
Yale Cancer Center
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MAGAZINE
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New Tools
Applied to Old Problems
spring | summer 2019

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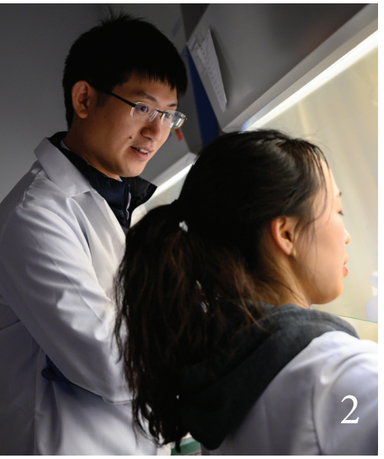

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director's letter

As cancer research evolves, not only are we looking at new drugs, new targets, and new combinations of therapies, our scientists are also reimagining old tools and reinventing new uses for them in our labs to advance cancer research. Dr. Sidi Chen's lab in the Systems Biology Institute at Yale West Campus is one example of pushing the boundaries of cancer research. Recently, he and his team have uncovered more efficient solutions to genetically engineer immune cells and have discovered a better understanding of the biology of cancer metastasis.

Neuro-oncologist Dr. Antonio Omuro joined Yale Cancer Center and Smilow Cancer Hospital earlier this year to lead our Brain Tumor Center. His direction has already united current brain tumor research throughout Yale University into a more cohesive effort, which will undoubtedly create new collaborations and ultimately increase research discoveries. At the same time, patients cared for through our Brain Tumor Center, like Valencia Opont, can feel confident that they receive access to the very best team, during the most challenging of circumstances.

I am extremely grateful to The Frederick A. DeLuca Foundation for their generous support of our hematology research and patient care with the launch of The DeLuca Center for Innovation in Hematology Research. The Foundation has already provided transformative support to better understand the optimal treatment for myeloproliferative neoplasms and to determine the mechanisms that lead to the development of myelodysplastic syndromes. I look forward to sharing the results of new research enabled by The DeLuca Center.

Smilow Cancer Hospital continues to build and expand on our network of patient care. We treat over 45% of cancer patients in the state, and ensure the quality of care each of our patients receives is at the highest excellence. Our radiation oncology team's recent recognition by the American Society for Radiation Oncology (ASTRO) Accreditation Program for Excellence (APEx) is a prime example. We are the first in the New England region to be awarded APEx, which indicates that patients who choose Smilow Cancer Hospital for radiation oncology receive care delivered with the highest safety and quality standards in the industry.

Together, our scientists and clinicians continue to strive for the very best with the common goal of our patients at the forefront every day. I am proud of their countless successes and look forward to sharing more progress with you in the coming months.

Sincerely,

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

Sidi Chen, PhD

NEW TOOLS APPLIED TO OLD PROBLEMS

Steve Kemper writer **Peter Baker** photographer

Sidi Chen, PhD, Assistant Professor of Genetics, is always looking for practical, more efficient solutions to familiar problems. When dissatisfied with a tool, for instance, he and his lab invent a better one. He has recently used this approach to make advances in fundamental genetics, genetically-engineered immune cells, and the biology of metastasis.

Fundamental genetics is a logical place to begin. In the February issue of *Cell Systems*, Dr. Chen and colleagues, most of them from his lab in the Systems Biology Institute on Yale West Campus, published the results of their extensive search for genes that either incite cancer cells or help them evade detection by the immune system. Both types are implicated in tumor growth.

Using the genetic editing tool CRISPR and mice models, they screened more than 20,000 genes through 80,000 sgRNA constructions. A dozen genes stood out as enablers of tumor growth. The champion that sparked the most aggressive tumors was also, until now, the most obscure—a gene called Prkar1a. It caused rampant growth by its absence. When the scientists removed Prkar1a from cells, tumors went crazy.

Dr. Chen explains: "The main reason patients get cancer is that some cells acquire mutations. A mutation can make a gene super active and drive cell proliferation, like if your gas pedal gets stuck. That's an oncogene. The opposite is a tumor suppressor gene. If a mutation destroys the function of this gene, you lose the power to suppress tumor growth, meaning you lose your brakes. Losing a tumor suppressor is at least as important as gaining an oncogene. Prka1a is a tumor suppressor."

Tumors without Prkar1a not only grew more rapidly, their cancer cells corrupted the host's innate immune system, tricking immune cells into accelerating tumor growth instead of fighting it.

If removing the gene speeds up growth, why not boost immunity by somehow saturating cells with the suppressor Prkar1a? "That's very difficult," said Dr. Chen. "Taking something out is easy, but if the cancer cell has already lost an important tumor suppressor like Prkar1a, it's really hard to give it back. This research is for basic understanding of why cancer progresses. It's hard to translate. That's why I'm also working on developing new strategies for immunotherapies, meaning you get rid of the brakes on immune cells so they can fight better. Therapeutically that's more achievable."

One such effort is Dr. Chen's work on chimeric antigen receptor CAR T-cells. These are T-cells that have been removed from the blood and genetically engineered to target an antigen in cancer cells. This is done by using CRISPR to insert a code in the T-cells' genome. Then these weaponized super-Ts are multiplied in a lab and reintroduced into the body to fight cancer. It's a fairly new and very promising immunotherapy, but so far is approved only for B-cell non-Hodgkin's lymphoma and B-cell acute lymphoblastic leukemia.

