Yale Cancer Center

centerpoint

MAGAZINE

Innovative Care & Brotherly Love Team Up

fall | winter 2017

contents fall | winter 2017

departments

On the Cover
Marc and John St. Martin

Lisa Garcia **photographer**

features

yale cancer center

Director
Charles S. Fuchs, MD, MPH

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

Director, Public Affairs & Marketing
Renee Gaudette

art + production

Design
Frankie Winter Design

Photographers
Peter Baker
Lisa Garcia

Writers
Steve Kemper
Emily Montemerlo
Kristin Rattini

submit your ideas...

Do you have an idea for a story you'd like to see featured in Centerpoint Magazine? Submit your ideas to: renee.gaudette@yale.edu

Yale Cancer Center
centerpoint
MAGAZINE

Centerpoint Magazine is published two times a year by Yale Cancer Center to inform the public and the Center's friends, volunteers, donors, and staff on current items of interest at Yale Cancer Center.

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

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

director's letter

The partnerships developed throughout Yale Cancer Center and Smilow Cancer Hospital continually push the boundaries of cancer research and patient care. It's my goal to leverage the great accomplishment and expertise across our clinical and scientific community and launch new initiatives, build new collaborations, and expand our pool of talent to drive forward our mission to better understand and treat cancer. Through all of this, team science and partnering in the care of our patients is fundamental.

Immunotherapy breakthroughs are transforming the care of patients worldwide, and laboratory and clinical scientists at Yale Cancer Center are leading the charge. In September, the FDA approved the first immunotherapy drug for advanced stomach cancer providing a new option for patients with a difficult to treat disease. Nonetheless, across all cancers, some patients who do respond to immunotherapy become resistant to the treatment, and others may not respond at all. In an important new finding, Dr. Katerina Politi used the resources and expertise of our Lung Cancer SPORE team to identify the protein that causes resistance to immunotherapy in non-small cell lung cancer with mutations in the EGFR pathway. With this new knowledge, the hope is that the resistance to immunotherapy treatment can be prevented.

While teams of scientists are working to solve inquiries in our laboratories, our clinical teams are focused on improving care for our patients. Drs. Rogerio Lilenbaum and Kerin Adelson, and Ms. Cathy Lyons, Vice President for Clinical Services, are leading a highly engaged, multidisciplinary team of physicians, nurses, pharmacists, administrators, and clinical staff to maximize quality and impact clinical care, while minimizing costs throughout Smilow Cancer Hospital and our Care Centers. Through the Oncology Care Model, we opened an Oncology Extended Care Clinic for our patients. This novel service provides acute care services and is the preferred alternative to the emergency department. Newly hired patient care coordinators and approved clinical pathways are also helping to improve access and care throughout our clinical teams.

The best combination is when we team up to care for our patients, like the story of Marc St. Martin. Mr. St. Martin had a long course of treatment for cutaneous T-cell lymphoma, under the care of Dr. Richard Edelson, which resulted in a curative stem cell transplant with a donation from his brother, John. Unfortunately, Marc was left with painful side effects from previous radiation treatments. After careful consideration, Dr. Deepak Narayan performed a revolutionary fat cell transplant, again using a donation from his brother John, to relieve Marc of his pain. Not only did Marc have an amazing team at Smilow but also a family that supported him in the most remarkable way. His story truly exemplifies why we work so diligently in the pursuit of new treatment options for our patients.

These articles and many other accounts exemplify the power of discovery and innovation at Yale Cancer Center.

Sincerely,

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

Innovations to IMPROVE QUALITY *and* CONTROL COST

Steve Kemper writer **Peter Baker** photographer

Dr. Kerin Adelson and Dr. Rogerio Lilenbaum

The U.S. healthcare system is the most expensive in the world, and the most expensive disease to care for, per person, is cancer. The National Cancer Institute estimates that by 2020 the annual bill for cancer care could reach $173 billion. The burden is unsustainable, and all the stakeholders involved—hospitals, physicians, businesses, insurers, and the government—are searching for ways to cut the financial impact of cancer care.

The federal government's Centers for Medicaid & Medicare Services (CMS) has initiated one promising experiment, a five-year program that began last July called the Oncology Care Model (OCM). CMS selected 192 group practices to take part in the program. Smilow Cancer Hospital is among those participating, and has about 3,500 patients in the program.

OCM's twin aims are to improve cancer care while reducing costs. To encourage innovations that achieve these goals, the program pays a monthly stipend of $160 for each Medicare patient on chemotherapy. Additional stipends are possible if a practice meets certain targets. OCM's underlying purpose is to shift cancer care away from the traditional fee-for-service model and move it toward a payment model that rewards quality rather than quantity.

Smilow is participating in OCM for two reasons, explained Rogerio Lilenbaum, MD, Professor of Medicine and Smilow's Chief Medical Officer. "First, we wanted to engage in a value-based payment model, because we believe that is where healthcare is going, and we wanted the opportunity to test the actual steps that an institution needs to take to be successful in that model."

