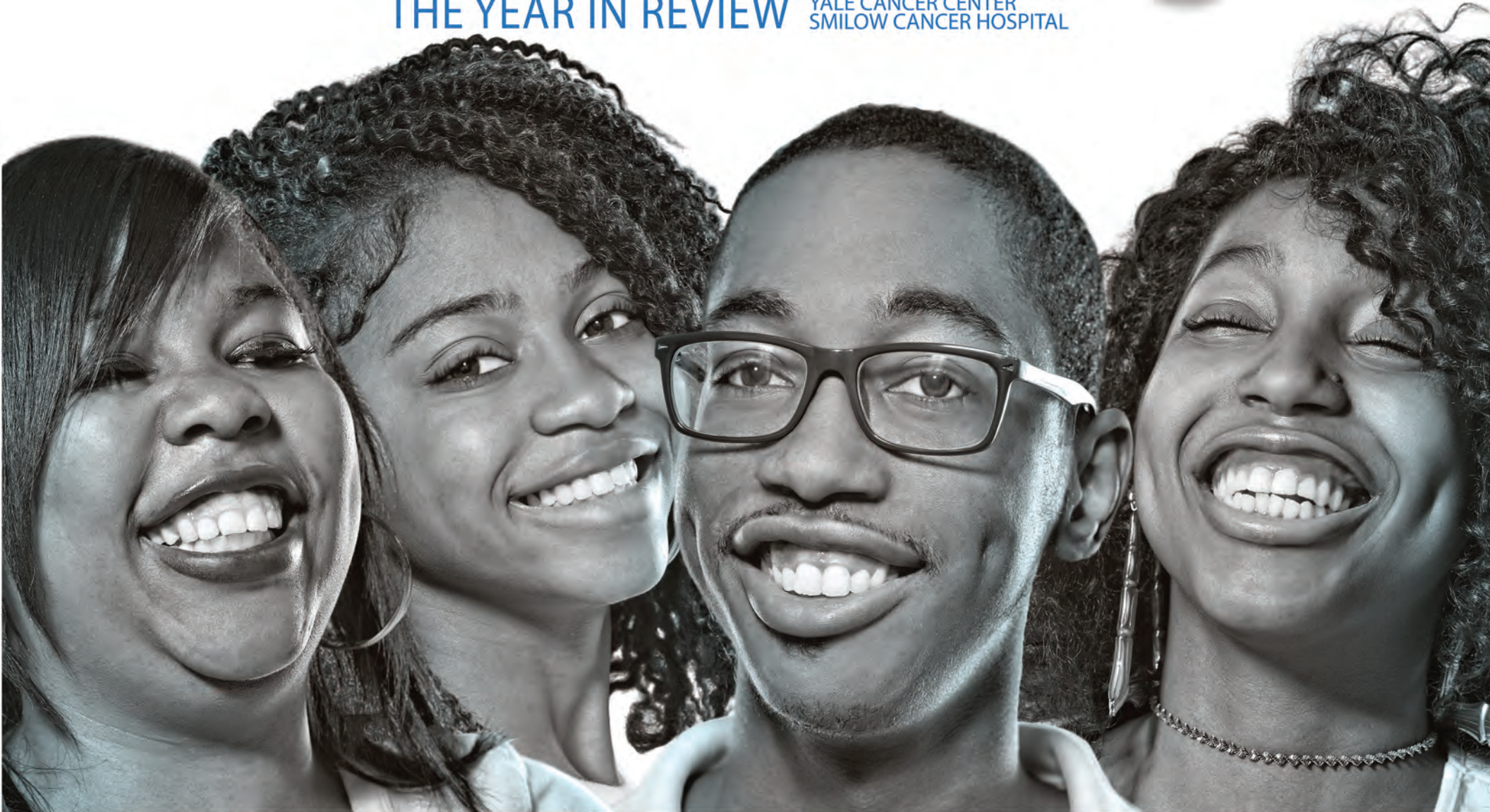


breakthroughs

THE YEAR IN REVIEW YALE CANCER CENTER
SMILOW CANCER HOSPITAL



The Wright Family's Journey to a Cure

yale cancer center

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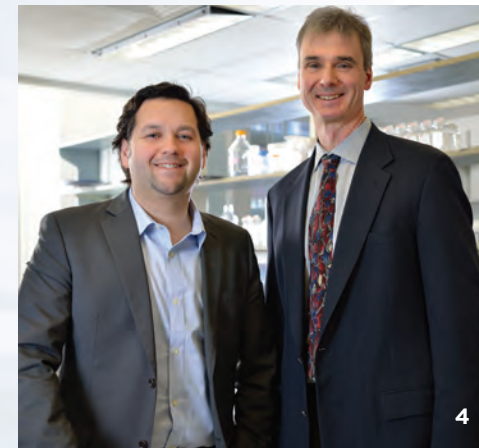
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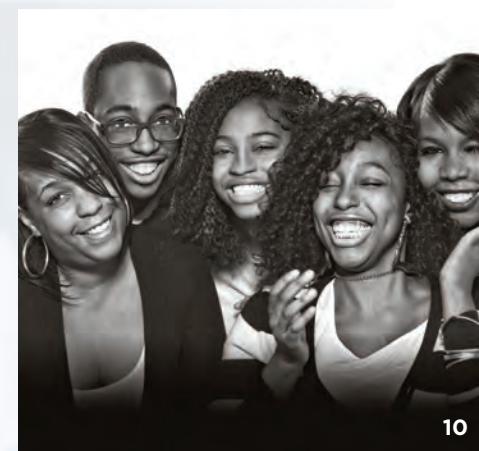
With research into biomarkers and immunotherapy surging at Yale Cancer Center, Dr. Kurt Schalper and others started developing standardized protocols and quantitative methods to carefully evaluate anti-tumor immune response. The result was a new Translational Immuno-oncology Laboratory.

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Dr. Patricia LoRusso's 5-year UM1 grant has launched more than a dozen new clinical trials at Smilow Cancer Hospital, with more coming. By the end of 2016, 10 supplemental grants, ranging in value from \$20,000 to \$1.3 million had been approved by the NCI for additional research and clinical trials.

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When Sharee Edmonds learned that three of her children had sickle cell disease, she prayed for a miracle that would cure them. That miracle came when her daughter Unity, now 17, was born. In an incredibly rare occurrence, her bone marrow was a perfect match for all three of her siblings.



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With the start of the New Year, I began my tenure at Yale Cancer Center and Smilow Cancer Hospital. In preparation of my start, I was traveling to Yale regularly and had the privilege of meeting with individuals representing the spectrum of professions that make up our Yale Cancer Center and Smilow Cancer Hospital community. We are fortunate to have dedicated and highly talented faculty and staff who are making vital contributions to our clinical and research enterprises and advancing our fundamental mission in clinical care, education, and research.

Smilow Cancer Hospital is recognized throughout the region as the leading provider of exceptional, compassionate, innovative patient-focused care, while Yale Cancer Center's research programs are advancing science across the compendium of basic, translational, population, and clinical research. This issue of *Breakthroughs* highlights some of the many strengths of our clinical and research programs.

As you will read, Yale is a national leader in the development of immunotherapy as a novel and effective treatment for cancer, and patients worldwide are benefitting from the translational research and clinical

trials that have paved the way to several new FDA approvals this year. Our Translational Immuno-oncology Laboratory is setting the stage for an increasing number of immunotherapy-based research studies led by our scientists. Much of the translational work is supported through Dr. Patricia LoRusso's UM1 grant from the National Cancer Institute, which funds new clinical trials available in our dedicated Phase I Infusion Center at Smilow Cancer Hospital.

Beyond efforts to lead innovation on our main campus, our Smilow Cancer Care Centers throughout Connecticut ensure that we provide exceptional care and access to clinical trials at 10 multispecialty locations across the state. This year, we will continue to strive to make the newest treatment options available to all patients through expanded clinical trial participation across all of our Care Centers.

Despite these achievements, it is widely recognized that cancer represents one of the greatest challenges that we face in medicine today. As we embark on 2017, I look forward to expanding our great talent; continuing to invest in critical infrastructure that will accelerate our basic, translational, clinical, and population research;

“I am grateful for the opportunity to lead Yale Cancer Center and Smilow Cancer Hospital and know that there will continue to be great successes to share with you from New Haven.”

and ensuring that our clinical, educational, and research programs are properly resourced to lead the next generation of innovation.