Dr. Chen and his lab have designed a new CAR T-cell technology that is safer, faster, more precise and efficient, more flexible and prolific, and more potent than the current platform. They call it CRISPR–Cpf1. Their paper describing it was published in March in *Nature Methods*.

"There are quite a few limitations with the current CAR T strategy," said Dr. Chen. "That's why we invented a new tool. It produces two, three, four times more CAR Ts than the current platform, more quickly and efficiently. We are even more excited that our tool can make more complicated CARs that recognize two antigens of the cancer cell instead of just one."

That's important because some patients who receive CAR Ts with only one antigen relapse after the cancer cells adapt by camouflaging the antigen to make it invisible to the CAR T. "But if the CAR T recognizes two antigens," said Dr. Chen, "then the cancer cell has a harder problem to hide them both."

The new tool is flexible enough to accommodate many different CAR Ts. Dr. Chen's team is testing variations, looking for the most effective combinations against different cancers. He is particularly intent on finding something that works against solid tumors, which have proven resistant to current CAR Ts.

It's much too early to bring this new platform to clinical trials, but Chen is confident it will reach that stage. "We think this technology will accelerate the entire process of T-cell engineering and therapeutic translation."

His newest paper, published in April in *Nature Methods,* addresses the thorniest problem in cancer research—metastasis. "Surgeons are now so good, they can remove any primary tumor or residual tumors, for most part," said Dr. Chen. "What kills most patients is cancer that metastasizes into vital organs like the lung, liver, brain, or upper body."

Scientists have been investigating the complicated mechanisms of metastasis for decades. Many single genes are known to speed it up or slow it down. Dr. Chen decided to approach the problem more systematically and comprehensively. He began with the belief that metastasis is driven by the interaction of two or more genes.

"But if you have 20,000 genes," he noted, "there are 400 million different combinations. To find and test the relevant pairs that might drive metastasis, we need two things. First, to narrow down which genes are potentially important." He did that by focusing on mutated genes in metastasis samples.

"Second, we need to computationally study those genes and their interactions."

Dr. Chen's team identified 26 genes as likely suspects, which meant 326 pairs—still lots of combinations. "We needed a way to test them all together," said Dr. Chen. "If you lose one pair, would the cancer cells metastasize faster? Or if you lose a different pair, would that change metastasis?"

He had an idea how to get this information, but first he had to invent another new tool. This one is called MCAP (massively parallel CRISPR–Cpf1/Cas12a crRNA array profiling). Using a library of roughly 12,000 DNA constructs, the tool allows high throughput screening of double knockout cancer cells in a mouse model. Each gene pair was targeted by 16 or more constructs.

"These cancer cells are not metastatic to begin with," said Dr. Chen, "but if you knock out a lot of combinations and inject the cells into the mice, in some combinations each cancer cell would lose two genes, meaning they are double mutants. If you see these two genes more frequently in the metastasis in the animal, then they drive metastasis together."

Next the team sequenced all the metastases and ranked the gene pairs according to potency. They created a map of the genetic interactions influencing the metastatic properties of the cancer cell. Lastly, they validated everything by comparing double knockouts to single knockouts to no knockouts.

Dr. Chen believes that MCAP and his findings will someday help determine if a mutation in a patient's primary tumor is more or less likely to become metastatic. First, that prognostic information could be vital for guiding treatment. Second, identifying the drivers of metastasis could provide targets for drug developers—perhaps the pathways to metastasis can be blocked or obstructed. Lastly, Dr. Chen thinks his tool could be used to develop immunotherapies that target metastatic cancer cells.

"Those three very different directions are enabled by this high throughput technology and what we have found so far. But we still don't see the limit of these tools. The sky is the limit," explained Dr. Chen.

TWO LIVES ON THE LINE

Paula Derrow writer
Peter Baker photographer

Valencia Opont

From the time she was a little girl in Bridgeport, CT, Valencia Opont was prone to headaches. "I'd get them a lot but it wasn't a big deal," said the 27-year-old nursing assistant. "My mother would give me Tylenol and they went away."

That was not the case when Valencia became pregnant with her daughter Jana, who will be two in May. "My headaches came back, and they were much more severe," she explained. Her ob-gyn prescribed a medication called Fioricet, which eased the pain. But in October of 2018, when Valencia became pregnant with her second child, a boy this time, the headaches returned with a vengeance, along with vertigo. "I was really worried," Valencia said.

So was her doctor, who sent Valencia to the local hospital for an MRI in January.

The scans revealed that Valencia, who was in her second trimester of her pregnancy at the time, had a brain tumor. Even so, local doctors were relatively reassuring. "They told me that the tumor was slow growing, and that because I was pregnant, the best thing to do would be to follow it and do nothing until I delivered the baby."

By the next month, however, Valencia's symptoms had grown worse. Besides the headaches, and the vertigo, she was also experiencing severe nausea and vomiting. "One day I came home from work and I was throwing up nonstop, even though I had not eaten," she explained. She asked her husband Jean to bring her to the ER, only she couldn't walk to the car; she was too dizzy.

Valencia ended up going to the ER by ambulance, where another MRI revealed that her tumor had tripled in size in just four weeks' time. Valencia was stunned. "There was nothing like this in my family and I'd always been healthy. The only time I'd ever been to the doctor was for checkups."