Second, he continued, OCM's monthly stipend allowed Smilow to add clinical infrastructure to improve the quality of care, regardless of whether the payment model succeeds. The main additions are a new Oncology Extended Care Clinic, available to all Smilow patients 16 hours every day, the hiring of seven senior oncology nurses to coordinate the care of OCM patients, and implementation of clinical pathways for care.

How will these enhancements meet the other half of OCM's mission, to reduce costs? Kerin Adelson, MD, Associate Professor of Medicine and Chief Quality Officer at Smilow, expects the Oncology Extended Care Clinic to cut down on unnecessary visits by cancer patients to Yale New Haven Hospital's Emergency Department (ED). Several years ago, Dr. Adelson and colleagues analyzed these visits over five months and found that about half of them could have been managed outside of the ED, at a much lower cost.

After an extensive multidisciplinary planning process, the Oncology Extended Care Clinic (OECC) opened on April 1, 2017. It is quiet, uncrowded, and staffed by oncology APPs and nursing staff and attending physician, Dr. Bonnie Gould Rothberg. Unsurprisingly, responses to the clinic from patients have been enthusiastic. Since its opening, the clinic completed more than 1200 visits, and nearly 70 percent of the patients were discharged home rather than hospitalized—another savings. "The expertise of our OECC staff results in focused and specialized supportive care to our patients when they are experiencing complications of treatment or disease," said Catherine Lyons, RN, MS, Vice President, Patient Services, Smilow Cancer Hospital.

Because Medicare patients in the OCM program are older, they often have co-morbidities. That's where the seven newly hired care coordinators are invaluable. They advocate for their patients throughout their entire medical journey, inside and outside the hospital. That might mean finding extra homecare, attending appointments with patients, acting as liaisons between inpatient and outpatient doctors, and clarifying prognoses and treatment options. The OCM care coordinators have a dual goal: to improve care for patients and to help them avoid unnecessary and expensive hospitalizations, ED visits, and aggressive late-stage treatments.

"When you look at the total cost of cancer," said Dr. Adelson, "30 percent is spent in the last year of the patient's life, and much of that 30 percent is spent in the very last month, when it's often futile."

"Nationally, we see high rates of hospitalization, admission to intensive care units and chemotherapy being given near the very end-of-life—interventions that don't improve outcomes," said Dr. Adelson. "This is not in the best interest of the patient, because it prevents them from spending time with their family, from saying goodbye, and from getting their affairs in order. End-of-life care is an area where improving the quality of care will also reduce cost."

The new Oncology Extended Care Clinic at Smilow is quiet, uncrowded, and staffed by oncology specialists 16 hours a day as an alternative to the ED.

"With clinicians, the conversation can't just be about dollars," said Dr. Lilenbaum, "because their focus is on quality of care. But if we set out to change practice patterns that cause pain and suffering to patients and families, such as going to the ED or spending time in the ICU within 30 days of death, that resonates with clinicians."

Dr. Adelson added, "There's a growing understanding that we need to prevent those hospitalizations both for the patient's wellbeing and for society's healthcare expenses. I think our physicians are starting to talk about good deaths, a peaceful death in hospice, as opposed to the ICU."

Such conversations are difficult for doctors, not just emotionally but professionally, because they must acknowledge that they have no disease slowing treatments left to offer the patient. Dr. Adelson and her team are educating doctors about how to have these discussions, and are encouraging them to think of this moment not as withdrawal of treatment, but as a shift to another form that's better for the patient—palliative care or hospice care.

"Lots of data show that patients who receive earlier palliative care have a better quality of life, and their family members have less grieving and depression," said Dr. Adelson. To that end, Smilow recently expanded from three clinical sessions of palliative care per week to ten.

Dr. Adelson is also collaborating with a healthcare technology company to create a dashboard that measures each doctor, disease team, and care center on certain metrics at the end of a patient's life. This feedback will help doctors improve their practice patterns and reduce unwarranted treatments, while ensuring that patients know all their options.

"Our care coordinators are experienced oncology nurses who are making a direct impact to ensure our patients have what they need to manage their treatment at home," explained Ms. Lyons. Deanna D'Agostino, RN, BSN, MS, is the coordinator for a patient who has endured several lines of chemotherapy and has now had disease progression. Her husband wanted her to keep receiving treatment, despite being exhausted from doing all the homecare himself. At a meeting with the couple and their oncologist, Ms. D'Agostino outlined other options—palliative homecare, regular homecare, hospice homecare. The oncologist explained that the patient couldn't tolerate another treatment and that he had nothing more to offer.

"The husband was having a hard time letting go," said Ms. D'Agostino, "despite his wife telling him that she just wanted to enjoy her remaining time at home, in comfort and not in pain. They finally agreed to a hospice program. She's at home now and comfortable."

