CENTER FOR CANCER RESEARCH
MILESTONES

Cancer Research with a Purpose

HIGHLIGHTS
2018–2019

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.**

On the cover, hairy cell leukemia cells (purple) are shown under attack by the cancer drug moxetumomab pasudotox, or Moxe (orange dots). In the foreground, Moxe, which is composed of a monoclonal antibody (gold) attached to a toxin (red), binds to a receptor on a cancer cell's surface (purple, foreground). Once it binds to the cancer cells, Moxe can deliver its attached toxin and induce cancer cell death, as shown in the lower right.

Credit: *Veronica Falconieri Hays, Falconieri Visuals*
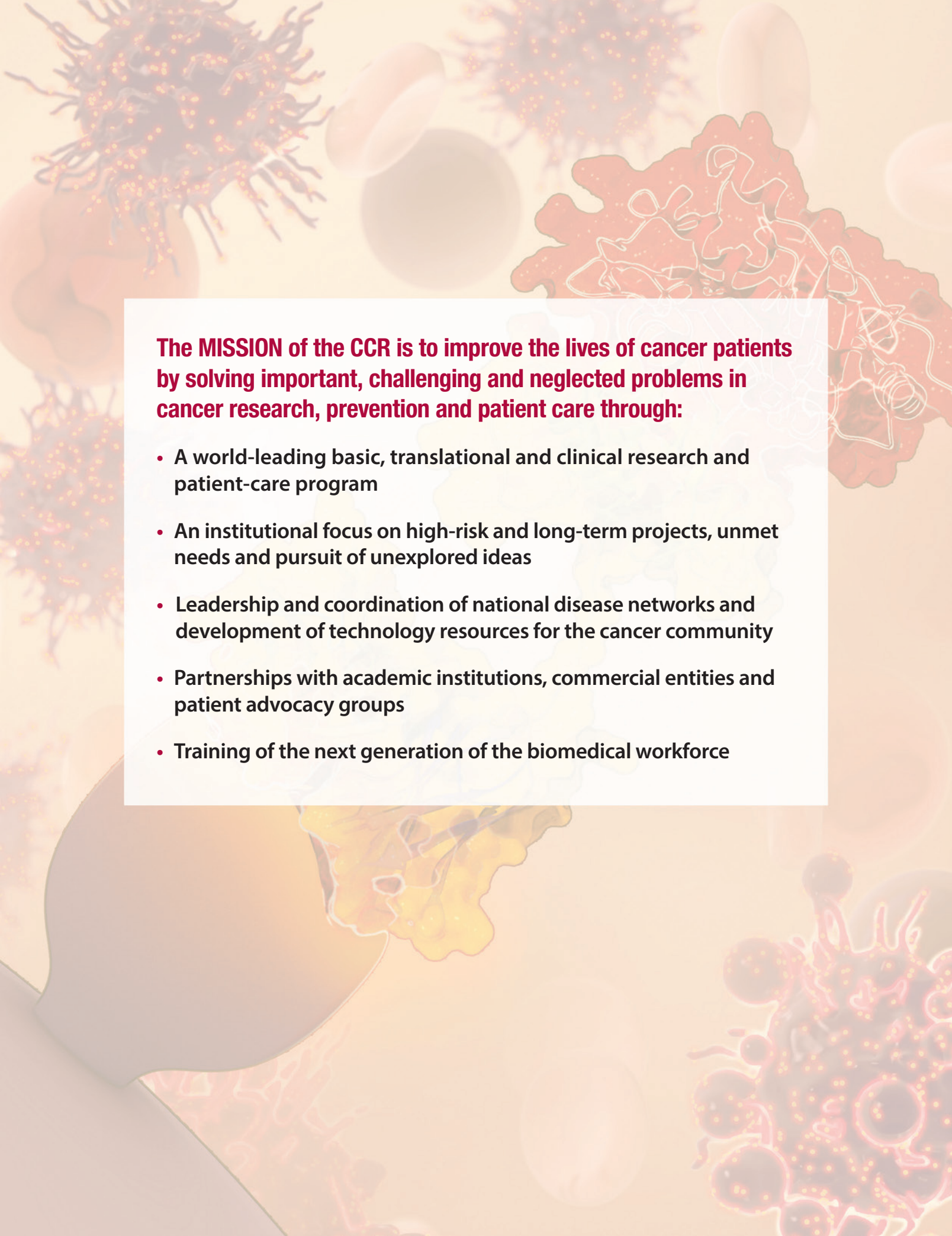
Contributors:

Brenda Boersma-Maland

Chia-Chi Charlie Chang

Veronica Falconieri Hays

Li Gwatkin

Abbie Harrison

Allen Kane

Joseph Meyer

Jennifer Michalowski

Mike Miller

Melissa Pandika

Lianne Priede

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

The science never stops in the NCI's Center for Cancer Research (CCR). Our labs and clinics bustle with activity at all hours of the day with the singular goal of better understanding, preventing, diagnosing and treating cancer. As a result, in the past year, CCR scientists have published more than 1,300 scientific publications, filed nearly a hundred invention reports and treated thousands of patients in the NIH Clinical Center. This issue of *Milestones* captures a few select highlights of this year's research activities.

Featured are achievements in areas where CCR has long been a leader, including immunotherapy, HIV research and cell signaling, but also in important new emerging areas such as big data science and chemical biology, in which CCR is making major investments. Many of the remarkable studies included in this issue represent high-risk projects or long-term endeavors, which CCR is uniquely positioned to undertake in the protected research environment of the intramural program.

It is also reassuring to see that many of this year's top advances come from our tenure track investigators, highlighting our dedication to training the next generation of cancer researchers. All of the advances summarized here, and indeed all progress in CCR, reflect the work of our dedicated and passionate scientists, clinicians, trainees and administrative staff.

Cancer research is paradoxical in its nature. On the one hand, we see continuous and rapid advances, yet progress is never fast enough, and there is much more to do. That is precisely why the science in CCR never stops.

Tom Misteli
Director
NCI Center for Cancer Research

EXPANDING
THE KINASE UNIVERSE

A new way of mining cancer genomes finds enzymes with tumor-suppressing roles.

John Brognard, Ph.D.
Laboratory of Cell and Developmental Signaling

Cancer biologists have long been interested in a family of enzymes called kinases. More than 500 different kinases are found in human cells where they transmit critical signals by adding phosphate groups to proteins. A handful of kinases have received a great deal of attention in cancer research because they are disrupted by genetic mutations that are well known to drive cancer. Most, however, remain poorly characterized. Now, CCR scientists have devised a clever new way to identify additional cancer-relevant members of this prominent class of proteins.

John Brognard, Ph.D., Investigator in CCR's Laboratory of Cell and Developmental Signaling, and Andrew Hudson, M.D., a former clinical fellow in his lab, devised an innovative strategy to sift through data describing the tens of thousands of mutations that have been found in cancer cells. Using data from The Cancer Genome Atlas, which was supported by NIH, and the Cancer Cell Line Encyclopedia, developed at the Broad Institute, their team searched for mutations in kinase genes in more than 11,000 patient tumors and 1,000 cancer cell lines.

Because they sought mutations that impact kinase function, Brognard's team limited its search to stretches of sequence known to be critical for the enzymes' activities, filtering out all other mutations. In this way, they identified several kinases with high frequencies of functional mutations across the large set of samples.
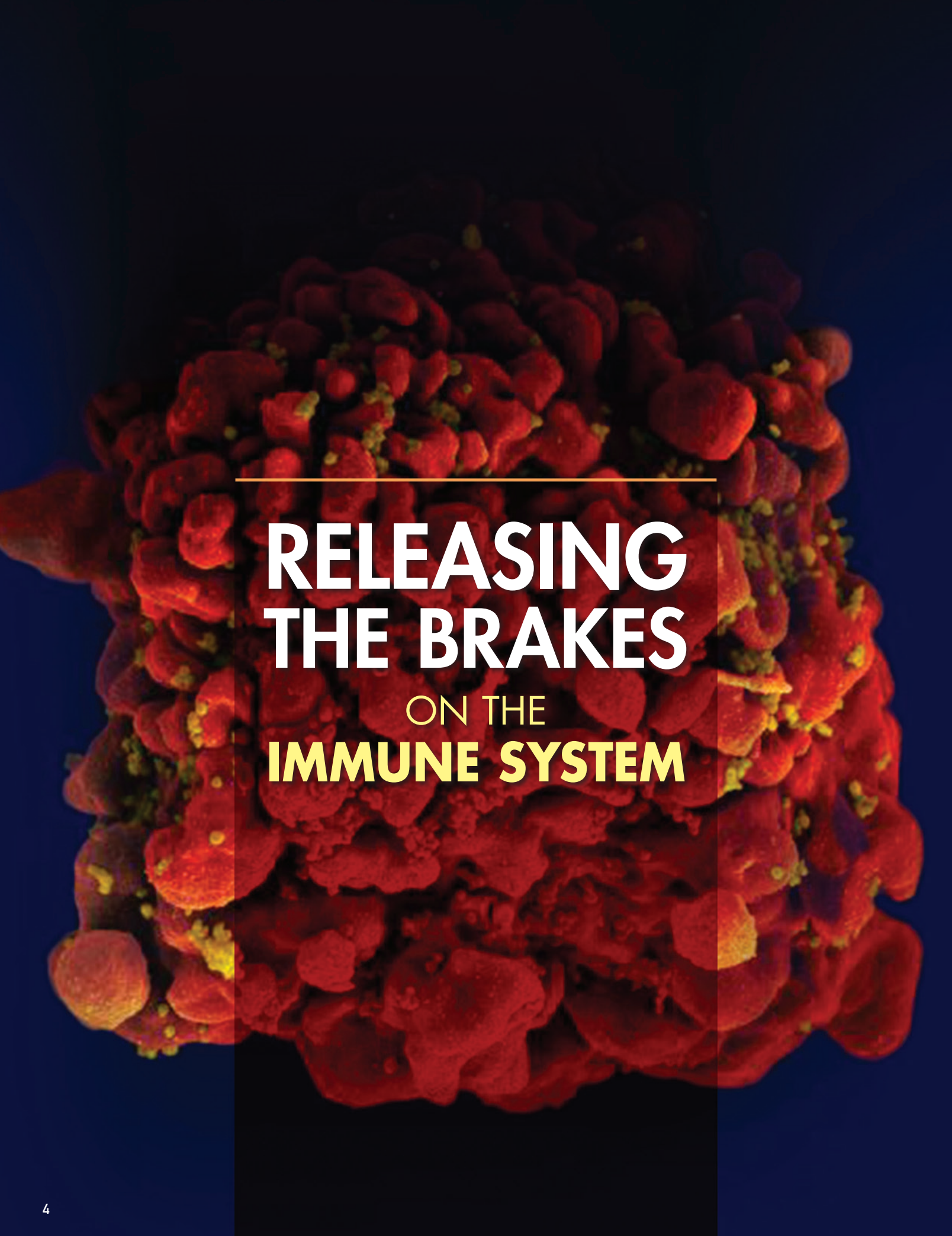
From this group, they focused on a kinase called MAP2K7, a component of the JNK signaling pathway that is known to be capable of both spurring cancerous growth and reining it in. The team's analysis showed that functional mutations in MAP2K7 were common among tumor samples from patients with gastric cancer. They went on to demonstrate that intact JNK signaling is important for keeping growth of gastric cells in check.