Her doctors were also shocked, and immediately referred Valencia to Jennifer Moliterno, MD, Chief of Neurosurgical Oncology for Primary Brain Tumors at Smilow Cancer Hospital. After reviewing the MRI, Dr. Moliterno was concerned Valencia had a medulloblastoma, which is a relatively rare, but aggressive type of brain tumor in adults. They can be commonly misinterpreted, as initially happened with Valencia. "By the time she came to me, the tumor was the size of a small tangerine, and had grown considerably in a short amount of time. It was now pressing on her brain stem and causing fluid buildup throughout the brain, which can be a life-threatening condition." The situation was indeed dangerous. After meeting with Dr. Moliterno on a Monday, Valencia was in surgery the next day. "We needed to remove it as soon and as safely as possible," said Dr. Moliterno.

Of course, performing brain surgery on a patient who was 26-weeks pregnant made an already complicated procedure even more challenging. Given the location of the tumor, the operation is typically done with the patient lying on his or her stomach as to provide adequate access. "That was impossible in Valencia's case of course because of the baby," explained Dr. Moliterno. Instead, she positioned Valencia on her side. "It wasn't ideal in any regard," she said.

Another concern was the amount of time the surgery would take. Ideally, the operation needed to be done as quickly as possible to minimize the effects of anesthesia and blood loss, not just for Valencia's well-being, but for her baby. "These types of tumors tend to be very vascular—very bloody," said Dr. Moliterno. "It can be a difficult surgery to perform to start with, and even more so when you have to modify it."

On the day of surgery, in addition to Dr. Moliterno and her team, there was an ob-gyn team in the operating room and on standby if needed for an urgent delivery during the brain surgery. "They had a fetal monitor attached to my belly to keep track of the baby's heart," recalled Valencia. "I was very scared." Both Valencia and the baby's heartbeats echoed throughout the operating room during the surgery.

Dr. Moliterno was mindful of the challenge at hand. "Instead of having one life on the line, we had two. That made it even more important that we remove the tumor quickly and safely." She did just that, removing the tumor in its entirety in a swift two hours. "We were able to remove all of it, and thankfully had Valencia on and off the table in a relatively short and safe amount of time," said Dr. Moliterno.

Valencia's tumor was classified as a Grade 4 medulloblastoma, confirming Dr. Moliterno's suspicions and explaining the relatively fast growth rate. Additional genetic testing, performed only at advanced centers such as Smilow, better categorized the tumor. When Valencia woke up in the Neuroscience Intensive Care Unit immediately following surgery, she felt a bit dizzy, but her headache was gone. And while she still gets headaches intermittently, "they are not as severe—they come and they go," she said.

Yet even with such a difficult diagnosis and journey ahead, Dr. Moliterno is optimistic for her patient. "Valencia had a very aggressive operation, which is a very good first start to treating this disease. That is certainly in her favor, and it gives us time to allow the baby mature and to be delivered before additional treatments are needed," she said. "We do a relatively high volume of brain tumor surgeries at Smilow, which allows for our experience to make a big difference in our patients' outcomes."

