NIH NATIONAL CANCER INSTITUTE

CENTER FOR CANCER RESEARCH

MILESTONES

Cancer Research with a Purpose

HIGHLIGHTS 2020–2021

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

CENTER FOR CANCER RESEARCH

The Nation's Cancer Center

The Center for Cancer Research (CCR) is the largest division of the NCI intramural research program and comprises nearly 250 basic and clinical research groups located on two campuses just outside of Washington, D.C.

For 20 years, CCR has been home to an extraordinary group of scientists and clinicians exploring the cutting-edge of cancer and HIV/AIDS research. Our scientists work on a wide spectrum of biological and biomedical problems, ranging from visualizing and understanding the structure of individual genes and proteins, developing novel methods for drug discovery, to inventing biomedical devices and technology and creating innovative ways to treat patients in the NIH Clinical Center.

Our scientists enjoy complete intellectual freedom and are expected to creatively and innovatively explore the most important questions in the field of cancer research and treatment. We support projects over a longtime horizon allowing our investigators to pursue some of the most difficult, high-risk problems in the field, and we are always on the lookout for new challenges and the most pressing problems in modern cancer research.

The success of CCR is grounded in an exceptionally strong discovery research program which provides the foundation for the seamless translation of insights into basic cellular and molecular processes to clinical applications and patient care. Examples of our success are the development of groundbreaking immunotherapy approaches, HIV/AIDS testing and the creation of a human papillomavirus vaccine.

The CCR is a unique place of science where we combine diverse expertise with the freedom to thoroughly pursue the most pressing questions in cancer biology and treatment.

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

This year's cover features members of our CCR community working safely during the COVID-19 pandemic to produce our scientific advances of 2020. For a complete list of images, see page 35.

***Credit:** Allen Kane and Joseph Meyer, Scientific Publications, Graphics and Media, Frederick National Laboratory, NCI, NIH and CCR staff; iStock*

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The **MISSION** of CCR is to improve the lives of all cancer patients by solving important, challenging and neglected problems in cancer research 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
- Research to eliminate cancer health disparities
- 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 the next generation of a diverse and inclusive biomedical workforce

Contents

Director's Note

2020 was certainly a year to remember. It will leave us with a lasting impression of a historic pandemic that dramatically and painfully upended our lives. The past year also shone a spotlight on longstanding racial inequities and brought polarizing political tensions and unrest.

But we will also remember the past year for the good: for standing together in times of crisis, for appreciating our daily lives and the small things in them, and for pulling together in our communities, none more impressive than how the scientific community worked across disciplines and national borders to tackle COVID-19.

It is those uplifting memories that guided our image selection of CCR staff and our science advances on the cover of this issue of *Milestones*. They illustrate the new ways in which we come together to get things done.

In CCR, we will also be able to look back at yet another year of outstanding science. In this issue of *Milestones*, we feature some of the major recent advances made by our scientists and clinicians.

Our basic discoveries form the foundation of our translational and clinical activities, and this year included the development of new computational tools to identify viruses in cancer genomes and the elucidation of the consequences of DNA damage. We learned how to use RNAs as molecular switches and how the *RAS* oncogene picks its protein interaction partners.

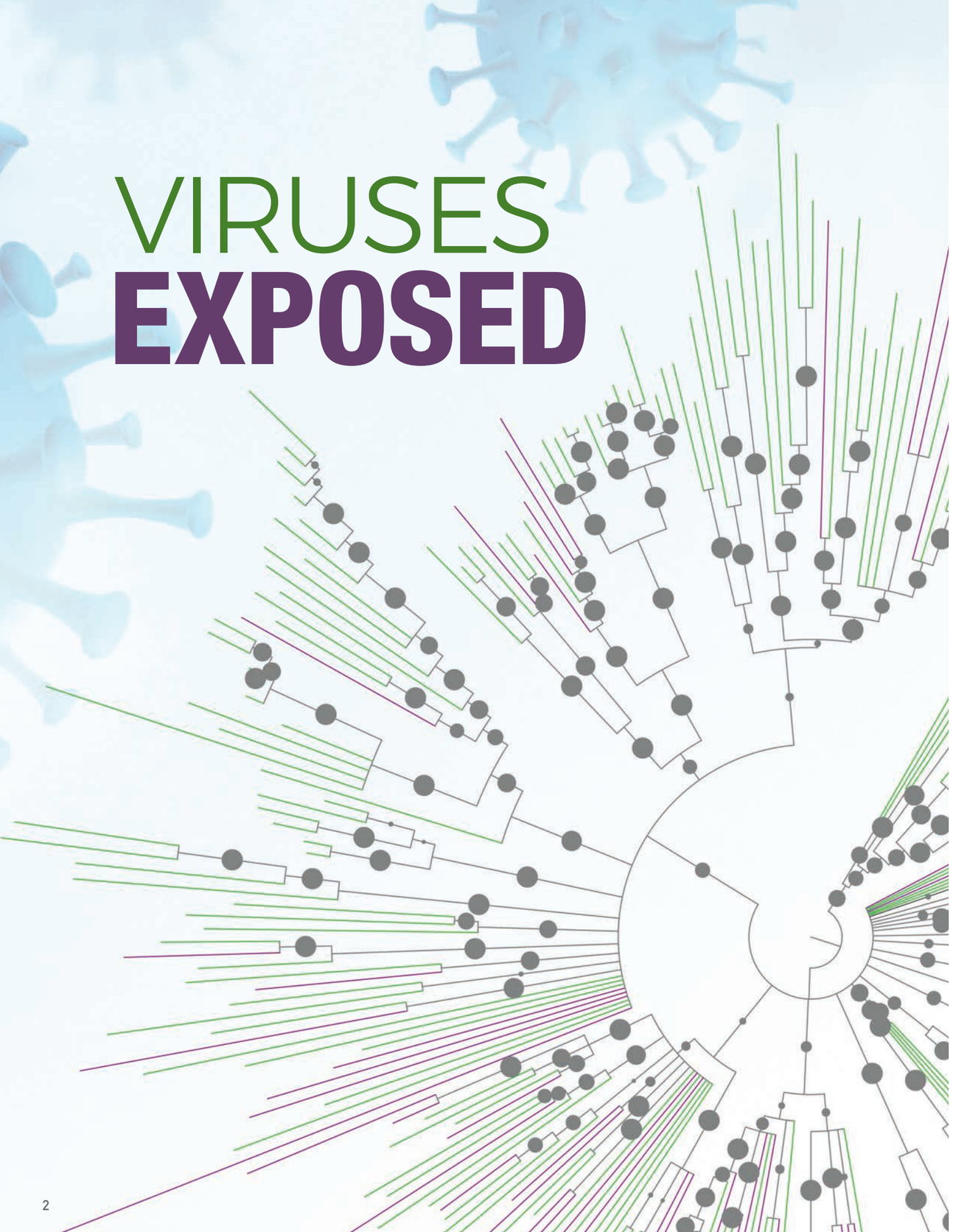
We also advanced our translational science by finding new ways to predict treatment outcomes in immunotherapy by reprogramming immune cells to better fight cancer and, as part of a growing effort in CCR, by identifying the molecular basis for ethnic health disparities in lung cancer.

We developed novel diagnostic tools, one to detect liver cancer using viral exposure history, another to precisely detect prostate cancer using sophisticated imaging technology. And following CCR's vision of "creating the medicines of tomorrow," we can offer new treatment options for patients with lymphoma, neurofibromatosis type 1 and Kaposi sarcoma, the latter two leading to approvals from the Food and Drug Administration.

This year has tested our resolve. What has become clear is that science is here to help, be it with a viral pandemic, environmental threats or cancer. Our science gives us hope and it creates solutions — it makes our lives better.

Tom Misteli
Director
NCI Center for Cancer Research

VIRUSES EXPOSED



A massive DNA search brings viral dark matter into the light.

Christopher B. Buck, Ph.D.
Senior Investigator
Laboratory of Cellular Oncology

It is thought that there may be hundreds of millions of different kinds of viruses in the world, most of which remain to be discovered. Some of these unknown viruses are likely to play a role in human cancers, but without thorough virus-hunting tactics, it's easy for them to go undetected.

Researchers led by **Christopher Buck, Ph.D.**, have long been interested in finding viruses that cause cancer, like papilloma- and polyomaviruses. Using a new computational tool that his team developed, he and his colleagues uncovered thousands of previously unknown viruses, which they reported in *eLife*. Many of the virus sequences they discovered share little genetic makeup with others in the catalog of known viruses. Now researchers will be able to identify these viruses if they are present in tumors or other patient samples, a vital step for exposing their potential contributions to disease.

Buck and research fellow Michael Tisza, Ph.D., set out to find unidentified viruses by scouring vast numbers of genetic sequences, generated by sequencing DNA from a variety of animals, including worms, fish, cows and people. Each sample was a complex mix of DNA from the animals' own genomes and the genomes of the many microbes and viruses with which they coexist. Although much of the DNA in samples like these is presumed to come from viruses, it is usually impossible to decipher many of the sequences' exact origins.

Tisza used NIH's supercomputing resources to search these DNA sequences for elements that encoded virus-like features. To narrow the search, he focused on circular DNA molecules, which are carried by certain viruses but are rare in animals.

The hunt yielded more than 2,500 viral genomes. Many appear to come from viruses that infect bacteria, whose effects on the microbiome can have consequences for human and animal health. Many represent entirely new families of viruses, and some offer unexpected insights into viral evolution. The team tested some of the most unusual suspected viral sequences in the laboratory, using cells to translate the genetic code into proteins. The proteins assembled into particles resembling the outer shells that enclose viruses' genetic material, supporting the idea that the sequences indeed represent viral genomes.

To ensure that other researchers can recognize the newly discovered viruses, these sequences are now included in GenBank, an essential public database widely used for genetic studies. Furthermore, the researchers say that adding this information about previously absent or poorly represented viral families to the database will make it easier to find additional family members. To facilitate future searches, Buck and Tisza have made their tool for analyzing and annotating genomic sequences, called Cenote-Taker, freely available to the research community.

