NATIONAL CANCER INSTITUTE

CENTER FOR CANCER RESEARCH

MILESTONES

Cancer Research with a Purpose

HIGHLIGHTS 2017–2018

U.S. Department of Health & Human Services | National Institutes of Health

CENTER FOR CANCER RESEARCH
THE NATION'S CANCER CENTER

As part of the federally funded National Cancer Institute (NCI), the Center for Cancer Research (CCR) is the nation's cancer center. Located in the suburbs of Washington, D.C., our scientists are unlocking the mysteries of cancer and discovering new ways to prevent, diagnose and treat it. The CCR collaborates with academic and commercial partners and advocacy groups across the world in efforts to find treatments and cures for cancer through basic, clinical and translational research. Our physician-researchers translate these discoveries from the lab to the clinic, and we treat thousands of people from around the country every year with novel therapies through our clinical trials program at the National Institutes of Health (NIH) Clinical Center.

For more about our science, our training programs and our clinical trials, visit **ccr.cancer.gov.**

About the cover: *Ten-year-old Travis Carpenter loves to play at The Children's Inn during his many visits to NIH. Travis has been participating in a clinical trial for neurofibromatosis type 1, or NF1, with Brigitte Widemann, M.D., Chief of CCR's Pediatric Oncology Branch, since November 2015. Travis was diagnosed when he was six months old, and a tumor developed on his lower back and left leg by the time he was two-and-a-half. This is the first time throughout his nine years of treatment for NF1 that his inoperable tumor has stopped growing and actually started shrinking. His energy level has increased, and his pain level has decreased.*

Credit: *Daniel Soñe*

Contributors:

Brenda Boersma-Maland
Chloe Gansen
Li Gwatkin
Abbie Harrison
Diana Linnekin
Jennifer Michalowski
Mike Miller

The MISSION of the CCR is to improve the lives of cancer patients by solving important, challenging and neglected problems in cancer research, prevention and patient care through:

- A world-leading basic, translational and clinical research and patient-care program
- An institutional focus on high-risk and long-term projects, unmet needs and pursuit of unexplored ideas
- Leadership and coordination of national disease networks and development of technology resources for the cancer community
- Partnerships with academic institutions, commercial entities and patient advocacy groups
- Training of the next generation of the biomedical workforce

Contents

Director's Note

In a recent conversation I had, CCR was referred to as "a place that changes lives." The statement could be taken as a mere cliché – but these words are true. All we need to do is watch Travis, seen on the cover, play happily while enrolled in a trial in the NIH Clinical Center for his neurofibromatosis type 1. We make a difference in the lives of our patients and their families. Through our research, we provide cutting-edge treatment, passionate care – and hope.

While our patients' well-being is the most evident sign of our impact, our clinical successes are built on groundbreaking, innovative laboratory research that identifies new molecular, diagnostic and therapeutic targets and inspires novel treatment strategies. Our basic research program is an engine for new knowledge that drives the development of novel clinical approaches.

This year's issue of *Milestones* once again captures the remarkable quality and spectrum of our work in the basic and clinical sciences. In the past year, CCR investigators elucidated a fundamental genetic mechanism in cancer using baker's yeast; characterized the molecular mechanisms of cancer stem cells; gained insights into how a tumor in one location in the body can prepare a far-flung site for metastasis; and developed novel and improved immunotherapy approaches, to mention just a few of the accomplishments described in this issue.

These advances are made possible by the creativity of the investigators, their fellows and students; the expert compassionate care of our nurses and clinical staff; and the support of our administrative personnel. They occur because of the vibrant intellectual environment and unmatched intellectual freedom created by the stable funding model of the NIH intramural program.

Each one of the CCR contributions in this issue of *Milestones*, and the many others not featured here, move us along the path towards preventing cancer and making the disease more manageable by developing effective treatments. Our journey continues, and with each scientific milestone we reach, we create an opportunity to make even more of a difference to many. The CCR, indeed, is a place that changes lives – and we are all proud to be part of it!

Tom Misteli

WHAT MAKES IMMUNOTHERAPY WORK

Understanding the genes tumor cells rely on to escape immune control could guide the way to immunotherapies that work for more patients.

Immunotherapies are changing the landscape of cancer treatment. They work by empowering a patient's immune system to attack difficult-to-treat cancers, often leading to complete disappearance of tumors. But many patients still fail to respond to these innovative treatments, and developing immunotherapies that work for more people is a high priority.

Senior Investigator **Nicholas Restifo, M.D.**, from CCR's Surgery Branch, and his team of researchers have addressed this issue in a systematic fashion and have created a complete compendium of human genes that affect how well immunotherapy works.

Restifo and his colleagues tested all of the nearly 25,000 protein-coding genes in the human genome to determine which ones must be working in tumor cells to make them vulnerable to immune attack. In a landmark publication in *Nature*, the team reported on 19 genes that appear to be essential for a successful anticancer immune response in patients. Their findings suggest that tumors that accumulate mutations in any of these genes might become less susceptible to immune control.

Current immunotherapies are designed to boost the ability of the immune system's T cells to find and destroy tumors. Restifo and colleagues used CRISPR, a powerful gene-editing technology, to generate melanoma cells with individual genes switched off. Then they allowed T cells to mingle with the modified melanoma cells and observed how the immune cells performed when their targets lacked any given gene. In this way, the researchers identified more than 100 genes that appeared to play a role in the T-cell response.

The team then accessed data from The Cancer Genome Atlas (TCGA), a publicly available resource collaboratively managed by NCI and the National Human Genome Research Institute. Using DNA sequence information from more than 11,000 patient tumors in TCGA, the team looked for evidence that the genes they identified in their laboratory experiments played a similar role in patients. By mining that data for patterns of gene activity that typically accompany cell death, the researchers linked 19 of the genes on their list to tumors' ability to avoid immune attack in patients.

Restifo's team has already zeroed in on one of these genes, *APLNR*, which encodes a cellular signaling protein, and discovered that it is critical for processing the markers on the surface of tumor cells that alert T cells to their identity. They found *APLNR* mutations in tumors from patients whose cancers had not responded to immunotherapy and showed that when melanoma cells contain mutations in *APLNR*, the immune system has a hard time finding tumors and keeping their growth in check.

Further studies should begin to unravel the other genes' contributions to a tumor's susceptibility to immune control. In addition to shedding light on how immunotherapy works, in the near-term, the catalogue of genes identified will help researchers predict which patients are most likely to benefit from specific immunotherapies. By exploiting the tumors' specific strategies for escaping the immune system, the catalogue could point the way to new therapies designed to counter those tactics.

Patel SJ, et al. *Nature*. 2017 Aug 31;548(7669):537-542.

This heat map graph shows the gene expression profiles of over 11,000 different tumors. The cluster of genes shown in red correlates with the presence of T cells.

Credit: *Nicholas Restifo, CCR, NCI, NIH*

EXPANDING IMMUNOTHERAPY'S REACH

New advances suggest opportunities to treat a broadening range of cancers with cell-based immunotherapies.

CCR scientists have long led the way in developing and testing immunotherapies, which strengthen patients' immune systems to confront their cancers head-on. Now, building on decades of laboratory and clinical findings, they are working to improve these revolutionary therapies and expand their potential.

Two recent advances highlight new opportunities. One, reported in the *New England Journal of Medicine* by a team led by **Steven Rosenberg, M.D., Ph.D.**, Chief of CCR's Surgery Branch, is the successful treatment of a patient with metastatic colorectal cancer using adoptive cell therapy (ACT). In ACT, a patient's own cancer-fighting immune cells are grown in the laboratory and then returned to the patient in larger numbers, bolstering the body's defenses.

An exciting aspect of this success is that the immune cells used for the treatment target cells with a mutation in a gene called *KRAS*. *KRAS* mutations are thought to drive the growth of 45 percent of colorectal cancers and 95 percent of pancreatic cancers. The specific mutation targeted in this study is estimated to occur in more than 50,000 new cancer cases in the United States each year.

Researchers have struggled for decades to develop therapies that rein in mutant forms of *Ras* proteins, but they have proved elusive targets. Now that Rosenberg's team has shown *KRAS*-targeting immune cells can lead to tumor regression in a patient with advanced disease, they hope this strategy can be used to treat other cancers with the same mutation.

CCR scientists are also exploring ACT as a treatment for cancers caused by the human papillomavirus (HPV). In 2015, a team led by Rosenberg and **Christian Hinrichs, M.D.**, an Investigator in CCR's Experimental Transplantation and Immunology Branch (ETIB), reported in the *Journal of Clinical Oncology* some success in a clinical trial for patients with advanced cervical cancer.

For two of the 18 women in that trial, ACT caused complete and lasting tumor regression. Now, Hinrichs and his colleagues have taken a closer look at the immune cells responsible for their recoveries and made a surprising discovery.

Women in the trial were treated with cancer-fighting immune cells that had been isolated from their own tumors and multiplied in the laboratory. Although the mixtures of cells selected for the treatment were chosen because they were particularly adept at targeting tumor cells bearing markers produced by HPV, the new analysis revealed that the dominant anticancer cells in their systems do not target HPV-specific antigens. Instead, they are sensitive to antigens produced due to mutations in the tumors' own genomes. The findings, published in *Science*, have important implications for the design of new cellular immunotherapies—not just for HPV-associated cancers but potentially for others as well.

The team found that a non-viral antigen that seemed to trigger a strong response against one patient's cervical cancer is produced by about 40 percent of cervical cancers. Other researchers have reported that the same antigen is found in many breast, lung and stomach cancers, raising the possibility that a therapy targeting this antigen could be effective for many cancer types.

Stevanović S, et al. *J Clin Oncol*. 2015 May (14):1543-50.

Tran E, et al. *NEJM*. 2016 December (375):2255-2262.

Stevanović S, et al. *Science*. 2017 Apr 14;356(6334):200-205.

