NIH NATIONAL CANCER INSTITUTE

CENTER FOR CANCER RESEARCH

MILESTONES

Cancer Research with a Purpose

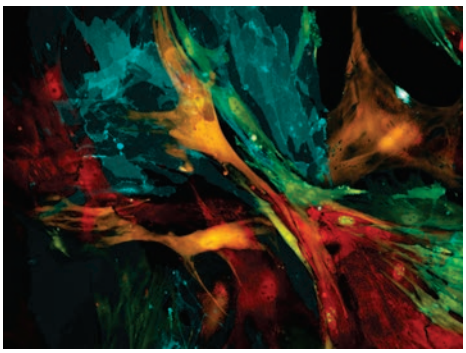
HIGHLIGHTS 2016–2017

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

CENTER FOR CANCER RESEARCH
THE NATION'S CANCER CENTER

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

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



About the cover: *The "confetti mouse" is the name given to a strain of mice genetically engineered so that their cells glow in various combinations of red, blue, yellow, or green markers, depending on what particular proteins those cells are producing. This color coding, demonstrated here in mouse kidney cells, can be especially useful in cancer research, shedding light on subtle molecular differences among tumors and providing clues to what may be driving the spread, or metastasis, of cancer cells beyond the original tumor site.*

Credit: *Heinz Baumann, Sean T. Glenn, Mary Kay Ellsworth and Kenneth W. Gross, Roswell Park Cancer Institute, Buffalo, NY*

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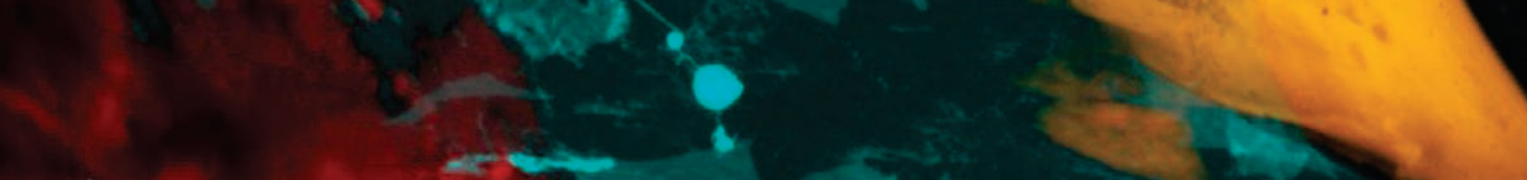
The MISSION of CCR is to improve the lives of cancer patients by solving important, challenging and neglected problems in cancer research and patient care through:

- 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 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 for the next generation of the biomedical workforce