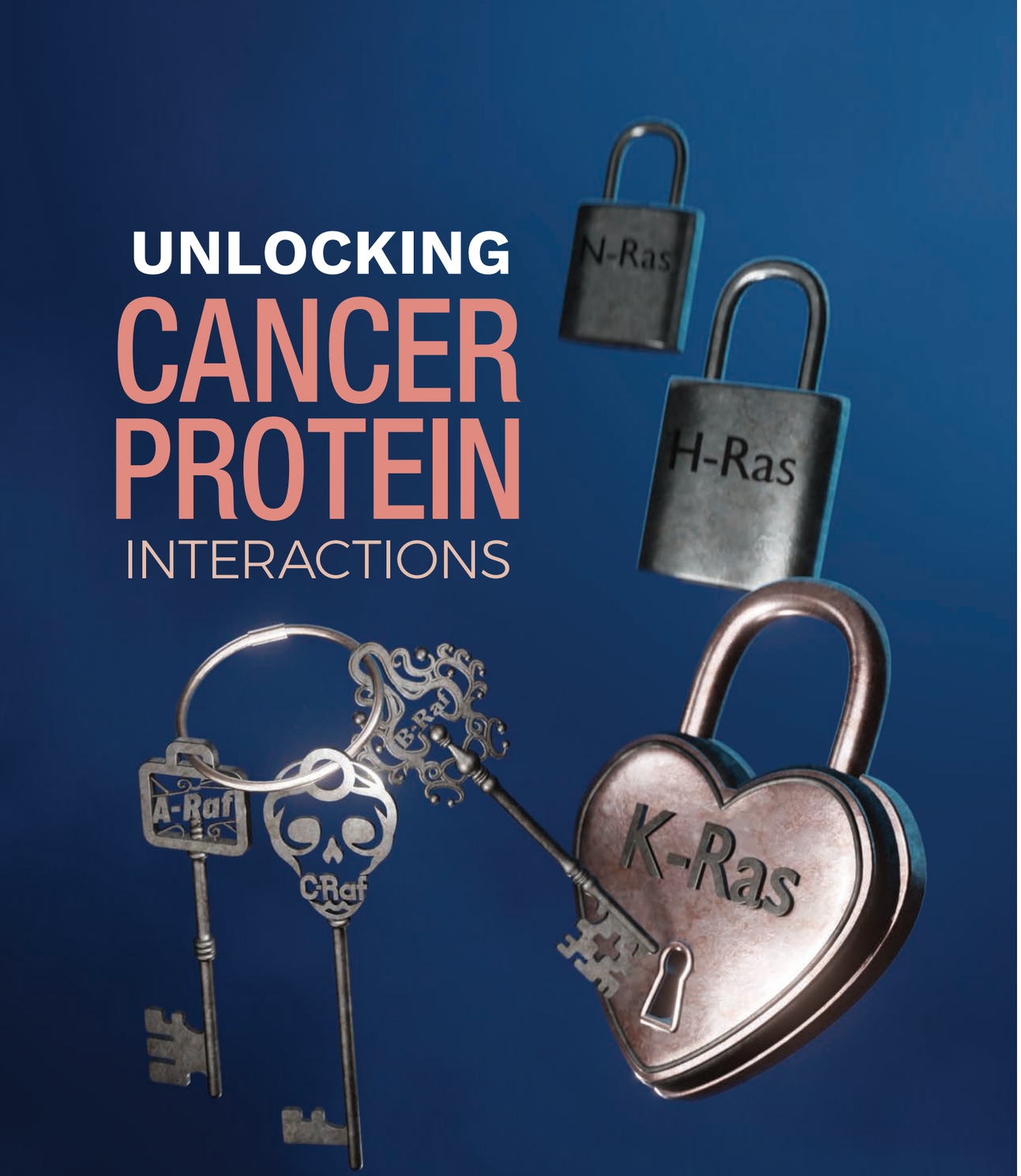
Buck and Tisza say that even after their discovery, the list of known viruses likely includes only a tiny fraction of those that exist in the world. They have already expanded their search and unearthed evidence of new viruses within additional sets of DNA sequences, including viruses that may be relevant to cancer.

Tisza MJ, et al. *Elife*. 2020 Feb 4;9:e51971.

A phylogenetic tree displays relationships between the sequences of capsid proteins, which form the outer shell of some types of viruses. Sequences identified by Christopher Buck, Ph.D., and his team are represented as green lines. Previously known sequences are represented as purple lines. Buck's tool for analyzing and annotating genomic sequences, called Cenote-Taker, is available at https://cyverse.org/discovery-environment.

***Credit:** Allen Kane, Scientific Publications, Graphics and Media, Frederick National Laboratory, NCI, NIH; iStock; Michael J. Tisza and Christopher B. Buck*

UNLOCKING CANCER PROTEIN INTERACTIONS



The Ras and Raf family members of proteins are depicted as locks and keys, respectively, to demonstrate how they interact with each other. Morrison and her team suggest that C-Raf is the skeleton key that binds all Ras family members with high affinity, whereas B-Raf exhibits a striking preference for K-Ras. The study helps explain why K-Ras *is the most commonly mutated* Ras *gene in human tumors and why certain* B-Raf *mutations often co-occur with* H-Ras *mutations in specific cancers. The findings suggest that Ras/Raf binding preferences need to be considered when treating patients.*

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

Within families of Ras/Raf proteins, individual preferences matter.

Deborah K. Morrison, Ph.D.
Chief
Laboratory of Cell and Developmental Signaling

Some of the most notorious proteins in cancer biology belong to a family of growth-promoting enzymes known as Ras. These proteins are essential for normal development, but when they become too active, they can drive excessive cell growth. Mutations in the genes that encode Ras proteins can send cells' growth-signaling pathways into overdrive and are thought to fuel more than 30 percent of human cancers.

Deborah Morrison, Ph.D., has long focused on understanding exactly how Ras proteins cooperate with signaling partners, known as Raf proteins, to drive cell growth. The fundamentals are well known: Ras proteins activate Raf proteins, which in turn trigger a cascade of signaling events that spur cell growth. But human cells have three different Ras proteins — H-Ras, K-Ras and N-Ras — and three different Raf proteins — A-Raf, B-Raf and C-Raf — and researchers have struggled to clarify each family member's particular role.

Morrison and Research Biologist Elizabeth Terrell, M.S., have now worked out exactly which of these proteins are most likely to interact with one another inside living cells. Their findings, reported in *Molecular Cell*, have implications for the treatment of patients whose cancers carry *Ras* or *Raf* gene mutations, as well as for understanding a group of rare developmental disorders caused by *Ras* gene mutations.

Until now, scientists have mostly used fragments of Ras and Raf proteins to study how these molecules interact. Morrison's team turned to a technique called bioluminescence resonance energy transfer (BRET) to instead monitor intact proteins' associations with one another inside living cells. Using BRET, which indicates when two proteins are in close proximity, the researchers were able to map out the binding preferences of each of the Ras and Raf proteins.

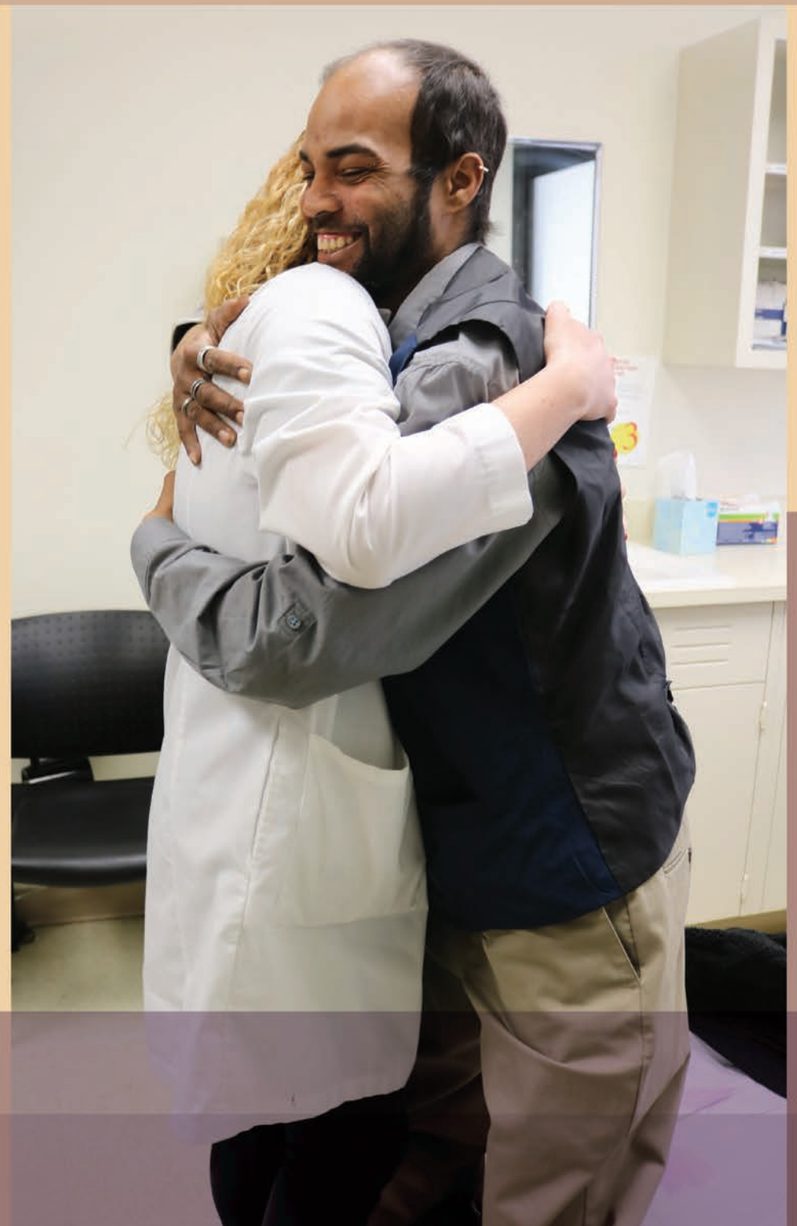
They found that B-Raf, which is the most potent activator of cell growth in the Raf family, binds readily to K-Ras but is much less likely to associate with other members of the Ras family. K-Ras, on the other hand, is able to bind to all of the Raf family members with high affinity. Morrison says these findings help provide an explanation for why *K-Ras* is the most commonly mutated *Ras* gene in human tumors and why certain *B-Raf* mutations often co-occur with *H-Ras* mutations in specific cancers.

The findings also shed light on how patients with mutations in certain *Ras* or *Raf* genes may respond to targeted therapies and suggests that Ras/Raf binding dynamics must be considered when treating patients. Binding preferences may explain, for example, why patients with melanoma have been found to be at risk of developing secondary, H-Ras-driven cancers if they are treated with drugs that inhibit B-Raf.

Finally, Morrison says her team's experiments demonstrated the power of BRET, not just to assess Ras/Raf interactions, but also to identify factors that either strengthen or interrupt them. They have begun using the method to search for small molecules that inhibit these interactions, with an eye toward developing new cancer treatments.