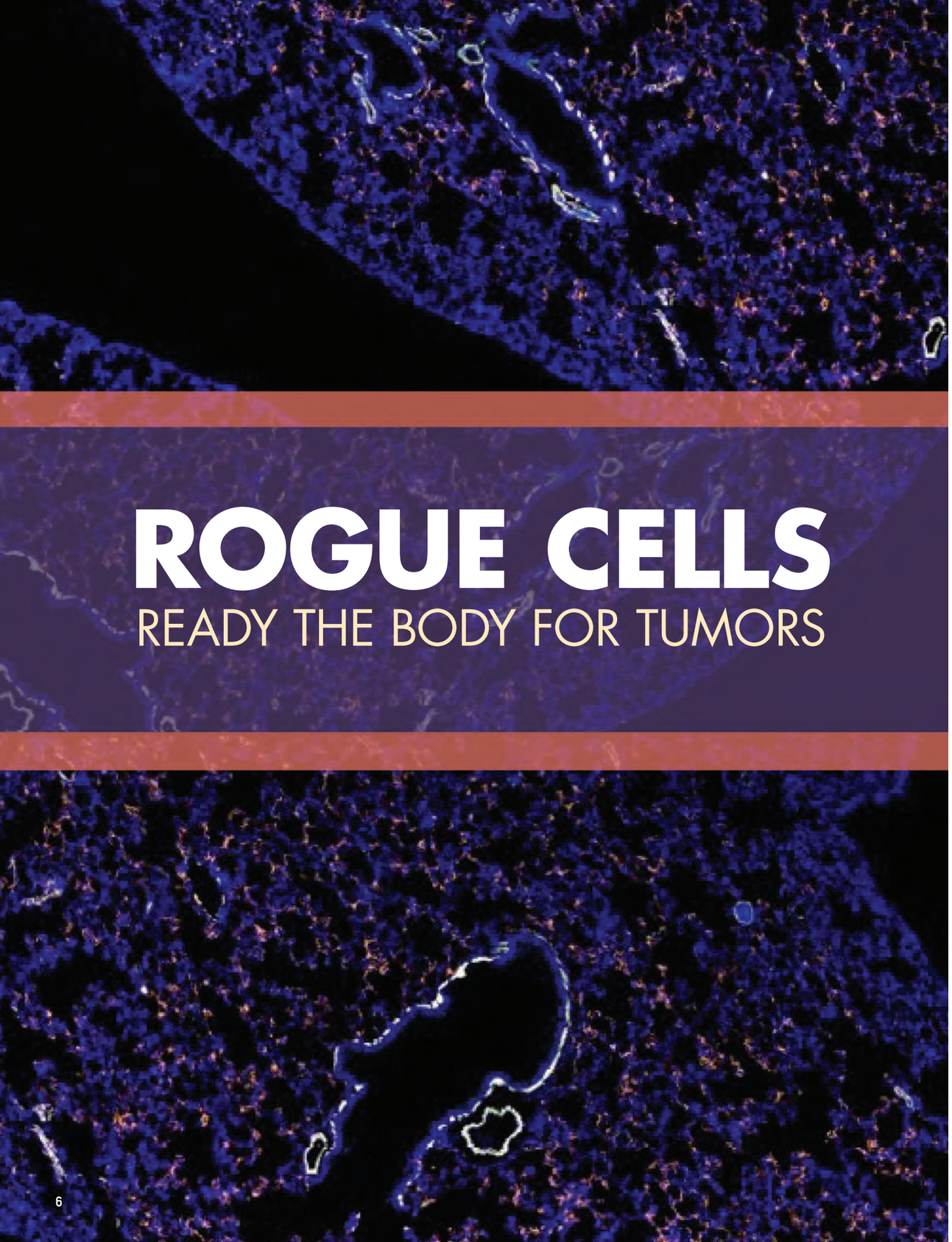
Lasting Immunotherapy Success in Lymphoma Patients

CCR scientists also continue to follow patients who have responded well to existing treatments. The longest follow-up to date of patients who have received chimeric antigen receptor (CAR) T-cell therapy, a treatment that modifies a patient's T cells in the laboratory to better recognize and eliminate tumor cells, was reported in *Molecular Therapy*. The study, led by ETIB investigator **James Kochenderfer, M.D.**, and Dr. Rosenberg, focused on patients with diffuse large B-cell lymphomas who received experimental treatment at the NIH Clinical Center. Five of seven patients in that study experienced complete remissions following treatment. Three years later, four patients' cancers remain in remission. The long-lasting responses raise the possibility that a single treatment with CAR T-cell therapy can be curative for this aggressive blood cancer.

Kochenderfer J, et al. *Molecular Therapy*. 2017 October (10): 2245-2253.

In this image from a genetically engineered mouse model, lung cancer driven by the KRAS *oncogene shows up in purple. As a key driver in many types of cancer, the* KRAS *gene makes a promising target for new cancer therapies.*

Credit: *NCI, NIH*



ROGUE CELLS
READY THE BODY FOR TUMORS

Keeping blood vessel–supporting cells in working order could reduce the risk of metastasis.

Tumors—even small ones that have not spread—trigger changes in the body well beyond their immediate surroundings. CCR scientists have now discovered that when a tumor grows locally in the body, cells in lung tissue dedicated to supporting blood vessels and regulating blood flow can take on a harmful new role: altering the structure of tissue to render it more hospitable to metastasizing tumor cells.

Rosandra Kaplan, M.D., an Investigator in CCR's Pediatric Oncology Branch, and her postdoctoral fellow Meera Murgai, Ph.D., found that they could dramatically reduce metastasis in mice by disabling this behavioral transformation in the distal renegade cells. Their findings, published in *Nature Medicine*, suggest a new strategy for preventing metastatic tumors from taking hold.

In animal studies, Kaplan and Murgai discovered that perivascular cells, best known for their role in maintaining healthy blood vessels, are critical for the establishment of a pre-metastatic niche for migrating tumor cells. These perivascular cells are usually found wrapped around the outside of blood vessels where they carry out a number of functions, including regulating the vessels' size and permeability. They also leave the periphery of blood vessels at times to aid in wound healing and tissue regeneration. Their functions beyond vascular support have been difficult to study, however, because when these cells take on alternate roles, they stop producing the surface markers that scientists typically use to identify them. As a result, their involvement in metastasis has been underappreciated.

To track the cells' behavior, Murgai studied mice whose perivascular cells had been engineered to produce an easy-to-follow fluorescent protein. When she injected tumor cells into the leg muscles of those mice, she saw bright yellow-tagged perivascular cells in the lungs leave the blood vessels and redistribute themselves through other parts of the lung tissue. The cells switched on new genes and changed their behavior, most notably generating large amounts of an extracellular matrix protein called fibronectin. Adding fibronectin to the extracellular matrix makes it easier for the cells to grab onto and crawl upon, creating a microenvironment tumor cells can more easily colonize, Kaplan explains.

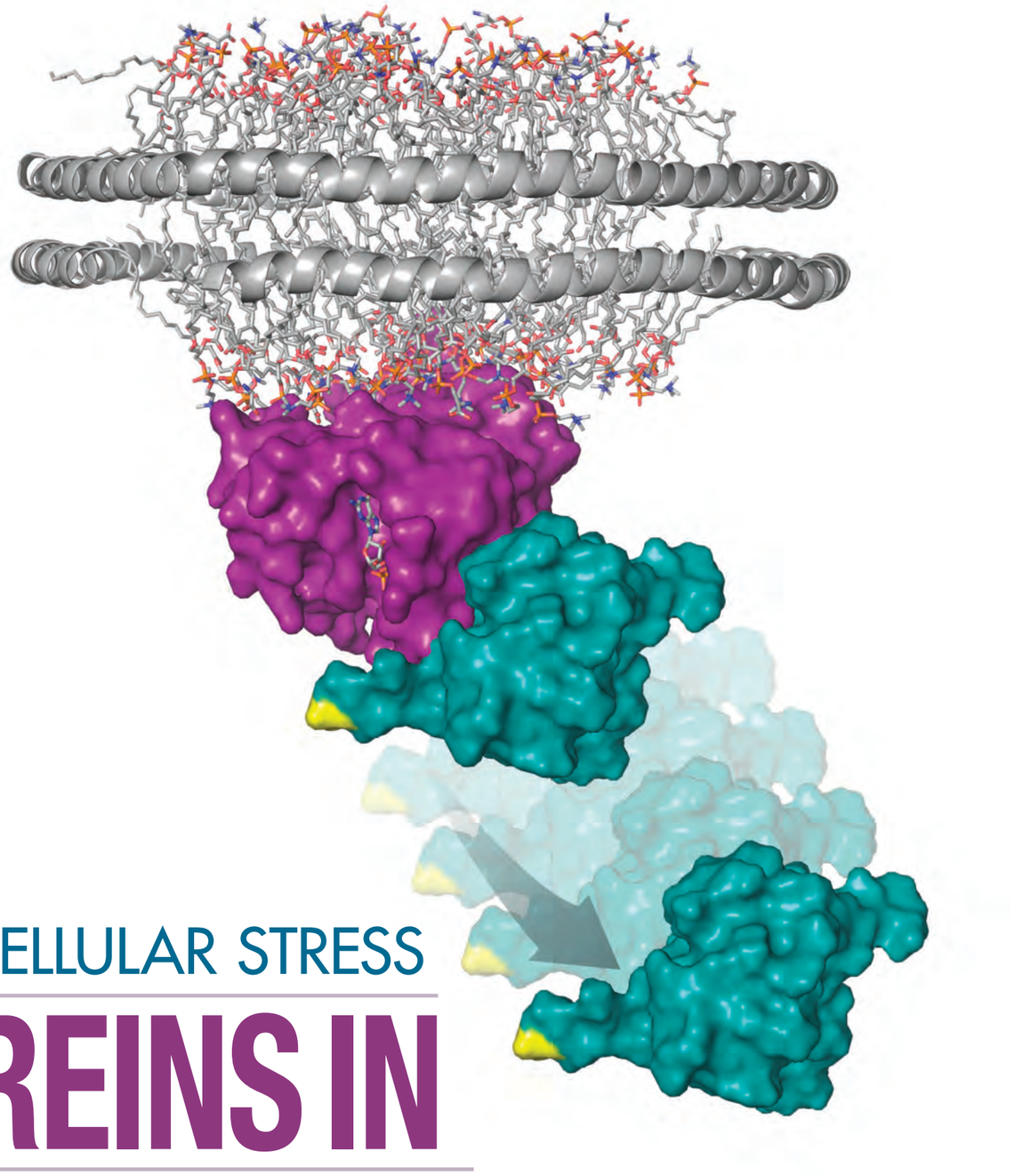
The researchers found they could prevent this behavior by switching off a gene called *KLF4*, which encodes for a gene regulatory protein that manages transcription of many other genes and is important for perivascular cells' ability to turn rogue. When they forced perivascular cells to maintain their usual roles by disabling *KLF4*, mice with tumors growing in their muscle tissue developed very few metastases in the lungs. Blocking tumor cells' ability to interact with fibronectin similarly reduced metastasis, suggesting a modified extracellular matrix is critical for tumor cells' survival once they reach the lungs.