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Director's Note

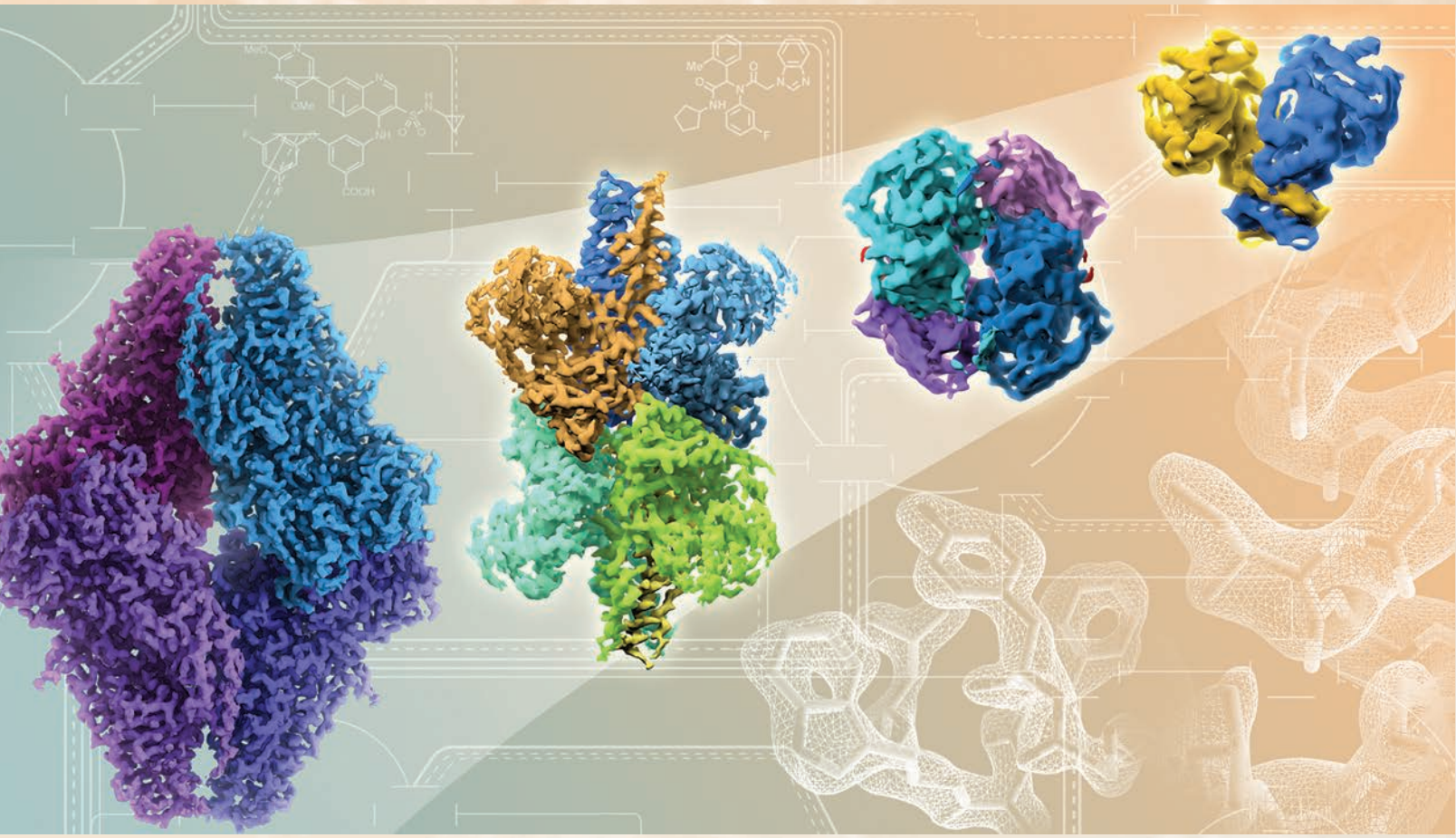
Every year, the Center for Cancer Research (CCR) makes remarkable contributions to the understanding, detection, treatment and prevention of cancer. The CCR scientists and staff publish approximately 2,000 scientific papers per year, run more than 200 clinical trials and care for hundreds of cancer patients in the National Institutes of Health Clinical Research Center. Each published study and clinical trial is a step forward on our journey to alleviate the burden of cancer.

Progress in cancer research often comes in unanticipated areas. As history has shown, it is difficult to predict how an individual discovery will contribute to future progress. Who would have thought that the basic exploration years ago of how the immune system works would one day lead to immunotherapy, one of today's most promising weapons in the fight against cancer? It is essential that research institutions create an environment where the unexpected is expected and where new areas of exploration can be freely pursued by its scientists. In CCR, we pride ourselves on our culture of creating an environment where the most important and difficult problems in cancer biology can be fearlessly pursued by our investigators.

In this magazine, we highlight some of the milestones CCR investigators have reached in the last year on the road to mitigating the dire consequences of cancer. The collection of research highlights presented here only scratches the surface of the many advances made by CCR scientists, but they showcase the broad spectrum of our activities and the ingenuity of our scientists. Be it groundbreaking methods to visualize the structure of proteins and RNAs that help us understand their function and allow us to design specific drugs, be it the molecular characterization of kidney cancer that will pave the way to new treatment approaches, or be it imaging methods that provide unprecedented precision in detection of prostate cancer, each of these are the result of daring and groundbreaking research that will ultimately benefit cancer patients. Through efforts like these, we are leading the cancer community in developing innovative approaches to clinical studies while also contributing to shaping the next generation of the biomedical workforce through our commitment to excellent training programs.