The impact of this work, which the researchers reported in *Science Signaling*, reaches beyond the important leads it has already turned up. The data-mining approach is not limited to kinases, Brognard says, and can now be used to search existing genomic data for cancer-driving mutations in other families of enzymes.

Hudson AM, et al. *Sci Signal*. 2018 Apr 17;11(526).

Advanced molecular dynamics is a method that helps researchers study the physical movements of molecules. The technique helps scientists to predict if cancer mutations will alter the structure of an enzyme, such as a kinase, in a manner that may alter the enzyme's function to promote cancer. These two different structures compare the normal enzyme (top) and a cancer-mutant enzyme (G265D) for the kinase MAP2K4 (bottom). The cancer mutant (G265D) has dramatically less movement, indicating the enzyme will not be functional, which is consistent with mutations in tumor-suppressing enzymes.

Credit: *John Brognard, CCR, NCI, NIH*

RELEASING THE BRAKES
ON THE
IMMUNE SYSTEM

Preventing interaction between two immune proteins could improve treatment of HIV infection with implications for cancer immunotherapy.

Mary Carrington, Ph.D.
Cancer and Inflammation Program

Medications now allow HIV-positive individuals to stay healthy for many years by keeping the viral infection in check. However, the virus almost always resurges if patients stop treatment. Research by CCR investigators suggests that targeting a receptor located on the surface of certain immune cells could help clear stubborn HIV reserves. The findings, published in *Science*, may also have implications for the response of cancer patients to immunotherapy.

A group of researchers led by **Mary Carrington, Ph.D.**, Senior Investigator in the CCR Cancer and Inflammation Program, set out to determine why some HIV-infected individuals are able to control the virus better than others in the absence of drug treatment. They examined proteins called human leukocyte antigens (HLA), which help disease-fighting natural killer and T cells recognize and destroy cells that have been infected by HIV. The researchers knew that HIV-positive individuals who express high levels of a certain type of HLA tend to have worse outcomes than those with low expression, but they did not understand why.

To find out, they analyzed blood samples from nearly 10,000 black, Hispanic and white HIV-positive patients from the United States, Botswana, South Africa, Zambia and Switzerland. They saw that the higher an individual's expression levels of two types of HLA (HLA-A and HLA-B21M), the higher their HIV viral load, indicating that they had poorer control of the virus.

How did elevated levels of these HLA proteins impair HIV control? Carrington and her team realized that they boosted expression of another type of HLA protein, HLA-E, which binds to a receptor called NKG2A, found on natural killer cells and a certain subset of T cells. Binding between HLA-E and NKG2A hampers these immune cells' ability to kill cells infected by HIV.

The findings suggest that drugs that block NKG2A would allow natural killer and T cells to eliminate HIV-infected cells, improving HIV-positive individuals' control of the virus. These drugs, possibly in combination with other therapies, could expand the drug arsenal against HIV by equipping the immune system to more effectively control the virus.

This study on HIV infection has intriguing implications for cancer because earlier research has indicated that dampening of the immune response by affecting HLA protein function may play a role in the disease. Clinical trials in cancer of an antibody that blocks NKG2A, known as monalizumab, are already underway. In addition, Carrington and her team have begun exploring whether HLA expression could predict response to cancer immunotherapy. She notes that this makes sense—one way immunotherapy works is by inhibiting the interaction between proteins that tighten the reins on the immune system, freeing it up to kill cancer cells.

Through these efforts, Carrington's team hopes to determine whether HLA expression could help identify which patients will respond to a given immunotherapy and which will not. If successful, HLA analysis will help clinicians determine which type of immunotherapy will most likely benefit a given patient.

Ramsuran V, et al. *Science*. 2018 Jan 5;359(6371):86-90.

HIV (yellow) buds from an infected immune cell.

Credit: *National Institute of Allergy and Infectious Diseases, NIH*

TRAINING THE IMMUNE SYSTEM TO
REMEMBER HIV

An infection-fighting white blood cell could be a key element in developing an effective vaccine treatment against HIV/AIDS.

Genoveffa Franchini, M.D.
Vaccine Branch

Treatment options for infection with the human immuno-deficiency virus (HIV) have greatly improved over the last 30 years, and current prevention tools, such as pre-exposure prophylaxis (PrEP), can work well, but the ultimate goal in HIV management remains the development of a preventive vaccine. CCR scientists have discovered that a certain type of white blood cell, known as a CD14+ monocyte, may be crucial in that quest.

In response to a foreign invader like HIV, the immune system can initiate an innate or an adaptive response. In the faster innate response, white blood cells recognize molecules found on a broad array of invaders. Once they home in on an invader, they destroy it and release chemical signals that trigger the longer lasting and more specific adaptive response. The adaptive response involves other types of white blood cells that secrete antibodies that bind to proteins found only on certain invaders.

AIDS arises when HIV infects white blood cells, called T cells, and thus impairs the adaptive response. The fact that the virus infects the very cells a conventional vaccine would seek to activate has complicated efforts to develop a vaccine. The virus' effects on the innate response have been difficult to study and remain unclear, making development of an HIV vaccine all the more challenging.

Research led by **Genoveffa Franchini, M.D.**, Senior Investigator in CCR's Vaccine Branch, and published in *Nature Medicine*, tackles this conundrum. Franchini and her team tested various vaccine regimens to determine whether they could lower infection of simian immunodeficiency virus (SIV), the primate version of HIV, in macaque monkeys.

After treating the macaques, the researchers analyzed samples of their blood. The team measured the number of immune system cells released after viral infection and the amount of antibody produced by the cells that recognize SIV. The vaccine regimen that produced the strongest immune response did not prevent infection. Instead, other approaches offered protection by balancing the activity of innate immune-response cells.
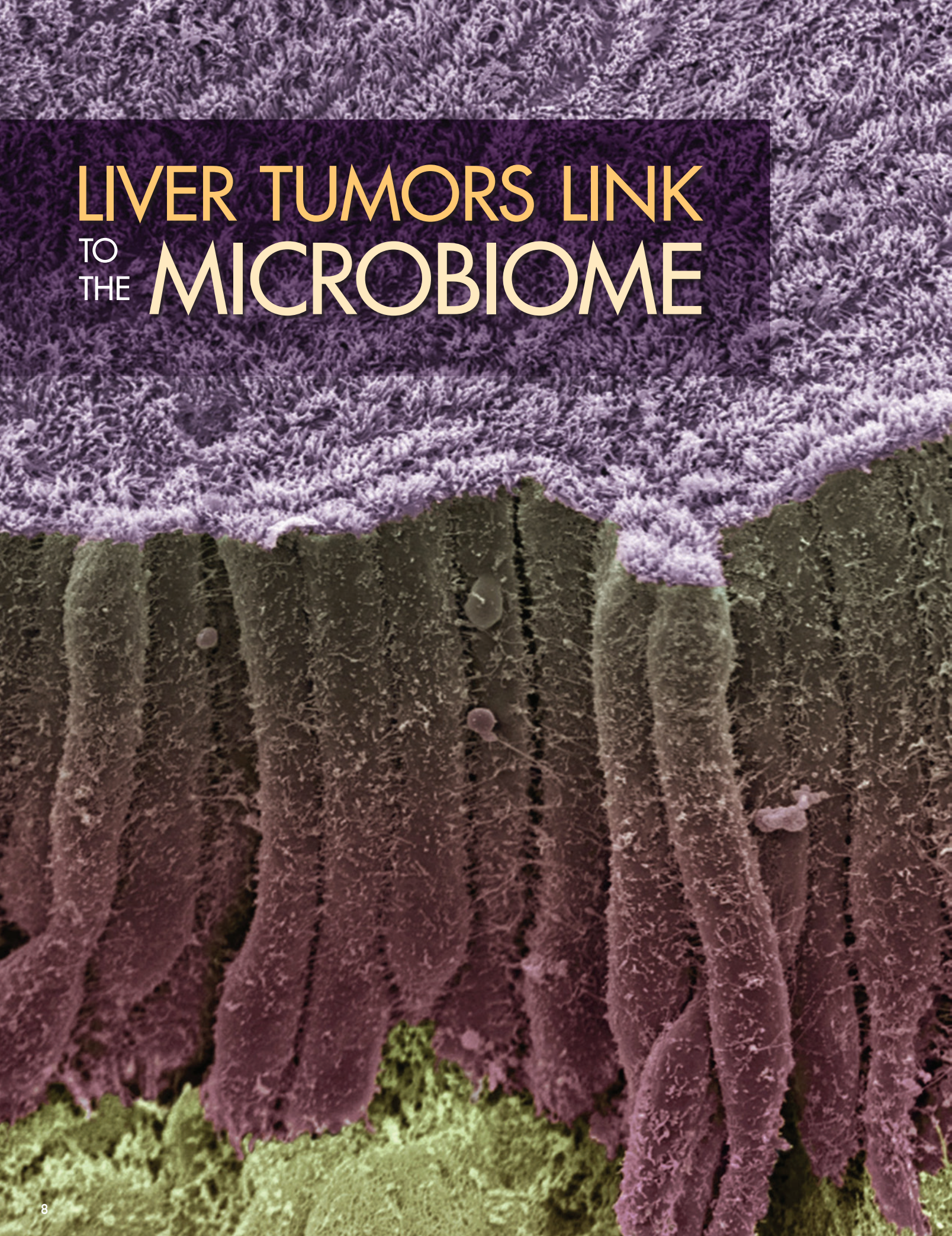
Macaques primed with DNA and boosted with another vaccine called ALVAC-SIV had more monocytes that expressed the CD14 protein and fewer that expressed the CD16 protein than macaques who were not protected against SIV infection. As it turns out, these CD14+ monocytes may be vital to mobilizing an innate response against SIV. Franchini thinks they do so by releasing a protein called IL-1beta, whose main function is to help immune cells involved in the innate response form a long-term memory of a foreign invader, so they can recognize it and activate the innate response if they encounter the invader again.

When immune cells that have formed a long-term memory of SIV encounter it again, they respond to it by secreting a protein called IL-10, Franchini hypothesizes. IL-10 lowers the levels of the CCR5 receptor on T cells to which SIV normally binds in order to infect them. Sure enough, vaccine regimens that protected against SIV infection resulted in T cells that express less CCR5 on their surface. Together, the findings suggest that an effective vaccine against HIV/AIDS would act via tipping the monocyte balance toward CD14+ monocytes and thus trigger an effective response of the immune system to the virus.