OCM has been the catalyst for innovations at Smilow that will affirm the hospital's position as a leader in cancer care while positioning it for leadership during the anticipated changes to the healthcare system that lie ahead. "Value-based performance is where healthcare is moving," said Dr. Adelson. "OCM gave us the chance to get early experience and to build the clinical infrastructure to transform care now and in the future. Being an early actor also gives us a voice in the national conversation about the changes coming in cancer care delivery."

Maureen Raucci, MSHA, BSN, Vanna Dest, MSN, APRN, and Bonnie Gould Rothberg, MD, PhD, MPH

Marc St. Martin

Emily Montemerlo writer **Lisa Garcia** photographer

INNOVATIVE CARE & Brotherly Love Team Up

When Marc St. Martin was diagnosed with cutaneous T-cell lymphoma (CTCL) in 2007, he had no way of knowing the impact it would have throughout his family. Over the course of five years, Marc underwent treatment with spot radiation therapy, total skin electron beam therapy, and chemotherapy, all in the hopes of achieving a durable remission. When this course no longer seemed to be working effectively, it was recommended by his dermatologist, Dr. Richard Edelson, Aaron B. and Marguerite Lerner Professor and Chairman of Dermatology at Yale School of Medicine, and an internationally-recognized pioneer in the research and treatment of CTCL, that Marc prepare for a stem cell transplant.

All five of Marc's siblings agreed to be tested to see if they were a match to be a stem cell donor and in 2012, Marc received a Hematopoietic Stem Cell Transplant (HSCT) using stem cells from his brother John, who was a 2-haplotype match. Marc commented that the transplant itself was relatively easy and painless, and it took a while before the effects of the transplant manifested. He developed a cytomegalovirus (CMV) infection and became very weak, but less than a year following the transplant, he was disease free and his brother's stem cells had taken over to fully rebuild his immune system.

"When I was first diagnosed in Florida, I was being treated for what they thought was psoriasis. I had no idea it would turn into a diagnosis of cancer," said Marc. Marc's dermatologist at the time, Dr. Anthony Fransway, was instrumental in confirming his diagnosis as CTCL and getting Marc to the right people from day one. "When my doctor suggested I meet with Dr. Richard Edelson at Yale, I knew I was being put into the best hands possible for my care. I didn't realize at that time just how much I would come to rely on his expertise, and the expertise at Yale, to not only save my life, but to give me a life worth living."

Part of the reason that it was suggested Marc undergo a transplant was to avoid any further exposure to radiation, which can damage DNA, proteins, and cell membranes leading

“Marc’s story is one of hope. Not only can you beat cancer, but you don’t have to suffer to be cancer free. There are so many options out there if you have the right team assembled.”

to cell death and ultimately resulting in painful skin ulcerations. Despite an initially successful procedure, Marc developed tumors in the hip, thigh, and chest regions, and following additional radiation to these sites, Marc noticed his skin breaking down in the treated areas. Although Marc was cured of the cancer, he now found himself suffering from the effects of his past treatments. Dr. Edelson referred him to Deepak Narayan, MBBS, FRCS, Professor of Plastic Surgery at Yale School of Medicine.

Dr. Edelson commented, “Marc had beaten the cancer, but found himself unable to live a full life because of the treatments that had kept him alive. His story is one of hope; not only can you beat cancer, but you don’t have to suffer to be cancer free. There are so many options out there if you have the right team assembled.”

The painful ulcers that developed, mainly on Marc’s hips and thighs, required him to take high doses of pain medication just to get through the day. The ulcers did not respond to normal treatment and were deemed unsuitable for free-flap reconstruction. Luckily, Dr. Narayan was able to propose an innovative solution. Knowing Marc’s history and the success of his recent stem cell transplant, Dr. Narayan recommended allogenic fat grafting using fat from his brother John, as a way to alleviate Marc’s pain and restore the skin. This method had never been used before in this way, and would require his brother John to undergo liposuction in order to provide the fat needed.

“There were several factors that had to be considered and discussed beforehand,” said Dr. Narayan. “Because of the multiple previous radiation treatments that Marc had undergone, he had minimal to no fat available to harvest from his own body. We were also concerned that the fat transfer may have adverse effects such as reactivating the CTCL or altering his genetic profile, but after weighing the risks, both Marc and John agreed to undergo the procedure.” Since it was an experimental procedure, and had never been attempted in this fashion before, Dr. Narayan obtained permission from the Human Investigation Committee at Yale before moving forward with the operation.

For Marc, a former pro golfer who still remained active, there was no question as to whether or not he would undergo the procedure. After spending three years on high doses of pain medication, he was ready to try anything. As for his brother John, he jumped at the chance to help his brother once again.

“Cancer is a family affair, and I was more than willing to help in any way that I could,” said John. “I was grateful when I learned that I was the one to match him and that I would have the opportunity to save my brother’s life. When he said he needed me to help relieve the severe pain he was in, I was happy to have the opportunity again.”