We are proud to have reached some critical milestones this year–but the journey goes on. All of us at CCR are committed to continuing the march towards our common goal of making cancer a preventable, curable and manageable disease.

Tom Misteli



SHARPER IMAGES
BETTER DRUGS

Improved imaging reveals protein structure in amazing detail, opening a path for accelerated drug development.

The laboratory of Senior Investigator Sriram Subramaniam, Ph.D., makes the invisible visible. His research team has produced astonishingly detailed images of biological molecules that are considered targets for potential cancer therapies.

Subramaniam has refined a technique called cryo-electron microscopy (cryo-EM), which produces images detailed enough to reveal individual atoms throughout key regions of a molecule. Although cryo-EM has long been used as a research tool, the increased power of the technique means it now stands to accelerate drug development.

Visualizing precise three-dimensional structures helps researchers understand how biological molecules work. For decades, the favored method for determining the structures of proteins and other molecules has been a technique called X-ray crystallography. This method offers very high resolution, but it is not suitable for studying all types of molecules because it requires the formation of small crystals of the molecule of interest, which can be difficult to produce. Cryo-EM excels at revealing the structure of molecules that are not compatible with X-ray crystallography either because they adopt more than one shape or because they cannot be coaxed into a crystalline form.

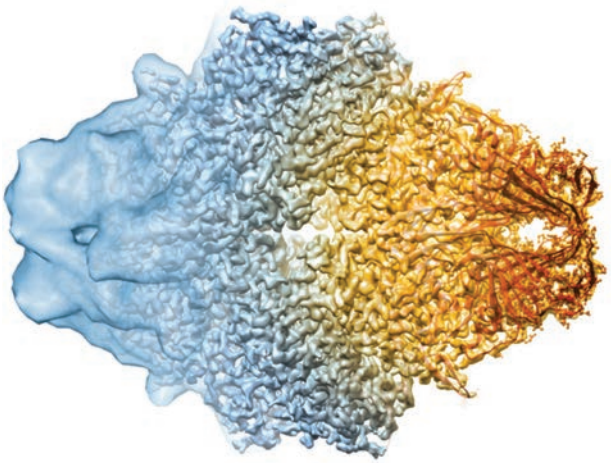
To perform cryo-EM, molecules are flash frozen in liquid nitrogen, put on a flat surface and then, inside the microscope, bombarded with electrons to capture their image. The trick to obtaining three-dimensional information is to take thousands of two-dimensional images from various angles then average them together to generate a final three-dimensional structure. This is similar to looking at a sculpture from different sides to capture all aspects of it.

In the last few years, Subramaniam and his laboratory have pushed the boundaries of what can be done with cryo-EM. In a groundbreaking 2015 study, Subramaniam's team overcame several major technical challenges to generate the highest-resolution image ever produced with cryo-EM—the structure of a bacterial enzyme called beta-galactosidase with near-atomic resolution. The structure offered details comparable to what, until then, could only be obtained with X-ray crystallography. In large part due to this study, the journal *Nature Methods* named cryo-EM its 2015 "Method of the Year" in recognition of the technique's potential impact on medicine and biology.

The images Subramaniam's team produced in 2016 are even better. The team reported in *Science* that they had used cryo-EM to produce a series of high-resolution structures of p97, an enzyme that influences protein levels inside cells. Interfering with p97's activity is considered a potential strategy for slowing the growth of cancer cells. The images show how p97 twists and shifts as it prepares to perform its work and how binding of an inhibitor prevents these essential shape changes.

Later the team reported in the journal *Cell* that they had used cryo-EM to determine the structures of several small metabolic enzymes, both alone and interacting with their small-molecule inhibitors, at near-atomic resolution. The genes for two of those enzymes, isocitrate dehydrogenase and lactate dehydrogenase, are commonly mutated in human tumors, and the proteins are considered targets for potential cancer therapies. Enzymes like these were previously considered too small to be imaged with cryo-EM.

Banerjee S, et al. *Science*. 2016 Feb 19;351(6275):871-5.
Meyerson JR, et al. *Nature*. 2016 Sep 22;537(7621):567-571.
Merk A, et al. *Cell*. 2016 Jun 16;165(7):1698-707.