Vaccari M, et al. *Nat Med*. 2018 Jun;24(6):847-856.

When exposed to simian immunodeficiency virus (SIV), vaccinated monkeys that produced more CD14+ monocytes (blue cells, right) than CD16+ monocytes (green cells, left) mounted a stronger immune response to the infection overall, indicating that vaccines able to elicit the correct balance of immune response will be more successful.

Credit: *Veronica Falconieri Hays, Falconieri Visuals*

LIVER TUMORS LINK
TO THE MICROBIOME

Bacteria in the gut rein in tumor-fighting immune cells in the liver.

Tim Greten, M.D.
Thoracic and GI Malignancies Branch

The bacteria, viruses and fungi that live in and on our bodies have a profound impact on our health. Researchers are just beginning to understand how this complex community, known as the microbiome, contributes to cancer. Now, a discovery from the laboratory of **Tim Greten, M.D.**, Deputy Chief of CCR's Thoracic and GI Malignancies Branch, offers a clear example of how bacteria that live in the gut can hinder the immune system's ability to control tumors in the liver.

Greten and his colleagues found that when they treated mice that are genetically predisposed to develop liver cancer with antibiotics to deplete the level of microorganisms in their guts, the animals developed fewer liver tumors. Antibiotic treatment also reduced the likelihood that tumors implanted elsewhere in the body would metastasize to the animals' livers. Searching for an explanation, they noted that these effects occurred along with a change in the immune system. Following the reduction in gut bacteria, critical cancer-controlling cells, called natural killer T (NKT) cells, began to flourish in the liver. The findings were published in *Science*.

The investigators traced this increase in NKT cells to a change in bile acids, digestive molecules that help break down fats.

These digestive acids, which are produced by the liver, can be modified by bacteria they encounter in the gut. The research team discovered that bile acids control the production of CXL16, a protein found on cells inside the capillaries, through which blood enters the liver. They showed that when CXCL16 is abundant, NKT cells accumulate to enable a stronger anti-tumor defense. Exposure to bile acids modified by bacteria drove cells to produce less CXCL16.

Greten's team traced the source of these effects to bacteria known as *Clostridium scindens*. The investigators found that they could overcome the effect of these bacteria by manipulating the bile acids present in the animals' livers—either by adding certain bile acids to their diet or by manipulating the bacteria in their guts. This shifted the numbers of NKT cells in the organ and, consequently, the numbers of tumors that developed there.

Based on these findings, Greten and colleagues are planning a clinical trial to investigate whether antibiotic treatment in combination with two immune-modulating drugs can reduce primary and metastatic liver tumors in patients.

Ma C, et al. *Science*. 2018 May 25;360(6391).

CCR's Liver Cancer Program

Liver cancer is the second most common cause of cancer-related death worldwide. In the United States, it is one of the few common cancers whose incidence and mortality continues to rise. CCR is confronting the problem with a new Liver Cancer Program, a multi-disciplinary effort that brings researchers and clinicians together to find better ways to detect, diagnose and treat the disease. The program co-directors are **Tim Greten, M.D.**, and **Xin Wei Wang, Ph.D.**

A colored scanning electron micrograph of a bile duct. The bile duct carries bile from the liver and the gallbladder to the small intestine.
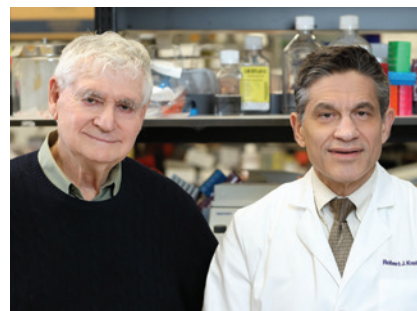
Credit: *Getty Images*

MOXE
FOR LEUKEMIA

After decades, a research endeavor produces an FDA-approved, toxin-based drug to treat relapsed or refractory hairy cell leukemia.

Ira Pastan, M.D.
Robert J. Kreitman, M.D.
Laboratory of Molecular Biology

The U.S. Food and Drug Administration's (FDA) approval of moxetumomab pasudotox (Lumoxiti) in September 2018 for certain adults with hairy cell leukemia (HCL) provides a promising new therapy to a group of patients who previously had few other options. It also marks the latest milestone in a decades-long journey that unfolded largely in CCR.

In HCL, a slow-growing cancer comprising 2 percent of leukemias, the bone marrow churns out abnormally high numbers of white blood cells called B lymphocytes. Although many patients enter remission with current treatments, most will eventually relapse. Moxetumomab pasudotox, or Moxe for short, can help patients whose HCL did not respond well to standard therapy and had several relapses.

Moxe is an immunotoxin, a drug that uses an antibody that recognizes a protein found on cancer cells, to deliver a toxin that gets engulfed by, and then kills, the target cancer cells. In Moxe, the antibody binds to CD22, a protein found on B lymphocytes and cancers derived from B lymphocytes, and brings a toxin into the cell made by the *Pseudomonas aeruginosa* bacterium.

Moxe's history stretches back to the 1980s. **Ira Pastan, M.D.**, Co-Chief of CCR's Laboratory of Molecular Biology, and his team showed that the *Pseudomonas* toxin, when attached to various human antibodies, could kill human cancer cells, but it killed other human cells, too. At the time, many in the scientific community were concerned that immunotoxins would prove too toxic for patients.

It was at this point that the CCR's unique research environment came into play, providing long-term support of Pastan and colleagues' high-impact, high-risk research. In meticulous work over the years, Pastan's team developed immunotoxins that efficiently killed cancer cells by shortening the toxin. By testing a range of cellular targets, they identified CD22 as the most potent target. They also re-engineered the immunotoxin's antibody portion to bind more tightly to CD22.

Moxe was licensed to MedImmune, a subsidiary of AstraZeneca, for commercial development, and Medimmune continued to work with CCR to further develop the drug. Clinical trials at the NIH Clinical Center were directed by **Robert J. Kreitman, M.D.**, Senior Investigator in Pastan's lab.

A phase I trial enrolled 49 patients with relapsed or refractory HCL. Fifty-seven percent of the patients had a complete response. These promising results, reported in *Blood*, convinced the FDA to allow CCR investigators to fast track Moxe to a phase III trial. After 17 months of follow-up, 75 percent of the patients had a complete or partial response. Most complete responders had no minimal residual disease, meaning no rogue cancer cells that can lurk in bone marrow and escape standard therapy, leading to relapse.

Based on these findings, published in *Leukemia*, the FDA approved Moxe for HCL that has recurred or progressed after at least two prior systemic therapies. Pastan notes this research probably could not have happened anywhere else.

Kreitman RJ, et al. *Blood*. 2018 May 24;131(21):2331-2334.

Kreitman RJ, et al. *Leukemia*. 2018 Aug;32(8):1768-1777.

Jeff Larioni participated in an NCI clinical trial of moxetumomab pasudotox (Moxe) for hairy cell leukemia conducted at the NIH Clinical Center and directed by Robert J. Kreitman, M.D. Originally diagnosed in 2012, Jeff began treatment on the Moxe trial in February 2016. He achieved complete remission, but residual disease was discovered about a year later. Kreitman and Jeff's primary care physician are currently monitoring his blood levels. Jeff says: "For now, I am feeling healthy and have an active lifestyle. I have complete faith in Dr. Kreitman."

Credit: *Chia-Chi Charlie Chang, NIH*

IMMUNOTHERAPY

vs.

BREAST CANCER

In a landmark study, a patient's advanced breast cancer regressed completely after treatment with immune cells that recognized products of mutations specific to her cancer.

Steven A. Rosenberg, M.D., Ph.D.
Surgery Branch

In an ongoing NCI-led clinical trial at the NIH Clinical Center, a patient with metastatic breast cancer has experienced complete regression of her disease after treatment with an experimental immunotherapy developed in CCR. Despite multiple prior cancer treatments, her cancer continued to enlarge and spread until she received this new treatment. The case report, published in *Nature Medicine*, highlights the potential of immunotherapy for difficult-to-treat solid tumors.

Although cancer immunotherapies have brought about complete regression of disease in some patients, certain types of cancer, including breast cancer, have been difficult to treat with these approaches. The experimental approach being tested in the current trial, developed by CCR Surgery Branch Chief **Steven A. Rosenberg, M.D., Ph.D.**, and colleagues, uses immune cells selected for their ability to recognize cells with mutations specific to a patient's tumor to fight their disease—a strategy that Rosenberg says may serve as a blueprint to treat many cancers.

This type of immunotherapy, called adoptive cell transfer (ACT), uses cancer-fighting cells from a patient's own immune system that are grown in large numbers in the laboratory and then infused into the patient. The specific form of ACT being investigated uses immune cells that have been isolated directly from a patient's tumor, known as tumor-infiltrating lymphocytes (TILs). The key to this approach is the identification and use of only TILs that specifically recognize proteins encoded by genetic mutations present in the patient's cancer.

The TILs used to successfully treat this patient's breast cancer were selected after researchers compared the DNA and RNA from one of her tumors to her normal tissue and identified 62 mutations unique to her cancer. Next, the TILs isolated from her tumor were tested for their ability to recognize the products of these mutations. TILs recognizing proteins encoded by four different cancer-specific mutations were then selected for treatment. Along with the tumor-specific immune cells, the patient was given pembrolizumab, an immune system checkpoint inhibitor that allows cancer-fighting cells to remain active in the microenvironment of a tumor, and interleukin-2, which promotes immune cell growth.

More than three years after the treatment, the patient's breast cancer has not returned. The team has also seen this type of immunotherapy trigger tumor regression in patients with liver cancer, colorectal cancer and cervical cancer, offering hope that it might be a broadly effective treatment strategy.

Zacharakis N, et al. *Nat Med*. 2018 Jun;24(6):724-730.

At the top of the image are cells isolated from a patient's tumor directly after it was removed by surgery. The sample includes a combination of dark tumor cells, tumor-infiltrating lymphocytes (TILs) and other inflammatory cells. Below, the same culture is shown after two to three weeks of growth. This is a pure sample of TILs and is used to select lymphocytes that are able to identify the products of mutations unique to the patient's tumor. Once multiplied, TILs are then infused into the patient.

Credit: *James Yang, CCR, NCI, NIH*

ARRESTING
METASTASIS

A compound that reduces the prevalence of an enigmatic cellular structure linked to metastasis blocks the spread of cancer in animals.
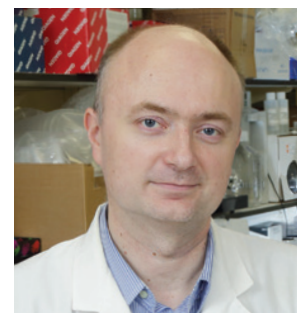
Udo Rudloff, M.D., Ph.D.
Pediatric Oncology Branch

Metastasis, the spread of cancer cells from a primary tumor to other parts of the body, is the cause of most cancer-related deaths. Finding an effective way to interfere with this complex process holds tremendous benefit for patients with a broad range of cancer types, but so far, there are no approved cancer therapies that specifically target metastatic cells. CCR scientists, in collaboration with researchers from the National Center for Advancing Translational Sciences (NCATS) and Northwestern University Feinberg School of Medicine, have now identified an experimental drug that may arrest metastasis.