In August of 2015, both brothers went in for surgery, not knowing if the procedure would work, but fully trusting in Dr. Narayan and his team. Two years later, Marc is back on the golf course and living the life he knew was possible, but had been out of reach. “I have been in remission for four years now, and am still working to recover fully from the effects of treatment, but I will take that over cancer any day,” said Marc. “I am able to get out and do the things I love. I am so blessed to have been connected with Yale from the start. I had the best of the best to treat my CTCL and then again to treat the radiation induced ulcers. I can’t imagine having gone through this anywhere else. I wouldn’t be where I am today.”

Dr. Narayan commented that this case provides a basis for a standard of care for the treatment of radiation-induced ulcers in patients with lymphoid malignancies with stem cell transplants. Not only did it restore the skin to the area, but it also alleviated the chronic neuropathic pain that was interfering with Marc’s life, with none of the adverse effects they were concerned about. “This is a game changer for patients dealing with similar effects,” said Dr. Narayan. “Not having to rely on pain medication gives new hope to patients that have beaten their cancer, but are still dealing with side effects.”

Back on the golf course, Marc and John both agreed that while this experience may have brought them closer together genetically speaking, not much else has changed in their relationship. They have always been a tight-knit family, willing to go above and beyond for each other. “I can never repay what my brother has done for me, and hope that I never have to,” said Marc. “I feel so fortunate to have a family where it wasn’t even a question if they would be tested. John just happened to be the winner of the bunch. I’m still dealing with pain and recurring infections, but it’s a long way from where I was. I credit the team at Yale with giving me my life back twice, and there’s no real way to say thank you for that.”

NEW INSIGHTS INTO PANCREATIC CANCER

Steve Kemper writer **Peter Baker** photographer

Mandar Muzumdar, MD

During the last decade, researchers have made tremendous progress in deciphering the biology of cancer, which has made targeted therapies, immunotherapies, and combination chemotherapies possible. These advances have improved the survival rates and the quality of life for people with many different cancers.

"In pancreatic cancer, unfortunately, we haven't had that," said Mandar Deepak Muzumdar, MD, a new Assistant Professor of Genetics at Yale who recently left Dana-Farber Cancer Institute to open a lab at Yale's Cancer Biology Institute. "In the past 10 or 15 years we have learned quite a bit about how pancreatic cancer works, in terms of its genetic features, and how it progresses from early stage to advanced stage, but we haven't been able to take advantage of this knowledge clinically."

As a result, pancreatic cancer remains one of the most deadly, with a five-year survival rate of less than 10 percent. Part of the explanation is that the disease rarely shows early symptoms, and there is no reliable way to detect its initial stages. Consequently, the disease often goes undiagnosed until after it metastasizes. This year, an estimated 53,000 Americans will die from this cancer.

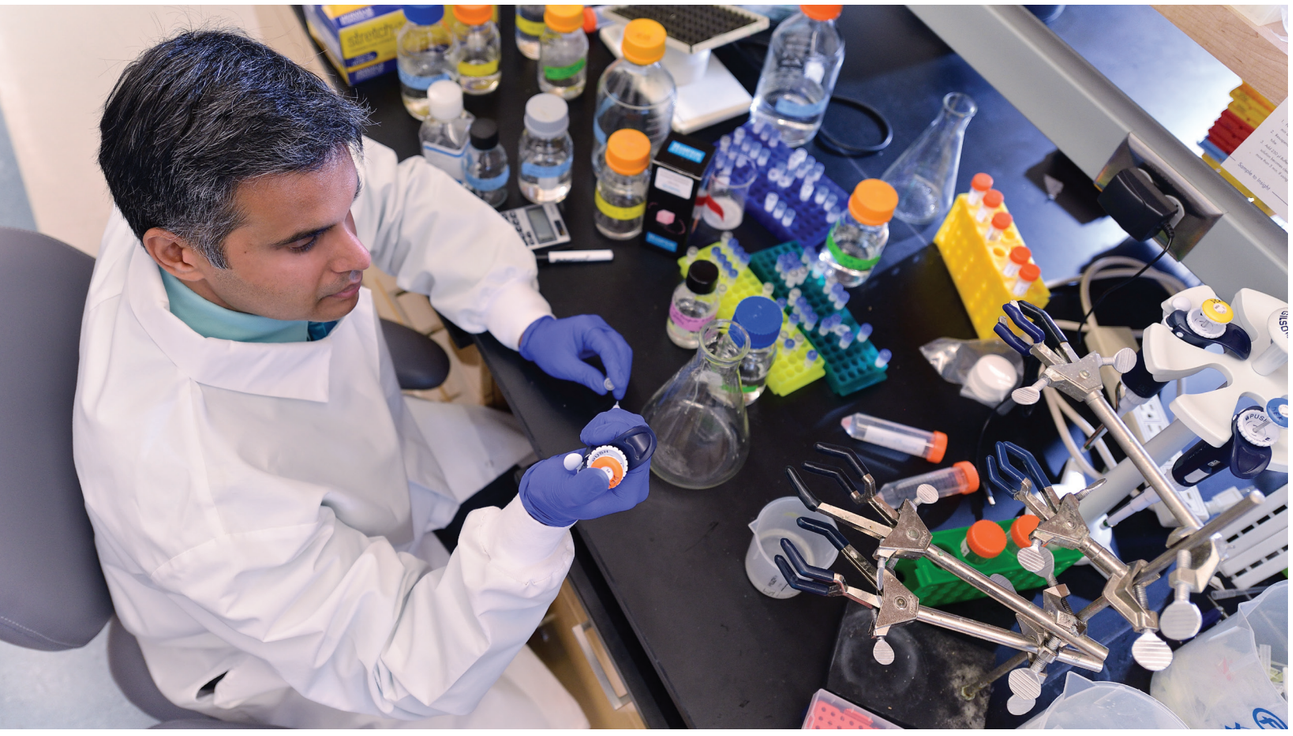
In his new lab, Dr. Muzumdar will continue his groundbreaking research into the genetic and environmental factors that underlie pancreatic cancer. His discoveries have altered science's understanding of this disease and also identified some promising possibilities for preventing and treating it.