Kaplan notes that the mice used for the study develop metastatic tumors quickly when *KLF4* is left intact, making them a good model for studying what happens in patients with highly metastatic disease. She is hopeful that preventing the detrimental shift in behavior of perivascular cells in patients may reduce the risk of metastatic disease.

Murgai M, et al. *Nature Medicine*. 2017 Oct;23(10):1176-1190.

This image represents the early changes that occur in the lung in response to a localized primary tumor distant from the lung. These changes involve perivascular cells (orange) that are normally found around blood vessels (yellow) where they support vessel development and function. In individuals that have a primary tumor, these perivascular cells move away from blood vessels and create an environment that supports tumor cells that have left the primary tumor for a new site, ultimately leading to metastasis.

Credit: *Rosandra Kaplan, CCR, NCI, NIH*



CELLULAR STRESS REINS IN *RAS* SIGNALS

Activating the cellular stress response puts the brakes on overactive signaling by one of cancer's most notorious growth promoters.

New research from **Deborah Morrison, Ph.D.**, Chief of the Laboratory of Cell and Developmental Signaling, shows that conditions of cellular stress can halt signaling from the growth-promoting *RAS* pathway, which drives the development of many cancers and has been notoriously difficult to stop.

More than a third of human cancers, including about 95 percent of pancreatic cancers and 45 percent of colorectal cancers, carry mutations in *RAS* genes. In healthy cells, the proteins encoded by these genes help relay growth-triggering signals from outside a cell to the gene regulators that spur appropriate cell proliferation. Mutations can lock *Ras* proteins into a position where they send their growth-promoting signals all the time, driving tumor development.

Researchers have tried for decades to develop drugs that stop tumor growth by blocking dysfunctional *RAS* signaling but have found the protein to be a particularly difficult target. Because creating effective new treatments for *RAS*-driven cancers would have such an enormous impact, in 2013 NCI established a major initiative to bring a wide range of resources and expertise to bear on this problem. Working together under the *RAS* Initiative, researchers in government, industry and academia are learning new details of how the *RAS* pathway works and laying the groundwork for drug development.

Morrison, a collaborator in the initiative, has long been teasing out the precise mechanisms that enzymes in the *RAS* pathway use to relay signals that regulate cell growth. An investigational drug called rigosertib, which blocks the growth of cancerous cells in the lab, caught her team's attention because it was reported to interfere with the *RAS* pathway, possibly by preventing *RAS* from interacting with its signaling partners.

When Morrison and her colleagues took a close look at the drug's effects, however, they found, as they reported in *Molecular Cell*, that its effects on *RAS* signaling are not so direct. Rather than interacting with proteins in the *RAS* pathway, rigosertib causes cellular changes that trigger a cell's stress response. The stress-response pathway, in turn, interrupts *RAS* signaling to put the brakes on cell growth.

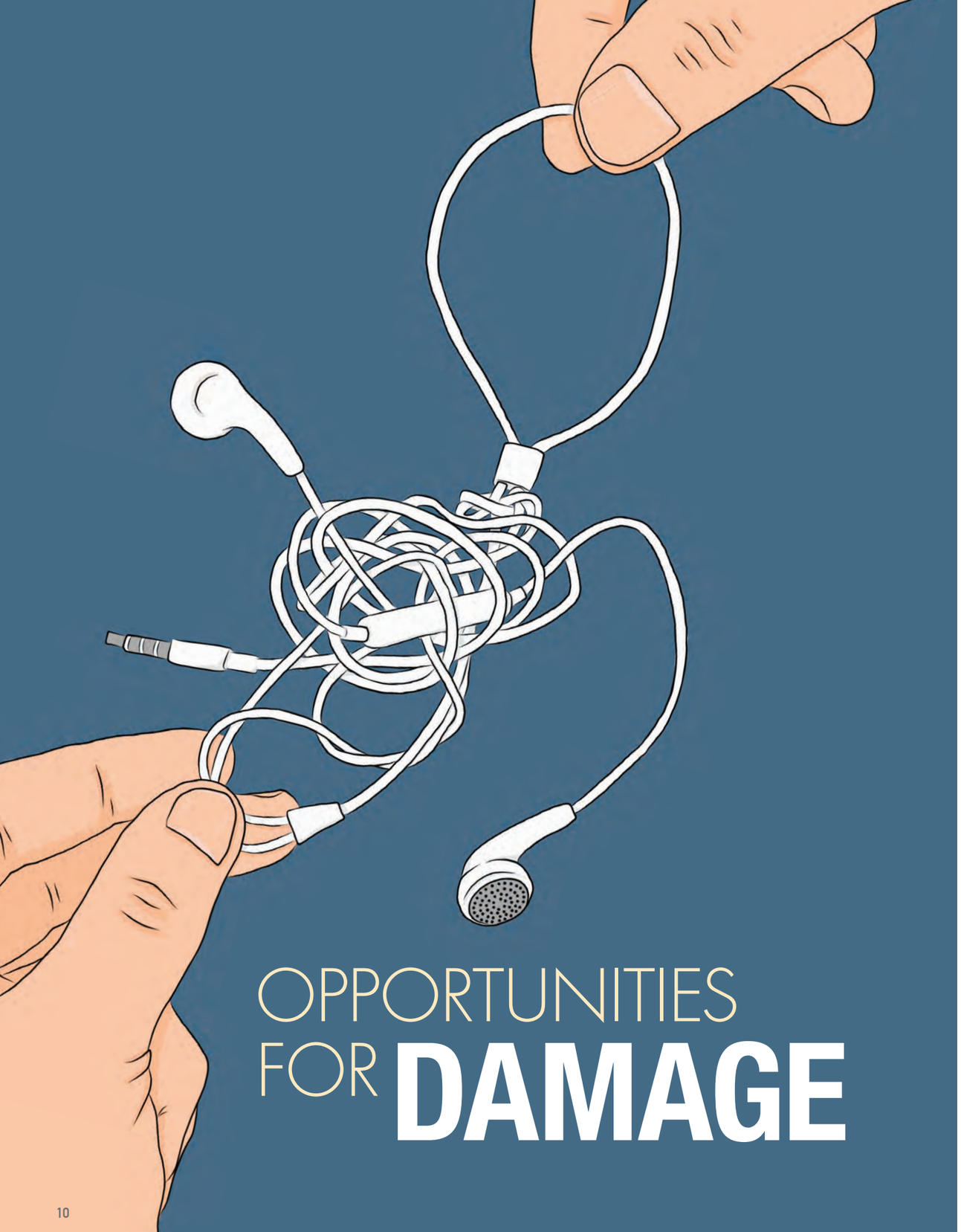
The interaction between the two pathways appears to be a signaling checkpoint that ensures that cells suspend their growth while they assess and respond to stressful conditions, Morrison says. In detailed biochemical experiments, she and *RAS* Initiative collaborators at the Frederick National Laboratory for Cancer Research teased out exactly how a stress-response pathway, called the *JNK* pathway, switches off specific signaling molecules in the *RAS* pathway, effectively blocking *RAS*-mediated growth signals.

Rigosertib is currently being evaluated in clinical trials as a treatment for myelodysplastic syndromes, in which immature blood cells in the bone marrow fail to mature. Morrison's team's findings could help researchers identify new ways to use the compound. In particular, she says, the new understanding of rigosertib's activity suggests that it might be useful in preventing or slowing the development of drug resistance caused by increased *RAS* signaling when used in combination with other cancer therapies.

Ritt DA, et al. *Mol Cell.* 2016 Dec 1; 64(5):875-887.

This model represents the structure of the Ras *protein (purple) attached to a membrane-like nanodisc with the Raf-RBD (teal) protein domain bound to* RAS. *In response to cellular stresses, like rigosertib treatment,* JNK *becomes activated and phosphorylates (or modifies) Raf on a specific site (shown in yellow) that disrupts binding between* RAS *and Raf.*

Credit: *Deborah Morrison, CCR, NCI, NIH*



OPPORTUNITIES FOR **DAMAGE**

Temporary breaks keep DNA organized but put chromosomes at risk for cancer-promoting rearrangements.

Packing an entire genome inside the cramped quarters of a cell nucleus involves organizing long chromosomes into smaller loop domains. This compaction can put chromosomes at risk for damage, according to new research led by **André Nussenzweig, Ph.D.**, Chief of CCR's Laboratory of Genomic Integrity. The findings, reported in *Cell*, suggest that DNA breaks are routinely introduced and then repaired as a cell folds and organizes its genome. When repair processes fail, these breaks can give rise to chromosomal abnormalities characteristic of cancer cells.

One of the most essential activities in a cell is the ability to repair broken DNA. Even temporary breaks created during routine cellular activities are opportunities for lasting damage. Broken DNA strands are usually swiftly repaired, but they can sometimes be reconnected inappropriately, fusing together bits of different chromosomes in an event known as a translocation. This can lead to an imbalanced regulation of genes. Some translocations spur cellular growth and support the survival of cancer cells.

It has long been known that certain chromosome translocations show up in cancer cells again and again. To assess whether these might be common because they arise at fragile sites where DNA breaks are common, Nussenzweig and his collaborators set out to identify all the sites in the genome where one DNA-cutting enzyme, called Topoisomerase 2 (*Top2*), creates such breaks.

Using a method developed in Nussenzweig's laboratory to identify all of the sites in the genome where *Top2* creates DNA breaks, the researchers uncovered a clear pattern. "We found that the initial breakage actually correlates very nicely with where the translocation eventually occurs," Nussenzweig says. The researchers also established that DNA cuts were frequently located near the base of loops that bring distant parts of a DNA strand together to facilitate chromosome organization.

Notably, Nussenzweig says, they found that DNA breaks often occured in genes that were not in active use by cells. "Prior to this finding, translocations have been linked to either transcription or replication problems," he says. "We were very surprised that the damage we saw was independent of both of those, but rather, related to problems during chromosome folding."

In a video found on Nussenzweig's profile at www.ccr.cancer.gov, Nussenzweig and his colleagues explain how the intricate architecture in the cell nucleus makes specific DNA sites more susceptible to breaks that, if not properly fixed, can lead to cancer.

Canela A, et al. *Cell*. 2017 Jul 27;170(3):507-521.