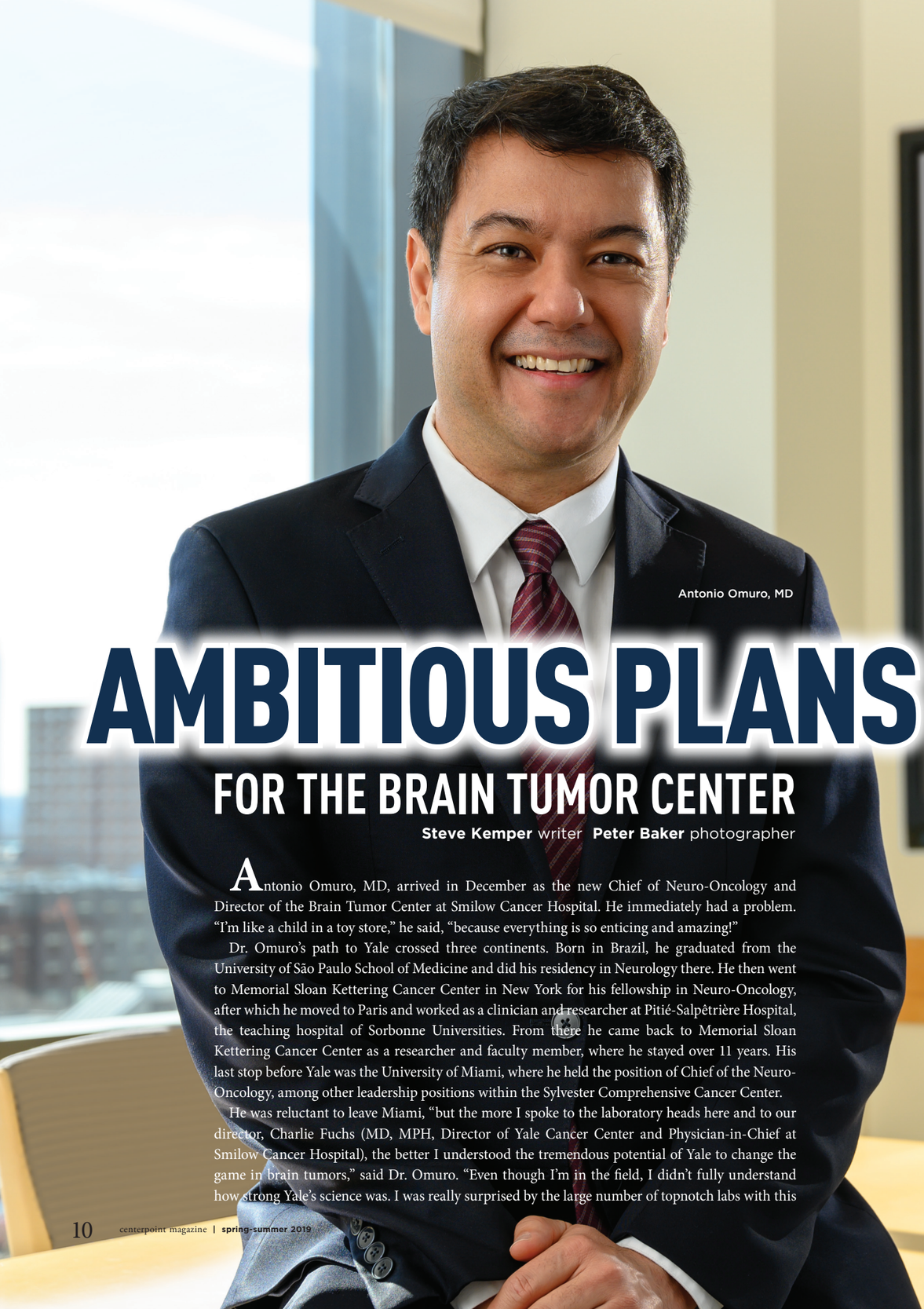
Dr. Moliterno also feels positive about the fact that Valencia ended up at Smilow Cancer Hospital. "Valencia's case really demonstrates all of the strengths of our Brain Tumor Center," she said. "For brain tumor surgery and brain tumor treatment, it definitely matters which hospital or center a patient seeks care from." One reason: As with all brain tumor patients at Smilow, Valencia's case was presented at a multidisciplinary tumor board, which includes a diverse panel of experts—neurosurgeons, neuro-oncologists, radiation oncologists, neuropathologists, neuroradiologists—all with specialized brain tumor expertise. "As you can imagine, when you have that many experts dedicated to once specific specialty, such as brain tumors, it makes a significant difference in the care that is offered," said Dr. Moliterno. Valencia's case was also reviewed as part of their Precision Brain Tumor Board, which considered the underlying genetic abnormalities of her tumor, to decide which treatment might be the most effective. "Genetic sequencing, which is performed on every primary brain tumor removed at Smilow, allows us to better understand the tumor on a molecular level and can affect their treatment and outcomes," explained Dr. Moliterno. "Our patients truly benefit from the expertise and cutting-edge care we provide, including robust clinical trials."

Home and taking care of her daughter, only a few weeks after her life-saving surgery, Valencia can do all the normal things that a mother-to-be does, including trying to come up with a name for her son, who will arrive early at 34 weeks to allow her to begin radiation and chemotherapy.

"Even despite the challenges, and the added pressure of hearing every heartbeat of the baby while I operated on Valencia's brain, they both did wonderful. I look forward to meeting this special little boy and seeing Valencia continue to fight this disease," said Dr. Moliterno.

INSTEAD OF HAVING ONE LIFE ON THE LINE, WE HAD TWO. THAT MADE IT EVEN MORE IMPORTANT THAT WE REMOVE THE TUMOR QUICKLY AND SAFELY.

– Dr. Jennifer Moliterno



Antonio Omuro, MD

AMBITIOUS PLANS

FOR THE BRAIN TUMOR CENTER

Steve Kemper writer **Peter Baker** photographer

Antonio Omuro, MD, arrived in December as the new Chief of Neuro-Oncology and Director of the Brain Tumor Center at Smilow Cancer Hospital. He immediately had a problem. "I'm like a child in a toy store," he said, "because everything is so enticing and amazing!"

Dr. Omuro's path to Yale crossed three continents. Born in Brazil, he graduated from the University of São Paulo School of Medicine and did his residency in Neurology there. He then went to Memorial Sloan Kettering Cancer Center in New York for his fellowship in Neuro-Oncology, after which he moved to Paris and worked as a clinician and researcher at Pitié-Salpêtrière Hospital, the teaching hospital of Sorbonne Universities. From there he came back to Memorial Sloan Kettering Cancer Center as a researcher and faculty member, where he stayed over 11 years. His last stop before Yale was the University of Miami, where he held the position of Chief of the Neuro-Oncology, among other leadership positions within the Sylvester Comprehensive Cancer Center.

He was reluctant to leave Miami, "but the more I spoke to the laboratory heads here and to our director, Charlie Fuchs (MD, MPH, Director of Yale Cancer Center and Physician-in-Chief at Smilow Cancer Hospital), the better I understood the tremendous potential of Yale to change the game in brain tumors," said Dr. Omuro. "Even though I'm in the field, I didn't fully understand how strong Yale's science was. I was really surprised by the large number of topnotch labs with this incredible talent. I knew about their work individually but had not tied them together around the Yale name, until now. It seems to be a bit of a kept secret, like a gem waiting to become a beautiful jewel. The intellectual capital and the resources here are unparalleled. It's just a matter of grouping them together and put them to the best use."

Dr. Omuro has lots of plans, and expansion of the Brain Tumor Center is central to them. He sees it as a clearinghouse for collecting and distributing information on the vast amount of research related to brain cancer that occurs throughout Yale. He also sees it as a meetinghouse where basic scientists can find clinical partners for projects that can turn research ideas into new therapies.