I am grateful for the opportunity to lead Yale Cancer Center and Smilow Cancer Hospital and know that there will continue to be great successes to share with you from New Haven. Many highlights from 2016 are featured in this edition of *Breakthroughs* and I look forward to sending updates of new research advances and outcomes from our laboratories to you in the year to come.

Sincerely,



Charles S. Fuchs, MD, MPH

Director, Yale Cancer Center

Physician-in-Chief, Smilow Cancer Hospital





Kurt Schalper, MD, PhD

A **HUB** for Translational Research in **ANTI-CANCER IMMUNOTHERAPY**

In just a few years, immunotherapy has become one of the biggest stories in cancer care. Some of the earliest clinical trials, as well as work on the biomarkers critical to these revolutionary treatments, were done at Yale.

“Immunotherapy can be used in many different tumor types, so the potential to treat a large number of patients across a range of cancer types is massive,” says Kurt Schalper, MD, PhD, Assistant Professor of Pathology and Director of the Translational Immunology Laboratory. “We realized there would be a great need for translational science to understand the biological determinants and exploit the potential of novel immunostimulatory therapies, including identifying predictive biomarkers that could improve patient care.”

With research into biomarkers and immunotherapy surging at Yale Cancer Center, Dr. Schalper and others started developing standardized protocols and quantitative methods to carefully evaluate anti-tumor immune response. Simultaneously, they discussed strategies to meet the demand for high-quality tumor samples for research and support of translational studies for immuno-oncology clinical trials. The result was Dr. Schalper’s Translational Immuno-oncology Laboratory.

Previously, if a Yale researcher wanted to undertake a

project requiring interrogation of immune markers in tumor samples, that scientist had to contact different investigators from diverse laboratories, departments, and/or “core” service facilities. Coordination was limited, frequently leading to inefficient use of samples and limited comparability across studies.

“It was difficult to know where to start and how to optimally integrate and communicate all the data,” explains Dr. Schalper, “and also difficult to put together a single project budget. We decided to standardize relevant immuno-oncology studies, harmonize protocols, and funnel the work through a single place.”

For example, Dr. Schalper is currently interacting with and supporting immune related molecular studies in diverse tumor types including lung, bladder, breast, head and neck, and digestive tract malignancies. He is also involved in projects with industry partners, in multi-institutional academic projects, such as AACR’s Stand Up To Cancer Lung Cancer Dream Team, and meets regularly with members of the Yale SPORE in Lung Cancer to discuss projects and to review and manage the tissue samples needed. All of which may require immunophenotyping, measurement of functional immune markers, analyses of nucleic acids, and integrated biostatistics and bioinformatics.

“We marry the researcher’s idea or the clinical project needs with an opportune biospecimen collection plan and execute or guide state-of-the-art cancer immunology molecular studies,” says Dr. Schalper. “Not infrequently, it’s a reality check between what the researchers aim to do and the resources that are required to get the job done.”

Asking the right questions beforehand is crucial. Does the study require blood or tumor tissue collection? Is tissue fresh, frozen, or fixed? If fresh, do they know how to preserve it after taking it from the patient? What sort of assays best suit the project’s purposes? Optimal execution of translational projects require careful planning, technical knowledge of the advantages and limitations of laboratory methods, and capacities to accurately envision the associated costs and potential problems.

“If samples aren’t prepared correctly or stored correctly, the researcher may miss an opportunity,” says Dr. Schalper. “Or if they’re measuring T-cells, some markers only measure the presence of the cells, some markers assess the function of the cells, and sometimes you have to do a combination.”



“We marry the researcher’s idea or the clinical project needs with an opportune biospecimen collection plan and execute or guide state-of-the-art cancer immunology molecular studies.”

“If an investigator isn’t familiar enough with the technical aspects of the proposed assessments, you may get, for example, DNA sequencing data that doesn’t match up, or the wrong type of sequencing to compare. This has to be coordinated up front, and there has to be enough knowledge about each of the different assays to make sure that at the end of the project, the data from each of those assessments can support each other and you can make conclusions about it,” adds Edward Kaftan, PhD, Associate Research Scientist, who helped Dr. Schalper launch the Translational Immuno-oncology Lab.

Careful planning is also essential to ensure that tumor samples are used efficiently. Researchers who aren’t quite clear about their goals or methods can waste tissue and/or exhaust limited sample supplies before all the necessary assays are done.

“Tissue samples are highly precious,” says Dr. Schalper. “They’ve become smaller and smaller over the years because of advances in medical technology and imaging, so we typically don’t receive big biopsies. The samples are shrinking but the number of questions and studies we have are growing. That’s why we need to coordinate the science with the collection of the sample in the right way.”

Dr. Schalper also helps researchers estimate a budget. It’s another reality check best done beforehand. Researchers often don’t understand the costs of the various assays, or

whether they can be done at Yale or must be outsourced. Dr. Schalper has much of this information, collects the rest, and advises the investigator as to what the project will cost and how long it will take.

“Having an early and clear view about the costs associated with the project is crucial to support the execution and success. This also helps adjusting to particular funding sources or requirements.”

After the planning comes the execution when all the assays and lab work are performed. Dr. Schalper coordinates this as well, and in many cases the assays are completed in his lab. When the projects need high throughput genomic sequencing, they are executed in the Yale Center for Genome Analysis or with external partners, but quality-control and analysis is completed by a Yale bioinformatician to make sure the analyses are standardized across samples, and to ensure the accuracy and comparability of the data.

Meanwhile he and his research team are looking ahead. They have validated assays for over 30 immune related biomarkers, and the number grows each week. “We are validating assays for the next generation of tumor targets,” he says, “which may become clinically relevant at any moment.”

NCI GRANT sparks explosion of EARLY PHASE TRIALS

When Patricia LoRusso, DO, Professor of Medicine and Associate Director of Innovative Medicine came to Yale in 2014, she not only brought 25 years of experience in developing new drugs, but also a prestigious National Cancer Institute (NCI) grant that has launched more than a dozen new clinical trials at Smilow Cancer Hospital, with more coming.

The grant, called a UM1, is a 5-year grant that funds investigator-initiated clinical trials. UM1s are highly competitive—nationwide, the award is given to only 11 principal investigators and institutions, who can select other academic sites for collaborations in research and recruitment of patients. As Yale’s associate sites, Dr. LoRusso chose Wayne State, Vanderbilt, and the Universities of California at San Francisco and San Diego. In North America, 44 academic sites are under the umbrella of the 11 UM1s.

The grants support the NCI’s Experimental Therapeutics Clinical Trials Network (ETCTN), whose purpose is to encourage early phase clinical trials of innovative cancer therapies. Dr. LoRusso’s UM1 is certainly having that effect at Yale.

“There has been what I would call an explosion of investigator-initiated research here in the last two years,” she says, “and in large part it’s because the UM1 helps support those projects and also helps with mentoring junior investigators to bring these projects to fruition.”

A key aspect of the UM1/ ETCTN is the NCI’s collaborative agreements with



Patricia LoRusso, DO



pharmaceutical companies, whose new therapies become part of the NCI’s portfolio of drugs. This allows the NCI to provide these drugs to UM1-funded researchers who need them for clinical trials. “It gives our researchers great access to drugs that otherwise can be hard to get,” explains Dr. LoRusso.

For instance, if exciting lab data generates an idea that includes testing a drug against a rare tumor, and if that drug is in the NCI’s pharmacopeia, the investigator can submit the idea to the NCI for review. If the NCI finds the idea is worth exploring, it requests a formal protocol. If the project is approved, the NCI gives the investigator the drug to study in a clinical trial, and the UM1 grant provides the funding.

Currently, a further benefit of the UM1 is that projects approved under this mechanism may also be



eligible for supplemental NCI grants to cover expenses related to an early phase clinical trial. “For instance, you might need to use or develop a biomarker to select a certain subset of patients or help to better understand how the drug is working against the tumors,” says Dr. LoRusso, “or you might need special imaging or biopsies or a special assay. You can apply for a supplement to cover that. So far we’ve been very successful in obtaining supplements to help us carry out the translational components of the clinical trials on the UM1.”