Terrell E, et al. *Mol Cell.* 2019 Dec 19;76(6):872-884.e5.

ONCE INFAMOUS,
NOW BENEFICIAL



Patient Brandon Lutrell greets Dr. Kathryn Lurain. Lutrell is a patient on the HIV and AIDS Malignancy Branch service with Kaposi sarcoma who has received pomalidomide. This photo was taken in March 2019 before the COVID-19 pandemic.

***Credit:** Lianne Priede, Center for Cancer Research, NCI, NIH*

A variation of a once-banned drug proves effective for patients living with AIDS-related Kaposi sarcoma.

Robert Yarchoan, M.D.
Chief
HIV and AIDS Malignancy Branch

First marketed in the late 1950s, thalidomide was widely prescribed to pregnant woman as a sedative to relieve morning sickness until tragedy struck. Although never approved in the United States, the drug was banned worldwide in the 1960s after thousands of babies were born with deformed limbs. Remarkably, since then, the drug has emerged as a treatment for leprosy as well as multiple myeloma.

Now, CCR investigators have shown that a derivative of thalidomide, known as pomalidomide (Pomalyst®), can treat Kaposi sarcoma, a rare cancer that grows on the skin as well as in lymph nodes, lungs and other regions of the body. In the U.S., about 2,000 people per year are diagnosed with the disease. Immunocompromised individuals, such as those with HIV, are most at risk.

In May 2020, the Food and Drug Administration (FDA) expanded the indication of pomalidomide. The expansion includes treatment of adult patients with AIDS-related Kaposi sarcoma that have not responded to highly active antiretroviral therapy as well as initial treatment of HIV-negative adult patients with Kaposi sarcoma. The approval was based on findings of a phase I/II clinical trial led by **Robert Yarchoan, M.D.**, that started enrollment in 2012.

Kaposi sarcoma patches consist of a class of blood vessel cells, known as endothelial cells, that grow uncontrollably. Yarchoan and his team hypothesized that thalidomide, which blocks blood vessel formation, could impact the disease. Their research showed that AIDS-related Kaposi sarcoma patients responded to thalidomide, but the side effects, which included fatigue and depression, outweighed the benefits, Yarchoan says.

Meanwhile, Yarchoan and his team had grown interested in less toxic derivatives of thalidomide which led them to pomalidomide. In collaboration with Celgene Corporation, now Bristol-Myers Squibb, they tested pomalidomide in Kaposi sarcoma in this phase I/II trial under a Cooperative Research and Development Agreement.

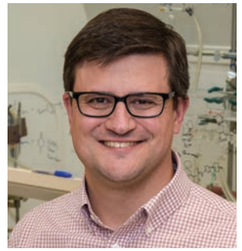
The trial ultimately led to FDA approval of pomalidomide for the treatment of Kaposi sarcoma. It enrolled 18 HIV-positive and 10 HIV-negative patients. Twelve of the HIV-positive patients had a complete or partial response to pomalidomide, which lasted an average of about one year. Eight of the HIV-negative patients had a complete or partial response, which lasted slightly less than a year, on average. In both groups, pomalidomide increased the number of T cells, an important class of immune cells destroyed by HIV. The treatment was well-tolerated, with relatively minor side effects, such as skin rash, vomiting and diarrhea.

Pomalidomide provides Kaposi sarcoma patients with a treatment option that is not only less toxic than chemotherapy, but also easier to administer. While other systemic drugs used to treat this cancer are delivered intravenously, pomalidomide is given orally, making it a more feasible option for people living in lower- and middle-income countries. The global AIDS Malignancy Consortium supported by NCI has recently begun testing pomalidomide for Kaposi sarcoma in Africa, where the disease is especially prevalent in young men.

www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-pomalidomide-kaposi-sarcoma

SWITCHING ON RNA

Learning how to design RNA-targeted therapeutics by manipulating a bacterial gene regulator.



John "Jay" Schneekloth Jr., Ph.D.
Senior Investigator
Chemical Biology Laboratory

One of life's most essential and versatile molecules, RNA, is best known as DNA's molecular messenger, relaying information encoded in the genome to the cellular machinery that builds proteins. However, only a small fraction of the RNA inside human cells plays that role. A vast assortment of additional RNAs perform a myriad of tasks that ultimately keep a wide range of cellular operations on track.

These activities exert a profound influence on health, and there is good evidence that dysregulation of RNA contributes to cancer and other diseases. Researchers expect that identifying ways to manipulate RNA molecules that contribute to disease could lead to a new generation of therapeutics.

John Schneekloth, Ph.D., is working to understand how small molecules interact with RNA. Collaborating with Adrian Ferré-D'Amaré, Ph.D., and colleagues at the National Heart, Lung, and Blood Institute (NHLBI), his team has engineered a molecule that potently activates a specific gene-regulating RNA found in bacteria. Their success, reported in *Cell Chemical Biology*, offers important clues into the discovery and design of molecules that interact with RNA targets and could point the way toward development of a novel class of antibiotics.

The synthetic molecule developed by the team targets a gene-regulating segment of RNA called a riboswitch. Riboswitches, which are found primarily in bacteria, act as cellular sensors that can be activated by small molecules, or ligands. When a riboswitch encounters and binds to its ligand, it adopts a new shape that changes the activity of its associated gene. Because they are more amenable to structural analysis than most other RNAs, riboswitches are useful models for understanding how RNA folds and interacts with other molecules, Schneekloth says.

Schneekloth and his colleagues set out to find a way to activate genes controlled by a group of riboswitches called ZTP riboswitches. They tested about 22,000 small molecules for their ability to bind to these switches and found some that did, but none that had the potent effects they were hoping for. So they tried a new strategy: if they couldn't find a molecule that strongly activated the riboswitch, they would make one.

Rather than starting from scratch, the team turned to the riboswitch's natural ligand, a metabolite called ZMP, and reengineered it. To guide their modifications of the natural molecule, NHLBI fellow Christopher Jones, Ph.D., generated a detailed structure of a ZMP-bound riboswitch. That structure revealed exactly how the metabolite nestles inside the folded RNA and suggested places for the team to tinker with ZMP to improve the interaction.

When the researchers administered their synthetic ligand to bacteria, it stimulated the activity of the ZTP riboswitch's target genes more potently than the natural ligand. The achievement represents a new way to engineer molecules that can control gene expression in bacteria. More broadly, it also gives researchers a deeper understanding of how to target not just riboswitches, but other types of RNA. This could help guide the development of new therapeutics that interact with RNA molecules to treat cancer and other diseases.

Tran B, et al. *Cell Chem Biol*. 2020 Oct 15;27(10):1241-1249.e4.

CCR scientists are developing small molecules that target RNA. This figure highlights a molecule interacting with a bacterial riboswitch that controls gene expression. Studying systems like this can provide the basis for developing new RNA-binding drugs.

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

GETTING IT JUST RIGHT

An adjusted chemotherapy regimen provides a less toxic treatment option for adults with Burkitt lymphoma.

Wyndham Wilson, M.D., Ph.D.
Senior Investigator
Lymphoid Malignancies Branch

Burkitt lymphoma is a rare, highly aggressive cancer that arises in a class of immune cells known as B cells. The cancer can affect the central nervous system, kidneys, bowels and other organs and is more common in children as well as in people who live with HIV. The disease is curable with high-dose chemotherapy, which was originally developed for use in children with the disease. Unfortunately, the standard high-dose treatment is often intolerable in adults, and thus may not be an option for older patients or those with serious health conditions, including HIV. The high-dose treatment can cause severe cardiovascular and neurological side effects in adult patients, who typically require hospitalization throughout the course of treatment, which can last several months.

In a multicenter phase II clinical trial, reported in the *Journal of Clinical Oncology*, a team led by **Wyndham Wilson, M.D., Ph.D.**, has shown that a less toxic chemotherapy regimen using low-dose treatment with individualized dosing is effective for adults with Burkitt lymphoma, regardless of their age or HIV status. Known as dose-adjusted (DA)-EPOCH-R, the regimen involves infusing chemotherapy drugs in several cycles of 96 continuous hours. Dosing in subsequent cycles is adjusted higher only if patients are able to tolerate it.

Wilson developed DA-EPOCH-R for Burkitt lymphoma after cell culture experiments in diffuse large B-cell lymphoma lines revealed that prolonged, low-dose exposure to chemotherapy drugs outperformed brief, high-dose exposure in rapidly proliferating lymphoma cells. His team hypothesized that the regimen might prove effective and indeed, after an average follow-up of about seven years, all 19 adults with Burkitt lymphoma who underwent DA-EPOCH-R in a 2013 pilot study survived, and almost none showed disease progression.

To validate these results, Wilson, Senior Clinician Mark Roschewski, M.D., and Staff Clinician Kieron Dunleavy, M.D., tested the regimen in their phase II trial in 113 patients at 22 cancer centers. The overall survival rate was 87 percent, with DA-EPOCH-R proving effective for people across all age groups and independent of HIV status. Nearly 85 percent of patients showed no signs of cancer after an average follow-up of about five years, and few experienced the side effects often seen with high-dose chemotherapy.

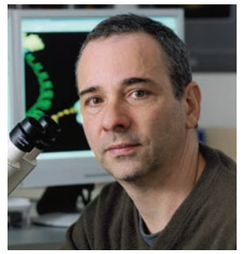
These findings have major treatment and quality-of-life implications for adults with Burkitt lymphoma. Roschewski points out that DA-EPOCH-R is now used to treat diffuse large B-cell lymphomas, and unlike with dose-intensive chemotherapy, this treatment can be given in an outpatient setting. This more gentle, yet still effective regimen can help patients avoid months of inpatient hospitalization and allow them to work and largely continue with their day-to-day lives.

Roschewski M, et al. *J Clin Oncol*. 2020 Aug 1;38(22):2519-2529.

Pictured is a thin slice of Burkitt lymphoma tissue as seen through a microscope. Researchers found low-dose chemotherapy treatment effective for adults with Burkitt lymphoma, regardless of their age or HIV status.

Credit: *Getty Images. Image by Steve Gschmeissner/SPL*

Long, repetitive sequences distort DNA and create a unique vulnerability in cancer cells.



André Nussenzweig, Ph.D.
Chief
Laboratory of Genome Integrity

Some cancers are particularly prone to accumulating genetic mutations due to failures in the DNA repair systems that cells use to find and fix errors in the genetic code. Although DNA damage is unavoidable, when repair systems fail and damage persists, the consequences can be dire.