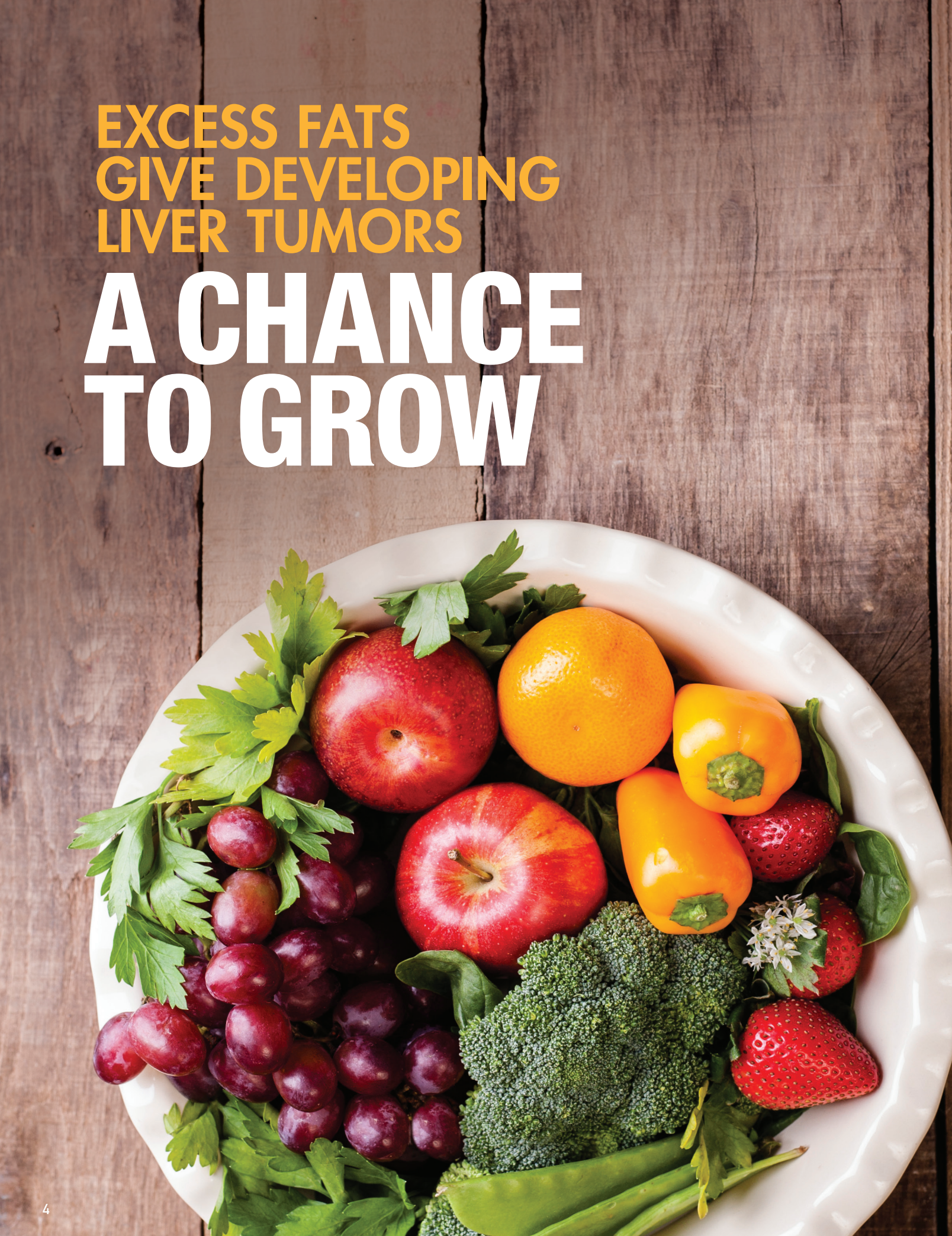


Above: *This composite image of beta-galactosidase shows how cryo-EM's resolution has improved dramatically in recent years. The older image is on the left and the more recent image is to the right.*

Left: *Rapid advances in cryo-EM technology, from left to right, show improving resolutions in atomic detail of proteins and drug binding.*

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

EXCESS FATS GIVE DEVELOPING LIVER TUMORS A CHANCE TO GROW



Understanding the immune response to tumors suggests that dietary changes may influence antitumor immunity.