By the end of 2016, the NCI had approved 10 supplemental grants for Yale researchers, ranging in value from \$20,000 to \$1.3 million for biomarker research and also to help develop later stage, or Phase 2, clinical trials.

Nearly all of the UM1 projects pair a senior investigator with a junior investigator, in keeping with the grant’s objective to encourage mentorships that train the next generation of clinical investigators. “It’s a great way for junior faculty and fellows to learn the intricacies of what it takes to do clinical and translational research, what it takes to get an idea from the lab into the clinic,” explains Dr. LoRusso.

All the trials supported by Dr. LoRusso’s UM1 have translational components. “We not only ask a pivotal question in the lab and come up with results,” says Dr. LoRusso, “we’re asking if that science means improved outcomes for patients in the clinic.”

She reels off several examples. Joseph W. Kim, MD, Assistant Professor of Medicine, is testing two drugs in combination against prostate cancer, pancreatic cancer, triple-negative breast cancer, and small-cell lung cancer. He is looking at biomarkers of angiogenesis and alterations on vascular biomarkers, and how those relate to drug response. Both drugs came from the

“There has been what I would call an explosion of investigator-initiated research here in the last two years and in large part it’s because the UM1 helps support those projects and also helps with mentoring junior investigators to bring these projects to fruition.”

NCI’s pharmacopeia. With support from the UM1, says Dr. LoRusso, Dr. Kim’s idea is moving forward into a clinical trial.

In hematology, Amer M. Zeidan, MBBS, Assistant Professor of Medicine, and Thomas Prebet, MD, PhD, Assistant Professor of Medicine, are working on UM1-funded concepts involving leukemia and lymphoma. Another project developed by Dr. LoRusso and Joseph M. McLaughlin, MD, a former medical oncology fellow who is now in private practice, is combining a PARP inhibitor with a checkpoint inhibitor against BRCA-mutant triple-negative breast cancer, again using drugs from the NCI pharmacopeia.

Michael Cecchini, MD, a second-year Clinical Fellow, illustrates how Dr. LoRusso and the UM1 nurture ideas with the potential to ripen into early phase clinical trials. Dr. Cecchini is interested in gastrointestinal malignancies. In late 2015, during a clinic with Dr. LoRusso, the two clinical scientists batted around ideas to explore. They noticed that a recent paper had mentioned a subset of gastric cancer patients who had a mutational signature characteristic of homologous DNA repair. This signature has been linked to several cancers, including pancreatic, breast, and ovarian, and has been countered with PARP inhibitors, which kill cancer cells by hindering them from repairing their damaged DNA.

But defective DNA repair hadn’t previously been associated with gastric cancer, so Dr. Cecchini and Dr. LoRusso saw an opportunity to try PARP inhibitors against it. They also speculated that adding an angiogenesis

inhibitor that suppressed the development of new blood vessels in the tumor could boost the PARP inhibitor’s effectiveness. This combination has shown promise against other cancers, especially ovarian.

The two submitted the idea to the NCI in spring of 2016 and were asked to submit a full protocol. The project was approved under the UM1 at the end of the year, and Dr. Cecchini says they expect to start enrolling patients in their clinical trial by mid-2017. The University of California at San Francisco will collaborate on the trial and several ETCTN sites will help to enroll patients.

Asked how important the UM1 grant has been to him as a junior investigator, Dr. Cecchini says, “It’s incredible. Any type of clinical trial is really challenging, and I’ve learned so much. We’re integrated with the NCI but also potentially working with 44 other centers, and we also have our collaborators at UCSF. As a junior investigator, I’m getting to interact with faculty across the country. Without the UM1, none of that would be possible. I haven’t heard of many other fellows getting such a unique opportunity. I feel really fortunate, and also fortunate that Dr. LoRusso is available as a mentor for me.”

Dr. LoRusso is in the third year of her five-year UM1, and she hopes that Yale and their UM1 consortium will be able to renew the grant again—she has successfully re-competed for the NCI’s early therapeutics grants for about 20 years. She is hopeful that this explosion of investigator-initiated research at Yale sparked by the UM1 will continue for years to come.



“We not only ask a pivotal question in the lab and come up with results, we’re asking if that science means improved outcomes for patients in the clinic.”



Images of the dedicated space for Phase I Trials Carl Kaufman photographer



The Wright Family's Journey *to a Cure*



Left to right: Alequis (recipient 1999); Cachet (recipient 2016);
Unity (donor); Kortne (recipient 2016); Sharee (mom)

When Sharee Edmonds learned that three of her children had sickle cell disease, she prayed for a miracle that would cure them. That miracle came when her daughter Unity, now 17, was born. In an incredibly rare occurrence, her bone marrow was a perfect match for all three of her siblings. Now with seven siblings in total, Kortne Wright, 26, Alequis Wright, 24, and Cachet Wright, 21, are the only three that had the disease, while six carry the trait.

“Transplant is the only curative therapy for patients with sickle cell disease and the earlier they can get it, the better the success rate.”

Sickle cell disease is a genetic disease that affects red blood cells in the body. Each year about 2,000 children are born with sickle cell disease in the United States, the majority of which are African American. When both parents have the sickle cell trait, there’s a 25 percent chance that their child will have sickle cell disease. Sickle cell disease can affect many different organ systems in the body. Important organs like the bones, brain, heart, and kidneys, which need a constant blood supply, can be damaged by sickle cells that do not move through the body as easily as normal cells. For the Wright siblings, it was very routine to have what they call ‘crisis,’ severe bone pain that was unpredictable in both duration and severity.

“Although they were diagnosed at birth, I didn’t start to notice symptoms until they were toddlers,” their mother Sharee says. “Fever were the most common sign until they got older and started experiencing severe pain. It was very difficult as a mother to watch your children go through this. You learned to avoid certain triggers like extreme temperatures and flu season, but it was hard with three young children.”

In 1999, Alequis, who was 7 at the time, suffered a stroke and needed a bone marrow transplant to save her life. Unity was just seven months old, but the doctors caring for Alequis tested her to see if she was an HLA (Human Leukocyte Antigen) match, which she was. HLA typing is used to match patients and donors for a bone marrow transplant by creating a DNA fingerprint. HLA are proteins found on most cells in the body, and the immune system uses these to recognize which cells belong in the body and which do not. The more similar they are, the less chance there is of rejection. Since half of HLA markers are inherited from the mother and half from the father, each full sibling has a 1 in 4 chance of being a match.

Alequis’ bone marrow transplant was performed at Yale New Haven Hospital and the family decided not to immediately schedule another transplant for another child, but to wait and see how Alequis recovered. In early 2015, when the time came for Kortne and Cachet’s transplants, they met with Dr. Michael Kent, Assistant Professor of Pediatrics and a member of the Pediatric Transplant Program at Yale. He worked to find a regimen that would be well tolerated. “Once a patient is over the age of seventeen, transplant becomes more toxic for them,” he explains. “Our first task was to determine whether or not they would benefit from transplant, and then find a regimen that would be well tolerated.” Kortne and Cachet both received a reduced intensity method with less chemotherapy given in advance of their transplant to reduce toxicity, while still ensuring an effective transplant. Kortne and Cachet received their transplants in the summer of 2016 and are more than 4 months post-transplant.

In June of 2016, Dr. Niketa Shah, Assistant Professor of Pediatrics, joined the Pediatric Transplant Program as Director. Dr. Shah came from a very high volume transplant program and brought with her the expertise and experience needed to treat patients like Kortne and Cachet and offer them a cure. Dr. Shah commented that up until the point of transplant, Kortne and Cachet’s disease was being managed by frequent blood transfusions and pain medication, and when those didn’t work, hospitalization was necessary. “They are both still on graft-versus-host disease (GVHD) prevention medication,” explains Dr. Shah, “but will eventually be weaned off of it completely. Unity’s cells have slowly stabilized in Kortne and Cachet’s bodies and they are not experiencing any further sickle cell disease related complications.” For patients that receive a transplant from a sibling, the cure rate is 80-90 percent. What



makes the Wright family’s case so unique is that three siblings were diagnosed with the disease, and one sibling was a donor match for all three. Dr. Shah commented that she has never seen a case like this before.