Genetic research into pancreatic cancer starts with mutations of the KRAS gene, which researchers have long suspected drives the disease. "KRAS mutations are found in more than 90 percent of human pancreatic cancers," explained Dr. Muzumdar, "and also in 40 to 50 percent of colon cancers, and 25 to 30 percent of lung cancers. Those are the three leading causes of cancer death in the United States, so there is considerable interest in developing inhibitors of KRAS molecules. But despite our knowledge of KRAS, for more than 30 years we haven't been able to develop drug inhibitors for it that are effective and reach the clinic."

To decode the gene's riddles, and to discern whether KRAS is even the correct target, Dr. Muzumdar has leveraged sophisticated genetic engineering techniques and a murine model that replicates what happens in human pancreatic cancer. "When we induce a KRAS mutation in the pancreas of a mouse," he said, "the mouse will develop cancer that looks like human pancreatic cancer under a microscope and behaves like it in terms of how it progresses from early to advanced stages, spreads, and responds to chemotherapy."

Though drugs have failed to inhibit KRAS mutations, Dr. Muzumdar wondered if he could simulate inhibition through genetic engineering, and if so, how that would affect the cancer. He used a new gene-editing tool called CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) to completely eliminate KRAS function in pancreatic cancer cells, something never done before.

"To our surprise," he said, "nearly 50 percent of the cancer cell lines that we profiled could survive that process and generate a subpopulation of pancreatic cancer cells that survived without functional KRAS." Dr. Muzumdar knew that similar behavior has been observed with the use of targeted inhibitors in other cancers. He used the surviving cancer cell lines to explore the next question: how did these cells evade KRAS inhibition? Once again he was surprised—more than 80 percent of the cell lines used the same escape mechanism.



"And that was true across species," he said. "Human pancreatic cancer cells and mouse pancreatic cancer cells all escaped in the same fashion. To maintain their growth and survive, they rewire how they signal within themselves, and reactivate some of the same downstream signaling pathways regulated by KRAS. And it turns out that this rewiring is targetable with drugs that are currently in clinical trials, using a PI3K inhibitor."

Dr. Muzumdar's discoveries are valuable for the development of drugs that target KRAS mutations. He has shown that simply inhibiting KRAS will likely allow roughly half of pancreatic cancers to evade the drug and survive. To be effective, a therapy must simultaneously inhibit KRAS and block the escape route, probably through a combination of drugs that might include a PI3K inhibitor.

Dr. Muzumdar also has made discoveries about the role played in pancreatic cancer by a tumor suppressor gene named p53, which is known to slow or prevent the growth of many different cancers. But when p53 is lost through mutation or malfunction, cancer cells can proliferate, and p53 loss is observed in about half of all cancers, including more than 75 percent of pancreatic cancers. What has not been well understood is when p53 functions to block the development and progression of disease.

"If we can understand these mechanisms, how normal cells progress to early and then advanced cancer," said Dr. Muzumdar, "maybe we can intervene to intercept or prevent cancer from ever getting to the advanced stage."

To investigate these mechanisms, Dr. Muzumdar applied a sophisticated genetic system that he helped design as a medical student. He uses KRAS mutations to create early-stage pancreatic tumors and then genetically engineers some cells to lose p53 and others to maintain it. He labels these cells with different fluorescent markers, which allow him to compare what happens to them over time and thus follow the cancer's progression from early to late stages.

"If we can understand these mechanisms, how normal cells progress to early and then advanced cancer, maybe we can intervene to intercept or prevent cancer from ever getting to the advanced stage."