Nearly one in three Americans have non-alcoholic fatty liver disease (NAFLD), a buildup of fat in the liver that can cause inflammation and scarring in the organ. The condition, which is common among people who are obese or have diabetes, is on the rise in developed countries. NAFLD usually causes no symptoms, but it puts people at risk for both liver failure and liver cancer.

Tim Greten, M.D., a CCR Senior Investigator in the Thoracic and Gastrointestinal Oncology Branch, and his team now have reported in the journal *Nature* that a type of fatty acid that accumulates in livers with NAFLD is toxic to cancer-fighting immune cells. Greten's observations suggest that elimination of these defensive cells from the liver gives tumors a better chance to grow because they avoid immune detection.

The team began their studies in mice, which develop NAFLD when they are fed a diet designed to disrupt fat metabolism. Like humans, mice with NAFLD are more likely to develop hepatocellular carcinoma, the most common type of liver cancer.

To explore the consequences of excess fat, Greten and his colleagues analyzed the presence of specific immune cells in the livers of mice with NAFLD. They found that the fatty livers were largely missing one cell type, helper T cells, which play a key role in antitumor immunity. These cells seek out infected and cancerous cells, and when they find them, they summon other immune cells to mount an attack. Without helper T cells in their livers, even mice without NAFLD have an elevated risk of developing liver cancer.

But why do these helper T cells disappear in NAFLD? Greten's team determined that a fatty acid called linoleic acid, which is abundant in fatty livers, is responsible for the death of helper T cells. When linoleic acid enters these cells, it perturbs energy-generating organelles called mitochondria, shifting cellular metabolism toward biochemical pathways that generate more cell-damaging free radicals, which ultimately leads to cell death. When the scientists fed mice a diet high in linoleic acid, there was a clear reduction of helper T cells in their livers, while killer T cells, another essential element of the immune system's anticancer defenses, were spared.

To determine whether their findings were of clinical relevance, the Greten team analyzed liver biopsies from patients. As they had seen in mice, they found that helper T cells are depleted from livers affected by NAFLD while killer T cells remain undisturbed. Greten and his colleagues also found that they could protect immune cells from the effects of linoleic acid by blocking the reactive oxygen species that build up in its presence. When they gave antioxidants to mice with NAFLD, helper T cell populations in the liver recovered and tumors developed more slowly than they did in untreated mice with NAFLD.

Taken together, these results reveal a novel aspect of the immune response to tumors and suggest that dietary changes may be a means to influence antitumor immunity and impact tumor growth.

Ma C, et al. *Nature*. 2016 Mar 10;531(7593):253-7.

As fats accumulate in the liver, the immune system weakens and limits our anticancer defenses. These results suggest dietary changes may alter tumor growth.

Credit: *iStock*

A FOX with No Footprints?

Activated hormone receptors and other gene regulators help one another find new gene targets in breast cancer cells.

Hormones and hormone receptors are critically important for normal development, but they are also involved in cancer. The female hormone estrogen plays a particularly important role in many breast cancers. Once activated by the hormone, estrogen receptors on tumor cells bind to sites throughout the genome and switch on target genes, many of which promote cell growth. Understanding the role of estrogen signaling in breast cancer has helped scientists devise treatments that inhibit the growth of hormone-dependent cancers by blocking the activity of the receptor or the production of estrogen.

Although the estrogen receptor plays a key role in the growth and progression of many breast cancers, it does not act alone. Other proteins influence the receptor's ability to find and activate its target genes. New research from CCR scientists shows how these molecules shape one another's interactions with a cell's DNA. The findings, from a team of scientists led by Gordon Hager, Ph.D., Chief of CCR's Laboratory of Receptor Biology and Gene Expression, indicate that the cellular systems for regulating hormone-responsive genes are more complex and dynamic than previously recognized, suggesting new opportunities for therapeutic intervention.

In their study, reported in the journal *Cell*, Hager and his colleagues investigated interactions between the estrogen receptor, another hormone receptor called the glucocorticoid receptor and a protein called FoxA1, which have all been implicated in breast cancer.