Certain DNA repair problems lead to a condition called microsatellite instability in which mutations accumulate in microsatellites, which are regions of the genome where short segments of genetic code are repeated many times. Microsatellite instability contributes to the development of various cancers, including some colorectal, ovarian, endometrial and stomach cancers.

While microsatellite instability has typically been linked to small changes in repetitive regions of the genome, **André Nussenzweig, Ph.D.**, and colleagues have discovered that these changes can be much larger in scope, expanding into stretches of disrupted DNA that are long enough to contort the genome into problematic shapes.

Their findings, reported in *Nature*, help explain a unique feature among cancers with microsatellite instability: their dependence on a DNA-unwinding enzyme called WRN. Most cells can survive without WRN, but when cancer cells with microsatellite instability lose WRN, they die.

When Nussenzweig's team examined microsatellite-unstable cancer cells, which develop widespread breakage in their DNA when WRN is missing, they discovered thousands of breaks at spots in the genome where the letters T and A were repeated over and over again. Sophisticated DNA sequencing technology was needed to detect this previously unrecognized type of microsatellite instability since standard methods cannot be used with highly repetitive DNA.

The team's experiments suggest that these long stretches of repetitive sequences distort the shape of DNA molecules inside cancer cells with microsatellite instability. This presents a physical obstruction to the enzyme that travels along a DNA strand when it tries to replicate the code into a second copy in preparation for cell division.

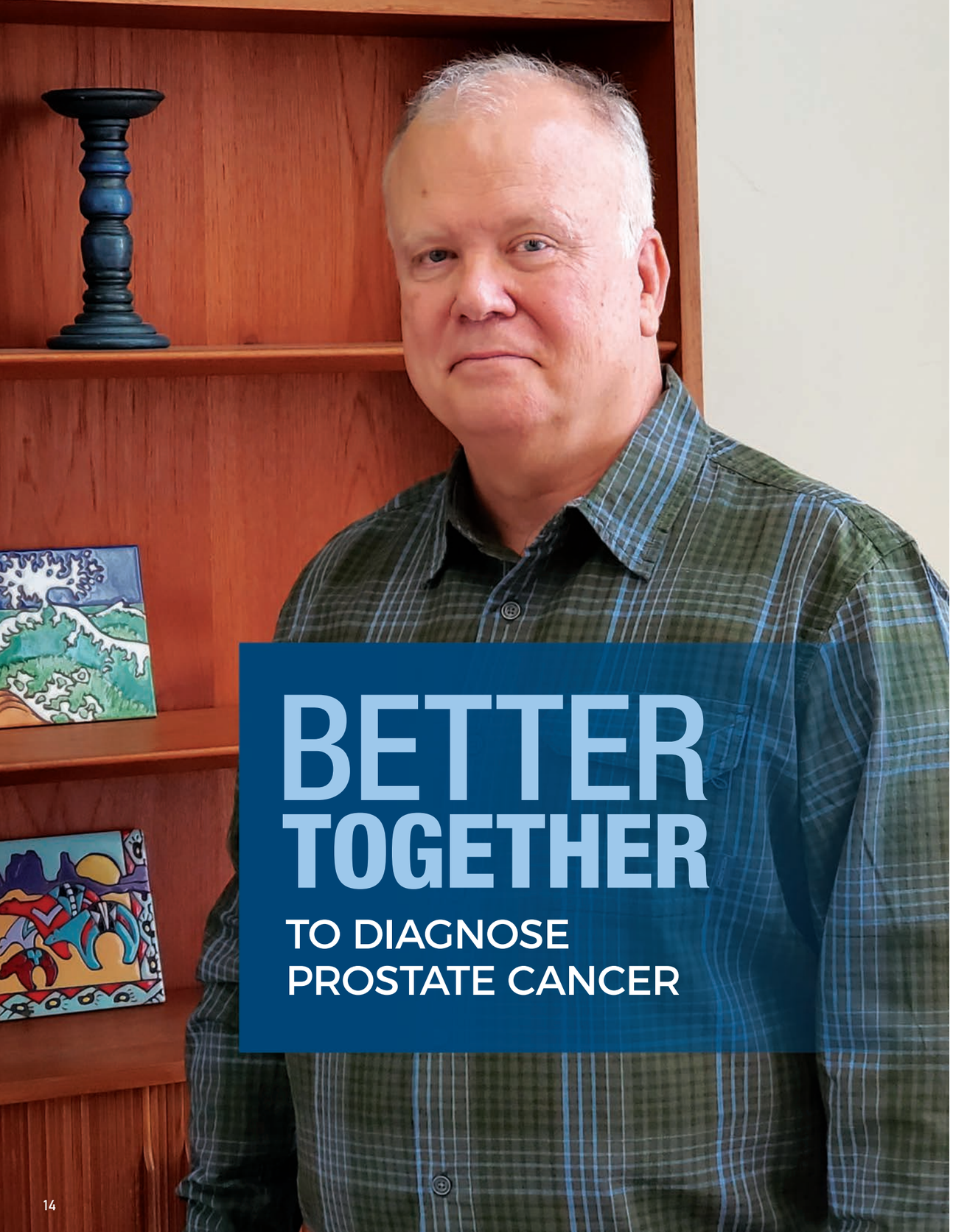
Based on their findings, the researchers propose that when DNA replication stalls at these sites, WRN can alleviate the obstruction by unwinding the tangled DNA. But without WRN, the blockage remains until another enzyme comes along and clips apart the DNA. In microsatellite-unstable cancer cells with long stretches of TA repeats, the absence of WRN leads to thousands of DNA breaks. The long strands of DNA that make up the chromosomes are shattered, and the cancer cells ultimately die.

It may now be possible to exploit this vulnerability and to develop drugs that inhibit the WRN enzyme. Nussenzweig says such drugs might be very effective at stopping the growth of microsatellite-unstable tumors, either alone or in combination with other therapies.

van Wietmarschen N, et al. *Nature*. 2020 Oct;586(7828):292-298.

Cancers with microsatellite instability depend on a DNA-unwinding enzyme called WRN. Without the enzyme, cancer cells die. The shattered plates represent the thousands of breaks at spots in DNA, specifically where T and A are repeated, that occur because of a lack of WRN in microsatellite-unstable cancer cells.

Credit: *iStock*



BETTER TOGETHER

TO DIAGNOSE PROSTATE CANCER

A combined biopsy method leads to more accurate prostate cancer diagnoses.

Peter A. Pinto, M.D.
Investigator
Urologic Oncology Branch

Early and accurate detection is often the key to successful treatment of cancers. Traditional biopsy techniques for men at risk for prostate cancer are limited and can lead to both under- and overtreatment. Researchers led by **Peter Pinto, M.D.**, have developed a new method that more accurately diagnoses prostate cancer, as described in the *New England Journal of Medicine*.

Prostate cancer can vary vastly in how fast it grows and spreads. Low-grade prostate cancer is associated with a low risk of cancer-specific death; higher grades spread more aggressively and are more lethal. Given this range of severity, the correct assessment of cancer grade is critical to guiding treatment.

The current primary diagnostic method for prostate cancer involves prostate-specific antigen screening, and if levels are elevated, a traditional systematic biopsy. Strategically spaced core-needle samples are taken from throughout the prostate gland in a manner that is "blind" to the tumor's location and are biopsied. Since these traditional systematic biopsies can miss tumors, doctors may overtreat patients with low-grade disease as a precaution against aggressive cancer that might have escaped detection. They may also undertreat patients with high-grade disease whose tumors are missed upon sampling. An alternative is MRI-targeted biopsy, which detects high-grade tumors better than traditional systematic biopsy.

The approach developed at CCR combines traditional systematic biopsy with MRI-targeted biopsy to yield the best of these two methods.

The study included over 2,000 men who received both systematic and MRI-targeted biopsies. Of this total, just over half were diagnosed with prostate cancer, and 404 underwent radical prostatectomy to completely remove the prostate. Pinto's team, including clinical fellow Michael Ahdoot, M.D., and Senior Clinician Ismail Baris Turkbey, M.D., found that combined biopsy led to 208 more cancer diagnoses and 458 upgrades in diagnosis to more aggressive cancer than either test alone.

They then evaluated the tumors of men who underwent radical prostatectomy to compare the grades assigned by systematic, MRI-targeted and combined biopsies against those determined by analyses of their prostate tissue after surgery.

Systematic biopsy alone underdiagnosed about 40 percent of cancers, and MRI-targeted biopsy alone underdiagnosed about 30 percent of the cancers, while combined biopsy underdiagnosed 14.4 percent of the cancers. When it came to diagnosing the most aggressive cancers, systematic biopsy underdiagnosed 16.8 percent and MRI-targeted biopsy underdiagnosed 8.7 percent of the most aggressive cancers, while combined biopsy missed only 3.5 percent of the most aggressive cancers.

The findings show that combined biopsy leads to more accurate diagnoses than MRI-targeted biopsy alone. MRI-targeted biopsy, although a vast improvement over the traditional systematic biopsy, may still leave some aggressive tumors undetected, Pinto explains. However, the addition of systematic biopsy can catch these misses.