"That hadn't been well-established previously," he said. "We know that cells that have lost p53 eventually go on to advanced stage. Now, because we have a separate fluorescent label for the cells that have retained p53, we can isolate both cell populations at various times and compare them using molecular or biochemical analyses to see the differences between the two. That could give us insight about the cellular features involved in progressing from early to advanced disease. Those features may be proteins that are increased or decreased, proteins that might be the important ones to block with drugs in order to prevent that progression."

Dr. Muzumdar is also investigating non-genetic factors implicated in pancreatic cancer. One of these is obesity, which puts a person at greater risk of developing the disease and being diagnosed at a more advanced stage, all of which shorten survival. Again, the mechanism behind these links is poorly known.

To explore this, Dr. Muzumdar combined genetic mouse models of obesity and pancreatic cancer. His studies confirmed that obese mice develop pancreatic cancer that progresses rapidly towards death. Dr. Muzumdar speculates that obesity might alter the immune system in a way that speeds up tumor progression.

He is particularly excited by another outcome from the mouse model: he was able to reverse obesity. "If we genetically make obese mice lose weight very early," he said, "we can alter how the tumor progresses to advanced disease and completely reverse it. Instead of making mice lose weight, if we interfere with other aspects of obesity such as changes in the immune system or diabetes, perhaps we can recapitulate the reversion of obesity. These pathways could be something we can target to prevent or treat pancreatic cancer."

Dr. Muzumdar decided to bring his research to Yale to take advantage of the resources and opportunities available at Yale Cancer Center and the Cancer Biology Institute. Another factor was Charles Fuchs, MD, MPH, Director of the Cancer Center and Physician-in-Chief of Smilow Cancer Hospital, who had been Dr. Muzumdar's division chief and mentor at Dana-Farber. "He was a big driver in choosing Yale," said Dr. Muzumdar.

Dr. Muzumdar is also looking forward to working with Smilow Cancer Hospital physicians, in the hopes of moving some of his basic research toward the clinic. "I'm also excited to join the group that Mark and Yossi (Mark Lemmon, PhD, FRS, and Joseph Schlessinger, PhD, co-Directors of the Cancer Biology Institute) have brought together at the Cancer Biology Institute," he said. "It's such a diverse group of great investigators, all with different expertise, with a focus on combatting cancer together."

PHOTO: RUBBERBALL

On the MAP

MAP:
Medication Assistance Program

Since 2010, the Medication Assistance Program (MAP) at Smilow Cancer Hospital has charted out a successful course for covering patients' high out-of-pocket costs.

A cancer diagnosis often delivers a one-two punch to patients: What does this mean for my health? And, how will I pay for my treatment? Through the Medication Assistance Program (MAP), Smilow Cancer Hospital has helped alleviate some of the financial concerns and burdens of thousands of patients with high out-of-pocket costs so that they can focus on their physical and mental well-being.

Each year, MAP provides between $8 and $12 million in direct financial assistance to patients with cancer and other diseases. The aid takes two forms: medication replacement, in which pharmaceutical companies provide medicine free of charge; and co-pay assistance, in which foundations or institutions cover a patient's co-pays.

"In 2016, around 2,000 patients participated in the Medication Assistance Program," said Howard Cohen, RPh, MS, FASHP, who oversees MAP as Smilow Cancer Hospital's Director of Oncology Pharmacy Services. "Our numbers continue to grow. Oncology has one of the highest costs of therapy. Cost is an issue that potentially interferes with patient compliance and adherence: If a patient can't afford the treatment, how do they get it? So supporting these patients through their therapy is paramount."

MAP started in 2010 with one coordinator. Today, six MAP coordinators work with patients across the Yale New Haven Health System, from Smilow Hospital, to the health system's in-house specialty pharmacy, to the regional Smilow Cancer Care Centers. Patients are referred to MAP by a variety of staff members across the healthcare spectrum: nurses, physicians, social workers, and other providers. Patient-account representatives who check patients' insurance coverage and request prior authorizations identify many. "If a patient receives a denial, we are the safety net that allows the patient to proceed with the doctor's preferred course of therapy," explained Jacqueline Caban, senior program coordinator.

Coordination is a huge understatement of the Herculean-juggling act that Ms. Caban and her colleagues perform on behalf of patients. Dozens of pharmaceutical companies, foundations, and other institutions offer either drug replacement or co-pay programs. Each program has different criteria. Some determine income limits based on the federal poverty level. Others have no income limit, but set other restrictions. Coordinators must stay alert for program changes that can, and do, happen at any given time. "Being a part of a program that understands and looks out for patients is so rewarding," Ms. Caban said. "Patients tell us, 'I would have had to choose whether to purchase medication or put food on the table. I couldn't have done this without you.'"

> **"Cost is an issue that potentially interferes with patient compliance. Supporting these patients through their therapy is paramount."**

Once enrolled, a patient can typically receive aid through the end of the current calendar year or for 12 months from the date of approval. Throughout that period, coordinators check in frequently with patients and handle the billing process for them. "We pull the explanation of benefits (EOB), along with our claim form, and send that off," Ms. Caban said. "We can process payments so that the charges are removed from their chart within 24 hours. It's a seamless process. We work hard to take any burden off the patient."