In this decade-long collaboration, researchers have identified and tested a potential anti-metastasis drug that they call metarrestin. Led by **Udo Rudloff, M.D., Ph.D.**, Investigator in the CCR Pediatric Oncology Branch, the CCR team showed that metarrestin prevents different implanted human tumor types from metastasizing in animals and significantly extends the lives of mice bearing aggressive human tumors. Their findings were published in *Science Translational Medicine*.

Metarrestin drew the researchers' attention because of its potential to eliminate a poorly understood subcellular structure that is found in cancer cells and not in normal cells. Under a microscope, that structure, known as the perinuclear compartment (PNC), appears as a tiny speck inside a cell's nucleus. The exact function of this tiny compartment remains unknown, but researchers do know that the more PNCs cancer cells have, the more likely they are to metastasize.

PNCs are such reliable indicators of a cancer cell's metastatic potential that the team hoped they might be able to use them to find a drug that stops metastatic cells in their tracks. Scientists at NCATS conducted a massive drug screen to find compounds that make PNCs disappear. After devising an automated microscopy method to assess the presence of PNCs in individual cells, they tested how their prevalence changed when metastatic cancer cells were exposed to each of about 140,000 potential small-molecule drugs. The most promising compound from the screen was chemically modified and improved to use as a drug to further enhance its PNC-reducing effects. The resulting compound was named metarrestin.

Experiments in Rudloff's lab yielded encouraging results. Metarrestin did not just reduce the number of PNCs in cancer cells and keep metastatic cancer cells from growing in laboratory dishes. It also blocked tumor metastasis in mouse models of cancer. Whereas untreated animals developed metastatic tumors in the livers and lungs, these organs were nearly tumor-free in mice that were treated with metarrestin. Mice with metastatic pancreatic tumors that were treated with metarrestin lived significantly longer than untreated animals. Many animals were considered cured if no disease developed after six months.

Rudloff and his colleagues are now preparing to evaluate metarrestin's effects in patients with metastatic cancers. The team hopes to launch an initial first-in-human trial of metarrestin at the NIH Clinical Center in 2019.

Frankowski KJ, et al. *Sci Transl Med*. 2018 May 16;10(441).

In the upper image, an electron micrograph at 1,000x magnification depicts the nucleus (with a thin, dark outline) of a metastatic human cancer cell with three nucleoli. Structures within the nucleoli actively fuel metastasis. In cells treated with metarrestin, like the one below, the nucleoli collapse, becoming highly dense, and develop a nucleolar 'cap' formation. While the nucleus and other components of the cell remain intact, the nucleoli are now unable to promote metastasis.

Credit: *Kunio Nagashima, CCR, NCI, NIH*

SORTING
LYMPHOMA SUBTYPES

Deepened understanding of what drives different blood cancers is paving the way to more precise treatments.

Louis M. Staudt, M.D., Ph.D.
Lymphoid Malignancies Branch

New knowledge about the molecular changes that drive different types of lymphoma is giving a more nuanced view of these cancers. Recent discoveries by CCR's Lymphoid Malignancies Branch Co-Chief **Louis M. Staudt, M.D., Ph.D.**, are enabling more precise diagnoses and suggest potential new treatment strategies for increasingly specific subsets of patients.

Pioneering molecular profiling efforts two decades ago by Staudt and colleagues changed how the most common type of lymphoma, diffuse large B-cell lymphoma (DLBCL), is diagnosed and treated. Although DLBCL was once considered a single disease, Staudt and colleagues discovered 18 years ago that most cases of the cancer can be placed into two major subgroups based on their gene expression patterns, and that each subgroup tends to respond differently to immunochemotherapy and targeted treatments.

With newer technologies, it has now become feasible to conduct more extensive genetic analyses on large numbers of patient samples, and Staudt and his colleagues have taken advantage of these tools to refine their classification system. Using several advanced methods of DNA sequencing and gene analysis to survey the genetic aberrations in 574 DLBCL tumor samples, they have now identified four distinct genetic subtypes of DLBCL.

Each subtype shares a group of genetic aberrations and differs from the others in its response to the standard treatment regimen for DLBCL. Patients with two of the subtypes, called BN2 and EZB, respond well to treatment, while those with the other two, MCD and N1, do not.

The new classification system, reported in the *New England Journal of Medicine*, will be valuable in assigning clinical trial participants to appropriate treatments based on their tumor classification and interpreting the results of clinical studies. It may also help researchers devise new treatment strategies that target the vulnerabilities of specific subtypes.

Along these lines, Staudt's laboratory has clarified what makes certain cases of DLBCL vulnerable to the molecularly targeted drug ibrutinib, which stops some cancer cells from dividing by binding to a signaling molecule called BTK. In a previous clinical trial, only a fraction of patients with DLBCL responded to the drug. In work reported in *Nature*, Staudt and colleagues have now discovered that ibrutinib-responsive DLBCL cells rely on a growth-promoting protein complex called My-T-BCR for their survival. This complex, which can be detected in biopsy samples, may be valuable for identifying patients likely to benefit from the drug.

Staudt and CCR colleagues are now collaborating with multiple cancer centers across the country to conduct an NCI Cancer Moonshot[SM]-funded clinical trial to test combinations of targeted drugs in patients selected according to Staudt's new classification system of lymphomas.

Schmitz R, et al. *N Engl J Med*. 2018;378(15):1396-1407.

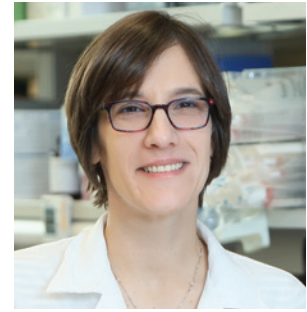Phelan JD, et al. *Nature*. 2018;560(7718):387-391.

Like the apples in this sorting line, scientists have now sorted the most common type of lymphoma, diffuse large B-cell lymphoma, into four distinct genetic subtypes.

Credit: *Pixabay*
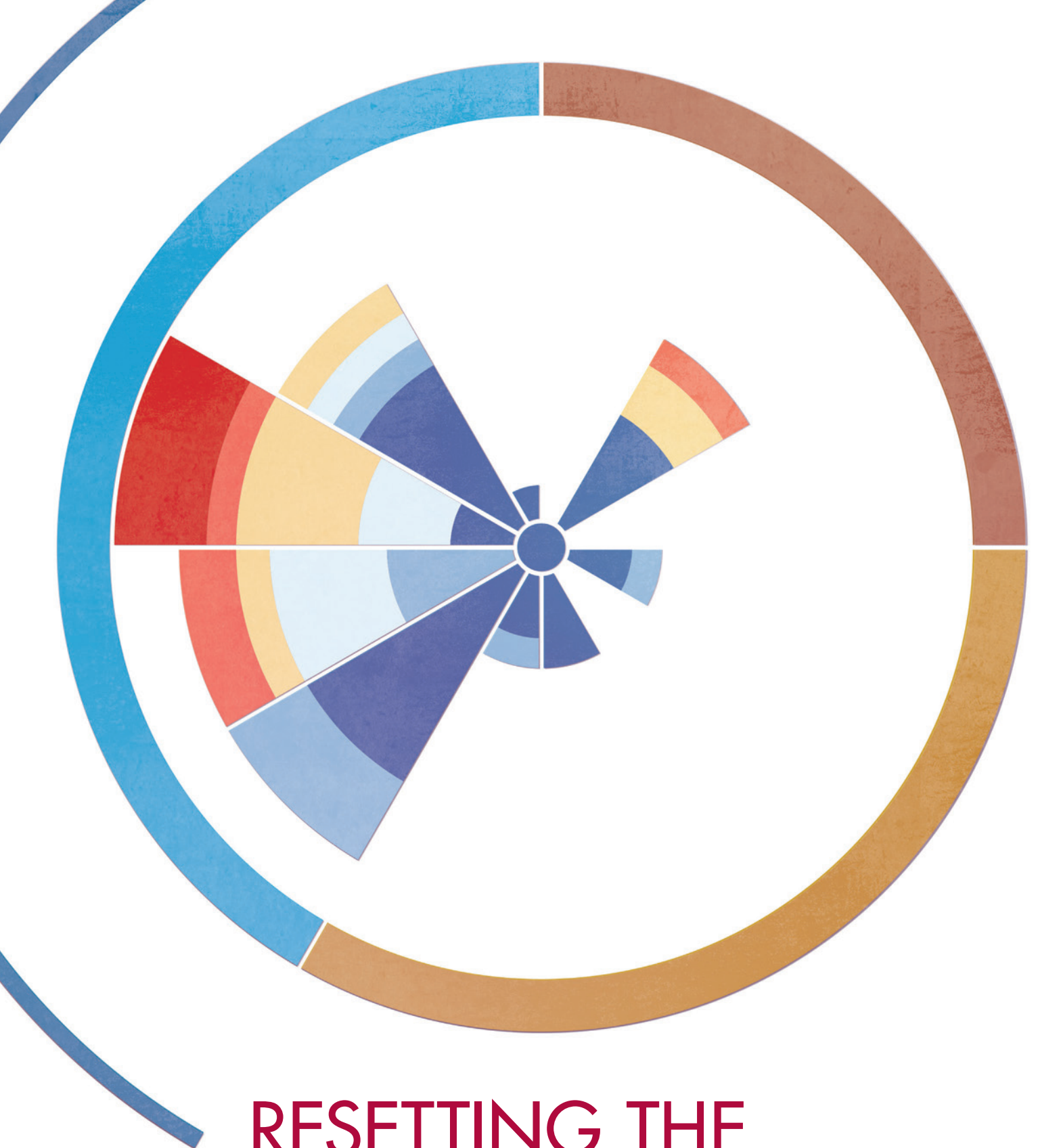
RESETTING THE
RAS PATHWAY

Inhibiting an enzyme in the growth-promoting *Ras* pathway could stop the childhood cancer rhabdomyosarcoma.

Marielle Yohe, M.D., Ph.D.
Pediatric Oncology Branch

CCR scientists have uncovered a potential new treatment strategy for rhabdomyosarcoma, a rare cancer that occurs mostly in children and arises from muscle progenitor cells that never properly mature. Their studies may lead to better options for patients with the disease who often experience severe side effects from chemotherapy.