The Pediatric Transplant Program at Yale is the only one in the State of Connecticut, and as Director, Dr. Shah’s goal is to grow the program regionally. Dr. Shah explained that the Transplant Program, as part of the Pediatric Hematology/Oncology Program at Smilow, performs various types of transplants for both malignant and non-malignant disorders of childhood. Dr. Shah comments, “Transplant is the only curative therapy for patients with sickle cell disease and the earlier they can get it, the better the success rate. Each sickle cell crisis causes damage to the body that can be irreparable. It’s important for both providers and patients to understand that if a patient has an HLA match donor, transplant can provide a cure.”

“I prayed for a miracle and instead, thanks to the team at Yale, I got four of them.”

A few years before transplant, Cachet developed an autoimmune disease that left her paralyzed. Despite all the challenges with sickle cell disease, all three siblings say they had a normal childhood and they had learned to live with their disease. When it interfered with school, they worked with tutors or completed home schooling to catch up. They avoided certain triggers and managed their pain when it came. Now after the transplant their lives have changed dramatically. They are learning to adjust

to normal life without having to constantly worry about sudden pain, cold, or fatigue. Both Cachet and Kortne will be attending Gateway Community College in the spring; Cachet plans to be a nurse and may return to Yale New Haven Hospital, but this time not as a patient.

The siblings joke that their sister Unity deserves an award for all the stem cells she has donated to her brother and sisters, and they realize what a different experience it was for each of them. However, they all agree that it was a part of their life and they got through it together. “This is the hardest thing I have been through in my life, and at the time I didn’t have a support system in place,” Sharee says. “All I had was my children and there were times when all three of them were in the hospital at the same time. I never stopped believing that all of my children would have the opportunity to be healed. I prayed for a miracle and instead, thanks to the team at Yale, I got four of them.”

Roy Decker, MD, PhD

Expanding the Treatment Options for Elderly Patients

In 1992, two meta-analyses of clinical trials established that for patients with limited-stage small cell lung cancer (LS-SCLC), the best treatment for cure and survival was chemotherapy combined with radiotherapy. This has remained the standard treatment for 25 years. But several of the analyzed trials in the meta-analyses excluded patients over 70 years of age, and in the subset of patients over 70 there was actually a survival detriment with the use of combined therapies. The analyses concluded that these older patients should be given chemotherapy only, and for the last 25 years that has remained the consensus recommendation for this group.

Roy Decker, MD, PhD, Associate Professor of Therapeutic Radiology and Disease Aligned Research Team Leader in Therapeutic Radiology, wanted to test the aging assumption behind the guideline. He reasoned that radiation technology and techniques have vastly improved, as have the supportive care options that limit toxicities.

“Our hypothesis was that in the modern era, we might find that patients over 70 were able to tolerate the treatments well and could benefit from them,” says Dr. Decker. He knew that some physicians were already prescribing chemoradiotherapy to this group despite the guideline, and he wondered if these patients had better survival rates.

These questions were important because older people make up a substantial portion of patients with this aggressive form of cancer. Each year, among all the new

diagnoses of the disease, 45 percent are patients over 70.

To test his hypothesis Dr. Decker turned to the National Cancer Database, which includes about 70 percent of all the newly diagnosed cases of cancer in the United States. “It’s very representative of how cancer is treated and what the outcomes are nationwide,” he says, “not only in academic settings but also in smaller community settings. So, it’s ideal for looking at how things actually occur rather than how they might occur in a very controlled clinical trial setting.”

Dr. Decker mined the database between 2003 and 2011 for patients over 70 with LS-SCLC. He identified 8,637 cases, by far the largest survey of this group ever undertaken. Among these patients, 44 percent had received chemotherapy alone and 56 percent had received chemoradiotherapy. The study’s findings were conclusive.

“We found that survival was significantly improved when these elderly patients were given the combined aggressive therapy,” explains Dr. Decker. “That was true in every subset of patients, including patients over 80 and those with significant medical comorbidities.”

The median survival rate for patients who received chemoradiotherapy was 15.6 months, compared to 9.3 months for those who got chemotherapy only. “For the average patient,” says Dr. Decker, “receiving radiation adds six months of survival, a very significant difference. So it seems that treating these patients with aggressive concurrent chemoradiation is a reasonable thing to do.

I think our paper also highlights that physicians are already doing a good job of selecting patients for this therapy, and I hope the study reinforces that. I also hope it makes physicians who aren’t using this aggressive therapy consider it for elderly patients.”

Dr. Decker sees other lessons in the study as well. When he trained, for instance, he was taught not to treat patients over 70, based on earlier clinical trials that mostly excluded them. Now there’s recognition that elderly patients should be included in trials so the results represent the whole population.

Another lesson is that the growing number of patient databases are rich resources that can answer broad questions economically unfeasible to study in a clinical trial. “The caveat is the data is retrospective and subject to selection bias,” says Dr. Decker, “but it complements clinical trials.”

The improved survival rates found by Dr. Decker reflect major advances in radiation technology and techniques. When the original studies were published, he notes, thoracic radiation exposed large areas of the heart and lungs to heavy doses of radiation, worsening side effects for patients.

“Today we’re imaging patients better with PET scans and CT scans,” he says, “so the area we treat is smaller, because we’re more confident that we’re targeting all the sites of known disease. And the techniques for doing that are better and better, with 3D conformal radiation and intensity-modulated radiation therapy. Now we can spare surrounding normal tissue while we target tumors.”

Two new clinical trials, led by Yale investigators, aim to increase survival for women with triple-negative breast cancer (TNBC). That result is long overdue—the last significant improvement in outcome against early-stage disease appeared more than 20 years ago.

Both trials will explore the effectiveness of immunotherapies against early-stage TNBC, says their designer and principal investigator, Lajos Pusztai, MD, DPhil, Professor of Medicine, Chief of Breast Medical Oncology, and Co-Director of the Cancer Center's Genomics, Genetics, and Epigenetics Program. Immunotherapy drugs, particularly immune checkpoint inhibitors, rev up the immune system against cancer cells.

"These drugs work remarkably well in lung cancer, melanoma, head and neck cancers, and bladder cancer, but breast cancer is a latecomer to this field," Dr. Pusztai explains. "About 7 years ago we and others noted that breast cancers with high levels of immune infiltration have excellent survival. However, at that time there were no drugs to test if this association represented a cause and effect relationship or a mere coincidence. This has changed with the development of immune checkpoint inhibitors."

Most current immunotherapy trials for breast cancer are focused on advanced, metastatic disease, not early-stage cancer, as the two groundbreaking trials do at Yale. "We need more effective treatments in early-stage disease, where the impact is greater," says Dr. Pusztai. "It's important to prolong a patient with metastatic breast

cancer's life for several months, or even years; but it is even more important to cure a person when her cancer is first diagnosed and prevent metastatic recurrence, as we can do in early-stage breast cancers."

Right now the best weapon against early-stage TNBC is chemotherapy that is often administered before surgery. After treatment, about a third of the patients show no traces of cancer at the time of surgery, which oncologists call a pathologic complete response. Unfortunately, the majority of patients don't achieve this.

One way to improve these outcomes is to increase the effectiveness of preoperative chemotherapy. One of the trials (NCT02489448) led by Dr. Pusztai aims to accomplish exactly this by adding durvalumab (MEDI4736), anti-PD-L1 immune checkpoint therapy, to the best currently available chemotherapy regimen. In December 2015, the first patient to receive the combination of standard chemotherapy plus anti-PD-L1 therapy as preoperative treatment for TNBC was on the clinical trial at Yale. The phase I part of the study is completed. The results haven't been published, but Dr. Pusztai says, "Our patients did well without major toxicities and there were many pathologic complete responses." The phase II part of the study will begin at Smilow Cancer Hospital early in 2017.

The second clinical trial (NCT02954874) is for TNBC patients who have extensive cancer after completion of standard preoperative chemotherapy. This is a national, randomized trial to test if one year of treatment with the

anti-PD-1 antibody pembrolizumab could improve survival in these patients. "If chemotherapy didn't work," says Dr. Pusztai, "maybe stimulating the immune system will, and perhaps it can eradicate the micro-metastatic cancers that survived the preoperative chemotherapy."