The headphones in this image depict the inherent 'knotting' problem that arises during chromatin loop formation as DNA is channeled through a cohesin-extrusion complex, represented here as a two-way slider. Loosely entangled DNA outside of the loops are converted to tighter knots as chromatin is continuously fed through the motor of the extrusion complex. The mass of jumbled DNA can only be resolved by the action of proteins like Topoisomerase 2B that act as enzymatic scissors to disperse the entanglement of intertwined DNA. The DNA breaks by Topoisomerase 2B occasionally serve as precursors that lead to chromosomal translocations.

Credit: *Ernesto Llamas, Sketching Science*

DIFFERENT AND THE SAME

Overlapping molecular profiles suggest a unified approach may improve diagnosis and treatment of two types of liver cancer.

CCR scientists have found surprising molecular similarities between two types of liver cancer, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (ICC), which were traditionally thought of as quite distinct. The finding suggests that a unified clinical approach could benefit patients with either type of liver cancer.

Liver cancer is the second leading cause of cancer death worldwide. In the United States, about 80 percent of liver cancers are HCC, which originates from the liver's primary cells, hepatocytes. ICC, which develops from the cells that line bile ducts (cholangiocytes), is much less common. HCC and ICC look different under a microscope and have long been considered distinct diseases.

Xin Wei Wang, Ph.D., Deputy Chief of CCR's Laboratory of Human Carcinogenesis, says different clinical guidelines are used to manage HCC and ICC, and different drugs are currently recommended for their treatment. Therapeutic options are limited for both diseases, however, and the prognosis for patients with liver cancer is generally poor. There is an urgent need for new therapies.

For many years, Wang has collaborated with clinical centers in Thailand where liver cancer is a primary cause of cancer-related mortality. Through the Thailand Initiative for Genomics and Expression Research in Liver Cancer (TIGER-LC), this consortium of researchers and clinicians from CCR and five cancer hospitals in Thailand is creating a comprehensive liver cancer biorepository of tumor samples and clinical data. Unlike in the rest of the world, the most common form of liver cancer in northeastern Thailand is ICC, enabling the consortium to investigate similarities and differences between that disease and HCC.

In research reported in *Cancer Cell*, Wang, the lead researcher on the study, and Mathuros Ruchirawat, Ph.D., Vice President of the Chulabhorn Research Institute (CRI) in Bangkok, analyzed the genome sequences, gene activity and metabolic profiles of 199 tumor samples from patients in Thailand. The CRI is actively led by Her Royal Highness Princess Chulabhorn Mahidol of Thailand, Ph.D.

The team used the data to identify molecular subtypes of either type of liver cancer. Surprisingly, Wang says, the molecular features that defined certain subsets of ICCs closely resembled subsets of HCC.

"Those subtypes not only have very similar gene expression fingerprints and similar tumor biology, they also have similar clinical outcomes," Wang says. Examining a broader set of liver tumor samples, the team found that several of the subtypes they identified in their original analysis were represented among patients of all ethnicities, but some occurred only among Asians.

Recognizing common molecular subtypes of liver cancer could help researchers treat the disease more effectively, regardless of whether a patient has been diagnosed with HCC or ICC. In the near term, Wang says, the findings will help researchers identify patients with particularly aggressive liver cancers and recommend appropriate treatments. Additionally, genetic mutations that the team has identified as possible drivers of specific subtypes may point researchers toward strategies for developing targeted treatments.

Chaisaingmongkol J, et al. *Cancer Cell*. 2017 Jul 10;32(1):57-70.

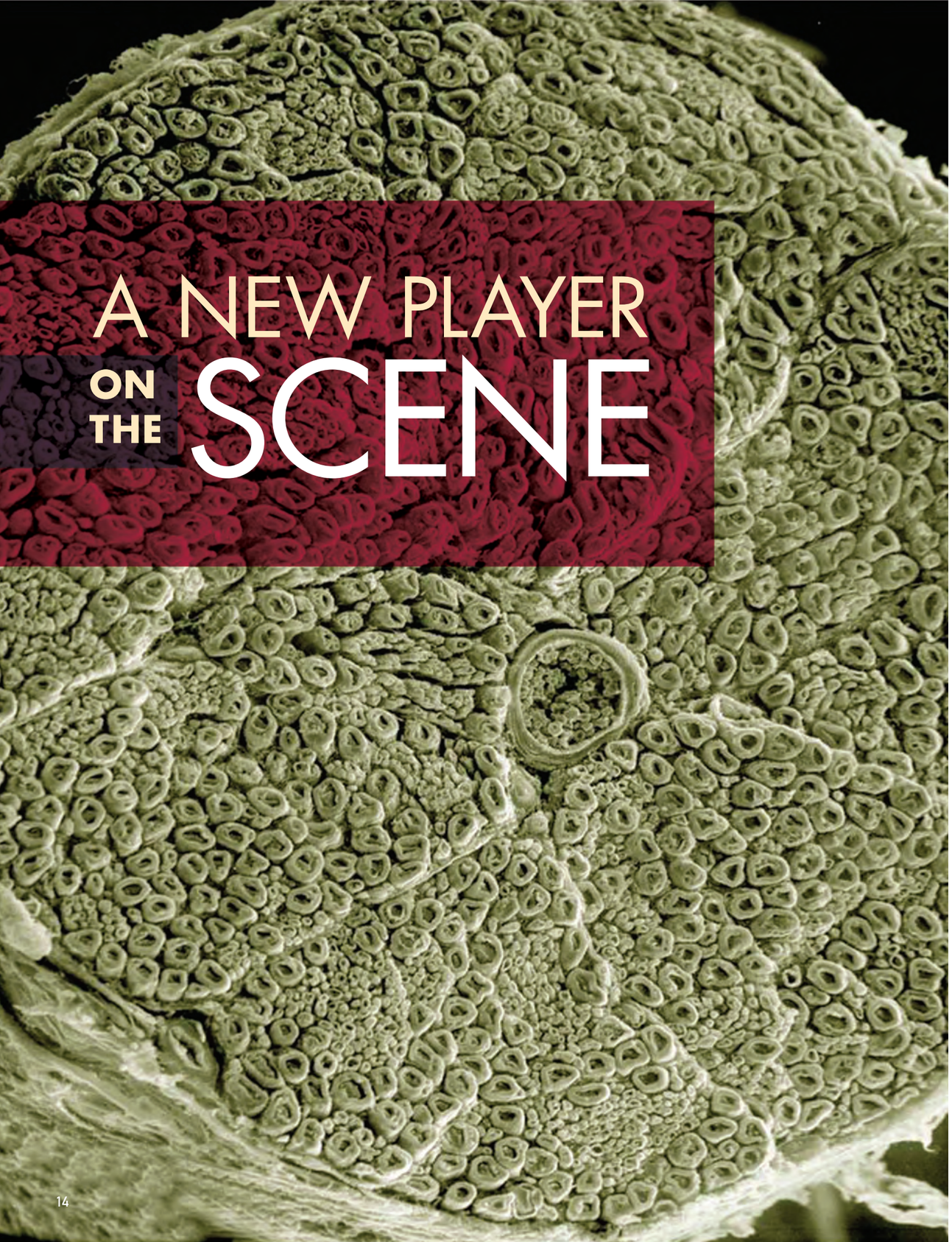
A New Player in Liver Cancer

Although cancer is generally thought to be driven by changes in a handful of genes, tumor cells often contain altered levels of thousands of different RNA molecules. A study from Wang's team, published in *Cancer Cell*, has identified a feature of liver cancer cells that may be to blame for these widespread disruptions: dramatic changes in the levels of RNA-binding proteins. After showing that RNA-binding protein levels were widely skewed in liver cancers, the team determined that excess levels of one of these proteins, negative elongation factor-E (NELF-E), enhances signaling of the oncogene *c-Myc*, which promotes cancerous growth. Disrupting NELF-E's interactions with its RNA targets or the c-Myc protein could be a strategy for new anticancer therapies.

Dang H, et al. *Cancer Cell*. 2017 Jul 10;32(1):101-114.

The Thailand Initiative in Genomics and Expression Research for Liver Cancer Consortium (depicted as a tiger) emerges from the foliage, representing molecular, clinical and epidemiological studies from teams in the U.S., Thailand and Japan, that generate a multilayered genomic and genetic liver cancer data ecosystem (represented by the tiger's tail). Although common molecular subtypes (depicted as bamboo stalks) are observed among liver cancer types, there are differences observed between Asian and Caucasian populations.

Credit: *Ethan Tyler, Medical Arts, NIH*



A NEW PLAYER ON THE SCENE

A screen for hundreds of epigenetic regulators has turned up a novel approach for treating a pediatric cancer.

Neuroblastoma is a rare disease, but it accounts for 15 percent of all childhood cancer deaths. Some neuroblastomas respond well to treatment, but about 40 percent of patients have a high-risk subtype, which tends to return even after chemotherapy. Frustratingly, DNA sequencing of patients' tumors has turned up few leads to point researchers toward strategies for developing more targeted therapies. **Carol Thiele, Ph.D.**, Deputy Chief of CCR's Pediatric Oncology Branch, and her team have now found new targets for better therapies for the most life-threatening form of this pediatric cancer.

Taking a new approach, as reported in *Cancer Cell*, Thiele and her colleagues screened hundreds of epigenetic regulators—enzymes that influence a cell's genetic activity by modifying DNA or the proteins that package it—in search of any that contribute to the growth of neuroblastomas. They found dozens that do, and their detailed analysis of one of these, a protein called *SETD8* that has not previously been linked to cancer, suggests a new strategy for stopping the growth of this aggressive tumor subtype.

Thiele and her colleagues turned to epigenetic regulators as a source of potential drug targets because it is widely known that these proteins play a crucial role in determining whether stem cells maintain their ability to divide, or instead, differentiate, taking on the characteristics of more mature cells. For stem cells in a developing nervous system, including the neuroblasts from which neuroblastomas arise, the ability to self-renew is critical, but cancerous cells that retain this ability spur tumor growth and can be particularly difficult to eliminate. It is well known, Thiele says, that the most dangerous neuroblastomas are those whose cells remain undifferentiated.

A tell-tale sign that a neuroblastoma cell has begun to differentiate is the development of long, thin extensions that project from its cell body. Thiele and postdoctoral fellow Veronica Veschi, M.D., Ph.D., worked with CCR's High-Throughput Imaging Facility to develop an automated method to analyze these projections based on microscope images so they could efficiently assess differentiation in large numbers of cells. Then they used genetic tools to switch off each of 400 different epigenetic regulators so they could determine how each one impacted the growth and differentiation of neuroblastomas.