Investigators **Marielle Yohe, M.D., Ph.D.**, in CCR's Pediatric Oncology Branch and **Javed Khan, M.D.**, in CCR's Genetics Branch, explored how mutations in the *Ras* family of genes, cancer-driving mutations that are present in about a third of human tumors, influence the growth of rhabdomyosarcoma. Their studies, published in *Science Translational Medicine*, suggest that blocking a protein in the *Ras* signaling pathway known as MEK may be an effective treatment for the subset of rhabdomyosarcomas that are driven by *Ras* mutations.

The team screened more than 1,900 drugs and found those that inhibited MEK signaling, including the FDA-approved cancer drug trametinib, dramatically slowed the growth of *Ras*-driven rhabdomyosarcoma cells. Cancer cells treated with trametinib not only stopped dividing, they began to take on the characteristics of more mature muscle cells, losing key features of the precursor cells, or myoblasts, from which rhabdomyosarcoma develops. When the team administered trametinib to mice with rhabdomyosarcoma tumors, they saw similar effects: cancerous myoblasts began to mature, and tumor growth slowed. In their experiments, mice treated with trametinib lived longer than those that did not receive the drug.

Yohe's team also conducted detailed experiments to reveal exactly how *Ras* and MEK affected muscle differentiation. They found that an enzyme activated by MEK called ERK2 not only switches on genes involved in cell division, it also keeps a gene called *MYOG*, which helps orchestrate myoblasts' transformation to more mature muscle cells, turned off.

Although these results were encouraging, the team found that rhabdomyosarcoma cells quickly developed resistance to trametinib. With a second drug screen, this time testing nearly 600 combinations of drugs, the researchers found that they could generate a more potent and prolonged response by combining trametinib with a compound called BMS-754807. Based on these findings, Yohe and her colleagues are now exploring the potential of combining trametinib with a BMS-754807-like drug to treat *Ras*-driven rhabdomyosarcoma in patients.

Yohe says that apart from its potential to reduce tumor growth, MEK inhibition might also be useful as a maintenance therapy to promote differentiation of any cancer cells that remain after patients with rhabdomyosarcoma complete chemotherapy.

Yohe ME, et al. *Sci Transl Med*. 2018 Jul 4;10(448).

This wind-rose plot taken from the study shows that MEK inhibitors are potent and selective for fusion-negative rhabdomyosarcoma as compared to fusion-positive rhabdomyosarcoma and normal cell lines. Each cell line investigated corresponds to a spoke of the plot.

Credit: *Berkley Gryder, CCR, NCI, NIH*

PREDICTING
IMMUNOTHERAPY RESPONSES
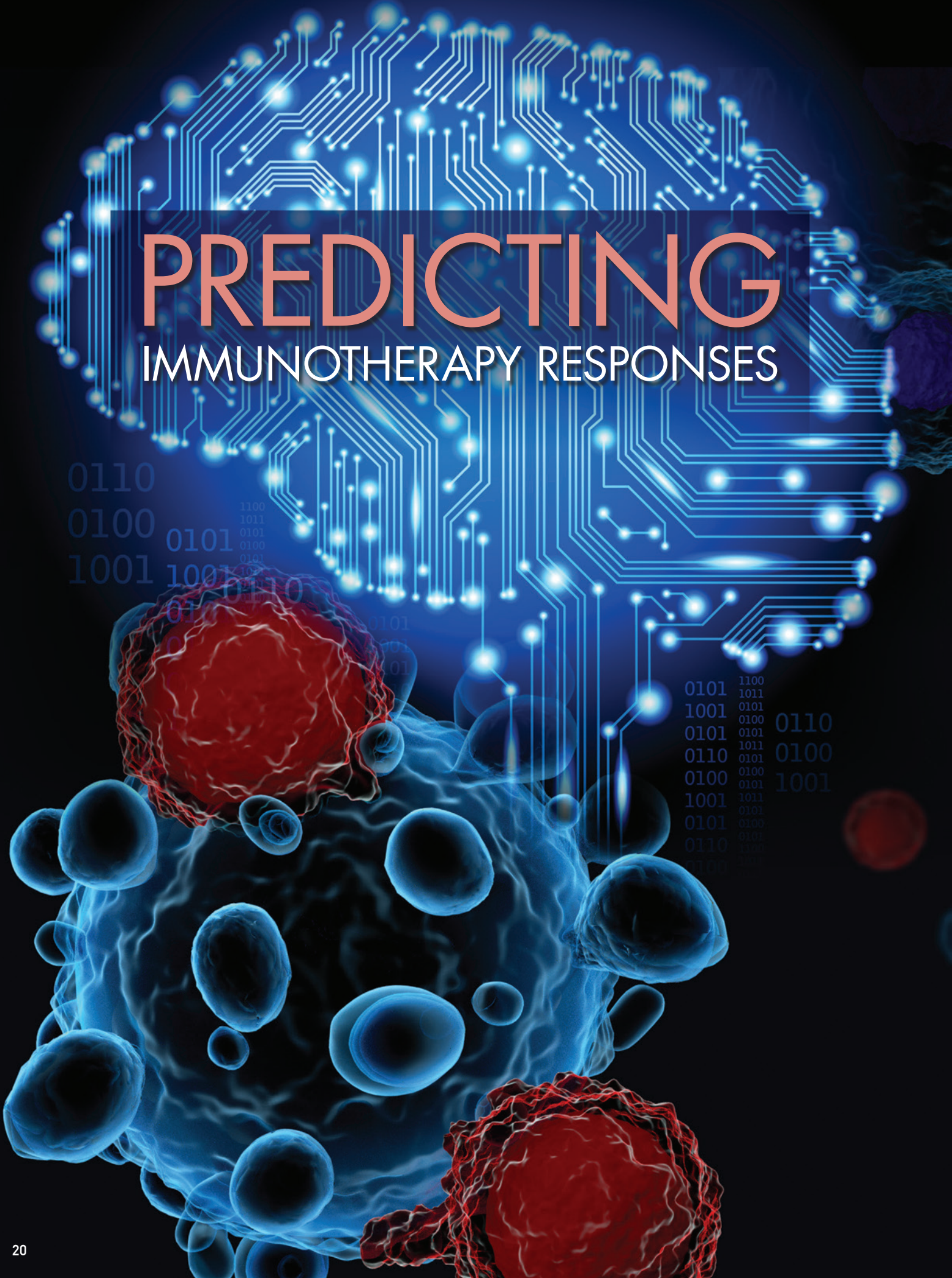
New computational tool analyzes gene expression to predict which melanoma patients will benefit from immunotherapy.

Eytan Ruppin, M.D., Ph.D.
Cancer Data Science Laboratory

Although immunotherapy is radically changing how we treat some cancers, these treatments, which boost the ability of a patient's own immune system to fight cancer cells, do not work for everyone. Clinicians need better tools to identify which patients are likely to benefit from immunotherapies available today.

A new computational method developed by CCR scientists and published in *Nature Medicine* may help patients with melanoma and their doctors decide whether to choose a form of immunotherapy that uses immune checkpoint inhibitors, which are effective for some but not all patients with late-stage melanoma and certain other types of cancer.

Led by CCR Senior Investigator **Eytan Ruppin, M.D., Ph.D.**, who heads CCR's new Cancer Data Science Laboratory, the team developed a predictive computational tool based on a small set of genes whose activity predicts whether a melanoma patient's cancer is likely to respond to the checkpoint inhibitors pembrolizumab (Keytruda), nivolumab (Obdivo) or ipilimumab (Yervoy). When tested on data from nearly 300 patients, the algorithm correctly identified nearly every patient whose melanoma responded to these drugs and more than half of those who did not.

The success is notable because predictive tools have been difficult to develop, in part because immunotherapy is so new that relatively few patients have received treatments. As a result, there are few datasets that researchers can mine for correlations between the molecular makeup of patients' tumors, their responses to immunotherapy and other factors that might influence that response.

Lacking a sufficiently large dataset from patients with melanoma treated with immunotherapy, Ruppin's team began their efforts by searching elsewhere for clues about features that might underlie an effective anticancer immune response. They looked at neuroblastoma, a cancer that starts in immature nerve cells and often regresses on its own in very young patients. This spontaneous regression is thought to be mediated by the immune system. The team's hope, explains Noam Auslander, Ph.D., a former graduate student in Ruppin's laboratory and the first author of this study, was that tumor samples from patients whose immune systems were able to control neuroblastoma might share certain defining features with the tumors of patients whose immune systems were, with the support of immunotherapy, capable of effectively attacking melanoma.

Analyzing gene expression data from patients with neuroblastoma, the team identified 15 checkpoint-related pairs of genes whose relative activity could be used to predict the effectiveness of the immune system's anticancer response, which they used to develop a predictive tool. When they applied this predictor to available data from patients with melanoma, it outperformed all other predictors of immunotherapy drug outcomes that had been reported so far.

The next steps will be to refine and validate the predictor before it can be used clinically and to test whether the same approach can be used to predict immunotherapy responses for patients with other types of cancer. Ultimately, tools like these will be critical in enabling a more personalized approach to cancer immunotherapy.
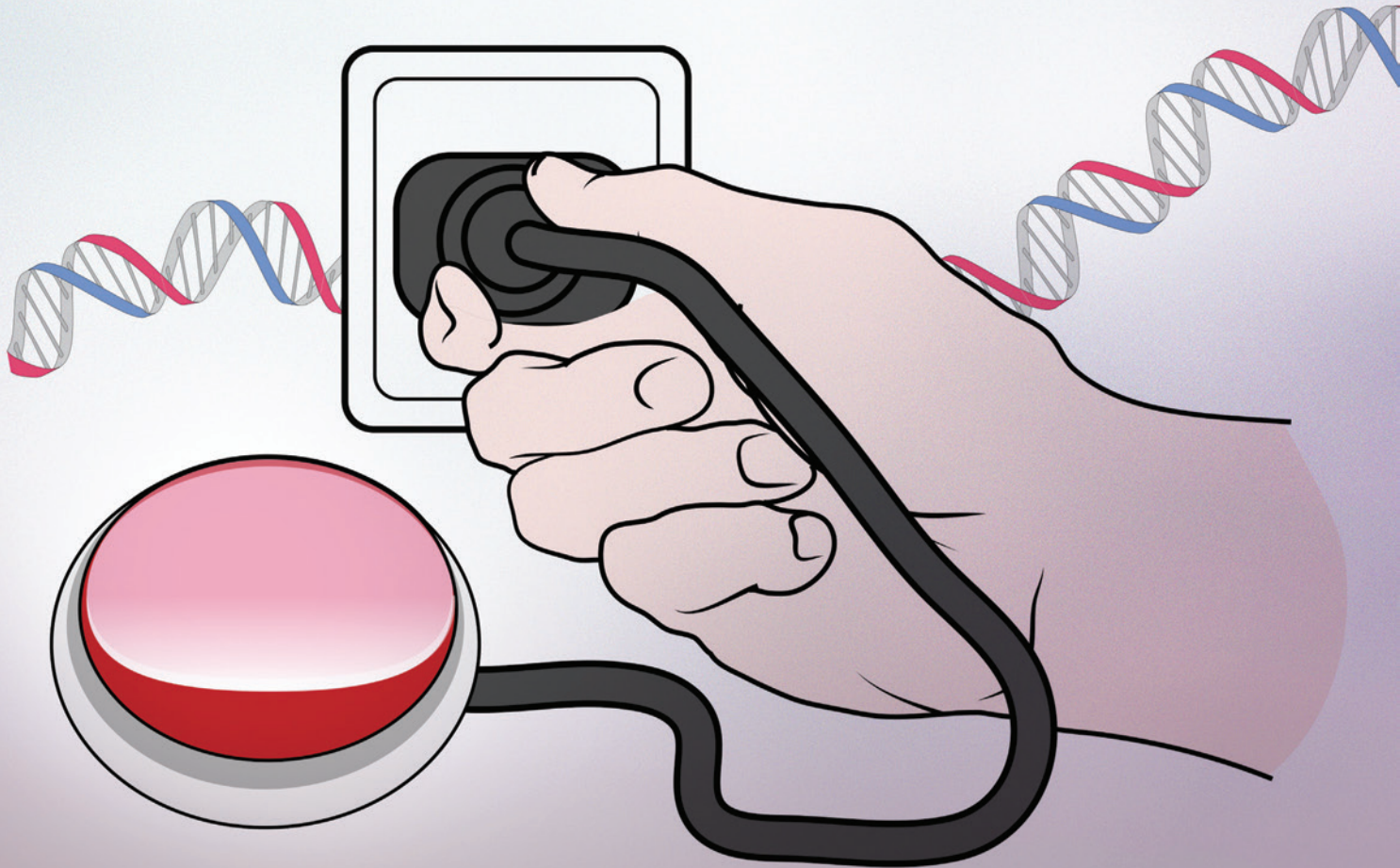
Auslander N, et al. *Nat Med*. 2018 Aug 20;24(10):1545-1549.