Advances in the treatment of brain cancers are desperately needed. "There hasn't been a major breakthrough for over 30 years," explained Dr. Omuro.

To begin, he has started to inventory all the labs throughout Yale University currently working on basic and translational research that could be applied to the treatment of brain tumors. So far he's up to over 20 labs. "And the list keeps growing," he said. "What is interesting is that many of these investigators were not aware of what the others were doing, and they didn't know how to get clinical support to help them develop their new ideas and test their hypotheses in patients. We are going to give these investigators a forum in which to present their work, exchange ideas, and establish collaborations. We are also providing them with advice to best determine the kind of experiments and select new treatments that are most likely to have a path forward for clinical development, and hopefully fund the best projects."

He ticked off several possibilities for collaborations. For example, the lab of Murat Gunel, MD, Chair of the Department of Neurosurgery, has been doing whole exome sequencing on all brain tumor patients operated on at Smilow for several years now. "A host of projects can come out of that genomic information," said Dr. Omuro. "We have investigators trying to understand the tumor and the role of each identified mutation. Yale is also very strong in immunology and brain microenvironment, and we have people trying to understand the interactions between the tumor and the host. It's a complicated process, and we have these ultra-specialists working on all aspects of it, but they have to talk to each other if we really want to make a difference."

Together with Dr. Gunel, Dr. Omuro has also been working on the arduous process of assembling an application for a SPORE grant (Specialized Programs of Research Excellence) from the National Cancer Institute. SPOREs are given to institutions of proven excellence who submit projects that show strong promise of moving quickly from basic scientific findings to clinical testing. SPORE projects require intensive multidisciplinary collaborations, so Dr. Omuro sees the application process as another opportunity for Yale scientists to share resources, exchange ideas, fine-tune research, and fast-track lab breakthroughs to the clinic.

Once all of Yale's labs are sharing their information on brain tumors, Dr. Omuro hopes to create a platform that uses artificial intelligence (AI) and machine learning (ML) to deepen and expand the application of the information. Some labs have started to use the enormous data science resources available at Yale, but others researchers have not accessed AI and ML yet. Dr. Omuro plans to set up a platform where investigators can learn which labs have these technologies and how they are being used, and can request help to meet their needs. He also wants to bring these technologies into clinical research and direct patient care.

"We have our own machine learning laboratory, led by Sanjay Aneja (MD)," said Dr. Omuro, "and he will help us with clinical developments and to improve the care of our patients, for instance by using AI resources to help physicians improve safety and predict outcomes."

He mentions a pilot project that is using deep learning methodologies to analyze patients with primary central nervous system (CNS) lymphoma. "We hope we will be able to predict, from the beginning, who will be cured and who will not be cured by existing treatments, based only on analysis of the first MRI scan," he said. "This type of technology is in its infancy when it comes to health care, but we want Yale to have a prominent role in its development, and we are ahead of most institutions."

The Center will also focus heavily on the development of clinical trials based on Yale science. Dr. Omuro singles out two projects. While investigating multiple sclerosis (MS) in his lab, David A. Hafler, MD, Chair of the Department of Neurology, discovered that expression of an immune check point called TIGIT was decreased in MS patients but increased in patients with glioblastoma. That is, TIGIT was protecting brain tumor cells by suppressing the immune system's T-cells. Dr. Hafler wondered whether targeting TIGIT would release T-cells to do their job against the cancer. He has been investigating that in laboratory models, and a clinical trial is expected to begin sometime this summer.

Dr. Omuro's other example is the work of Ranjit Bindra, MD, PhD, Associate Professor of Therapeutic Radiology and Experimental Pathology. Dr. Bindra discovered that a PARP inhibitor called olaparib can suppress the IDH-1 mutations common in gliomas. This innovative and promising immunotherapy is now in Phase 2 clinical trials at Yale and elsewhere. Dr. Bindra is one of the Brain Tumor Center's co-directors, along with Jennifer Moliterno, MD and Veronica Chiang, MD. The center's leadership team is working together to transform all these ideas and vision into real progress for the benefit of brain tumor patients.

"These are the kinds of opportunities that Yale makes possible," said Dr. Omuro, as enthusiastically as a child in a toy store.

Stephanie Halene, MD, PhD

Nikolai Podoltsev, MD, PhD

Transforming Research For Blood Malignancies

Steve Kemper writer **Peter Baker** photographer

In June 2013, Nikolai Podoltsev, MD, PhD, Assistant Professor of Medicine (Hematology), began caring for newly-diagnosed patient Fred DeLuca, co-founder of the global SUBWAY restaurant chain. Dr. Podoltsev and other staff at Smilow Cancer Hospital cared for Mr. DeLuca as he underwent treatment for leukemia leading to remission, which allowed him to proceed with an allogeneic stem cell transplant under the care of Stuart Seropian, MD, Associate Professor of Medicine (Hematology). When his disease later recurred, Dr. Podoltsev and other Yale specialists, including Stephanie Halene, MD, PhD, Associate Professor of Medicine (Hematology), treated Mr. DeLuca until his death in September 2015.

In April 2016, Mr. DeLuca's wife, Elisabeth DeLuca, met with Dr. Podoltsev and offered to support his research into blood malignancies through a grant from The Frederick A. DeLuca Foundation. She soon expanded this offer of support to fund research by Dr. Halene, Dr. Seropian, and others at Yale Cancer Center and Smilow Cancer Hospital. These grants have already fostered research collaborations and resulted in the publication of nine manuscripts, which illuminate new findings in hematological cancers.