Pembrolizumab, an anti-PD-1 antibody, has already been approved against several advanced cancers, and has also been tested against metastatic TNBC in one phase I trial, done at Yale and elsewhere. In that study, the tumors shrank in about 20 percent of the patients, comparable to, or even better than chemotherapy could do in a similar situation. Remarkably, many of the patients who responded to the treatment remained on therapy for close to a year, indicating prolonged disease control, which is rarely seen with chemotherapy in this clinical setting.

Dr. Pusztai is testing immunotherapy drugs against TNBC partly because it often contains more tumor-infiltrating lymphocytes (TILs) than other subtypes of breast cancer. That could be good news in terms of immunotherapy, since more TILs mean more T-cells that can be activated to attack the cancer. In a small fraction of TNBC, TILs account for 50 percent or more of the cells in the micro-environment of the cancer and the prognosis for such patients, after chemotherapy and surgery, is excellent. But, the majority of TNBC contains much fewer TILs. The idea behind these trials, says Dr. Pusztai, is to force tumors with a low percentage of lymphocytes to act like tumors with 50 percent or more.

Lajos Pusztai, MD, DPhil

Boosting the Immune System to Fight Breast Cancer



Amy Justice, MD, PhD

Mining Long-term Patient Data for Scientific Discovery

The Veterans Administration cares for more people with human immunodeficiency virus (HIV) than any other organization in the country. All of these patients are included in the Veterans Aging Cohort Study (VACS), the nation's largest longitudinal study of people with HIV. Now 20 years old, VACS monitors more than 50,000 patients with HIV and, as a control, more than 100,000 patients uninfected with the virus. The extensive long-term data collected by VACS has altered research and treatment in many areas of medicine, including cancer.

The Principal Investigator on VACS is Amy Justice, MD, PhD, Professor of Medicine and Public Health and a member of Yale Cancer Center's Virus and Other Infection-associated Cancers Research Program. Dr. Justice has been researching HIV and its associations with other diseases, including cancer, for more than 25 years. Much has changed. "When I started working on HIV the median survival after an AIDS diagnosis was six months. Now, because of antiretrovirals, it's 30 years," she says.

This astonishing success has created new complications. Patients with HIV began living long enough to develop other medical problems. Dr. Justice wanted to know if HIV contributed to them, and also how the disease intersected with the process of aging.

"Even if we can suppress the virus with treatment, the virus does substantial damage to the immune system at the beginning of the infection and it often remains active in viral reservoirs," she explains. "So people have ongoing

inflammation, hypercoagulability, monocyte dysfunction, and immune dysfunction, which sets them up for all kinds of conditions associated with aging, cancer common among them."

In fact, older HIV patients rarely die from AIDS-defining conditions; the main cause of death is non-HIV-related cancers. Studying the relationship between HIV and cancer may open a window into the etiology of cancer that could benefit all cancer patients. In April, Dr. Justice and a colleague received a \$3 million grant from the National Cancer Institute to study liver cancer in veterans both with and without HIV to determine whether the cancer functions differently in these two groups.

For this project and others, VACS data will be mined for insights. Because of VACS, notes Dr. Justice, we know that people with HIV have more virally-related or infectious-related cancers than do people without HIV. This is true even when VACS controls for risk factors associated with HIV such as drugs, alcohol, tobacco, race, and socio-economic status.

"Folks with HIV just have more of these cancers, across the age spectrum," she says, "and because we have this big sample, we can pinpoint what is really driving outcomes for people aging with HIV." For instance, the standard measure of an HIV patient's health is the number of CD4 T-lymphocytes in a blood sample—the higher, the better. "But through VACS," says Dr. Justice, "we've shown that CD4 count alone doesn't really tell you much. Also considering

kidney function, liver function, bone marrow function—tells you a lot more."

That's why Dr. Justice and colleagues developed the VACS Index, a diagnostic tool that combines measures from major organ systems to predict various medical events. The Index has been validated to work not only for the average patient with HIV but also for all the main subgroups broken down by race, gender, age, and other factors. Given the patient's age, race, gender, and routine laboratory values, the program calculates a risk score which can be translated into an overall risk of mortality.

"HIV causes subtle injury to organ systems over time," explains Dr. Justice, "and it also increases your risk of many comorbid conditions. To understand how sick a patient really is, you need a measure of their overall burden of disease."

Dr. Justice is extending what she has learned from VACS. She is developing an even larger cohort—all veterans under VA care born between 1945 and 1965, roughly six million people. She also has a grant from the VA's Million Veteran Program, which so far has enrolled more than 500 thousand veterans, who have provided DNA samples and full access to their electronic records. By combining the phenotypes developed and validated in VACS with this trove of genomic information, she says, "We'll be able to characterize a tumor and then link it to the patient's longitudinal record and full genome. That will create an invaluable resource for discovery."

Mice injected with human genes may transform research into cancers of the immune system, multiple myeloma, and other hematologic cancers. Yale scientists designed this groundbreaking mouse model by removing six genes from mice and inserting key genes found in human bone marrow, where myeloma develops. This revolutionary mouse model is providing researchers and clinicians at Yale and beyond with multiple possibilities to advance both research and treatment.

To build this mighty mouse took more than a decade, says Richard Flavell, PhD, Sterling Professor of Immunobiology. Previous researchers had succeeded in putting human cells into mice, but unless the immune system of the mouse was disabled, it attacked the human cells and impeded their ability to develop. But even when the mouse immune system was knocked out, the human immune cells did not populate the mouse well. Dr. Flavell attributed this to chemical differences in the growth factors (proteins that bind to receptors on cell surfaces) found in the immune systems of mice and humans. He set out to design a mouse model that mimicked the human immune system so that researchers could use mice to study that system and its responses to infections and cancers.

“We identified the growth factors we thought were important for immune cell development,” he says. “Then we chopped out the mouse genes and put in the human genes.” He and his colleagues built a separate mouse model for each of the five factors. Each one took more than a year to

create. In 2012, they combined all five into a new model and introduced it to the world in a 2014 paper. They named it MISTRG, an acronym for its five human genes. “That’s been a very valuable mouse for a lot of people,” says Dr. Flavell.

Next they improved MISTRG by knocking in another growth factor, human Interleukin-6 (IL-6), to create a new mouse called MISTRG6. They added IL-6 because it’s a critical growth factor for myeloma, a cancer of the bone marrow whose cells will not grow in vitro, making it difficult to study. “So now we have a mouse that makes this human protein,” explains Dr. Flavell, “in a very specific way, in the right amount, at the right time, in the right place, because it’s in the same gene environment—the bone marrow—where the mouse gene was. We figured that if we put myeloma cells from a patient into the bone marrow of these mice, maybe the cells would grow and allow people to study this terrible disease.”

They tested their assumption together with the lab of Madhav V. Dhodapkar, MBBS, Arthur H. Bunker and Isabel Bunker Professor of Medicine (Hematology), Chief of Hematology, and Professor of Immunobiology. The injected myeloma cells behaved in the mice much as they do in humans. “So now we can grow patients’ tumor cells, we can study them, we can look at their genetic evolution and the way they behave hematologically,” Dr. Flavell notes. That work has started at Yale.