A new predictive computational tool developed by CCR scientists analyzed gene expression in melanoma to determine if the patient's cancer is likely to respond to immunotherapy. This image shows a melanoma cell being attacked by immune cells.

Credit: *iStock*

KEEPING
DNA REPLICATION
IN CHECK

A protein called RepID is key to regulating DNA replication and preventing cancer when the process goes awry.

Mirit Aladjem, Ph.D.
Developmental Therapeutics Branch

Each time a cell divides, it must first duplicate its genetic material in a process called DNA replication. Because defects in this process can cause mutations that eventually lead to cancer, understanding the details of how replication works could point to possible cancer treatments. Now, CCR scientists have added to this understanding by describing novel aspects of DNA replication that involve a protein called RepID.

Cells have a number of molecular checkpoints in place to prevent DNA replication from going awry, including some to ensure that cells replicate their DNA only once before each division. Occasionally, these checkpoints get disrupted. As a result, cells can become cancerous through a variety of mechanisms, such as increased copies of genes that drive cancer growth or through uncontrollable cell division, which is a hallmark of cancer.

DNA replication errors, especially those occurring at regions that are hard to replicate, called fragile sites, can cause breaks in DNA. This can lead to cancer, primarily by making it more likely that fragments of chromosomes rearrange themselves, activating genes that lead to uncontrollable cell division.

A team led by **Mirit Aladjem, Ph.D.**, Senior Investigator in CCR's Developmental Therapeutics Branch, and Sang-Min Jang, Ph.D., a postdoctoral researcher in Aladjem's lab, reported in *Nature Communications* that the RepID protein sets off a chain reaction of protein signaling and recruitment to prevent DNA replication from getting out of control. They showed that RepID recruits the enzyme CRL4 to chromatin before DNA replication begins. Once CRL4 is bound to chromatin, it causes a protein called CDT1 to break down, keeping it from kick-starting replication more than

once each time cells divide. If CRL4 is not working properly, though, a buildup of CDT1 can occur, allowing DNA replication to proceed unchecked, resulting in excess replication of segments of the genome.

Oftentimes, portions of DNA replication checkpoints are disrupted in cancer cells. A number of drugs under investigation inhibit the remaining functional checkpoints in these cells, triggering excessive DNA replication. This places an excessive burden on the cancer cells, leading to improper separation of their chromosomes when they divide. The ultimate result is programmed cell death, or apoptosis. In other words, malfunctioning DNA replication checkpoints may actually help kill cancer cells because they render them more sensitive to this class of drugs.

Aladjem and her team tested one such drug, and they found that the drug triggered severe excess DNA replication in cells depleted of RepID. As a result, a greater proportion of RepID-depleted cells than RepID-containing cells underwent apoptosis. These results point to RepID expression levels as a way to gauge cancer cells' sensitivity to replication inhibitors.

Aladjem notes that her team's research explains the underlying mechanisms cells use to prevent DNA from replicating more than once each cell cycle. These basic findings will improve our understanding of not only how normal cells avoid becoming cancerous, but also how certain drugs can exploit excessive DNA replication to kill cancer cells.

Jang SM, et al. *Nat Commun*. 2018 Jul 17;9(1):2782.

The electrical socket in this image represents specific sites on chromatin (replication origins) that can bind a protein (RepID, depicted as a hand) that recruits a regulator complex (CRL4, a red button). Without RepID (top panel), the regulator complex is absent, and replication might start at the same chromosome sites more than once (right). With RepID (bottom panel), the controller CRL4 plugs into chromatin and prevents replication from starting more than once at each genomic location, ensuring that the entire genome replicates exactly once before each cell division.

Credit: *Sang-Min Jang, CCR, NCI, NIH and Erina He, Medical Arts, NIH*

CLOTTING THE SPREAD OF CANCER

A blood-clotting protein on the surface of tumor cells enables metastasis, the leading cause of death in cancer patients.
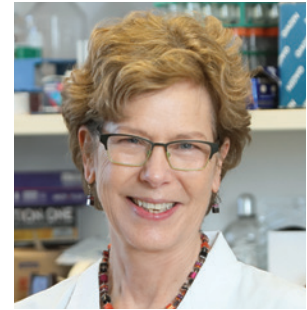
Kathleen Kelly, Ph.D.
Laboratory of Genitourinary Cancer Pathogenesis

CCR scientists have discovered that a protein on the surface of tumor cells activates blood-clotting cell fragments known as platelets, thus allowing tumor cells to spread to distant tissues in a process known as metastasis. Given that cancer metastasis is the leading cause of cancer-related deaths, the ability to inhibit this poorly understood process presents a potentially powerful approach to cancer treatment.

Earlier studies have shown that interactions between tumor cells and platelets in the blood played some role in metastasis, but how that happens has not been fully understood. In research published in *Cell Reports*, a team led by **Kathleen Kelly, Ph.D.**, Chief of CCR's Laboratory of Genitourinary Cancer Pathogenesis, hypothesized that a protein called CD97 plays a central role in this process. CD97 belongs to a class of proteins that can mediate adhesion between cells and resides at high levels in the cell membrane of tumor cells in several cancer types, including breast, prostate and thyroid cancer.

Using cultured cells, the researchers showed that CD97 activates platelets, causing them to release the signaling molecule lysophosphatidic acid (LPA), which, in turn, triggers the release of enzymes that allow tumor cells to more easily migrate through tissue. At the same time, these activated platelets make blood vessels more permeable, enabling the tumor cells circulating within them to escape into the surrounding tissue and to metastasize.

These findings were extended into a mouse model of thyroid cancer as well as in metastasis models using human prostate cancer cells and mouse breast cancer cells. In these in vivo settings, tumor cells needed to express CD97 in order to make blood vessels in the lungs more permeable and to form metastases.

The findings by Kelly and her team may point to a new target in research efforts to stop or slow metastasis. The team's study suggests that blocking the interaction between CD97 and platelets could prevent metastasis.

Ward Y, et al. *Cell Reports*. 2018 Apr 17;23(3):808-822.

In order to metastasize, cancer cells must enter the circulatory system and then exit at another site. CCR researchers have discovered that platelets (light blue) play a key enabling role in allowing cancer cells (orange) to escape blood vessels (red) in new locations away from the primary tumor (top left).

Credit: *Veronica Falconieri Hays, Falconieri Visuals*

DIVING DEEP

INTO THE

RED
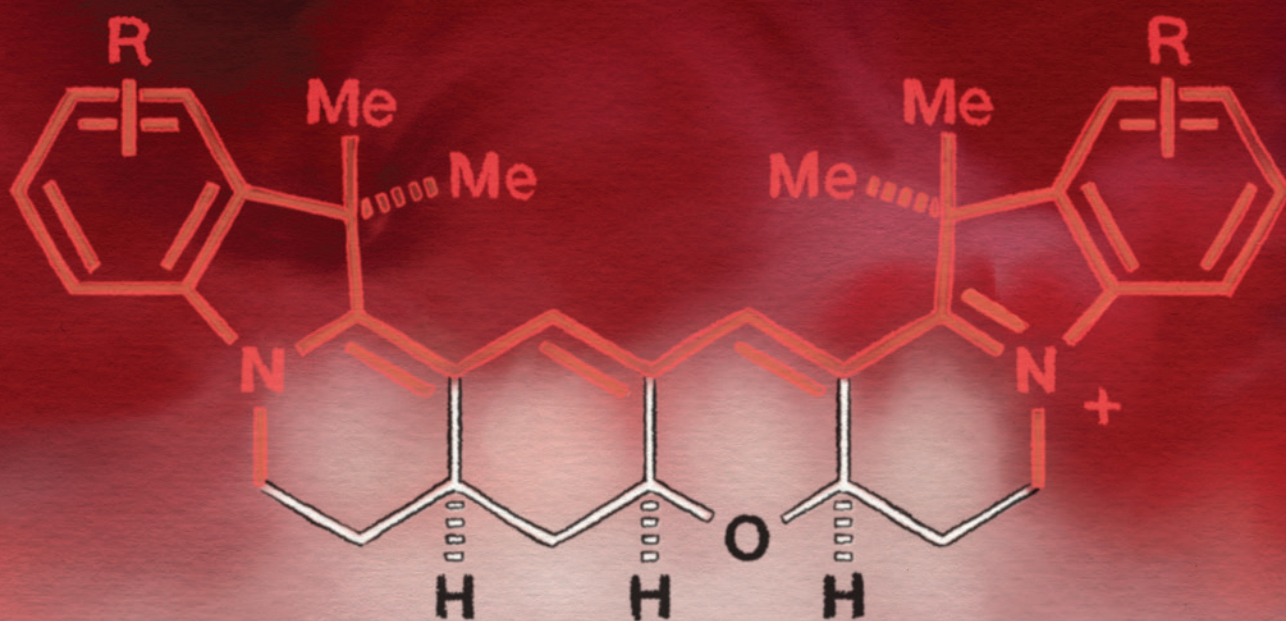
A new class of fluorescent probes peers deeper into live tissues.