FoxA1 binds directly to specific sites along DNA, including many of the sites to which the estrogen receptor binds. Because FoxA1 is thought to promote local changes in DNA packing that must occur before a gene can be activated, it has been considered a "pioneer factor."

Many studies have suggested that the estrogen receptor cannot bind to the regulatory elements of certain genes until FoxA1 arrives on the scene. However, Hager and his colleagues determined that although FoxA1 can act as a pioneer factor for estrogen and glucocorticoid receptors, these roles can also be reversed. To determine how these factors work together to influence the behavior of breast cancer cells, the researchers mapped footprints left on the DNA where FoxA1 and the receptors bind and determined how the binding patterns changed in the presence of other regulators. They found that FoxA1, the estrogen receptor and the glucocorticoid receptor can all change the binding capabilities of the others. Further analysis suggested that, in some locations in the genome, estrogen or glucocorticoid receptors can bind first and ready DNA for the arrival of FoxA1. Using single-molecule tracking, they also found that FoxA1 and the receptors have very brief residence times on the DNA, a finding consistent with the lack of footprints.

The results suggest a new level of complexity in how these factors influence one another and interact with regulatory sites of the genome in breast cancer cells. The hope is that understanding this interplay will help researchers develop better ways to rein in growth-promoting genes not only in breast cancer cells but in all types of cancer cells.

Swinstead EE, et al. *Cell*. 2016 Apr 21;165(3):593-605.

Hager et al. determined the FoxA1 factor leaves no detectable footprints at its binding sites throughout the genome, suggesting a more dynamic interaction with its environment.

Credit: *iStock*

ENDURING COMMUNITIES

Communities of microbes that make their homes in the diverse environments on human skin can persist for years.

Human skin is a complex ecosystem in which trillions of bacteria, fungi and viruses mingle and interact with the cells of their host. Microbes blanket the palms, nestle between toes and huddle in crevices formed by hair follicles and sweat glands. According to new research, once they settle in, they tend to stay.

Microbes influence our metabolism, modulate our immune systems and likely impact human biology in ways we do not yet understand. Their presence may influence individuals' susceptibility to cancer or their response to cancer treatments. Eventually, researchers hope to find ways to prevent or treat disease by manipulating the composition of the human microbiome, but first they need to understand the composition of these communities and evaluate their natural variability.

In 2014, CCR Investigator Heidi Kong, M.D., and her colleagues surveyed the bacteria, fungi and viruses present at different sites on the skin of healthy adult volunteers and found unique microbial communities wherever they looked. In addition to distinctions between different body sites, Kong and her colleagues found variations between individuals such that each person had a microbial "fingerprint" that was distinctly their own.

That study provided detailed information about a diverse array of microbial communities. Because skin is directly exposed to the outside world and comes into constant contact with soaps, sanitizers and other microbe-covered surfaces, however, it was unclear whether these communities remain constant or whether their members come and go.

In 2016, Kong and her colleagues extended their study and reevaluated the skin's diverse microbial communities to investigate how they change over time. After inventorying the microbes present at multiple sites on the bodies of healthy adults, the team repeated the analysis for each individual two to three months later and again after one to two years. The team used sophisticated DNA-sequencing technology to examine the microbial DNA at each site and analyzed the genetic data to generate a profile of the community members. They reported their findings in the journal *Cell*.

The researchers found that, even after a year or two, most sites on the body hosted the same types of microbes that were present at the outset of the study. Some sites, like the feet, were more variable, and certain microbes were less likely to have stayed put than others. They also found that some study subjects tended to have more variable microbial communities than others. Overall, Kong and her colleagues found the skin microbiome to be remarkably stable.

Despite their apparent stability, illness and changes in immune function are known to disrupt microbiome communities. Antimicrobial treatments, changes in diet, probiotics and even relocation to a new living environment could cause an individual's microbiome to shift. Kong's work lays the foundation for future studies investigating the factors that perturb the skin microbiome and the health consequences of these changes, especially as they pertain to cancer.

Oh J, et al. *Cell*. 2016 May 5;165(4):854-66.

This normal human skin cell was treated with a growth factor that triggered the formation of specialized protein structures that enable the cell to move. We depend on cell movement for such basic functions as wound healing and launching an immune response.