That screen identified more than 50 epigenetic-regulating genes that help keep neuroblastoma cells in a dangerous state of self-renewal, including 16 that also seem to block their differentiation. The team was most interested in genes whose products could be blocked with the kinds of small molecules that make effective drugs, so they conducted another screen, this time using a library of 21 chemicals known to target epigenetic regulators.

Of those, the compound with the most profound effect on the growth and differentiation of neuroblastoma cells blocked the *SETD8* protein. Working with colleagues in CCR's Laboratory of Cell Biology, Genetics Branch and NCI's Center for Biomedical Informatics and Information Technology to investigate *SETD8*'s function, the team learned that the protein dials down production of p53, an important tumor suppressor.

Thiele and her colleagues are hopeful that blocking *SETD8* in patient tumors might reactivate the p53 pathway and inhibit the growth of neuroblastomas. The inhibitor used in the team's experiments needs further development before it can be considered for clinical testing, but the team has already shown that blocking *SETD8* slows the growth of human neuroblastoma tumors implanted in mice.

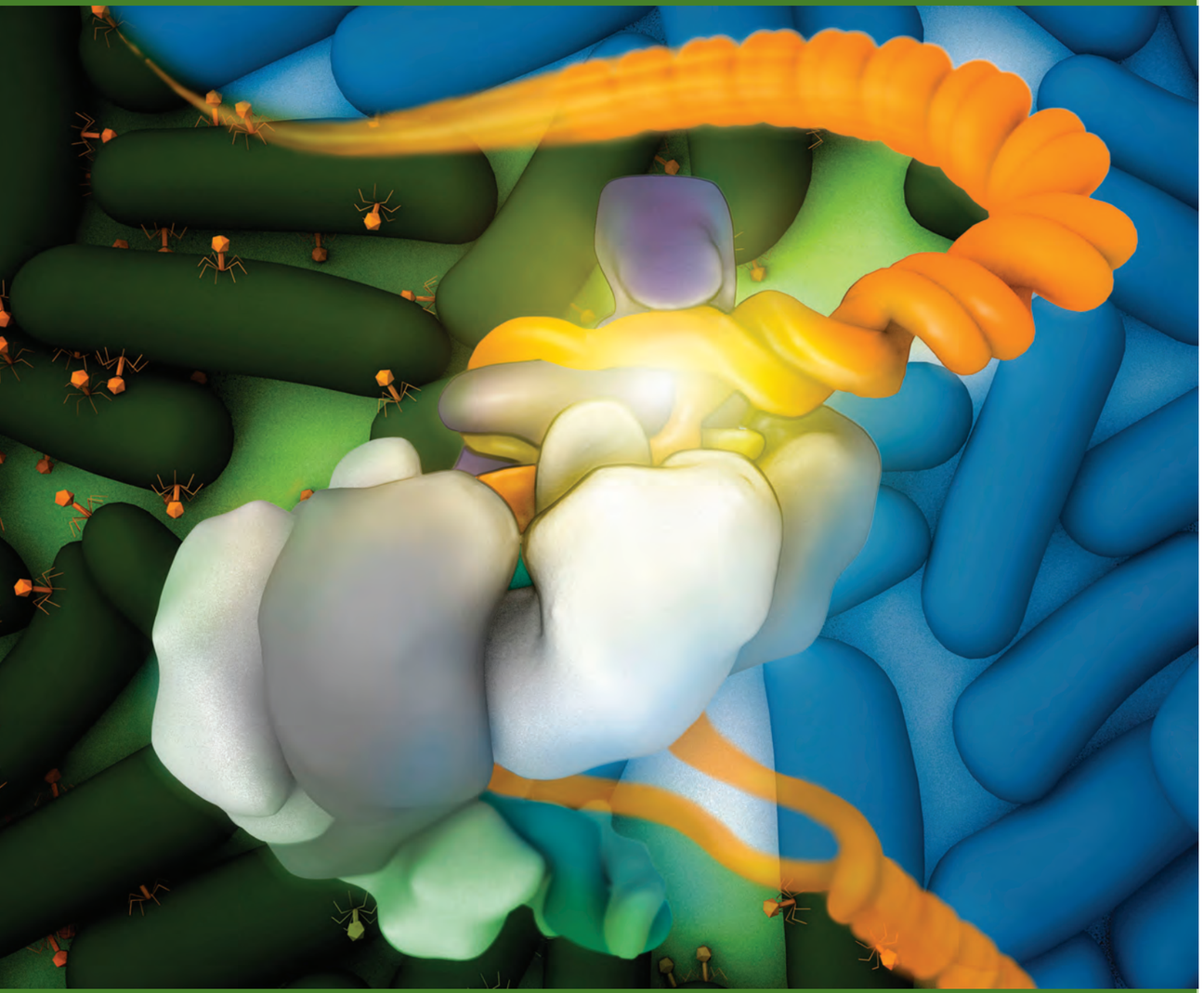
Veschi V, et al. *Cancer Cell*. 2017 Jan 9;31(1):50-63.

A scanning electron micrograph of a section through a human spinal nerve. In the center is a blood vessel filled with red blood cells. Neuroblastoma occurs in certain types of nerve tissue, including tissue in the neck, chest, abdomen or spine.

Credit: *Tom Deerinck, National Center for Microscopy and Imaging Research, University of California San Diego*

SNAPSHOT

OF A **CELLULAR MACHINE**



The Csy complex bound to DNA (orange); the DNA fork is coordinated by the "hook" (purple), overlaid on a field of healthy (blue, upper right background) and virally infected (green, lower left background) bacteria.

Credit: *Veronica Falconieri, Subramaniam Lab, CCR, NCI, NIH*

Visualizing a DNA-cutting complex in extraordinary detail reveals how it binds to target DNA and changes its shape.

Using the Nobel-prize winning technique of cryo-electron microscopy (cryo-EM), researchers led by CCR Senior Investigator **Sriram Subramaniam, Ph.D.**, have captured a series of highly detailed images of a protein complex that bacteria use to recognize and destroy foreign DNA.

The DNA-cutting complex is part of the CRISPR system that bacteria use to protect themselves against viruses and other foreign invaders. As part of this defense system, the surveillance complex recognizes foreign DNA and triggers its destruction. In recent years, researchers have adapted the CRISPR system into a powerful tool for genome editing, which is used for a wide variety of applications, including correcting disease mutations.

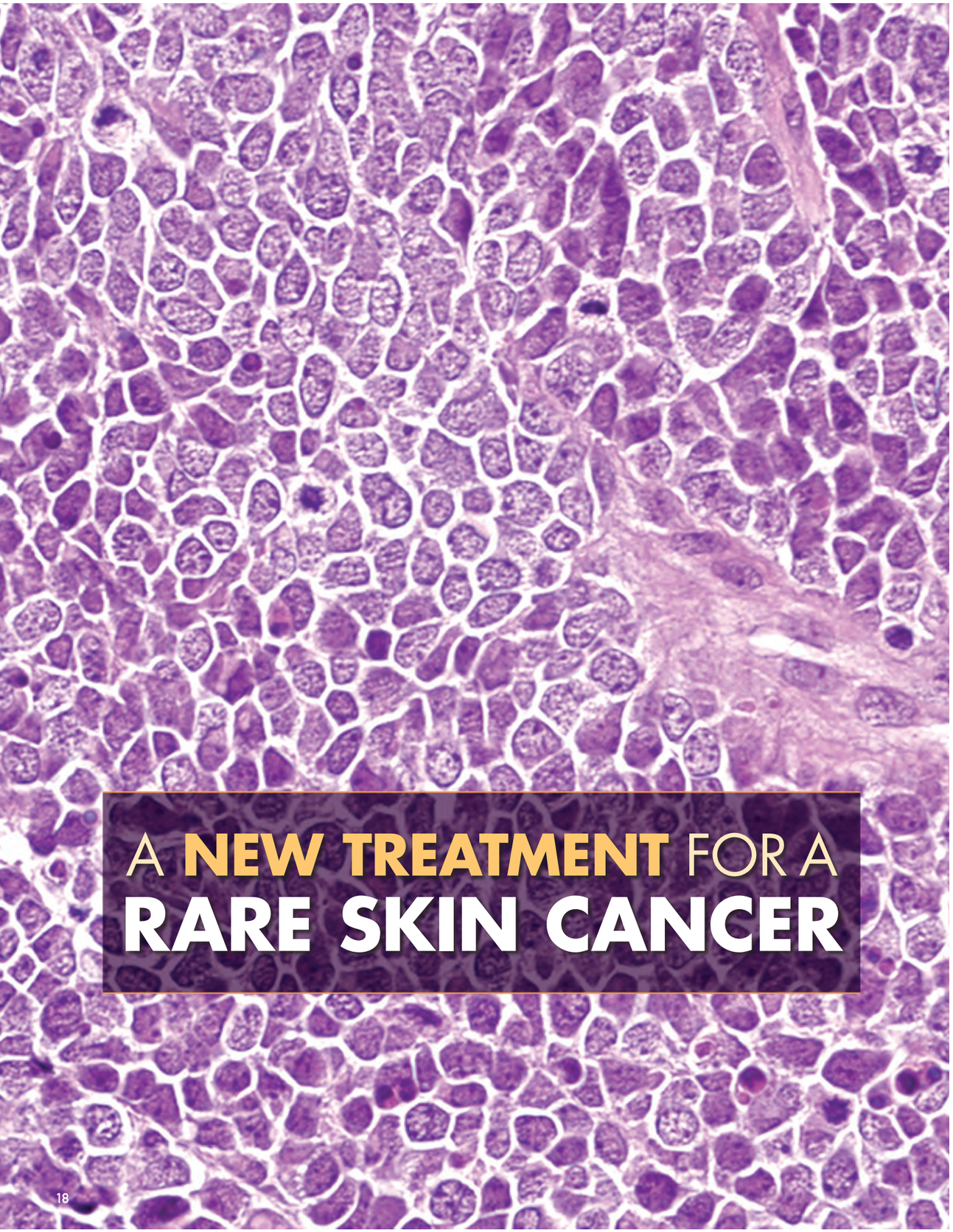
In a new study reported in *Cell*, Subramaniam and his team, including postbaccalaureate student Tai Wei Guo and CCR Associate Scientist Alberto Bartesaghi, Ph.D, collaborated with Memorial Sloan Kettering Cancer Center's Dinshaw Patel, Ph.D., and his postdoctoral fellow Hui Yang, Ph.D., to investigate the structural basis of one CRISPR surveillance complex's interaction with DNA. They learned how anti-CRISPR proteins produced by a viral invader block the system's ability to recognize its target.