Martin Schnermann, Ph.D.
Chemical Biology Laboratory

Fluorescent probes are workhorse molecules used by biologists to illuminate the inner workings of cancer cells. By lighting up cell components of interest, researchers can then observe cells in action through high-powered microscopes. CCR investigators have synthesized a novel class of far-red fluorescent probes that could allow live tissue to be imaged in greater depth and detail than is possible with current techniques.

Martin Schnermann, Ph.D., Senior Investigator in CCR's Chemical Biology Laboratory, and his team succeeded in developing a method to generate bright, far-red and near-infrared fluorescent probes, which they described in the *Journal of the American Chemical Society*. The making of such probes has eluded chemists for decades and only moderately bright dyes could be synthesized prior to this breakthrough.

Using cutting-edge synthetic chemistry techniques, Schnermann and his team solved this longstanding puzzle. They built a system of chemical ring structures and attached them to a certain class of fluorescent probes in order to block the rotation responsible for restricting the probes' brightness. The ring structures made them much brighter.

The Schnermann lab, with help from collaborators, including Jadranka Loncarek, Ph.D., of CCR's Laboratory of Protein Dynamics and Signaling, showed that their probes have an improved ability to go from a dark to bright state, making their signal clean and easy to distinguish from background fluorescence. Schnermann notes that this feature makes the probes ideal for single-molecule localization microscopy (SMLM). In SMLM, molecules in a tissue sample—such as tumor cell-surface markers—are fluorescently labeled and turned on to a bright state one at a time within a sample, allowing researchers to count them and determine their location with more precision than fluorescence-activated cell sorting or other existing methods.

Schnermann and his team's bright, far-red and near-infrared fluorescent probes are less toxic than currently available counterparts, suggesting they could be used for imaging live tissue. They also emit long, deeply penetrating wavelengths, which could allow them to be used for imaging deep into thick tissues, such as tumors. These promising properties point to several applications, such as tracking tumor cells in live tissues, which could lead to a better understanding of how cancer behaves in a living system. They also suggest a number of clinical applications, such as diagnostic imaging. For example, surgeons could use these probes to guide the removal of tumors from cancer patients, Schnermann says.

Michie MS, et al. *J Am Chem Soc.* 2017 Sep 13;139(36):12406-12409.

Fluorescent molecules are used frequently to dye and illuminate cells to be studied. Fusing a ring system (shown in white) onto an existing chromophore (the part of the compound responsible for absorbing light, shown in red) makes the new molecule much brighter. These new dyes, which are assembled using recently discovered organic chemistry techniques, will allow researchers to peer more deeply into living systems with unprecedented resolution.

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

New Faculty

Kenneth Aldape, M.D.

Kenneth Aldape, M.D., has joined CCR as Chief of the Laboratory of Pathology. His research interests focus on the molecular pathogenesis and classification of brain tumors, particularly malignant gliomas and meningiomas.

Chongyi Chen, Ph.D.

Chongyi Chen, Ph.D., has joined the Laboratory of Biochemistry and Molecular Biology as a Stadtman Tenure Track Investigator. His works explore the interface between DNA sequence, chromosome organization and gene expression in both bulk samples and single cells from a genome-wide perspective.

Yamini Dalal, Ph.D.

Yamini Dalal, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Receptor Biology and Gene Expression. Her laboratory is investigating how histone complexes adopt alternate structural conformations in cancer cells and the functional consequences of such alterations on the cancer epigenome.

S. Perwez Hussain, Ph.D.,

S. Perwez Hussain, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Human Carcinogenesis. His research is focused on identifying novel therapeutic targets in pancreatic cancer, one of the most lethal malignancies.

Jennifer Jones, M.D., Ph.D.,

Jennifer Jones, M.D., Ph.D., has joined the Laboratory of Pathology as a Stadtman Tenure Track Investigator. As a radiation oncologist, her current research is aimed at developing immune-based therapies that synergize with radiation to produce optimal anti-tumor immune responses.

Christopher Kanakry, M.D.

Christopher Kanakry, M.D., has been appointed as an NIH Lasker Scholar Tenure Track Investigator in the Experimental Transplantation and Immunology Branch. He pursues basic, translational and clinical research related to allogeneic hematopoietic cell transplantation.
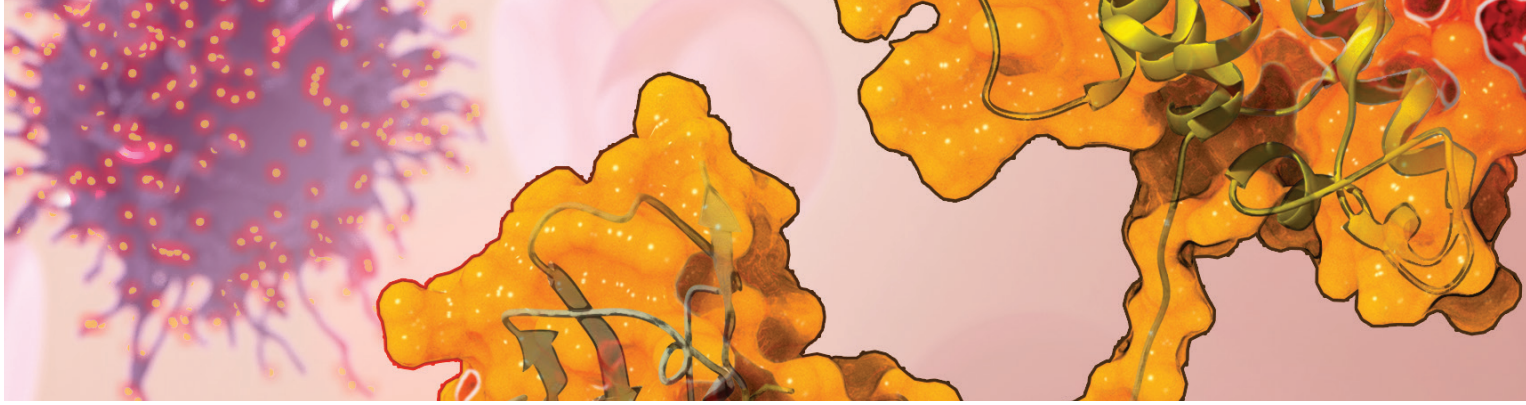
Eros Lazzerini Denchi, Ph.D.

Eros Lazzerini Denchi, Ph.D., has joined the Laboratory of Genome Integrity as a Stadtman Tenure Track Investigator. His research focuses on two fundamental aspects of telomere biology: the mechanism by which functional telomeres prevent DNA damage activation and the in vivo consequences of telomere dysfunction.

Andres Lebensohn, Ph.D.

Andres Lebensohn, Ph.D., has joined the Laboratory of Cellular and Molecular Biology as a Stadtman Tenure Track Investigator. He will develop a research program on understanding how signaling pathways are used, reused and repurposed to drive the myriad cellular processes that give rise to and maintain tissues and organs. Based on this understanding, he hopes to devise more selective therapies to target tumors driven by dysregulated WNT signaling.

Ravi Madan, M.D.

Ravi Madan, M.D., has been appointed as a Senior Clinician in the Genitourinary Malignancies Branch. His clinical research investigates immune-stimulating therapies and prostate cancer. Specifically, Dr. Madan's clinical trials are designed to develop a better understanding of how immune-stimulating therapies can improve clinical outcomes and be combined with other therapies.

Frank Maldarelli, M.D., Ph.D.

Frank Maldarelli, M.D., Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the HIV Dynamics and Replication Program. He develops and implements clinical protocols to elucidate mechanisms underlying the emergence of HIV drug resistance in vivo, the dynamics of infection under treatment and the role of resistance mutations in the efficacy and failure of subsequent treatments.

Claudia Palena, Ph.D.

Claudia Palena, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Tumor Immunology and Biology. Her laboratory studies the immunological targeting of drivers of tumor dissemination and resistance to therapy.

New Faculty continued

Arun Rajan, M.D.

Arun Rajan, M.D., has been appointed as a Senior Clinician in the Thoracic and GI Malignancies Branch. In his clinical research he develops new therapies for patients with lung cancer and thymic malignancies.

Mark Roschewski, M.D.

Mark Roschewski, M.D., has been appointed as a Senior Clinician in the Lymphoid Malignancies Branch. His research focuses on the management of aggressive B-cell lymphomas including diffuse large B-cell lymphoma, Burkitt lymphoma, mantle cell lymphoma and primary CNS lymphomas.

Sergio Ruiz Macias, Ph.D.

Sergio Ruiz Macias, Ph.D., has joined the Laboratory of Genome Integrity as a Stadtman Tenure Track Investigator. Dr. Ruiz Macias seeks to elucidate mechanisms of cell plasticity, pluripotency and differentiation with the goal of understanding embryonic development, cell transformation and cancer.

Eytan Ruppin, M.D., Ph.D.

Eytan Ruppin, M.D., Ph.D., has joined CCR as the Chief of the newly established Cancer Data Science Laboratory. He develops and harnesses data science approaches for the integration of multi-omics data to better understand the pathogenesis of cancer, its evolution and treatment.

Samira Sadowski, M.D.

Samira Sadowski, M.D., has been appointed as an Assistant Clinical Investigator in the Surgical Oncology Program. Her research will identify diagnostic and prognostic markers for endocrine tumors and develop new therapies for such tumors.

Martin Schnermann, Ph.D.

Martin Schnermann, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Chemical Biology Laboratory. His research group designs and synthesizes the molecules needed to craft new near-infrared optical drug delivery and imaging methods.
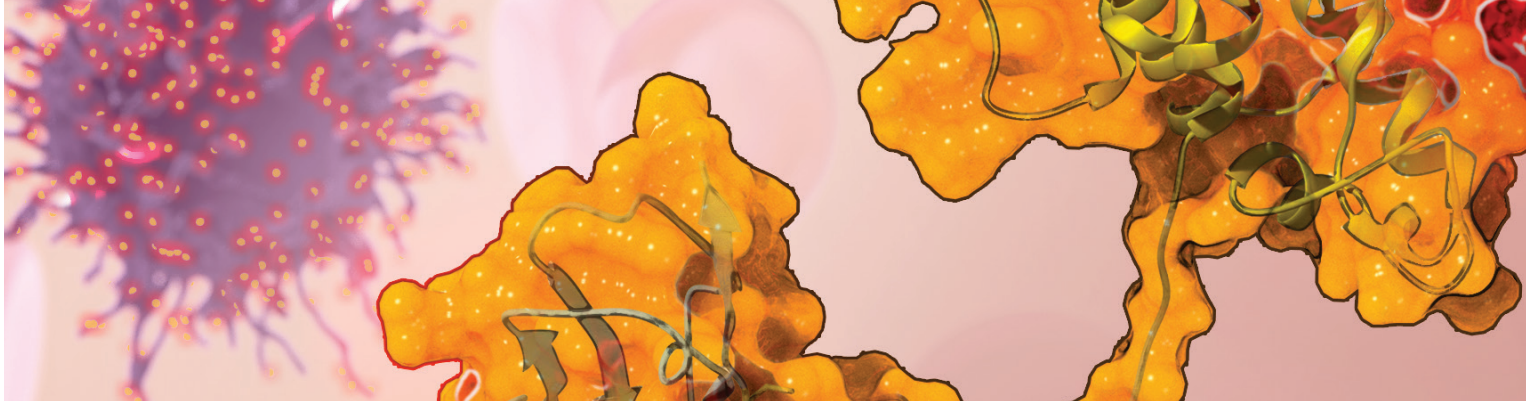
Jack Shern, M.D.