Myeloma may be foreshadowed by a precursor stage called MGUS (monoclonal gammopathy of undetermined

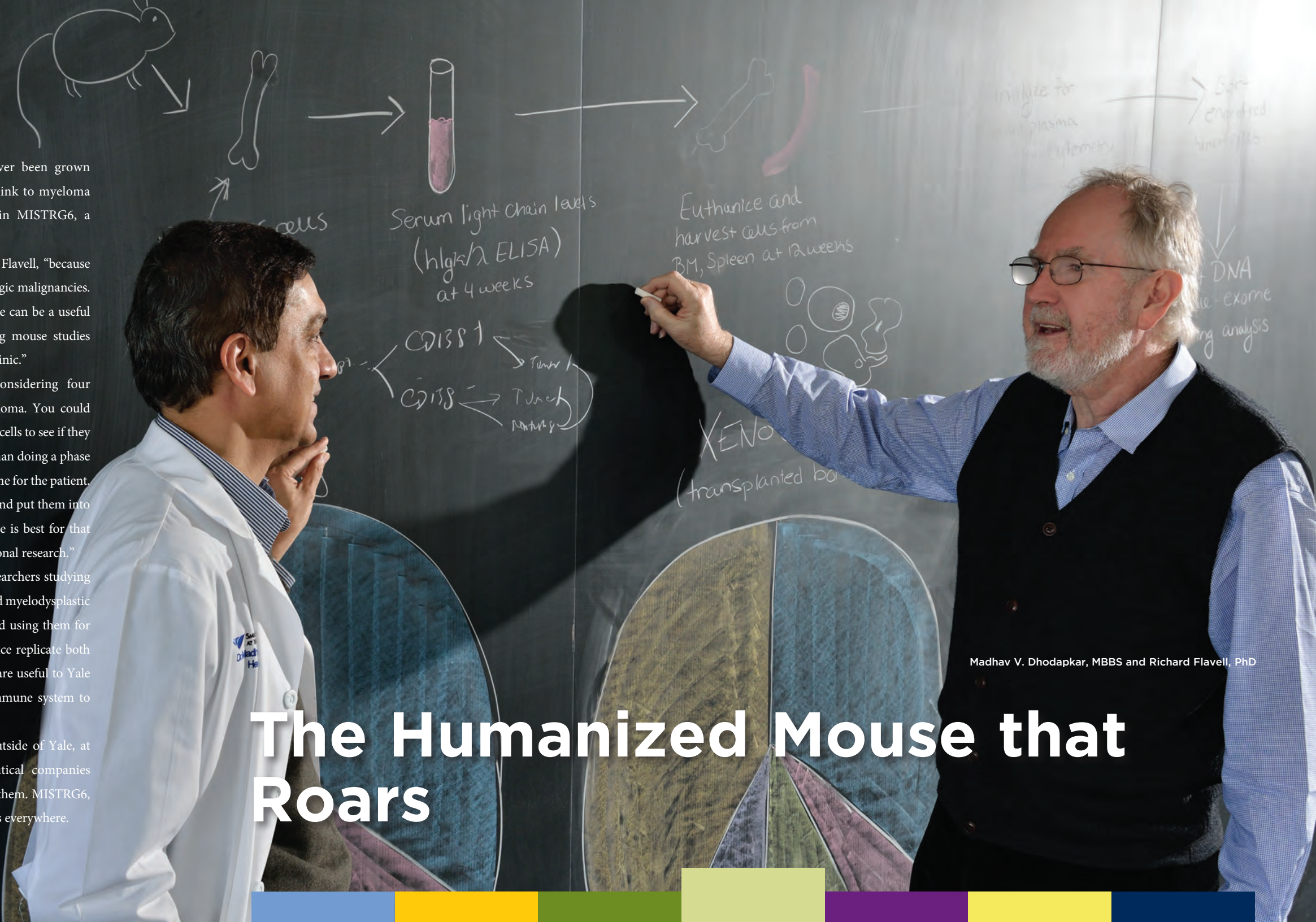
significance). But MGUS cells had never been grown successfully, so their development and link to myeloma remained unclear. But MGUS grows in MISTRG6, a scientific first.

“This was really wonderful,” says Dr. Flavell, “because it’s a general paradigm for other hematologic malignancies. We’re very excited. These humanized mice can be a useful intermediate point between people doing mouse studies and people working with patients in the clinic.”

Imagine, he adds, that you are considering four experimental drugs to treat human myeloma. You could test them on an individual patient’s tumor cells to see if they respond. “That’s a lot easier and cheaper than doing a phase I or II clinical trial, and a lot less burdensome for the patient. Or you could take a patient’s tumor cells and put them into 20 mice to test therapies to see which one is best for that patient. It’s an additional kind of translational research.”

The mice are already serving Yale researchers studying bone marrow cancers such as myeloma and myelodysplastic syndromes. Another researcher has started using them for research into lung cancer. Because the mice replicate both malignant and normal human cells, they are useful to Yale scientists studying ways to trigger the immune system to attack tumor cells.

Interest in the mice is also strong outside of Yale, at both academic centers and pharmaceutical companies who plan to do their own research using them. MISTRG6, created at Yale, will benefit cancer patients everywhere.



Madhav V. Dhodapkar, MBBS and Richard Flavell, PhD

The Humanized Mouse that Roars

Harriet Kluger, MD, Barbara Burtness, MD, and Roy S. Herbst, MD, PhD

Building on Immunotherapy's Success

Yale scientists have long been at the forefront in the development of new anticancer drugs, notes Barbara Burtness, MD, Professor of Medicine, Disease Aligned Research Team Leader for the Head and Neck Cancers Program, and Co-Director of the Developmental Therapeutics Research Program. She mentions that chemotherapy was first used against cancer in the 1940s by Yale pharmacologists Louis S. Goodman and Alfred Gilman, who altered toxic mustard gas into a chemical agent against lymphoma.

The challenge for Yale's researchers in developmental therapeutics hasn't changed. "When you have an exciting new compound or have figured out how to go after a target," says Dr. Burtness, "how do you turn that into something that can be studied in patients and become clinically useful?"

Yale's commitment to therapeutic innovations has recently become even stronger, she adds, exemplified by huge investments in leading-edge facilities and the recruitment of outstanding senior and junior scientists.

"In the Developmental Therapeutics Program," says Dr. Burtness, "we have really built out our capacity to do early phase trials. We have great creative pharmacologists who develop the new drugs, and also the clinical expertise to translate that to patients. There's the new Phase I Clinical Trial Infusion Center, and we have hired a lot of staff to run early phase trials here ourselves."

She is particularly excited about Yale's leadership in developing new immunotherapies against solid tumors.

"There are FDA drug approvals in head and neck cancer and in lung cancer that come directly out of the activities of our program," she says. "There are a number of us in Developmental Therapeutics who have played pivotal roles in testing immune checkpoint inhibitors in solid tumors." She describes some highlights:

Scott Gettinger, MD, Associate Professor of Medicine, reported a large dose-finding study about nivolumab, a targeted antibody that blocks PD-L1. Dr. Gettinger's trial showed that when used against non-small cell lung cancer, a highly deadly form of the disease, the median survival was 10 months. "That was unprecedented," says Dr. Burtness, "and has led to a randomized trial establishing nivolumab as part of the standard of care in non-small cell lung cancer."

Roy Herbst, MD, PhD, Ensign Professor of Medicine and Professor of Pharmacology, Chief of Medical Oncology, and Associate Director for Translational Research, then led a landmark trial showing that non-small cell lung cancer expresses immune suppressing ligands called PD-L1, and that an anti-PD-L1 checkpoint inhibitor called pembrolizumab can turn the immune system back on and is superior to the chemotherapy. "That was published in *The Lancet*," notes Dr. Burtness, "and pembrolizumab has become the new standard."

Harriet Kluger, MD, Professor of Medicine, mostly treats melanoma; Sarah Goldberg, MD, MPH, Assistant Professor of Medicine, mostly treats lung cancer—but they both noticed something unexpected when their patients

were given immunotherapies. Even the cancers that had metastasized to the brain responded to the treatment. This led to a clinical trial to study the effects of pembrolizumab on patients with brain metastases.

Then there's Dr. Burtness herself, whose primary area of research is head and neck cancers. These are notoriously resistant to treatment, and no new drugs have been approved since 2006. But Dr. Burtness sees great promise in immunotherapy. She and Paul Eder, MD, Professor of Medicine, participated in a multi-center trial of pembrolizumab against head and neck cancer in patients who expressed the biomarker PD-L1. Though the overall response rate was a modest 18 percent, it represents a striking improvement over previous treatments for this stubborn disease. In August, the FDA approved pembrolizumab for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma, despite being treated with platinum-containing chemotherapy.

Dr. Burtness is confident that further improvements aren't far off, probably through combination therapies. For instance, she is excited about a promising phase III trial she is chairing for head and neck cancer that combines pembrolizumab with chemotherapy, in comparison to pembrolizumab alone.