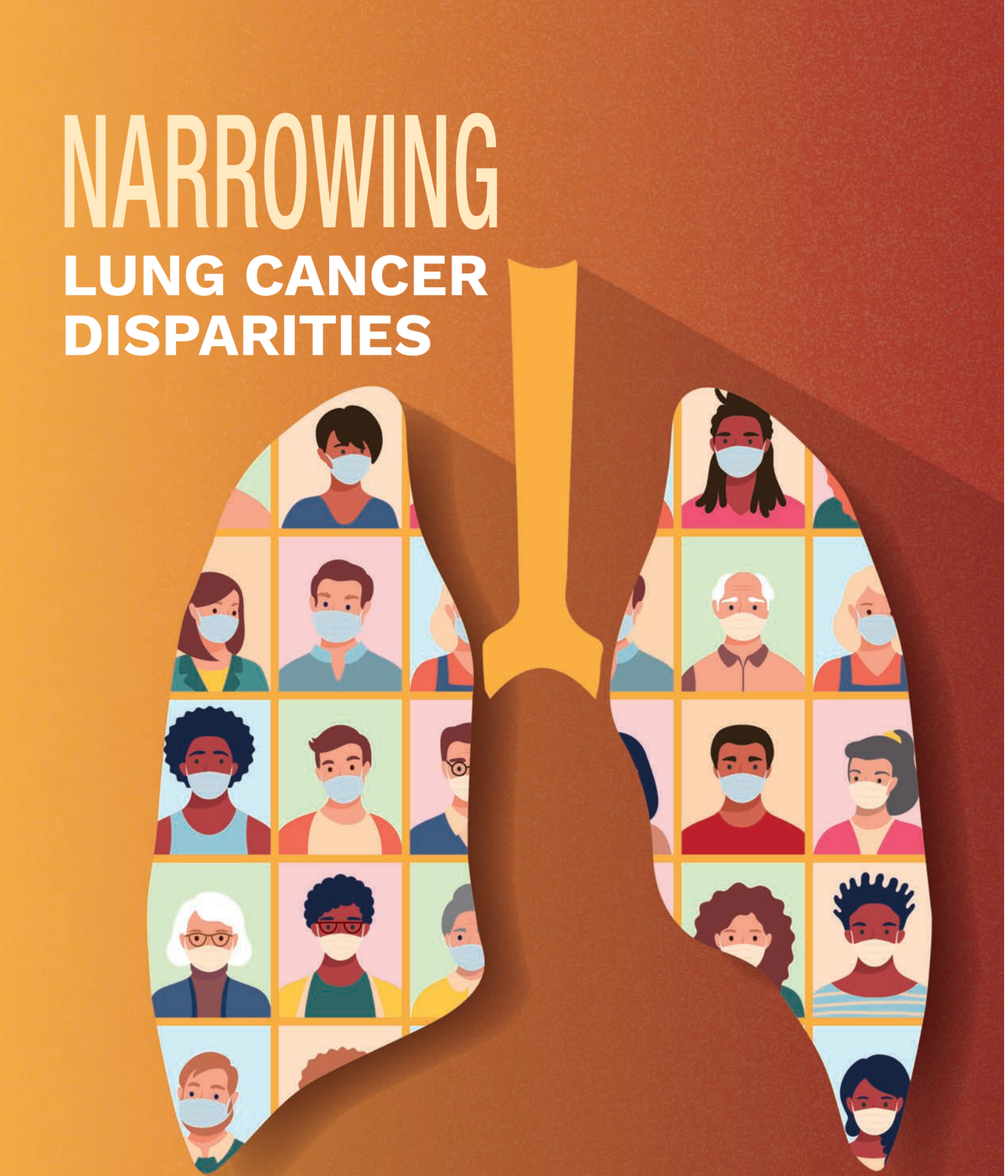
Pinto and his CCR colleagues spent more than 15 years developing the medical device to perform MRI-targeted prostate biopsies in collaboration with Philips Medical. The device is now commercially available.

Ahdoot M, et al. *N Engl J Med*. 2020 Mar 5;382(10):917-928.

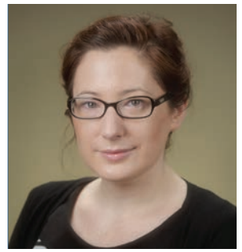
Jack Bilby, 69, underwent four separate systematic biopsy sessions between 2004 and 2013. Each yielded negative results yet his levels of prostate-specific antigen, often elevated in men with prostate cancer, continued to climb. After his fourth biopsy procedure, his urologist told him he could undergo the same biopsy a fifth time or enroll in Dr. Pinto's clinical trial. Bilby chose the latter. MRI-targeted biopsy located a tumor on the anterior side of the prostate, inaccessible to the prior biopsies, and confirmed an aggressive cancer that had grown to nearly one-third the size of his prostate. He underwent a radical prostatectomy at the NIH Clinical Center in 2014. Seven years later, he remains cancer-free. "If it wasn't for the NIH and their program, I don't know that I would have had such a positive outcome," Bilby says. "I was just so happy that it was able to be found, to be removed, and I could have a chance at continuing to have a normal life."

Credit: *Jack Bilby*

NARROWING
LUNG CANCER DISPARITIES



Deficiencies in DNA repair may lead to higher cancer rates in African Americans diagnosed with a type of lung cancer.



Bríd M. Ryan, Ph.D., M.P.H.
NIH Stadtman Investigator
Laboratory of Human Carcinogenesis

Lung cancer is the second most common cancer in the United States and the leading cause of cancer-related death. African Americans have the highest incidence and death rates from the disease when compared to other racial or ethnic groups, even after exposure to smoking is taken into account. The underlying causes of this disparity are complex and cannot be addressed until they are fully understood.

As part of CCR's growing commitment to address health disparities, **Bríd Ryan, Ph.D., M.P.H.**, raises the possibility, in a study published in *Nature Cancer*, that ancestry-related differences in genomic instability and homologous recombination deficiencies (HRD) may contribute to higher incidence and mortality in non-small cell lung cancer in African Americans compared to European Americans.

Homologous recombination is a mechanism for repairing DNA damage. Deficiencies in this mechanism result in DNA repair errors and consequently greater genomic instability, which is often related to a high frequency of mutations and other genome changes that favor cancer to develop.

Ryan, along with predoctoral fellow Sanju Sinha, B.S., and postdoctoral fellow Khadijah Mitchell, Ph.D., M.S., used advanced sequencing analysis to comb through the genomes of 222 non-small cell lung cancer tumor samples. They found significantly higher genomic instability and HRD in tumors from African Americans than in tumors from European Americans. These trends held up in several other cancer types, including invasive breast and head and neck cancers.

Normal cells from African Americans with squamous cell carcinoma, a skin cancer, also had a higher rate of mutations in genes associated with HRD, which may explain the observed genomic instability. Future research will test whether people who have these mutations are more likely to develop the disease.

The results may have therapeutic implications. Tumors with higher HRD are particularly susceptible to drugs known as PARP inhibitors — already used to treat breast, prostate and other cancer types — which suggests that they might be more effective in African Americans with squamous cell carcinoma.

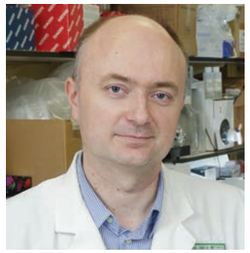
Therapeutic advances have been based largely on tumor samples from European Americans, but their efficacy may differ in underrepresented populations. Ryan's study helps fill a knowledge gap on tumor biology in African Americans, and the findings underscore the need to include racial and ethnic minorities in cancer genomics research and clinical trials. Through her work, Ryan and her colleagues want to ensure that any future advances in precision medicine benefit all populations.

Sinha S, et al. *Nat. Cancer.* 2020 Jan 13;1(1):112-121.

Biological factors may contribute to why African Americans experience higher incidence and death rates from lung cancer than other racial and ethnic populations. In this study, tumors from people with African ancestry and European ancestry, depicted in this image, were analyzed to better understand disparities in lung cancer.

Credit: *Allen Kane, Scientific Publications, Graphics and Media, Frederick National Laboratory, NCI, NIH; iStock*

Turning tumor-protecting immune cells into killer cells can strengthen the body's fight against cancer.



Udo Rudloff, M.D., Ph.D.
Senior Investigator
Pediatric Oncology Branch

Revolutionary cancer immunotherapies have become a successful strategy for treating certain cancers, but they are not effective for everyone. To extend their benefits to more patients, **Udo Rudloff, M.D., Ph.D.**, is developing a new type of immunotherapy that reprograms immune cells that normally interfere with treatment to instead join the anti-cancer fight.

The new therapeutic strategy, reported in *Science Translational Medicine*, emerged from studies in which Rudloff and his collaborators at Tuskegee University in Alabama became interested in small molecules called host defense peptides. These small peptides help protect a wide range of organisms, from fungi to humans, against infection and other threats. There was reason to believe that drugs that mimic their function might be useful for treating disease, Rudloff says.

To zero in on the most important features of host defense peptides, Rudloff and his collaborators began by searching for elements that are widely shared within this group of molecules. They examined the makeup of more than 2,000 host defense peptides, looking for short segments whose building blocks, or amino acids, shared certain physical properties such as charge and size. After identifying one such segment, the team engineered a synthetic version they named RP-182 and then tested its effect on immune cells.

The results were dramatic. When treated with the synthetic peptide, tumor-protecting immune cells, called M2 macrophages, transformed into cancer cell killers. After adding the peptide to the macrophages in laboratory dishes, Rudloff and colleagues watched as the reprogrammed immune cells approached cancer cells and then consumed them, completely engulfing them in a process known as cancer cell phagocytosis.

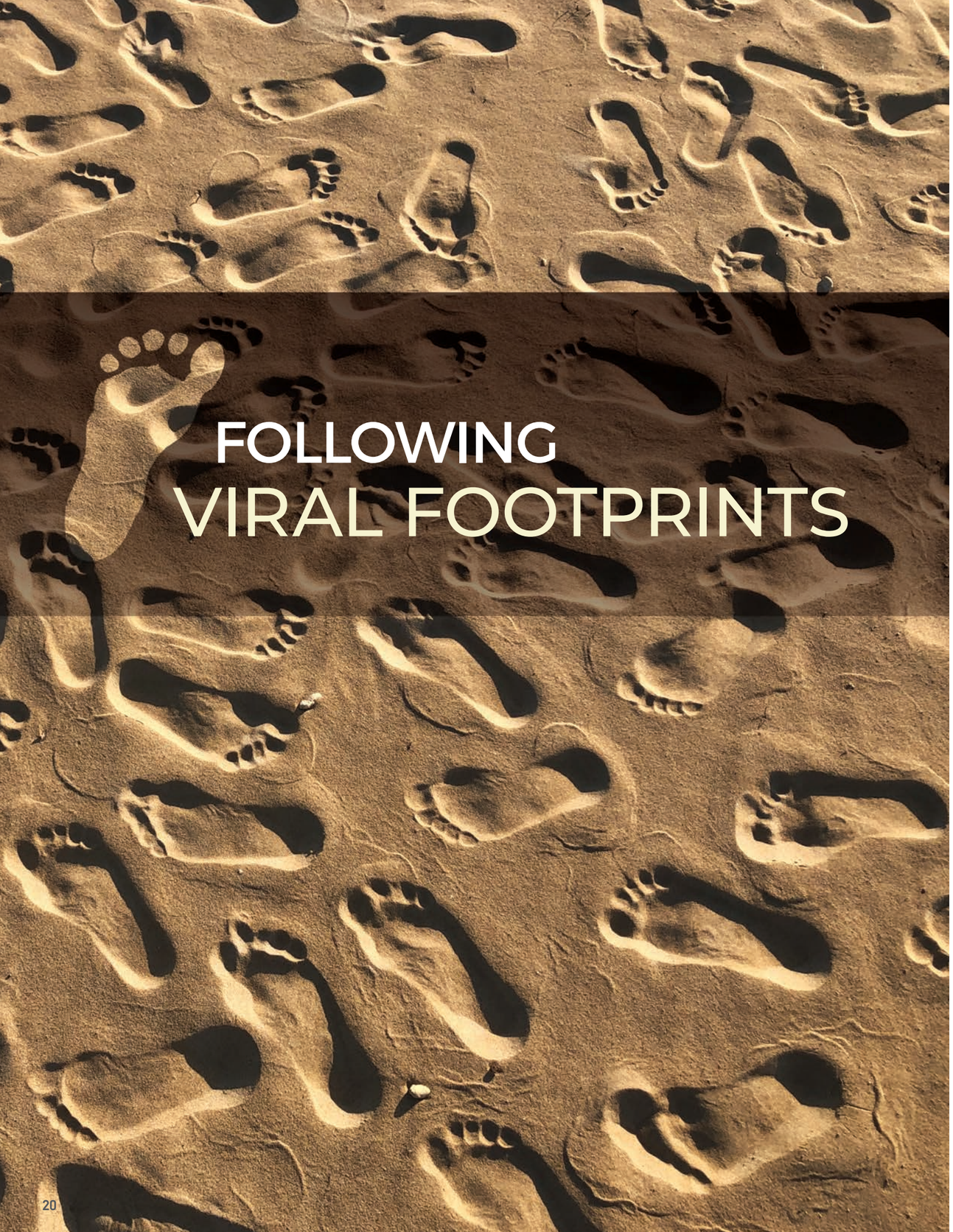
The peptide also showed promising results when administered to several different mouse models of cancer, including pancreatic, colon, breast, prostate and melanoma. The treatment not only converted immunosuppressive macrophages into cancer fighters, it also reduced the presence of other immunosuppressive cells in the tumor environment and enhanced other cancer-fighting immune cells. The result was an overall shift in immune response that suppressed tumor growth and extended the animals' lives.