To illuminate how the CRISPR complex changes its shapes as it does its job, Subramaniam and his team took advantage of cryo-EM, which can produce molecular images with high resolution and distinguish multiple states of a molecule. "This allows us to obtain snapshots of the complex in action and really explore molecular mechanisms," Subramaniam explains.

The team generated images that show how the CRISPR surveillance complex used by the common bacterium *Pseudomonas aeruginosa* undergoes a dramatic shape change when it binds to DNA, unwinding its twisted form. The shift probably helps trigger destruction of the bound DNA, the researchers say. They also produced images that show different ways viral proteins can block the interaction of the surveillance complex with DNA, thereby helping an invader elude detection.

The findings give insight into the molecular mechanisms that bacteria use to protect themselves against invaders as well as the defenses that viruses have evolved in response. There are likely hundreds of different surveillance complexes at work throughout the bacterial and animal kingdoms, Subramaniam says, and his team plans to continue exploring their mechanisms. A more comprehensive view of surveillance complex tactics might suggest ways for researchers to refine CRISPR-based genome editing tools, making them even more powerful and precise.

Guo TW, et al. *Cell*. 5 October 2017; 171 (2): 414–426.



A NEW TREATMENT FOR A RARE SKIN CANCER

Four years after CCR investigators began testing avelumab, the drug became the first approved for treatment of a rare disease.

In 2017, four years after early-phase clinical trials of the new immunotherapy drug avelumab began at the NIH Clinical Center, the U.S. Food and Drug Administration (FDA) approved the therapy for the treatment of Merkel cell carcinoma. It is the first FDA-approved treatment for this rare but aggressive skin cancer, which is diagnosed in about 2,500 people a year in the United States.

A large team of CCR scientists was instrumental in testing avelumab, generating preclinical evidence of the drug's effects and conducting its first-in-human trials. A collaboration between CCR and EMD Serono Inc., the manufacturers of avelumab, ensured that testing proceeded efficiently, allowing patients quicker access to the new drug.

Avelumab, which is marketed as Bavencio, boosts the immune system's ability to destroy cancer cells by binding to a molecule on tumor cells called PD-L1, which, if unbound, blocks T cells from mounting an attack. Avelumab's presence prevents PD-L1 from interacting with immune cells, freeing them to destroy their tumor targets.

Preclinical research led by **Jeffrey Schlom, Ph.D.**, Chief of the Laboratory of Tumor Immunology and Biology, showed that avelumab improves T cells' ability to kill tumor cells. His team also found that avelumab helps identify tumor cells as targets to the immune system's natural killer cells, initiating a second line of activity not triggered by other approved PD-L1 inhibitors.

These findings, along with evidence that Merkel cell carcinomas are susceptible to immune control, suggested avelumab might be an effective treatment for this cancer. In cooperation with EMD Serono, investigators led by Schlom and **James Gulley, M.D., Ph.D.**, Chief of the Genitourinary Malignancies Branch, planned a clinical study.

Because Merkel cell carcinoma is so rare, no potential treatment for the disease had yet been successfully evaluated in a clinical trial. But the CCR team was able to get the first trials underway quickly at the NIH Clinical Center, which specializes in rare diseases and draws patients from all over the world. Within eight months, the team obtained the safety and dosing data needed for the next phase of the study.

Ultimately, 88 patients with chemotherapy-resistant Merkel cell carcinoma participated in the clinical study, which included 35 cancer centers worldwide. Avelumab caused tumor regression for 33 percent of participants, including eight whose tumors disappeared entirely. **Isaac Brownell, M.D., Ph.D.**, an Adjunct Investigator at NCI and Head of Cutaneous Development and Carcinogenesis Section at the National Institute of Arthritis and Musculoskeletal and Skin Diseases, led the trial at the NIH Clinical Center. Brownell and his colleagues reported their results in *Lancet Oncology*, showing that 27 of the 28 patient responses lasted for at least six months and many lasted over a year.

Based on these results, the FDA granted accelerated approval for avelumab in March 2017. Trials are ongoing, and at the American Society for Clinical Oncology annual meeting in June 2017, Brownell and colleagues reported preliminary data suggesting that when the drug is given as a first-line therapy for Merkel cell carcinoma, response rates are even higher than those achieved in the original trial, which tested patients on avelumab only after their previous treatments had stopped working.

Testing avelumab first in patients with this rare disease helped speed the drug's initial approval by the FDA. While the Merkel cell carcinoma trials were underway, Gulley, Andrea Apolo, M.D., an Investigator in the Genitourinary Malignancies Branch, and colleagues were also investigating the drug's effects in patients with advanced bladder cancer. In that trial, tumors shrank in 18 percent of patients after six months of treatment, and the FDA approved the drug for use in patients with advanced bladder cancer in May 2017. Now, more than 80 clinical trials are investigating whether this new immunotherapy will be an effective treatment for a wide range of other cancers. The combined efforts in CCR that led to the approval of avelumab in two cancers received a 2018 Federal Laboratory Consortium for Technology Transfer National Award.

Boyerinas B, et al. *Cancer Immunol Res*. 2015 Oct;3(10):1148-1157.

Kaufman H, et al. *Lancet Oncol*. 2016 Oct;17(10):1374-1385.

Heery CR, et al. *Lancet Oncol*. 2017 May;18(5):587-598.

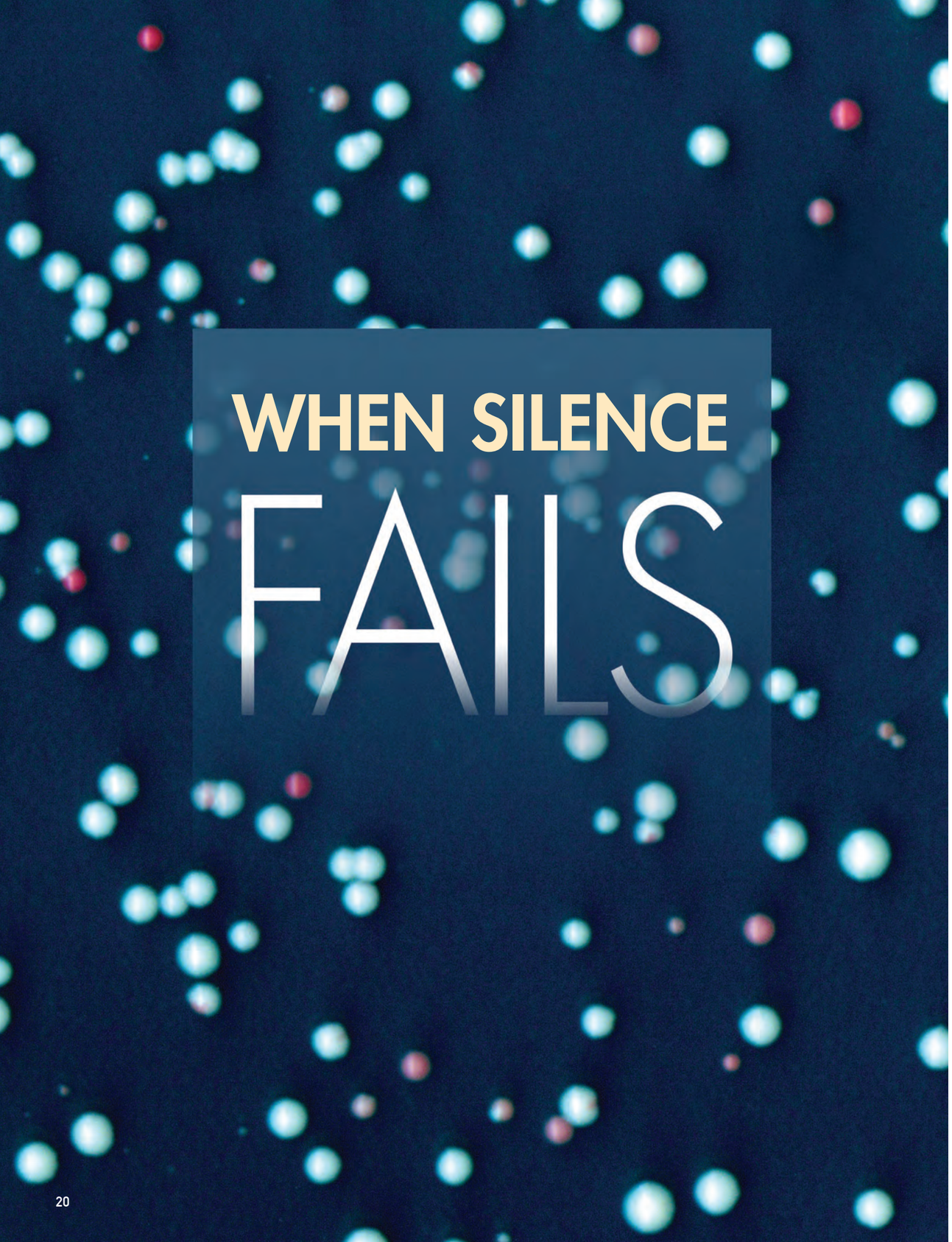
Donahue, RN, et al. *J Immunother Cancer*. 2017 Feb 21;5:20.

D'Angelo S, et al. *J Clin Oncol*. 2017 May;35:15_suppl, 9530-9530.

Apolo A, et al. *J Clin Oncol*. 2017 Jul;35(19):2117-2124.

Hematoxylin and eosin staining of a tissue section from a Merkel cell carcinoma tumor from a patient treated with avelumab at NCI.

Credit: *Isaac Brownell, CCR, NCI, NIH*



WHEN SILENCE FAILS

Inappropriate gene activity disrupts chromosome segregation and generates a chromosomal abnormality, known as uniparental disomy, present in many cancer cells.

There are a lot of ways things can go wrong when a gene gets switched on at the wrong time or place. New research from the Laboratory of Biochemistry and Molecular Biology, under the guidance of Chief **Shiv Grewal, Ph.D.**, shows that when a gene whose activity should be reserved for the production of sex cells becomes active, cells can't properly sort their chromosomes when they divide. As a result, new cells may wind up with too many chromosomes from one parent and not enough from the other—a genetic disruption that is common in cancer cells.