Credit: *Torsten Wittmann, University of California, San Francisco*

MANAGING DNA'S TOPOLOGY TO KEEP

GENES ACTIVE

The discovery of a gene-activating enzyme's role in reshaping DNA while it works suggests a new strategy for drug development.

Inside cells, the graceful twist of DNA's familiar double helix is frequently distorted. Its two strands must routinely be separated to make way for enzymes that copy the genetic code, forcing extra twists and kinks into nearby parts of the molecule. The resulting mechanical stress places strain on the genome that must be relieved.

That task is handled by enzymes called topoisomerases. Topoisomerases create a break in overtwisted DNA, which frees it to swivel into a more relaxed state. Then they repair the cut to ensure that a cell's DNA remains intact. Many cancer drugs interfere with the final step of this process and prevent topoisomerases from resealing the breaks they create. Unresolved breaks build up until cells are overwhelmed by the damage and die.

Preventing topoisomerases from mending their breaks kills cancer cells, but it also damages DNA in normal cells. A better understanding of how these enzymes work might enable researchers to design a new generation of topoisomerase inhibitors that kill cancer cells with fewer side effects. New research led by Laura Baranello, Ph.D., a senior research fellow, and David Levens, M.D., Ph.D., Senior Investigator in CCR's Laboratory of Pathology, revealed a surprising aspect of topoisomerase function that could help with that goal.

The discovery, published in the journal *Cell,* came from experiments in which Levens and his team investigated how topoisomerase 1 (Top1) relieves the stress introduced into DNA during the process of transcription when DNA's twin strands are separated so a gene can be copied into RNA. This process, executed by an enzyme called RNA polymerase II, is the essential first step in producing the protein encoded by a gene.

The team mapped Top1's activity throughout the genome and noticed that while the enzyme frequently binds to the regulatory regions near genes' start sites, it does not seem to be active. Instead, it only cuts DNA inside genes. This prompted the researchers to investigate how the enzymes transitioned from their inactive state into a form in which they are able to snip and repair DNA whose shape has been distorted by transcription.

They found that the very enzyme responsible for creating overtwisted DNA, RNA polymerase II, also directs topoisomerase to relieve that stress. Their experiments indicated that the polymerase activates the topoisomerase once transcription is under way. By coordinating topoisomerase's activity with its own, the polymerase can produce RNA copies of genes without being slowed by the shape changes it forces into the DNA.

Because cancer cells tend to transcribe more genes than normal cells, they are likely to depend heavily on Top1 to rid their DNA of kinks and buckles introduced by RNA polymerase II. Levens and his colleagues think their discovery will lead to the development of drugs that disrupt the two enzymes' interactions. Such drugs might block the Top1 activity that is needed by cancer cells without creating DNA damage. The hope is that this approach, based on a deep understanding of how topoisomerases work, will lead to drugs with less toxicity than the topoisomerase inhibitors currently used to treat cancer.