"The most significant point about these new therapies," says Dr. Burtness, "is that they prolong life for patients with metastatic and recurrent disease who in the past had relatively short life expectations."

Researchers first linked the epidermal growth factor receptor (EGFR) to cancer in the 1980s. The signal transduction pathways through which this receptor tyrosine kinase activates cancer are understood well enough that targeted therapies are in use to thwart it, including antibodies such as cetuximab and kinase inhibitors such as erlotinib and gefitinib. But despite this long and steady accumulation of knowledge, many aspects of EGFR remain enigmatic.

One of the protein's most tenacious explorers is Kathryn M. Ferguson, PhD, Associate Professor of Pharmacology and a faculty member of Yale's Cancer Biology Institute. She has unlocked many of EGFR's doors only to find more locked gates behind them.

"What has sustained our interest in this protein over the years," she says, "is that we fundamentally want to understand how it works – how it transfers messages across the cell membrane – and we still don't. Even with all the studies that have been done, we still have a lot to learn about how it's activated by its different ligands, how the signal is turned on and off, and how the receptor is aberrantly activated in cancer. And since EGFR is implicated in a large number of cancers—breast cancer, lung cancer, head and neck cancer, colorectal cancer, glioblastoma—it's clearly very important from a clinical perspective."

About a decade ago, Dr. Ferguson and Mark Lemmon, PhD, FRS, David A. Sackler Professor of Pharmacology and Co-Director of the Cancer Biology Institute, solved the

X-ray crystal structure of the extracellular region of EGFR. That breakthrough revealed that EGFR does not simply sit down and wait for the ligand to activate it, but rather is constantly altered by conformational changes. EGFR is a shape-shifter, flexible and adjustable, and far more complex than previously realized.

"That has really colored the way we think about the receptor," explains Dr. Ferguson. "The molecule's flexibility changes the way we need to think about how it is activated and what we need to do to inhibit it in cancer patients." Dr. Ferguson intends to investigate this in glioblastoma, in which poorly understood activating mutations in the EGFR extracellular domain have been described. Her hypothesis is that these mutations alter the protein's conformational flexibility, and that this is responsible for activation. To test this hypothesis she needs to move beyond the extracellular region where most of her research has been focused and find a way to open another locked door.

"We are now generating the whole receptor for structural studies," she says, "not just the extracellular region but also the parts that go across the membrane and act inside the cell – so that we can begin to understand how conformational changes and mutations in the extracellular region influence the receptor's activity inside the cell." Truly deciphering the mechanism of transmembrane communication would open possibilities for approaches, and new kinds of antibodies that might limit the ability of the receptor to switch to an activated conformation.

EGFR's frequent conformational changes might also explain why some cancers become resistant to the effects of cetuximab, a widely used antibody that blocks EGFR function in head and neck, colorectal, and other cancers. Alterations in EGFR emerge in cetuximab-treated cancers that appear to hinder the ability of the antibody drug to bind EGFR, rendering the treatment ineffective. The mechanism behind this resistance is another door that Dr. Ferguson hopes to pry open.

"We think that fully understanding EGFR will lead to more information that can be applied rationally in the clinic," she says, "both for better uses of the treatments that already exist and for developing better ways of 'silencing' cancer-causing mutations."

She is also studying other receptor tyrosine kinases related to EGFR, in particular one called TIE2. Like EGFR, it is proving far more complex than previously expected.

Since coming to Yale a year ago from the University of Pennsylvania, Dr. Ferguson has established a new lab in the Advanced Biosciences Center on Yale's West Campus. "One of the most exciting things about being here is the Cancer Center's strength in signal transduction," she says, "and also the feeling that basic science done at Yale really impacts clinical work and approaches to patient treatment. This unique strength of Yale opens up opportunities for collaborations with other basic and clinical scientists doing clinical trials right here on the molecules we're interested in."



Kathryn Ferguson, PhD

Unlocking the Secrets of EGFR

Steven L. Bernstein, MD

Leading the Fight Against Tobacco Addiction from the ED

In the 1980s, when Steven L. Bernstein, MD, Professor of Emergency Medicine and of Public Health (Health Policy), began working in hospital emergency departments (EDs) in New York City, he noticed that among the people he treated, whether for emphysema or hypertension or stroke, almost 40 percent were smokers. That was double the national average of adults who used tobacco. Dr. Bernstein realized that whatever malady brought patients to the emergency department, the underlying cause was smoking, yet they were being sent home with that cause untreated.

“Emergency departments were reservoirs of unrecognized, untreated, undiagnosed smokers,” he says. “So I thought maybe I could do good for patients by tackling smoking in this nontraditional setting.”

The problem is large. Smoking-related diseases, including various cancers, kill about 480,000 Americans each year, and smoking remains the country’s principal cause of preventable health problems and deaths.

Dr. Bernstein believes that emergency departments are excellent places to initiate change. There’s never a shortage of patients. EDs handle 130 million visits every year. About 20 million smokers are admitted, some of them multiple times. Yale New Haven Hospital’s ED sees 90,000 patient visits a year.

People who use EDs tend to come from medically and socially disadvantaged backgrounds, and are more likely to engage in unhealthy behaviors such as smoking. “So if

you’re interested in the social and behavioral determinants of health, which is how I think about this work,” says Dr. Bernstein, “then the ED is a great place to be.”

He also believes that emergency departments present an opening for medical intervention. “Patients are stuck there for a couple of hours, they’re sick or injured,” he says. “If I can empathically and therapeutically explain to them that they’re there because of tobacco dependence, and that changing that might improve their health, and if I also give them an alternative or aftercare, that moment can be very impactful, especially if we can start treatment right then and there.”

That was the idea behind Dr. Bernstein’s recent randomized clinical trial of 778 patients, conducted over two years at Yale New Haven’s ED. The trial offered patients a combination of therapeutic treatments that had not been grouped together before.

The package had four components. First, each patient received six weeks of nicotine patches and gum, tailored to the amount they smoked. More important, the patients were given the first nicotine treatment in the ED, which is atypical. Dr. Bernstein partly wanted to show patients that these medications are easy to use and well tolerated, but he also wanted, “to break the paradigm of tobacco treatment. When patients come in with hypertension or diabetes or other chronic diseases, we don’t ask them if they want to treat it,” he says, “we just start them on something. But in tobacco we check their motivation and tiptoe around the

problem. A number of us are trying to change the default to immediate treatment.”

Second, each patient was referred to a quitline, a toll-free phone number where a smoker can talk to a counselor about how to stop smoking. Typically, patients are simply handed a brochure or phone number. “But we faxed a referral form right from the ED to the quitline,” explains Dr. Bernstein, “so the quitline had the smoker’s name and phone number and would call.”

Third, a counselor interviewed each patient to explore why the patient smoked and to motivate reduction or cessation. Lastly, the counselor called the patient three days later to follow up and reinforce the motivational interview. Patients in the trial’s control group received the standard treatment, a brochure about the quitline.

At three months, 12 percent of the patients who received the combined therapies had stopped smoking, compared to five percent of the control group. “That means that if you treated 14 smokers in the ED with my protocol, you would have made one more quitter,” says Dr. Bernstein. “And if do that over the 40 or 45 million Americans who smoke, many of whom use the ED every year, you end up making a whole lot of quitters over the course of a year. So that seven percent difference may not sound like a lot, but when you look at it over the whole population of smokers, it’s a lot of people. In terms of years of lives saved, and quality of lives, it’s an exciting result.”