Now, thanks to the Foundation, research in the field of blood malignancies by Cancer Center scientists is about to multiply and accelerate. In April, a substantial gift launched the new DeLuca Center for Innovation in Hematology Research. "It's transformative for us," said Dr. Podoltsev.

Leukemias and lymphomas are the most familiar subtypes of blood cancers, but the list is long. Dr. Podoltsev's research and medical practice, for instance, address not only acute myeloid leukemia (AML) but also lesser-known blood malignancies such as myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPNs).

One of the papers supported by the Foundation was published in October 2018 in *Blood Advances*. Dr. Podoltsev and his co-authors from Yale School of Medicine (Hematology Section) and Yale School of Public Health performed a nationwide statistical analysis of two standard treatments for older patients with an MPN called polycythemia vera (PV). PV occurs when bone marrow makes too many red platelets, thickening the blood and slowing its flow. This can lead to clots, embolisms, heart attacks, and strokes.

One standard treatment is therapeutic phlebotomy, in which excessive blood is removed to prevent thrombosis or blood clots. Another is hydroxyurea (HU), a 150-year-old drug that suppresses the production of blood cells. The National Comprehensive Cancer Network (NCCN) recommends HU as a first-line therapy for older PV patients, but some physicians won't prescribe it because of doubts about its efficacy or misplaced fears that it can lead to acute leukemia.

Dr. Podoltsev and his co-authors used the massive SEER-Medicare database to analyze the history of 820 PV patients. Phlebotomy cut the risk of thrombosis nearly in half and reduced the risk of death by 35 percent. For patients who took HU, the data was equally striking. There was a direct correlation between the length of time a patient took HU and the decreased risks of thrombosis and death.

In short, the study strongly confirmed the guideline recommendations. That wouldn't normally be news, but the researchers also found that, despite the clear benefits of these therapies, only 64 percent of PV patients received phlebotomies and only 60 percent were prescribed HU. "We hope this convinces some physicians that they should use HU for PV patients who are at risk of developing clots," said Dr. Podoltsev. "Our study adds to the evidence that it works—we just have to use it."

A second paper, published this March in the *Journal of the National Comprehensive Cancer Network*, did a similar statistical analysis on high-risk patients with another MPN, essential thrombocythemia (ET). ET is also a blood malignancy caused by excessive production of platelets, with complications similar to those of PV. Using the SEER-Medicare database, the researchers investigated the use of HU among 1,010 patients. They found, once again, that HU was associated with a 49 percent drop in the risk of thrombosis, and a 48 percent drop in mortality. Yet a quarter of the high-risk patients didn't receive treatment with HU.

Dr. Halene also has benefitted from the support of The Frederick A. DeLuca Foundation. Among her research interests are the mechanisms that lead to MDS and acute myeloid leukemia (AML). AML and MDS are difficult to study because blood stem cells don't grow well in cultures and only few cell lines that model a patient's primary disease exist.

That's changing because of "humanized" mice designed by Richard Flavell, PhD, FRS, Sterling Professor of Immunobiology. Dr. Flavell's "MISTRG" mice have been genetically modified to have a human immune system so they won't reject grafts of human cells, including blood stem cells. The benefits for researchers such as Dr. Halene are immense.

In a paper published in *Nature Communications* in January, she and her co-authors described how they successfully engrafted human MDS cells into MISTRG mice and were able to reproduce the clonal complexity of those cells and follow the progression of the disease. "Now we can study these primary human cells," said Dr. Halene, "and see how the mutations occur and how they alter hematopoiesis"—the production of blood. "And then, importantly, we can test targeted treatments."

She is working on that with Ranjit Bindra, MD, PhD, Associate Professor of Therapeutic Radiology. The scientists are testing PARP inhibitors in combination with other drugs against mutations of a common enzyme in MDS called isocitrate dehydrogenase (IDH). With Dr. Thomas Prebet, MD, PhD, Associate Professor of Medicine (Hematology) and Associate Director of the Myeloid Malignancies Program, they hope to bring their research to a clinical trial by this fall. New therapies for MDS are needed. Currently the only cure is a bone marrow transplant, which isn't possible for everyone.

Drs. Podoltsev and Halene are excited that the new Center will facilitate recruitment of new faculty and provide grants to young scientists eager to develop promising ideas. It will also foster collaborations between clinicians and basic scientists to test new therapies. A major focus of the Center will be a bio-specimen bank of samples taken from patients with blood malignancies.

"We will be able to annotate patient samples much better, which will lead to new hypotheses, new approaches, new ideas on what to tackle," said Dr. Halene.

It's all happening because Fred DeLuca became Dr. Podoltsev's patient in 2013. "I sent him to both Dana Farber and Memorial Sloan Kettering for opinions, and he saw very distinguished leukemia physicians," said Dr. Podoltsev, "but he always came back. I think this new Center is Mrs. DeLuca's response to the care he received here, not just by me but by Stephanie and the nurses and our transplant team and the whole staff. We're extremely appreciative of her generosity and looking forward to share the results of the research the Center will enable."

We're extremely grateful for The DeLuca Center for Innovation in Hematology Research and look forward to sharing the results of new research the Center will enable.