For patient Edward Lent, the MAP coordinators' concern for his well-being was as valuable as the financial assistance he received for his medication. "When you become handicapped, you have a feeling of vulnerability, that you're in this alone," he said. "The coordinators really reach out to you and give you a hug. They think about you as a whole person, not just a patient number. It is so much more personalized. They are in my corner, looking out for me."

As Mr. Cohen, Ms. Caban, and the MAP team have continuously spread the word about the program, representatives from other medical institutions across the country have called and visited to learn how to establish their own versions of MAP. Ms. Caban's expertise on the subject has made her a frequent presenter at medical conferences, and she's developing a symposium on the program.

"MAP is one of our signature programs that distinguishes Smilow from many other hospitals," said Catherine Lyons, RN, MS, Vice President of Patient Services at Smilow Cancer Hospital. "It is a wonderful service to our patients."

Edward Lent wholeheartedly agrees. "The MAP coordinators went through incredible leaps and bounds to find the resources that covered my medication," he said. "They provide miracles."

PETER BAKER

Overcoming Resistance to Immunotherapy

Katerina Politi, PhD

For some cancer patients, the road to remission and healing can have its share of speed bumps. That's particularly true of patients with non-small cell lung cancer (NSCLC) who develop a secondary, or acquired, resistance to immunotherapy, which initially was effective against their tumors. A team at Yale Cancer Center, led by cancer biologist Katerina Politi, PhD, has made a breakthrough in identifying genetic changes that occur during immunotherapy treatment and enable tumors to evade therapy in certain patients.

Immunotherapy has emerged as a promising treatment for NSCLC patients who are not a match for targeted therapies. The regimen acts on immune checkpoints so that T cells can identify and kill cancer cells. "Studies have found that patients can have very durable responses to immunotherapy," explained Dr. Politi, an Associate Professor in the Departments of Pathology and Medical Oncology. "And, they seem to have fewer and different toxicities than standard chemotherapy." Yale Cancer Center played a key role in the development of immunotherapy. Extensive clinical trials at Smilow Cancer Hospital paved the way for FDA approval of the groundbreaking immunotherapy drugs Nivolumab and Pembrolizumab for patients with NSCLC.

Some NSCLC patients have primary resistance to immunotherapy; the tumor doesn't respond at all to therapy. In her latest study, Dr. Politi's lab focused on acquired resistance. "It's a major problem," she said. "It's fascinating to see how a tumor evolves through therapy. As we began to learn more about how immune checkpoint inhibitors work in lung cancer, we began wondering how resistance would occur with these therapies that target the immune system."

The "we" that Dr. Politi refers to is the cross-disciplinary team of Yale Cancer Center experts who worked with her on the study: pathologists, cancer biologists, medical oncologists, geneticists, immunobiologists, and bioinformaticians. The team examined NSCLC patient tissue samples that were collected at two distinct points during treatment: before the patient was treated with the immunotherapy that caused the tumor to shrink, and after the tumor had developed resistance to the therapy and stopped responding. "Those samples and biopsies are critical for us to be able to understand what's happening throughout the course of therapy," she explained. "We're grateful to everyone who contributes to this research effort, because they have a huge impact."

The team sequenced each tissue sample's genome and looked for differences in the before-and-after samples. In one patient's samples, a mutation occurred in a vital protein known as B2M. "What happens when you don't have B2M is that T cells can't recognize the tumor cells," Dr. Politi said. "Even if you activate the T cells with immunotherapy, it won't work. The tumor escapes therapy." Their further research using mice and tumors grown from resistant tissue grafts confirmed a connection between the B2M protein and resistance.

"What we're doing now is trying to understand if there are other ways in which tumor cells can downregulate this pathway so that the T cells don't recognize the cancer cells," she said. "Are there other resistance mechanisms that aren't genetic that can do this?"

The B2M discovery is currently in press at *Cancer Discovery* and echoes strides made by Dr. Politi and her 11-member laboratory in their studies of resistance to targeted therapies. Their work on mutations in the Epidermal Growth Factor Receptor (EGFR) gene in patients with lung adenocarcinomas and related work earned Dr. Politi the Early Career Investigator Award from the American Society for Investigative Pathology.

"The discovery of a specific resistance mechanism to targeted therapies in EGFR mutant lung cancer allowed scientists to focus their efforts on figuring out ways to overcome such resistance," she explained. "We now have new therapies that target tumors with resistance to EGFR targeted therapies. Similarly, with immunotherapy, if we understand resistance, we can direct our efforts to overcome and prevent that resistance."