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Signal Transduction

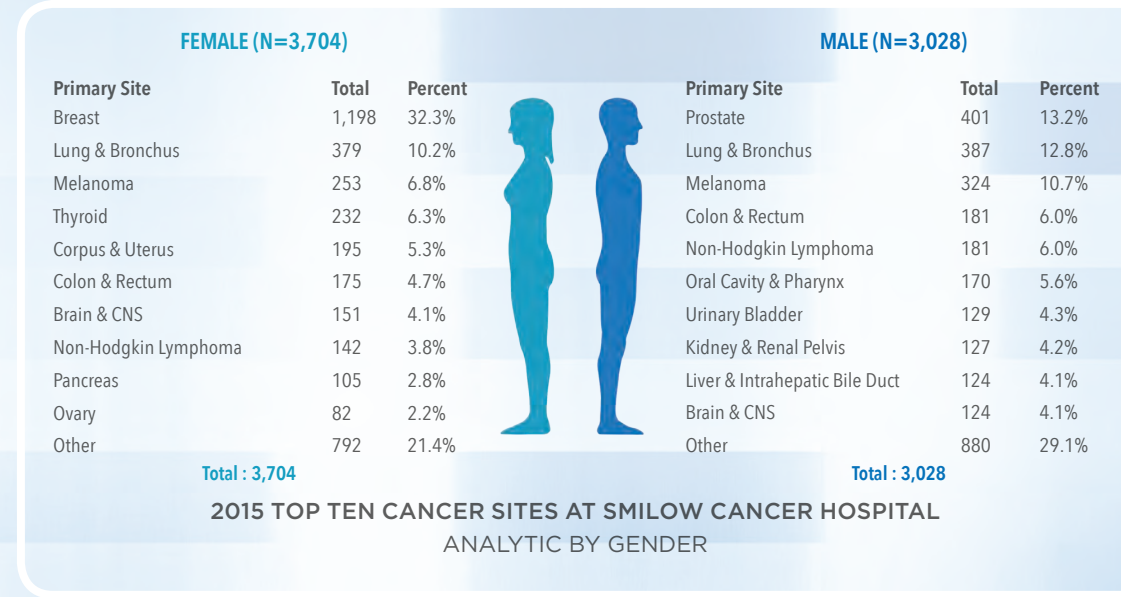
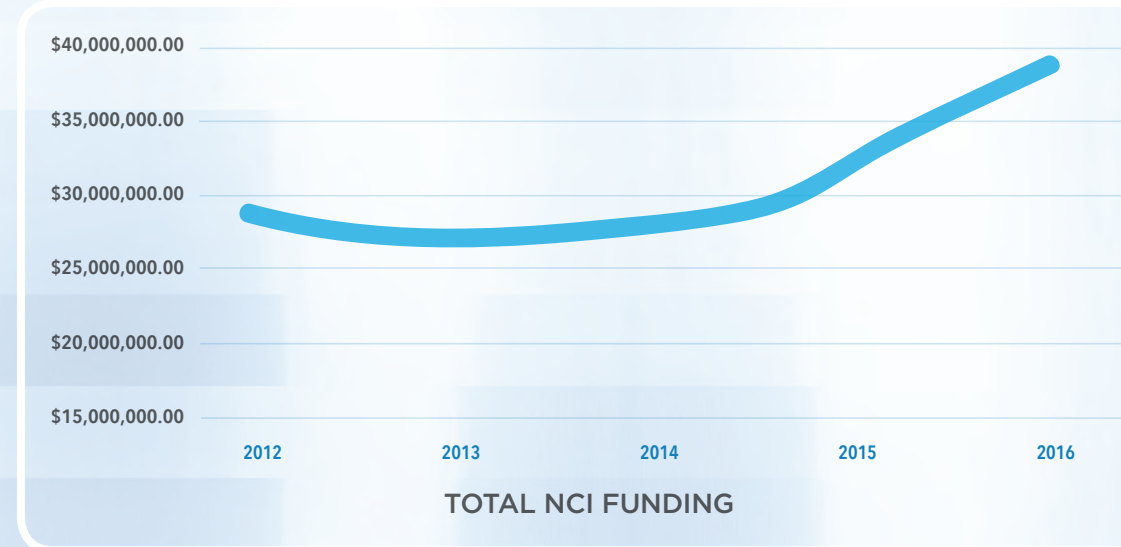
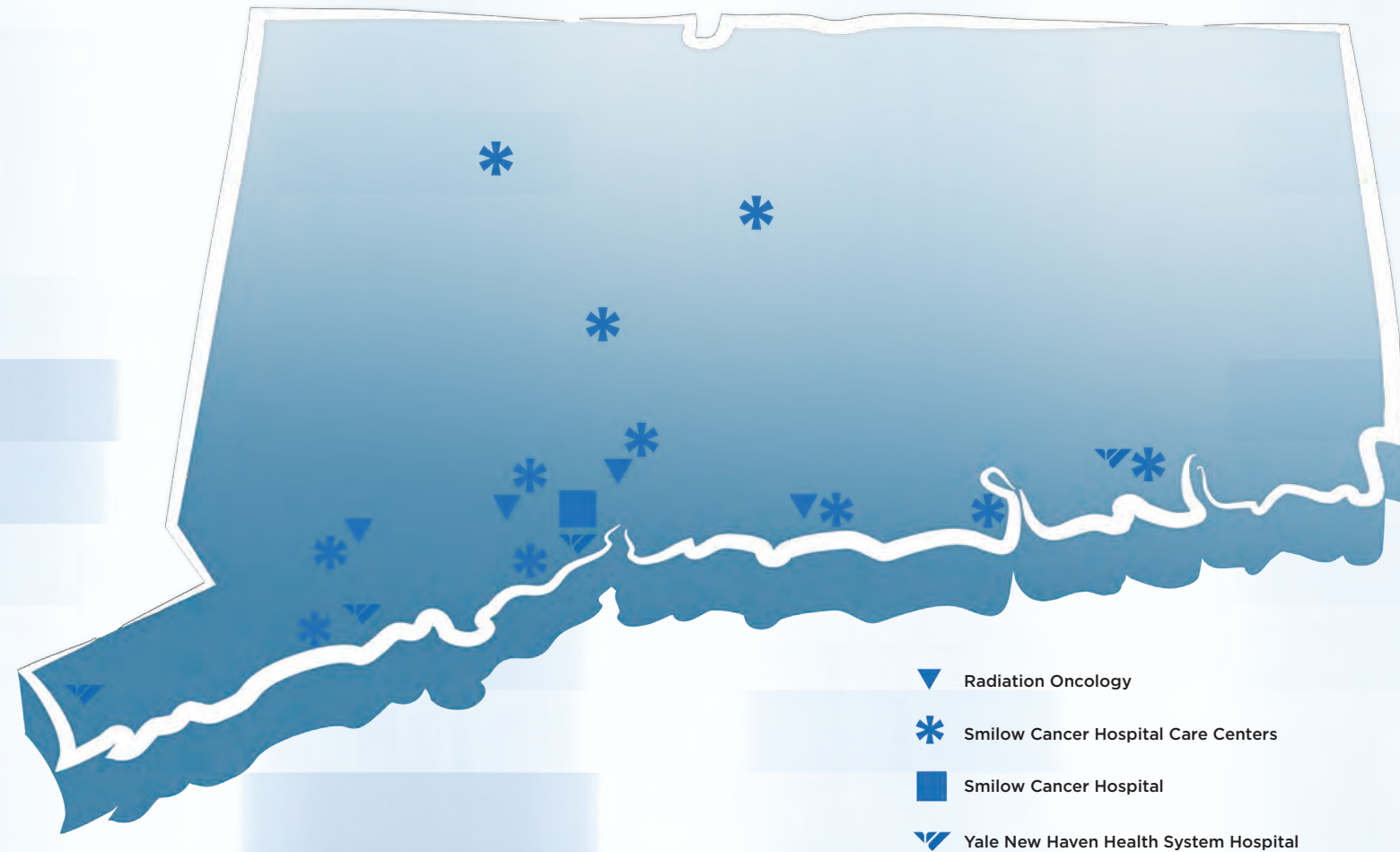
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 Titus Boggon
 David Calderwood
 Toby Chai
 Gary Desir
 Michael DiGiovanna
 Rong Fan
 Kathryn Ferguson
 Clare Flannery
 John Geibel
 Sourav Ghosh
 Valentina Greco
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 Joseph Schlessinger
 Martin Schwartz
 David Stern
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Yale Cancer Center and Smilow Cancer Hospital



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283 - High Impact Publications IF>10

- 39 - *Journal of Clinical Oncology*
- 9 - *New England Journal of Medicine*
- 27 - *Cell*
- 17 - *Science*
- 26 - *Nature*
- 35 - *Nature specialty journals*
- 18 - *Journal of Clinical Investigation*
- 28 - *Journal of the National Cancer Institute*
- 23 - *Molecular Cell*
- 16 - *Immunity*

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