Working with colleagues at Tuskegee University and NIH's National Center for Advancing Translational Sciences, Rudloff's team traced these effects to RP-182's activation of a protein on the surface of macrophages called CD206. The findings suggest that drugs that activate the CD206 receptor may be an effective way to reprogram a patient's immune system and reduce tumor growth. This new strategy in immunotherapy may also be useful for treating other diseases in which inflammation and macrophages play a role, including diabetic eye disease and fibrosis of the lungs.

Jaynes J, et al. *Sci Transl Med*. 2020 Feb 12;12(530):eaax6337.

A similar chain of amino acids exists in many species, from the honeybee to humans. Researchers replicated this sequence and developed a synthetic peptide called RP-182 that is now a template for a new class of cancer drugs. The Molly wheel, pictured here, is a code used to identify this conserved chain. The code explains the biophysical and chemical properties of each amino acid, including their size, charge and the energies required to move them. The color indicates if an amino acid is hydrophobic or hydrophilic.

Credit: *Allen Kane and Joseph Meyer, Scientific Publications, Graphics and Media, Frederick National Laboratory, NCI, NIH; iStock; Jesse M. Jaynes and Udo Rudloff*



FOLLOWING VIRAL FOOTPRINTS

A new blood test measures lifetime virus exposure to help predict risk of developing liver cancer.

Xin Wei Wang, Ph.D.
Deputy Chief
Laboratory of Human Carcinogenesis

The most common type of liver cancer is hepatocellular carcinoma (HCC). This deadly disease has limited treatment options, and death rates are increasing rapidly in the United States. Various factors, including hepatitis B and C, obesity, fatty liver-related chronic liver disease and cirrhosis elevate the risk of HCC. Individuals with these risk factors are advised to undergo ultrasound screening for HCC every six months with or without a blood test that looks for a tumor marker known as alpha-fetoprotein (AFP).

This screening method has limitations, however. Not everyone at high risk for HCC develops the disease, and long-term outcomes for HCC patients remain poor regardless of whether patients get screened. Most are diagnosed once their cancer has already reached an advanced stage.

Now, a team led by **Xin Wei Wang, Ph.D.**, has developed a screening method to help identify those most at risk of developing HCC based on their past exposure to certain viruses. The method predicts HCC risk more accurately than an AFP test and up to a decade earlier, the researchers reported in *Cell*.

Cancer screening methods typically detect specific features of tumor cells. The problem is, these cells constantly change, and even cells within a given tumor can differ vastly. Instead, Wang, together with postdoctoral fellow Jinping Liu, Ph.D., and Associate Scientist Wei Tang, Ph.D., focused on interac–tions between viruses and the immune system, which growing evidence suggests can influence the development of cancer. They hypothesized that viral infections a patient may experience over their lifetime may reflect the immune system's ability to destroy cancer cells and thus provide a window into when early onset of HCC could occur.

To test this paradigm shift, they used a blood test known as VirScan™, which detects antibodies churned out by the immune system in response to past infections with viruses and other foreign invaders. Analyzing blood samples from about 900 people at high risk of HCC, they identified a set of antibodies specific to 61 viruses. The presence or absence of each virus in the blood samples revealed "footprints" of viral exposure which, when combined, could accurately differen-tiate between people with and without HCC.

Next, they tested this viral exposure signature on blood samples from chronic liver disease patients enrolled under a long-term surveillance program, with some people eventu-ally diagnosed with HCC. When they used samples collected at the time of cancer diagnosis, they identified those who had developed HCC with near-perfect accuracy. They also identified these individuals from blood samples collected up to 10 years prior to diagnosis.

The findings suggest that along with current screening methods, the viral exposure signature can predict who is most at risk of developing HCC. This could help detect and treat the disease earlier, when it is more likely to be cured.

Wang and his team are testing their screening method in multiple clinical trials, including prospective studies to vali-date the test's ability to predict if high-risk individuals will go on to develop HCC and whether the test provides a survival benefit. They also plan to investigate whether they can apply their approach to other types of cancer, such as esophageal, biliary, pancreatic, colon and stomach.

Liu J, et al. *Cell*. 2020 Jul 23;182(2):317-328.e10.

This image represents the viral "footprints" left behind in a person's blood by antibodies produced from past viral infections. The footprints create a unique pattern in each person known as a viral exposure signature. By examining blood samples for viral footprints, researchers were able to identify who was at risk of developing the most common type of liver cancer, hepatocellular carcinoma.

Credit: *iStock*

A FIRST FOR KIDS WITH NF1

A new drug shrinks tumors and improves quality of life in children.

Brigitte C. Widemann, M.D.
Chief
Pediatric Oncology Branch

Plexiform neurofibromas are tumors which grow along nerves and occur in approximately 50 percent of children with the genetic disorder neurofibromatosis type 1 (NF1). Many plexiform neurofibromas grow relentlessly during early childhood, cannot be removed by surgery and result in severe problems including disfigurement, chronic pain, breathing difficulties and other symptoms depending on the tumor location. Until recently, there was no effective medical treatment for plexiform neurofibromas.

In a phase II multicenter trial led by **Brigitte Widemann, M.D.**, the drug selumetinib (Koselugo™) shrank NF1-associated plexiform neurofibromas in the majority of patients and often reduced pain and improved overall quality of life. Based on the findings published in the *New England Journal of Medicine*, the Food and Drug Administration approved selumetinib for children two years and older with NF1 and symptomatic, inoperable plexiform neurofibromas.

These results are the culmination of research that started 30 years ago with the identification of the gene causing NF1. Starting in 2000, Widemann and colleagues followed patients with NF1 to understand the progression of the disease. They also conducted trials with various drugs hoping to stop the growth of these tumors or shrink them. However, they were unsuccessful until their phase I trial of selumetinib showed tumor shrinkage in 17 of 24 patients.

The subsequent phase II trial of selumetinib was designed to confirm tumor shrinkage and to assess if children had clinically meaningful benefit. This trial enrolled 50 children, ages three to 18, between 2015 and 2016. Plexiform neurofibromas shrank by 20 percent in size in 68 percent of patients, which was sustained for at least one year in 56 percent of patients. In addition to reduced pain, children and their parents reported an improvement in range of motion, strength and airway function. Some patients were even able to stop taking pain medications altogether, says Assistant Research Physician Andrea Gross, M.D.

Plexiform neurofibromas have been very challenging to treat. Selumetinib provides the first approved medical therapy for these tumors. Widemann and colleagues are currently developing a trial to determine whether administering selumetinib earlier can prevent severe symptoms in the first place. She says CCR's commitment to rare diseases and high-risk, long-term projects allowed her team to thoroughly characterize the growth of NF1 tumors and to identify selumetinib as a promising drug candidate.