Grewal and his colleagues reported in *Nature* that the incorrect expression of gametogenic genes—those involved in meiosis, the specialized cell division process that gives rise to sperm and eggs—can result in this chromosomal abnormality known as uniparental disomy (UPD). Instead of inheriting one member of each paired chromosome from mom and dad as they should, cells affected by UPD receive both copies of a particular chromosome from the same parent. Although it has been known for years that UPD contributes to several human diseases and may support the uncontrolled growth of cancer cells, its cause has been elusive.

Because cells affected by UPD contain the expected number of chromosomes, the phenomenon is not easy to recognize and study in human cells. Grewal and his colleagues chose to investigate the causes of UPD in fission yeast, an organism whose genetic material is easier to track since the fission yeast genome is contained on only three chromosomes. Fission yeast also shares many features of chromosome structure and gene regulation with human cells, making it a useful model for studying cell division and genetic processes.

The new discovery grew out of an observation Grewal made nearly 20 years ago. His insight dawned while studying how components of a gene-regulating system called RNA interference (RNAi) influenced DNA packaging inside cells. When yeast cells divide and the system is impaired, they often produce new cells with incorrectly segregated sets of chromosomes, including cells affected by UPD.

Grewal initially suspected the chromosome problems in the impaired cells had something to do with DNA packaging. But when he and Staff Scientist H. Diego Folco, Ph.D., investigated, they found no such link. Instead, they discovered that the chromosome problem arose from the failure of the RNAi machinery to carry out another critical role: keeping unneeded genes turned safely off.

Fission yeast typically turn on their meiotic genes when stressful living conditions trigger a shift from asexual to sexual reproduction. At other times, they are actively repressed. Folco's experiments revealed that the untimely expression of just one meiotic gene during times of asexual growth could disrupt chromosome segregation and lead to UPD.

Grewal proposes similar disruptions could cause UPD in human cells. Hundreds of human genes encode proteins that are needed exclusively for meiosis. These genes are present in every cell in the body, but they are only used to produce sperm and eggs, so outside the ovaries and the testes, they are usually kept off. Our cells' gene-silencing systems may become less reliable as we age, however, increasing the risk that meiotic genes will become active and trigger UPD. In fact, researchers have noticed that many genes usually expressed only in the testes are frequently active in tumor cells, although the impact of this abnormal gene activity has not been clear.

By uncovering the cause of UPD, Grewal and his team have provided a foundation for understanding its role in cancer. They now plan to search for small molecules that can interrupt UPD in yeast, a step toward identifying a way to intervene in UPD-associated disease processes.

Folco HD, et al. *Nature*. 2017 Mar 2;543(7643):126-130.

Uniparental disomy occurs when cells contain two copies of a chromosome from one parent and none from the other parent. In this picture, uniparental disomy has occurred in the red and pink yeast colonies but not in the white colonies.

Credit: *H. Diego Folco, CCR, NCI, NIH*

CAR Ts FOR LEUKEMIA

Study results suggest combining immunotherapies could make it harder for cancer cells to become treatment-resistant.

Strategies in which patients' own immune cells are genetically modified to fight their cancer, called chimeric antigen receptor (CAR) T-cell therapies, have emerged recently as revolutionary new therapies. In 2017, two such treatments were approved by the U.S. FDA, including one that causes remissions in children with acute lymphoblastic leukemia (ALL). Now, CCR scientists led by **Terry Fry, M.D.**, an Investigator in the Pediatric Oncology Branch (POB) at the time the work was done, and Crystal Mackall, M.D., another former POB member, have had success in treating ALL with a new, related approach. Their results raise the possibility of combining multiple immunotherapies to improve patient outcomes.

The recently approved CAR-T immunotherapies arm the immune system to destroy cancer cells carrying a surface marker called CD19. The newer treatment is a CAR T cell that targets a different marker, CD22, found on many leukemia and lymphoma cells. After Fry and Mackall's team tested the CD22 CAR therapy in mice, a phase I trial was launched at the NIH Clinical Center to test the therapy in patients. Fry and colleagues have shown that targeting CD22 can lead to responses similar to those targeting CD19 in patients with ALL. That raises the intriguing possibility that a patient's remission may be prolonged by developing a CAR T-cell therapy that targets both CD19 and CD22.

Although CD19-targeted CAR-T therapies have generated complete remissions in children whose cancers relapsed or failed to respond to chemotherapy, many patients eventually relapse as their cancers develop resistance to the CAR-T treatments. Typically, this is because their cancer cells have lost the CD19 marker that flags them as targets to the engineered cancer-fighting T cells.

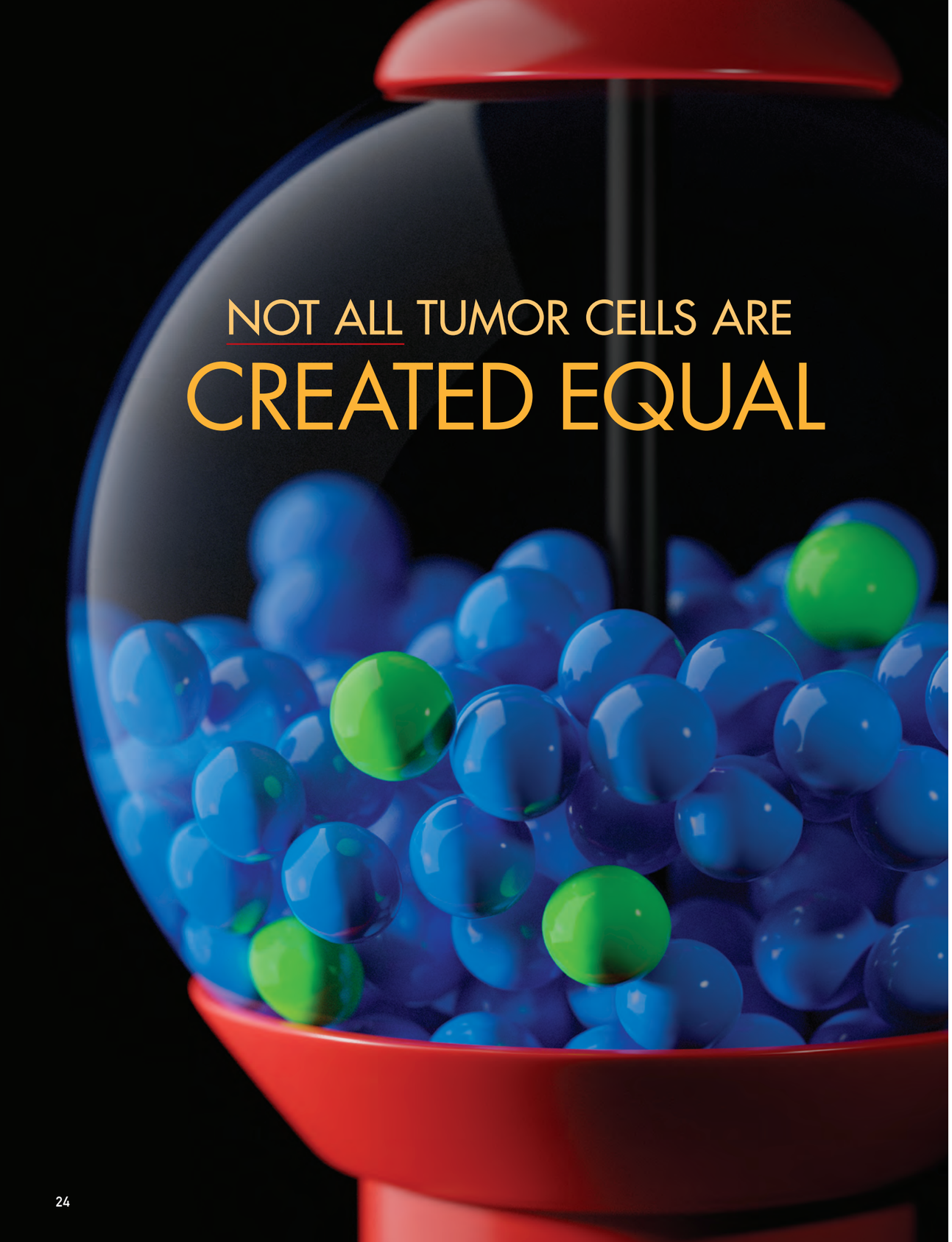
The research team, which also included **Nirali Shah, M.D.**, an Associate Research Physician in the Pediatric Oncology Branch, reported in *Nature Medicine* that 12 of 22 patients achieved complete remissions after receiving the engineered T cells. Notably, the treatment was effective in patients who had relapsed after treatment with CD19-targeted therapies and in patients whose cancer cells lacked the CD19 marker.

Now that it is clear that CAR T cells can effectively target CD22-bearing leukemia cells, Fry and colleagues are optimistic that they can achieve even better results for patients by developing a combined approach targeting both CD19 and CD22. The first combinatorial trial to test CD19 and CD22 opened in February 2018.

Fry T, et al. *Nature Medicine*. 2017 Nov 20; (24):20–28.

Terry Fry, M.D., a former Investigator in the Pediatric Oncology Branch, discusses treatment with Bo Cooper. Bo was featured in the 'First in Human' documentary series from Discovery Channel as a patient on Dr. Fry's clinical trial using the CD22 CAR T-cell therapy. Bo passed away in 2016 after a long battle with acute lymphoblastic leukemia.

***Credit:** 'First in Human,' Discovery Channel*



NOT ALL TUMOR CELLS ARE CREATED EQUAL

Like the contents of this gumball machine, tumors are highly heterogeneous and a few specialized cells (green) drive the growth of the entire tumor. Ongoing studies seek to understand the molecular differences between the various types of cells in a tumor.

Credit: *Joe Meyer, Scientific Publications, Graphics and Media, Frederick National Laboratory, NCI, NIH*

Loss of a genome-organization factor gives a subset of cancer cells the ability to self-renew.

The molecular makeup and biological properties of cancer cells can vary significantly, even within the same tumor. This heterogeneity agrees with the recent realization that usually only a small subset of the cells in a tumor have the capacity to sustain the tumor's growth. Now, CCR scientists have uncovered a key determinant of these growth-sustaining cells: loss of a DNA-packaging protein called linker histone H1.0.

The research was initiated when Paola Scaffidi, Ph.D., a former postdoctoral fellow in the laboratory of CCR Director **Tom Misteli, Ph.D.**, and now a group leader at the Francis Crick Institute in London, sought an explanation for why some tumor cells can spur tumor growth and give rise to new tumors when they are transplanted into animals while other cells from the same tumor cannot.