The team's discovery of the B2M mutation is a shining example of the collaborative spirit of the Yale SPORE in Lung Cancer, an $11-million effort funded by the National Cancer Institute. Short for Specialized Programs of Research Excellence, the SPORE brings together experts across the Yale campus to work on projects focused on NSCLC, one of the world's most prevalent forms of cancer. In addition to the support from the SPORE, the Beatrice Kleinberg Neuwirth Fund for Pancreatic and Lung Cancer Research and the Diane and David B. Heller Charitable Foundation provided funds for the project.

> **"It's fascinating to see how a tumor evolves through therapy. As we began to learn more about how immune checkpoint inhibitors work in lung cancer, we began wondering how resistance would occur."**

"The progress that we have made on identification of B2M alterations is a shining example of the work that can be accomplished through the team assembled by a SPORE. The team's ability to sequence the tissue samples, before and after treatment with immunotherapy, relies on colleagues' support, beginning with our medical oncology team in Smilow, and through to our bioinformatics team," said Roy S. Herbst, MD, PhD, principal investigator of the Yale SPORE in Lung Cancer, Ensign Professor of Medicine, Chief of Medical Oncology, and Associate Director for Translational Research at Yale Cancer Center. "Their collective effort propelled this research forward to discovery."

PETER BAKER

Smilow Cancer Hospital Care Center - Waterford

PRACTICE AT A GLANCE

- A patient-centered focus on exceptional cancer care
- Over 1,000 patient visits per month in medical oncology and 1,100 in radiation oncology
- 750 infusion visits per month
- 78 staff members
- 100% Oncology Certified Nursing Staff
- Nutrition Counseling, Genetic Counseling, Social Work, Breast Cancer Support Group, "Look Good, Feel Better," Wig Bank, Financial Counseling, Patient Navigators, Gentle Touch Therapy, Pet Therapy, Exercise Program for Survivors, Healing Garden

SMILOW CANCER HOSPITAL CARE CENTER AT WATERFORD
230 Waterford Parkway South
Waterford, CT 06385
Phone: (860) 444-3744

"The Waterford Care Center provides our patients access to a beautiful facility for their cancer care and a full team of Yale Cancer Center and Smilow Cancer Hospital medical and radiation oncologists and support staff. Our ability to offer cancer treatment, clinical trials, and collaboration with our colleagues at our main Smilow Cancer Hospital location in New Haven and at Lawrence + Memorial Hospital in New London, is a true benefit to patients throughout southeastern Connecticut and Rhode Island."

— Dr. Jane Kanowitz, Medical Director

PETER BAKER

meet the physician

Alessandro D. Santin, MD

Professor of Gynecology, Obstetrics & Reproductive Sciences; Disease Aligned Research Team Leader, Gynecologic Oncology Program

You care for women with gynecologic cancers. How have the surgical treatment options expanded and improved for women over the last several years?
The introduction of da Vinci robotic-assisted surgery for gynecological surgeries has greatly improved the care and outcomes for our patients. Women diagnosed with ovarian, cervical, or endometrial cancers who are recommended for surgery are now able to have the procedure done minimally invasively. The robotic surgeries provide the same outcomes as traditional surgery, but with minimal pain. Following surgery, our patients can usually return to the comfort of their home within 24 hours for recovery.

One area of research that you're focused on is the use of precision medicine treatment. How is precision medicine providing new treatment options to women with ovarian and uterine cancers?
As we better understood the genetic landscape of disease over the past 5-10 years, precision medicine has expanded dramatically. We are now able to provide patients with personalized therapy that specifically targets their tumor's exact mutations. I believe a major advantage for our patients at Smilow Cancer Hospital and our Care Centers is that each of them receives genetic analysis of their tumor tissue before treatment is planned; this analysis allows the care team to decide the best course of treatment, whether it be targeted therapy or immunotherapy, because we have specifically identified the tumor type and matched it to the therapy it will best respond to. This personalized path of treatment planning has considerably changed outcomes for our patients with metastatic, refractory, and aggressive disease.

In addition to new treatment options, your lab is also studying the genetic origins of these cancers. What progress has been made?
My laboratory team is studying the genetic signature of gynecologic cancers and creating models of the diseases in the lab. We're working to create signature tumor types, which will enable us to treat a tumor in the lab to validate a specific treatment type in advance of patient care. By validating treatments before we prescribe them to a patient, we will have the pre-clinical data to show the treatment's success on a particular tumor type.

Our team is also taking advantage of the genetic biology of the disease by studying the use of circulating tumor DNA – by looking for tumor DNA in patient's blood samples – to monitor a patient's response to treatment and possible relapse.

YaleNewHaven**Health**
Smilow Cancer Hospital

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

CHRIS VOLPE PHOTOGRAPHY

Closer to Free Ride

Presented by: Bank of America

Thank you! This year's ride raised over $2.5 million to support cancer research and care at Yale Cancer Center and Smilow Cancer Hospital thanks to our 1,800 riders and 500 volunteers. Mark your calendars for September 8, 2018!