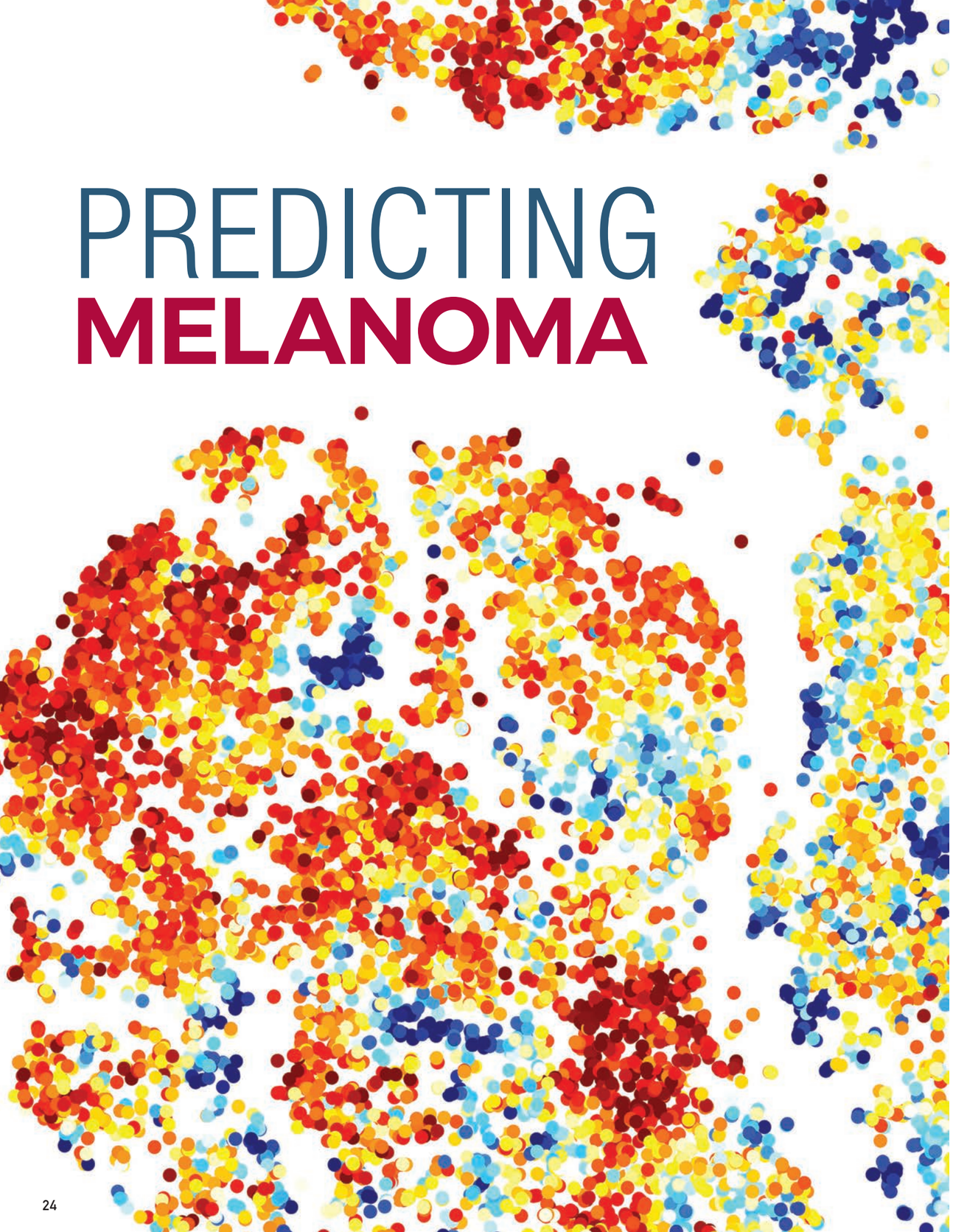
As is often the case in bringing new drugs to patients, this effort was highly collaborative. The NCI Cancer Therapy Evaluation Program sponsored the phase I and II selumetinib trials under a Cooperative Research and Development Agreement with AstraZeneca. Patients were enrolled at four centers, and the Neurofibromatosis Therapeutic Acceleration Program and the Children's Tumor Foundation supported aspects of trial conduct at participating sites. Widemann and her colleagues are especially grateful to the children and families who participated in the selumetinib and prior trials for NF1 plexiform neurofibromas.

Gross AM, et al. *N Engl J Med*. 2020 Apr 9;382(15): 1430–1442.

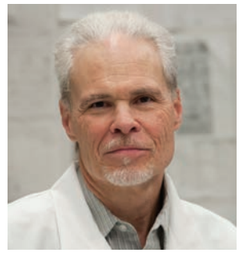
Autumn Schierling was diagnosed with NF1 shortly after birth. She was enrolled in her first NCI clinical trial with the Pediatric Oncology Branch when she was just 21 months old. After a year of treatment, there was no change in her tumor. She began the phase II clinical trial with selumetinib in 2015. That treatment led to shrinkage of her tumor and has since allowed her to open her right eye more fully. She continues taking selumetinib to this day and makes regular visits to the NIH. Both she and her mother, Lindsay Revenew, pictured here at the Children's Inn at NIH in Bethesda, Maryland, feel that the tumor is softer and smaller than when she started treatment. "We are so proud of her," Revenew says. "It's a big deal to be a part of something that actually got approved, and now other people will be able to benefit. That's something that's been pretty awesome for our family."

Credit: *Getty Images; photo by Marvin Joseph/*The Washington Post

PREDICTING MELANOMA



New mouse models recreate the diversity found in human melanomas.



Glenn Merlino, Ph.D.
Senior Investigator
Laboratory of Cancer Biology and Genetics

A form of immunotherapy that releases the natural brakes on the immune system has become the first-line treatment for metastatic melanoma. The treatment uses a group of drugs called immune checkpoint inhibitors to boost the body's ability to destroy tumors and to stop the spread of some aggressive cancers. They do not work for most melanoma patients, however, and clinicians need better tools to predict how individuals with this deadly cancer will respond to these treatments.

Led by CCR's **Glenn Merlino, Ph.D.**, a team of scientists has spent more than a decade developing and characterizing mouse models that replicate key features of human melanoma. Because no single model can capture the biological and clinical diversity of melanomas seen among patients, Merlino's team assembled a set of four mouse models and used them in combination to study immunotherapy responses, as they reported in *Nature Medicine*.

While the four models are genetically very similar, differences in cancer-promoting gene mutations and immune system composition make each model distinct. Their responses to immunotherapy reflect the variations seen in outcomes among patients with metastatic melanoma, where only about a third respond to checkpoint inhibitors like pembrolizumab (Keytruda), nivolumab (Opdivo) and ipilimumab (Yervoy). Immune checkpoint inhibitors slowed or blocked tumor growth in two of the models but were ineffective in the other two.

By comparing mice that responded to these treatments to those that did not, postdoctoral fellow Eva Pérez-Guijarro, Ph.D., found that many of the genes most strongly associated with immunotherapy outcomes were involved in the development of melanocytes, the pigment-producing cells from which melanoma begins. The more closely the activity of 45 key genes resembled that of melanocytes' precursor cells, rather than that of fully developed melanocytes, the less likely a tumor was to respond to immune checkpoint inhibitors.

The team examined the activity of this same set of genes in clinical data and found that this relationship held true among patients. Those whose melanoma responded best to immunotherapy had gene activity in their tumors that paralleled that of mature melanocytes, as seen in the mice. This suggests that monitoring the activity of these developmental genes, particularly when combined with other biomarkers of immunotherapy response, might help clinicians predict which patients will respond to immune checkpoint inhibitors.

Beyond their potential to identify the best candidates for existing immunotherapies, the findings also offer hope that it may be possible to develop more effective treatments that make melanoma cells more sensitive to immune checkpoint inhibitors by pushing them toward a more mature developmental state.

Pérez-Guijarro E, et al. *Nat Med*. 2020 May;26(5):781-791.

This image exemplifies the diversity of the immune cells found within tumors among four mouse models that replicate key features of human melanoma. The level of expression of an immune checkpoint marker (PD-1) on each cell, represented as dots in the image, was measured by a technique known as high parametric flow cytometry and is shown in a colored scale where darker red indicates higher expression of PD-1 and darker blue indicates the lower expression.

Credit: *Allen Kane, Scientific Publications, Graphics and Media, Frederick National Laboratory, NCI, NIH; Romina E. Araya*

New Faculty

Grégoire Altan-Bonnet, Ph.D.

Grégoire Altan-Bonnet, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Integrative Cancer Immunology. Dr. Altan-Bonnet and his team develop actionable models of the immune system and its response to cancer, with the goal of designing and optimizing new immunotherapies.

Christina M. Annunziata, M.D., Ph.D.

Christina M. Annunziata, M.D., Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Women's Malignancies Branch. Dr. Annunziata translates bench research to clinical trials focusing on mechanisms underlying NF-kappaB molecular signal transduction in ovarian cancer.

Erin L. Davies, Ph.D.

Erin L. Davies, Ph.D., has joined the Cancer and Developmental Biology Laboratory as a Stadtman Tenure-Track Investigator. She is investigating the embryonic origin and regulation of adult pluripotent stem cells required for tissue maintenance, whole-body regeneration and reproduction in planarian flatworms.

Thomas Gonatopoulos-Pournatzis, Ph.D.

Thomas Gonatopoulos-Pournatzis, Ph.D., has joined the RNA Biology Laboratory as a Stadtman Tenure-Track Investigator and is a member of the NIH Distinguished Scholars Program. His lab utilizes functional genomics to uncover RNA regulatory mechanisms that underlie cell fate decisions and how disruption of these processes contribute to disease states.

Christian S. Hinrichs, M.D.

Christian S. Hinrichs, M.D., was awarded tenure at NIH and appointed to Senior Investigator in the Genitourinary Malignancies Branch. Dr. Hinrichs discovered personalized cellular and gene therapies for HPV+ cancers and researched immunotherapy for HPV+ cancers including cervical, oropharyngeal, anal, vulvar, vaginal and penile malignancies.

Kazusa Ishii, M.D., M.P.H.

Kazusa Ishii, M.D., M.P.H., has joined the Genitourinary Malignancies Branch as part of CCR's Physician-Scientist Early Investigator Program. Dr. Ishii researches cell therapy for various hematologic malignancies and non-malignant diseases.

James N. Kochenderfer, M.D.

James N. Kochenderfer, M.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Surgery Branch. Dr. Kochenderfer is a physician-scientist working to develop immunotherapies for lymphoma, leukemia and multiple myeloma.

Jadranka Lončarek, Ph.D.

Jadranka Lončarek, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Protein Dynamics and Signaling. Dr. Lončarek studies the fundamentals of centrosome biology: their biogenesis, architecture and cellular processes associated with their activity.

Christian T. Mayer, Ph.D.

Christian T. Mayer, Ph.D., has joined the Experimental Immunology Branch as a Stadtman Tenure-Track Investigator. His research explores immunoregulatory networks, particularly those involving cell death, in health and disease.

Jordan L. Meier, Ph.D.

Jordan L. Meier, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Chemical Biology Laboratory. Dr. Meier's work focuses on the development of chemical approaches to study epigenetic signaling and its relationship to cellular metabolism.

New Faculty continued

Barry R. O'Keefe, Ph.D.

Barry R. O'Keefe, Ph.D., has been appointed Director of and Senior Scientist in the Molecular Targets Program. Dr. O'Keefe pioneered the discovery of biotherapeutics from natural products. He also specializes in the analysis and exploitation of protein-ligand interactions for both high-throughput screening and compound characterization.

Udo Rudloff, M.D., Ph.D.

Udo Rudloff, M.D., Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Pediatric Oncology Branch. Dr. Rudloff's work is focused on the discovery, translation and early phase clinical testing of novel therapies for patients with pancreatic and other solid organ cancers.

Christina I. Schroeder, Ph.D.

Christina I. Schroeder, Ph.D., has joined the Chemical Biology Laboratory as a Stadtman Tenure-Track Investigator. Her research uses bioactive peptide engineering of complex venom-derived peptides in order to investigate the therapeutic potential of ion channels upregulated in cancer.

Brad St. Croix, Ph.D.

Brad St. Croix, Ph.D., has been appointed as a Senior Scientist in the Mouse Cancer Genetics Program. His research focuses on the molecules involved in human tumor angiogenesis and utilizes mouse models to translate new molecular information on angiogenesis into the development of novel diagnostics and cancer therapeutics.

Travis H. Stracker, Ph.D.