PETER BAKER

Tom Felton with Virginia Clinchy-Jarmoszko, RN

Smilow's Patient Navigator Program Walks with Patients, Every Step of the Way

When Tom Felton was diagnosed with stage four colon cancer, it was an overwhelming conversation with his oncologist, recalls his wife Sharon. Two years and four surgeries later, the cancer has metastasized, but he's still in great spirits and is laughing in the background recalling his experience while his wife talks on the phone.

"My husband has had so many odd things that have happened to him that we kid Ginny she should write a book," said Mrs. Felton.

Ginny is Virginia Clinchy-Jarmoszko, one of seven Care Coordinators across the Smilow Cancer Hospital Network who support Medicare patients undergoing treatment for cancer. Care Coordinators are one of the strategies Smilow has employed to improve services to patients in the Oncology Care Model (OCM), a value-based payment program launched and funded by the Centers for Medicare and Medicaid Services (CMS) Innovation Center. Care Coordinators proactively follow up with high-risk cancer patients to track symptoms and intervene early to prevent hospitalizations and emergency department visits. They also support care transitions from inpatient to outpatient settings, and to hospice when necessary.

Smilow Cancer Hospital was selected as one of 176 practices to pilot the program, which began in July 2016 and will run through June 2021. So far, it has worked: there has been a 21.1 percent decrease in the hospitalization rate and 8.4 percent decrease in emergency department visits, according to Naralys Estevez Sinanis, OCM Program Manager at Smilow.

"Care Coordinators serve as the patient's main point of contact across the care continuum for both new and existing patients," said Ms. Sinanis. "They are the missing piece, especially in oncology, for helping to track patients so they have less fragmented care."

Like all seven Care Coordinators, Ms. Clinchy-Jarmoszko is a registered nurse. She also has a background in critical and ICU care, and case management. "Just hearing the word 'cancer,'" she said of her patients, "they don't know where to begin."

While Ms. Clinchy-Jarmoszko reviews background information provided to her about her patients, she believes in asking questions when they first meet. She aims to learn what her patients understand about their cancer, their treatment, their options. She also tries to clarify important details in how they wish to manage their care, like their living situation and who will support them throughout their treatment.

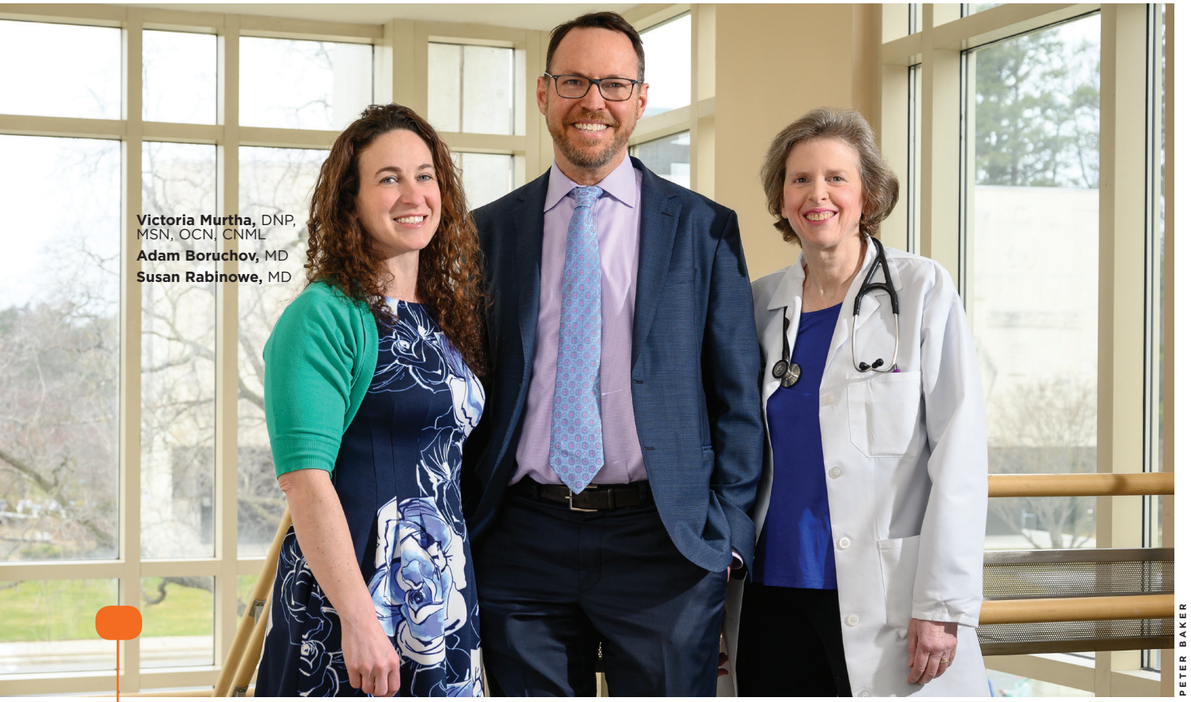
After that initial consultation, she likes to keep in touch with patients at least once a week with phone calls, or by visiting when they have an appointment or treatment scheduled. Ms. Clinchy-Jarmoszko said she tries to "be a cheerleader to help her patients through, especially with symptom management, so they can withstand their treatment." Along with coordinating with each patient's medical and oncology teams, she often brings in a nutritionist, a social worker, and other supportive care services to ensure the care team is all on the same page.