Jack Shern, M.D., has been appointed as an NIH Lasker Scholar Tenure Track Investigator in the Pediatric Oncology Branch. His research is aimed at defining and developing precision therapies targeting the genetic mutations that drive tumorigenesis.

Yousuke Takahama, Ph.D.

Yousuke Takahama, Ph.D., has joined the Experimental Immunology Branch as a Senior Investigator. His research focuses on understanding the molecular mechanisms involved in building functionally competent thymus microenvironments and in governing thymic selection to generate a functionally competent repertoire of mature T cells.

Naomi Taylor, M.D., Ph.D.

Naomi Taylor, M.D., Ph.D., has joined CCR as a Senior Investigator in the Pediatric Oncology Branch. During the next few years, she aims to combine fundamental and translational approaches to respond to key questions addressing the metabolic regulation of T-cell effector function and hematopoietic stem cell (HSC) differentiation in pediatric cancer patients and develop intrathymic-based strategies that enhance thymocyte differentiation and T-cell function.

Joana Vidigal, Ph.D.

Joana Vidigal, Ph.D., has joined the Laboratory of Biochemistry and Molecular Biology as a Stadtman Tenure Track Investigator. She will work toward understanding the mechanisms through which small noncoding-RNA pathways regulate gene expression during animal development, tissue homeostasis and disease.

Jing Wu, M.D., Ph.D.

Jing Wu, M.D., Ph.D., has been appointed as an NIH Lasker Scholar Tenure Track Investigator in the Neuro-Oncology Branch. She is interested in translational research in neuro-oncology focusing on developing preclinical testing and hypothesis-based clinical trials of glioma treatments.

Awards & Honors
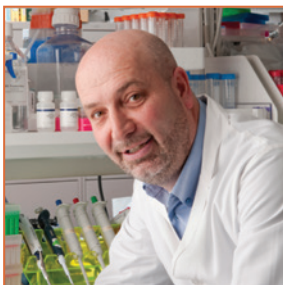
Stefan Ambs, Ph.D., received a Department of Defense Prostate Cancer Research Program Impact Award.
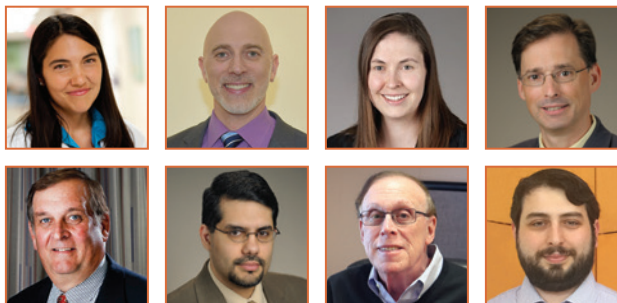
Andrea Apolo, M.D., Isaac Brownell, M.D., Ph.D., Renee Donahue, Ph.D., James Gulley, M.D., Ph.D., John Greiner, Ph.D., Ravi Madan, M.D., Jeffrey Schlom, Ph.D., and Julius Strauss, M.D., received a Federal Laboratory Consortium for Technology Transfer Excellence in Technology Transfer Award for Avelumab, New Therapy for Metastatic Merkel Cell and Urothelial Carcinomas.

Cristina Bergamaschi, Ph.D., received the Milstein Young Investigator Award.

Jay Berzofsky, M.D., Ph.D., gave the European Academy of Tumor Immunology honorary lecture.

Marijo Bilusic, M.D., Ph.D., James Gulley, M.D., Ph.D., Christian Hinrichs, M.D., and Ravi Madan, M.D., were members of the NCI team that received a Federal Laboratory Consortium Mid-Atlantic Region Award for the NCI Immunotherapy Fellowship co-sponsored by the Society for Immunotherapy of Cancer.
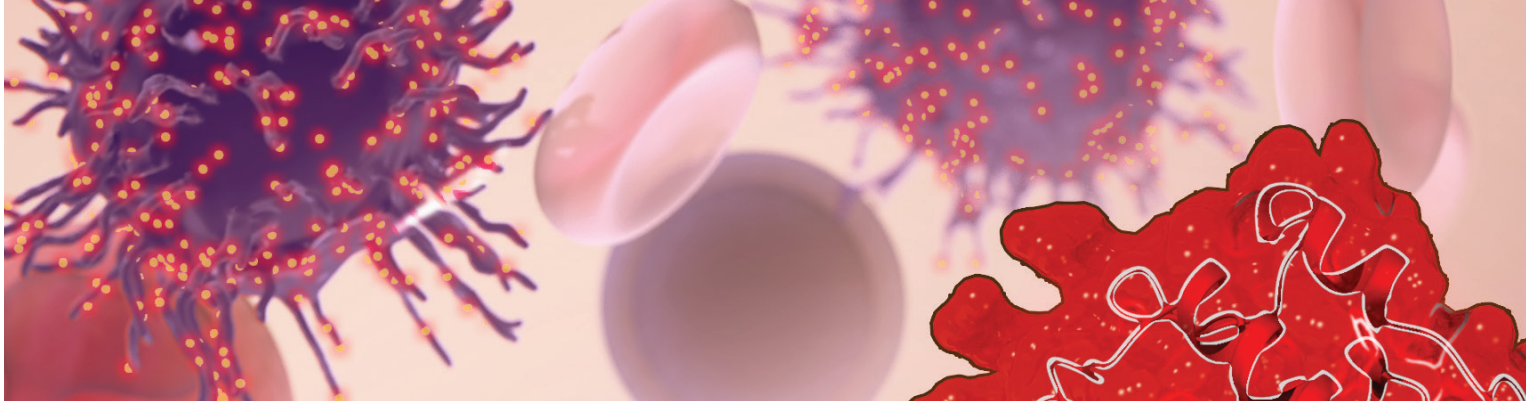

C. Norman Coleman, M.D., received the Ellen L. Stovall Award for Innovation in Patient-Centered Cancer Care from the National Coalition for Cancer Survivorship.
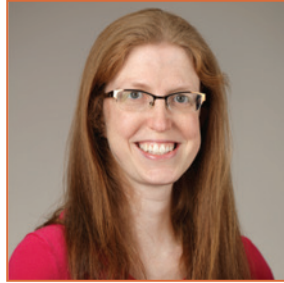

Eric Freed, Ph.D., received the KT Jeang Retrovirology Prize.

Terry Fry, M.D., and Nirali Shah, M.D., received a Clinical Research Forum Top Ten Clinical Research Achievement Award.

Michael Gottesman, M.D., was elected to the National Academy of Sciences and received the Dr. Nathan Davis Award for Outstanding Government Service from the American Medical Association.

Andrea Gross, M.D., received a Conquer Cancer Foundation of ASCO Young Investigator Award and the ASCO Bradley Stuart Beller Endowed Merit Award.

Jennifer Jones, M.D., Ph.D., received a Young Investigator Award from the Prostate Cancer Foundation and the Pamela Anne Cafritz Renal Cell Carcinoma Award.
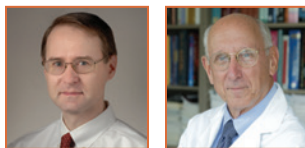
James Kochenderfer, M.D., and Steven Rosenberg, M.D., Ph.D., received a Federal Laboratory Consortium for Technology Transfer Excellence in Technology Transfer Award for FDA Approval: Personalized Cancer Treatment to Cure Deadly Blood Cancers.

Kenneth Kraemer, M.D., received the Environmental Mutagenesis and Genomics Society Award.
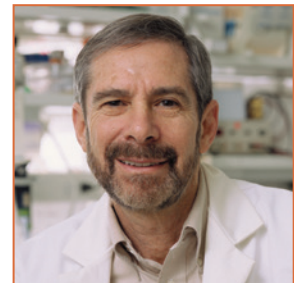
Douglas Lowy, M.D., received ASCO's Science of Oncology Award and Lecture.

Douglas Lowy, M.D., and John Schiller, Ph.D., received the Maryland Tech Council Lifetime Achievement Award and the Szent-Györgyi Prize for Progress in Cancer Research.

Tom Misteli, Ph.D., gave the Mendel lecture and received the Mendel Medal from Masaryk University in Brno, Czech Republic.

Ruth Nussinov, Ph.D., received the International Society of Computational Biology's Accomplishment by a Senior Scientist Award.

Awards & Honors <superscript></superscript>continued

Barry O'Keefe, Ph.D., Michael Boyd, M.D., Ph.D., (retired) and James McMahon, Ph.D., (retired) received a Federal Laboratory Consortium for Technology Transfer Excellence in Technology Transfer Award for Development of Large-Scale Production, Anti-HIV Microbicide in Soya Beans.

Steven Pavletic, M.D., was named a member of the Croatian Academy of Arts and Sciences.

Yves Pommier, M.D., Ph.D., was named a fellow of the American Association for the Advancement of Science.

Jason Redman, M.D., received an NCI Immunotherapy Fellowship from the Society for Immunotherapy of Cancer.

Steven Rosenberg, M.D., Ph.D., received the Albany Medical Center Prize in Medicine and Biomedical Research and the Jacobson Innovation Award from the American College of Surgeons.

The NIH Pediatric and Wildtype GIST Clinic received the Jeroen Pit Science Award from The Life Raft Group.

Jack Shern, M.D., received the James B. Nachman Endowed ASCO Junior Faculty Award in Pediatric Oncology.

Kandice Tanner, Ph.D., was named a Scialog Fellow of the Research Corporation for Scientific Advancement.

Giorgio Trinchieri, M.D., received the International Cytokine & Interferon Society-BioLegend William E. Paul Award.

Scott Wilkinson, Ph.D., received a Young Investigator Award from the Prostate Cancer Foundation.

CCR by the Numbers

74 | **New Employee Invention Reports**

36 | **Issued U.S. Patents**

76 | **New Technologies Licensed**

592 | **Active Licenses**

~1,300 | **Articles in Peer-Reviewed Journals**

1,346 | **Trainees**

30 | **New Cooperative Research and Development Agreements (CRADAs)**

188 | **Active CRADAs**

251 | **Open Clinical Trials**

40 | **New Trials Opened**

2,240 | **New Patients**

*Numbers are for FY2018.

Center for Cancer Research

NATIONAL CANCER INSTITUTE