Travis H. Stracker, Ph.D., has been appointed as a Tenure-Track Investigator in the Radiation Oncology Branch. Dr. Stracker's research focuses on understanding how cells respond to DNA damage and maintain genomic stability.

Kandice Tanner, Ph.D.

Kandice Tanner, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Cell Biology. Dr. Tanner's research focuses on understanding the metastatic traits that allow tumor cells to colonize secondary organs.

Christopher J. Westlake, Ph.D.

Christopher J. Westlake, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Cell and Developmental Signaling. Dr. Westlake studies membrane trafficking pathways important in ciliopathy, which are diseases linked to primary cilia dysfunction and cancer.

Matthew T. Wolf, Ph.D.

Matthew T. Wolf, Ph.D., has joined the Laboratory of Cancer Immunometabolism as a Stadtman Tenure-Track Investigator. He studies immunomodulatory biomaterials to augment cancer immunotherapy.

Colin C.C. Wu, Ph.D.

Colin C.C. Wu, Ph.D., has joined the RNA Biology Laboratory as a Stadtman Tenure-Track Investigator. His research explores the role of the ribosome in stress response signaling pathways and translational regulation to collect insights that can be used to guide the prevention and treatment of human diseases.

Ryan Young, Ph.D.

Ryan Young, Ph.D., has joined the Lymphoid Malignancies Branch as a Stadtman Tenure-Track Investigator. He uses proteogenomic technologies to elucidate novel modes of pathogenic signaling in multiple myeloma and lymphoma.

Awards & Honors

Andrea B. Apolo, M.D., received the Arthur Flemming Award.

Melissa Bronez, M.P.A., received the HHS Secretary's Award for Excellence in Management.

Terrence R. Burke Jr., Ph.D., received the Hillebrand Prize from the Chemical Society of Washington.

Sheue-yann Cheng, Ph.D., received the 2020 HHS Dr. Francisco S. Sy award for Excellence in Mentorship.

Peter L. Choyke, M.D., F.A.C.R., was elected to the National Academy of Medicine.

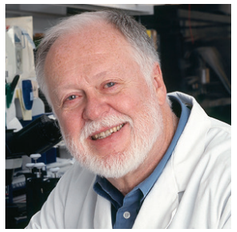
Joseph Clara, M.D., received the SITC-Merck Cancer Immunotherapy Clinical Fellowship.

William L. Dahut, M.D., received the Georgetown University Founders Alumni Award.

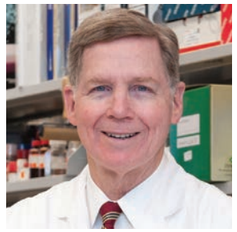
Jeremy L. Davis, M.D., received the USF Health Morsani College of Medicine Alumni Society Early Career Achievement Award in Academics.

Stephanie L. Goff, M.D., received the 2020 NIH Clinical Center Staff Clinician of the Year and the Alan S. Rabson Award for Clinical Care.

James L. Gulley, M.D., Ph.D., received the SITC Collaborator Award.



Curtis C. Harris, M.D., received the Environmental Mutagenesis and Genomics Society Award.



W. Marston Linehan, M.D., received the HHS Secretary's Award for Meritorious Service.

Doug R. Lowy, M.D., received the AACR Distinguished Public Service Award.

Kathryn A. Lurain, M.D., M.P.H., received the ASH Clinical Research Training Institute Award.

Jordan L. Meier, Ph.D., received the 2021 Eli Lilly Award in Biological Chemistry.

Ruth Nussinov, Ph.D., was named a fellow to the American Physical Society.

Ira Pastan, M.D., received the HHS Secretary's Award for Distinguished Service and the Paul A. Volcker Career Achievement SAMMIE.

James N. Kochenderfer, M.D., was elected to the American Society for Clinical Investigation and has been named a Top Ten Clinical Research Achievement Awardee by the Clinical Research Forum for "Development of CAR T-Cell Therapy for Myeloma."

Awards & Honors continued

Steven A. Rosenberg, M.D., Ph.D., received the 2020 AACR-CRI Lloyd J. Old Award in Cancer Immunology.

Samira M. Sadowski, M.D., received the 2020 American Association of Endocrine Surgeon Paul Lo Gerfo Award.

John T. Schiller, Ph.D., was elected to the National Academy of Sciences.

Louis M. Staudt, M.D., Ph.D., was elected to the National Academy of Medicine.

Patricia S. Steeg, Ph.D., received the 2020 AACR-Women in Cancer Research Charlotte Friend Lectureship.

Kandice Tanner, Ph.D., was named a fellow to the American Physical Society.

Sue Wickner, Ph.D., received the ASM Award for Basic Research.

Ying E. Zhang, Ph.D., was inducted as a fellow to the American Institute for Medical and Biological Engineering.

Group Awards

Christian S. Hinrichs, M.D., and Steven A. Rosenberg, M.D., Ph.D., received the FLC 2020 Excellence in Technology Transfer Award for "New, First-in-Class Immunotherapy, for Treatment of Recurrent, Metastatic Cervical Cancer."

Mark R. Gilbert, M.D., Michael Pollack, Ph.D., and Jing Wu, M.D., Ph.D., received a 2020 Excellence in Technology Transfer Award for "Zotiraciclib, FDA and EMA Orphan Drug Designation for Glioma."

Daniel Arango, Ph.D., and Melissa Fernandez, Ph.D., M.Sc., received the Dr. Eddie Méndez Scholar Award.

Scott Abrams, Ph.D., Clint T. Allen, M.D. (NIDCD), David Colcher, Ph.D., M.P.H., William L. Dahut, M.D., Renee N. Donahue, Ph.D., Sofia R. Gameiro, Ph.D., John W. Greiner, Ph.D., James L. Gulley, M.D., Ph.D., Duane H. Hamilton, Ph.D., Patricia H. Hand, Ph.D., Christopher R. Heery, M.D., James W. Hodge, Ph.D., M.B.A., Caroline Jochems Frohlich, M.D., Ph.D., Ravi A. Madan, M.D., Claudia M. Palena, Ph.D., Arun Rajan, M.D., Helen Sabzevari, Ph.D., Jeffrey Schlom, Ph.D., Julius Strauss, M.D., and Kwong Yok Tsang, Ph.D., were the CCR members who received the SITC Team Science Award.

CCR by the Numbers

234 Open Clinical Trials
45 New Clinical Trials
1,547 New Patients

236 Principal Investigators
11 New Faculty Recruits
7 Newly Tenured Investigators
345 Staff Scientists/ Staff Clinicians

~500 Technical Lab Staff
~800 Postdoctoral/ Clinical Fellows
327 Postbaccalaureate/ Predoctoral Students

>1,000 Articles in Peer-Reviewed Journals

47 Technology Facilities and Platforms

Technology Transfer Activities

70 New Employee Invention Reports
61 Issued U.S. Patents
28 New Cooperative Research and Development Agreements (CRADAs)
7 New Clinical CRADAs
183 Active CRADAs
87 Clinical CRADAs
9 Umbrella CRADAs
17 New Clinical Trial Agreements (CTAs)
88 Active CTAs

110 New Licenses for CCR Technologies
559 Active Licenses

2 FDA Approvals
1 FDA Breakthrough Drug Designation
1 FDA Orphan Drug Designation

The **NCI Technology Transfer Center (TTC)** works to enable and guide collaboration, invention development and licensing to advance today's discoveries into tomorrow's medical care. The TTC supports technology development activities for NCI in therapeutics, diagnostics, research tools, vaccines, devices and software, and facilitates partnerships with outside organizations so that NCI discoveries can reach the public in a timely manner.

For information on licensing and co-development opportunities, contact the TTC Invention Development and Marketing Unit (**ncitechtransfer@mail.nih.gov**), or visit **techtransfer.cancer.gov** for more information.
Numbers are for FY2020.

Captions & Resources

Front Cover Captions

Row 1 (left to right)

Peter Pinto's patient Gene Grabowski and his wife Kathy. Credit: Gene Grabowski

CCR Director Tom Misteli, Ph.D., working at his home office. Credit: Tom Misteli

A cluster from a sequence similarity network analysis of genes from dark matter circular sequences. Credit: Michael J. Tisza and Christopher B. Buck

A sign of hope seen in her neighborhood. Credit: Elaine Jaffe

Heba Al Khamici, Ph.D., working safely in the lab. Credit: Luanne Lukes

A molecule interacting with a bacterial riboswitch that controls gene expression. Credit: SPGM, FNL, NCI, NIH

Row 2

Preschool in the home of Bríd Ryan, Ph.D., M.P.H. Credit: Bríd Ryan

Brunilde Gril, Ph.D., M.P.S., working from home with her cat, Lola. Credit: Brunilde Gril

Lillian Yang, M.B.A., wearing a mask made by her mom in Hawaii. Credit: Lillian Yang

"Mimi, that man said social distancing!" – Paxton Holliday. Credit: Lori Holliday

Stained tissue slide showing a Burkitt lymphoma starry sky pattern. Credit: Elaine Jaffe

Row 3

Art of CAR T-cell immunotherapy. Credit: Veronica Falconieri Hays

Combined systematic and MRI-targeted biopsy for prostate cancer, developed at CCR. Credit: SPGM, FNL, NCI, NIH

Center for Advanced Preclinical Research staff and their children during a virtual meeting. Credit: Shyam K. Sharan

Row 4

Laboratory Animal Sciences Program staff social distancing. Credit: Matthew Breed

Nicolas Melis, Ph.D., working safely in the lab. Credit: Lakshmi Balagopalan

One of four mouse models that replicates key features of human melanoma that shows diversity of immune cells found in tumors. Credit: Romina E. Araya

Audra Addison and Amy Toner after surgery. Credit: Jeremy Davis

CD206 docking station that changes its structure and reprograms macrophages when attached to synthetic peptide RP-182. Credit: Jesse M. Jaynes and Udo Rudloff

CCR Resources

For more information on CCR and the topics mentioned in these stories:

Center for Cancer Research
https://ccr.cancer.gov

CCR Clinical Trials
https://ccr.cancer.gov/clinical-trials

NCI CCR Liver Cancer Program
https://ccr.cancer.gov/liver-cancer-program

Cancer Immunology and Immunotherapy at CCR
https://ccr.cancer.gov/research/immunology-and-immunotherapy

NCI CCR Prostate Cancer Multidisciplinary Clinic
https://ccr.cancer.gov/clinical-trials/prostate-cancer-clinic

CCR front-line clinical providers receiving COVID-19 vaccinations.

Top left and right: Andrea Apolo and James Gulley
Bottom left and right: Freddy Escorcia and Terri Armstrong

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