Using sensitive single-cell analysis methods, including imaging, Scaffidi and her colleagues measured H1.0 in tumor samples from six different types of cancer. In every tumor, they found that levels of the histone varied significantly among cells. What's more, glioblastoma and breast cancer samples that had the highest proportion of cells with low levels of H1.0 tended to be aggressive tumors. The team turned to The Cancer Genome Atlas, a resource collaboratively managed by NCI and the National Human Genome Research Institute, for additional genetic, molecular and clinical data and determined that low levels of H1.0 also correlated with poorer outcomes in patients with liver cancer, kidney cancer, melanoma and low-grade gliomas.

Histone H1.0 is one of the major proteins that organize DNA into the fibers of genetic material known as chromatin. By influencing how DNA is compacted into chromatin, histones help determine which of a cell's genes are turned on and which are turned off. Histone H1.0 is usually most abundant in specialized cells with little ability to divide, where most growth-promoting genes are kept safely off. Various extracellular signals can influence how much H1.0 a cell produces, and the researchers speculated that interactions with the tumor microenvironment could cause some cancer cells to stop producing this critical protein.

Although the study was initiated in Dr. Misteli's lab, it was led by Dr. Scaffidi and also included Eran Meshorer, Ph.D., another former NCI postdoctoral fellow in Dr. Misteli's lab, who is now a professor at the Hebrew University of Jerusalem.

How then does a chromatin protein affect the tumor potential of individual cells? A hint comes from the finding that when tumor cells stop producing H1.0 histones, chromatin structure is altered and growth-promoting genes become reactivated. As a result, these cells regain the ability to self-renew. Supporting this idea, Scaffidi and colleagues also noted that histone H1.0 is consistently low in cancer stem cells, which have an unlimited potential to divide.

Encouragingly, the effects of H1.0 loss appear to be reversible. The researchers found that they could drive tumor cells to differentiate and lose their proliferative potential by restoring H1.0 production. The findings, reported in *Science*, suggest that it may be possible to stop tumor growth clinically with interventions that modify H1.0 levels or otherwise alter the chromatin landscape of tumor cells.

Torres CM, et al. *Science.* 2016 Sep 30;353(6307).

New Faculty

H. Efsun Arda, Ph.D.

H. Efsun Arda, Ph.D., has joined the Laboratory of Receptor Biology and Gene Expression as a Stadtman Tenure Track Investigator. Her research focuses on understanding the genomic information that governs development, differentiation and function of pancreatic cell lineages.

Steven Cappell, Ph.D.

Steven Cappell, Ph.D., has joined the Laboratory of Cancer Biology and Genetics as a Tenure Track Investigator. Dr. Cappell's laboratory research focuses on understanding how signal transduction networks are wired to form logical circuits to understand how these networks function in space and time to regulate diverse aspects of human physiology.

Freddy Escorcia, M.D., Ph.D.

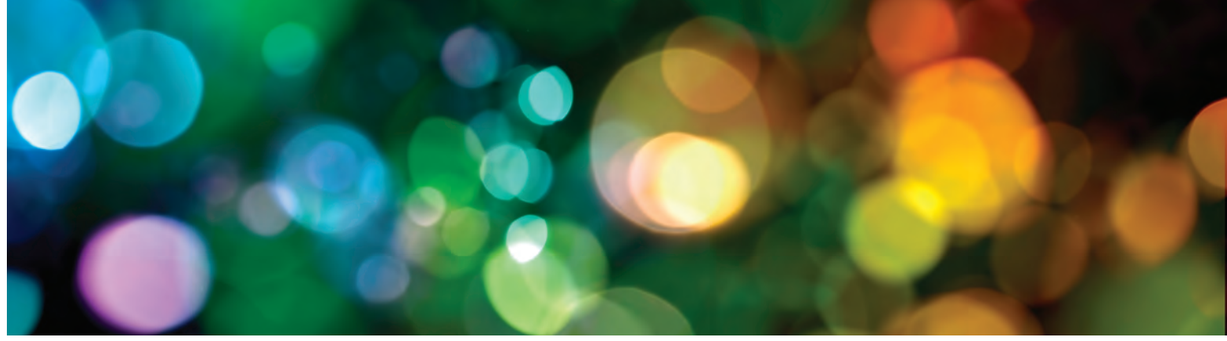
Freddy Escorcia, M.D., Ph.D., has been appointed as an Assistant Clinical Investigator in the Molecular Imaging Program. Dr. Escorcia's work focuses on tumor-targeted, personalized cancer treatment. Dr. Escorcia is also a clinically trained radiation oncologist and treats patients with all tumor types amenable to radiation therapy.

Anupama Khare, Ph.D.

Anupama Khare, Ph.D., has joined the Laboratory of Molecular Biology as a Stadtman Tenure Track Investigator. Dr. Khare's research focuses on understanding how different microbial species co-exist in the same environmental niche and the molecular interactions in such communities.

Natalie Porat-Shliom, Ph.D.

Natalie Porat-Shliom, Ph.D., has joined the Thoracic and Gastrointestinal Oncology Branch as a Stadtman Tenure Track Investigator. Dr. Porat-Shliom's research focuses on utilizing intravital microscopy for imaging and understanding the biology of human cancer.



Vassiliki Saloura, M.D.

Vassiliki Saloura, M.D., has been appointed as an Assistant Clinical Investigator in the Thoracic and Gastrointestinal Oncology Branch. Dr. Saloura's laboratory investigates the role of histone and non-histone protein methylation in tumor growth, therapy resistance and immunogenicity in squamous cell carcinoma of the aerodigestive tract.

Anish Thomas, M.B.B.S., M.D.

Anish Thomas, M.B.B.S., M.D., has been appointed as an NIH Lasker Scholar Tenure Track Investigator in the Developmental Therapeutics Branch. The goal of Dr. Thomas' research is to systematically develop more effective therapies for patients with small cell lung cancer and similar chemotherapy-refractory tumors.

Sandra Wolin, M.D., Ph.D.

Sandra Wolin, M.D., Ph.D., has joined CCR as a Senior Investigator and as the inaugural Chief of the newly established RNA Biology Laboratory on the Frederick campus. She will continue the world-class research program she established at Yale University and will play a leading role in developing an integrated program in RNA biology in CCR.

Chuan Wu, M.D., Ph.D.

Chuan Wu, M.D., Ph.D., has joined the Experimental Immunology Branch as a Stadtman Tenure Track Investigator. Dr. Wu's research focuses on differentiation of autoreactive T cells and the mechanism of neuro-immune crosstalk in autoimmunity.

Zhengping Zhuang, M.D., Ph.D.

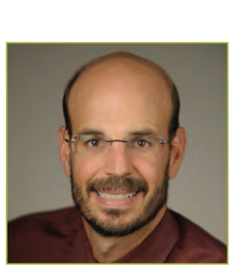
Zhengping Zhuang, M.D., Ph.D., has joined the Neuro-Oncology Branch as a Senior Investigator. Dr. Zhuang's research focuses on functional genomics and molecular signaling in central nervous system tumors to identify the critical genes and molecules in cancer formation and progression.

Awards & Honors

Kevin Camphausen, M.D., was named a Fellow of the American Society for Radiation Oncology.

Zbigniew Dauter, Ph.D., received the Patterson Award from the American Crystallographic Association.

William Douglas Figg Sr., Pharm.D., received the Tyler Prize for Stimulation of Research Award from the American Pharmacists Association.



Terry Fry, M.D., was elected as a member of the American Society for Clinical Investigation.

Stephanie Goff, M.D., was named a Fellow of the American College of Surgeons.

Michael Gottesman, M.D., was elected to the Japanese Order of the Rising Sun.

Susan Gottesman, Ph.D., received the Herbert Tabor Research Award from the American Society for Biochemistry and Molecular Biology.

Shiv Grewal, Ph.D., was named a Foreign Fellow of the Indian National Science Academy.

Stephanie Harmon, Ph.D, received a Young Investigator Award from the Prostate Cancer Foundation.

Richard Hodes, M.D., received the Lifetime Achievement Award from the American Association of Immunologists.

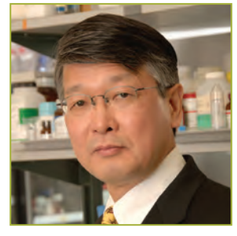
Fatima Karzai, M.D., received a Young Investigator Award from the Prostate Cancer Foundation.

James Kochenderfer, M.D., received the Outstanding New Investigator Award from the American Society of Gene & Cell Therapy.

Marston Linehan, M.D., received the Distinguished Career Award from the International Society of Urology.

John Schiller, Ph.D., and **Douglas Lowy, M.D.,** received the Lasker-DeBakey Clinical Medical Research Award.

Tom Misteli, Ph.D., was named a Fellow of the American Society for Cell Biology.



Hiroaki Mitsuya, M.D., Ph.D., was elected to the Association of American Physicians.

George Pavlakis, M.D., Ph.D., was named a Fellow of the National Academy of Inventors.

Awards & Honors continued

Nicholas Restifo, M.D., received the American Society for Microbiology Award in Clinical and Diagnostic Immunology.

Mark Roschewski, M.D., was named the Public Health Service Research Physician of the Year.

John Schiller, Ph.D., was named a Fellow of the National Academy of Inventors.

Haneen Shalabi, D.O., received the Next Gen Award from the Children's Cancer Foundation.

Louis Staudt, M.D., Ph.D., received the AACR Princess Takamatsu Memorial Lectureship from the American Association for Cancer Research.

Sriram Subramaniam, Ph.D., was named a Fellow of the Biophysical Society.

David Vander-Weele, M.D., Ph.D., received a Young Investigator Award from the Prostate Cancer Foundation.

Thomas Waldmann, M.D., was named a Fellow of the National Academy of Inventors.

Robert Yarchoan, M.D., was named a fellow of the American Academy of Microbiology.

CCR by the Numbers

89 **New Employee Invention Reports**

60 **Issued U.S. Patents**

35 **New Cooperative Research and Development Agreements (CRADAs)**

189 **Active CRADAs**

54 **New Technologies Licensed**

617 **Active Licenses**

245 **Open Cinical Trials**

45 **New Trials Opening**

~1,500 **Articles in Peer-Reviewed Journals**

2,290 **New Patients**

1,131 **Trainees**

All numbers are FY 2017.

Center for Cancer Research

NATIONAL
CANCER
INSTITUTE

NIH Publication No. 18-CA-8030