Care Coordinators also work with patients to take advantage of the Smilow Extended Care Center, which is another part of the OCM strategy. Instead of waiting until symptoms such as dehydration and nausea are so dire that emergency intervention is needed, Ms. Clinchy-Jarmoszko's goal is to keep an open line of communication so patients reach out early. She keeps patients aware of alternative solutions, like outpatient urgent care.

When cancer is not curable, Ms. Clinchy-Jarmoszko emphasizes to each of her patients that they are in control of their care and treatment. "I want to be sure that every patient, and their family, understands that there are choices along the way," she said. So far, "each patient has passed in the manner in which they wanted to."

"She really is remarkable," Mrs. Felton added of Clinchy-Jarmoszko. "She's just so comforting and professional. We're just blessed to have her."

Care Coordinators serve as the patient's main point of contact across the care continuum for both new and existing patients. They are the missing piece, especially in oncology, for helping to track patients so they have less fragmented care.



PETER BAKER

Victoria Murtha, DNP, MSN, OCN, CNML
Adam Boruchov, MD
Susan Rabinowe, MD

Smilow Cancer Hospital at Saint Francis

CENTER AT A GLANCE

- A patient-centered focus on exceptional cancer care
- Over 110 staff members; 13 oncology board-certified clinicians
- Medical Oncology: Over 2,000 patient visits per month
- On site oncology pharmacy and clinical trials, in collaboration with Yale Cancer Center
- Access to supportive care clinicians, including oncology nurse coordinators, social workers, dietician, clinical research staff, palliative care, and survivorship planning
- Access to Integrative Medicine Services including massage, Reiki, acupuncture, music therapy, and psychology

Saint Francis Hospital is fortunate to collaborate with Smilow Cancer Hospital and Yale Cancer Center to give our patients access to innovative cancer care in Hartford County. We partner with our colleagues at Smilow Cancer Hospital to offer genomic analysis, personalized treatment plans, and clinical trials, when appropriate."

— Adam Boruchov, MD
Medical Director

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PETER BAKER

meet the physician

Mario Sznol, MD

Professor of Medicine (Medical Oncology)
Co-Director, Cancer Immunology Program

The changes that immunotherapy has brought to the treatment of melanoma over the last 20 years have been remarkable. What has been the biggest impact on treatment advances since Interleukin-2 was established for treatment?
The introduction of anti-CTLA-4 had a small impact on patient response, but the single most effective agent for melanoma treatment is anti-PD-1 (nivolumab or pembrolizumab). Using either anti-PD-1 alone or in combination with anti-CTLA-4, we can expect 5-year survival for patients with advanced disease to be approximately 50%. Before these agents were available, the 5-year survival rate for our patients was 5-10%. Even more encouraging, many of the patients alive at five years will not relapse and are probably cured of their disease.

You are currently President of the Society for Immunotherapy of Cancer. What are some of the biggest challenges facing the research field as immunotherapy treatments and our knowledge evolves?
The single biggest challenge is to define the mechanisms of resistance, and to be able to identify which of the many possible mechanisms of resistance are responsible for lack of treatment benefit in an individual patient. Without a biomarker to identify why treatment did not work in an individual, it is very difficult to select among the many different potential second-line treatments for a patient, and to conduct clinical trials to approve new agents.

What are the research priorities for you and your team for our patients with melanoma?
We are, of course, trying to identify and test new agents, which will benefit the group of patients who don't receive long-lasting benefit from anti-PD-1 and/or anti-CTLA-4 therapies. Part of this effort is to collect tumor samples before and after treatment to understand why treatment is not working. We believe that modifying the function of certain other types of immune cells within the tumor can help a subset of these patients and we are also trying to study various types of cell therapies.

Within our team, Dr. Harriet Kluger is investigating the reasons why melanoma will often form metastases in the brain and is developing new approaches for treating those resistant brain metastases. And of course, not all patients will respond to immune therapies, so our colleagues, including Dr. Ruth Halaban, are focused on new targets based on defining abnormal molecular pathways that drive melanoma cells. Dr. Marcus Bosenberg and Dr. Harriet Kluger lead our NCI SPORE in Skin Cancer grant to translate laboratory findings from their labs and other labs into our clinics.

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Smilow Cancer Hospital

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A Comprehensive Cancer Center Designated by the National Cancer Institute

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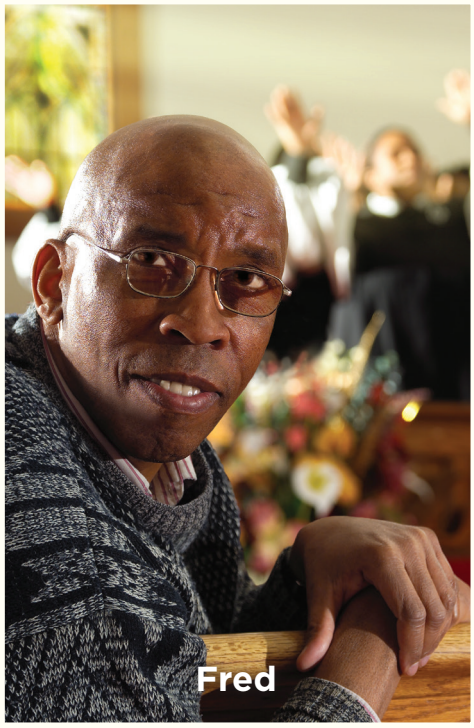

Read their stories:
yalecancercenter.org/survivors