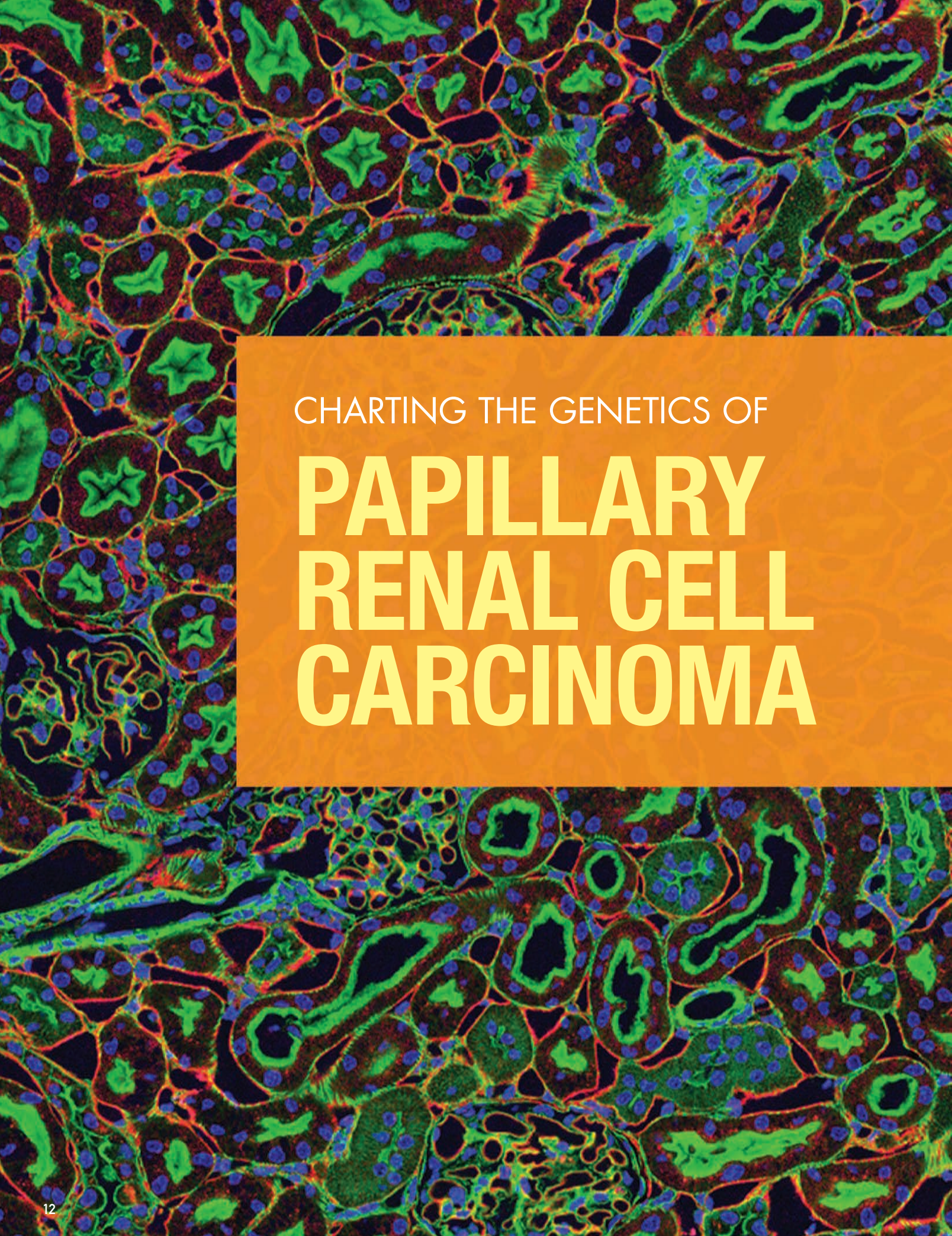
Baranello L, et al. *Cell*. 2016 Apr 7;165(2):357-371.

Topoisomerases create a break in over-twisted DNA, which frees it to swivel into a more relaxed state.

Credit: *NIH 3D Print Exchange*

DNA double helix.

Credit: *National Human Genome Research Institute, NIH*



CHARTING THE GENETICS OF

PAPILLARY RENAL CELL CARCINOMA

A comprehensive molecular analysis of the second-most-common type of kidney cancer sets the stage for more precise diagnoses and more tailored treatments.

More than 60,000 people are diagnosed with kidney cancer in the United States every year. About 20 percent of these patients have papillary renal cell carcinoma, the second-most-common type of kidney cancer. Currently, papillary renal cell carcinomas are classified into one of two subtypes based on their appearance under a microscope. Even within the same subtype, some of these cancers are much more aggressive than others, and clinicians need better tools for differentiating between these tumors and identifying the best treatments for individual patients.

Marston Linehan, M.D., Chief of CCR's Urologic Oncology Branch, teamed up with his colleagues Kimryn Rathmell, M.D, Ph.D., from Vanderbilt University and Paul Spellman, Ph.D., from Oregon Health and Science University and The Cancer Genome Atlas (TCGA) Research Network, a collaborative effort supported and managed by NCI and the National Human Genome Research Institute, to search for clues to help researchers devise better ways to diagnose and treat these tumors. Their comprehensive molecular analysis of 161 papillary renal cell carcinoma tumors, reported in the *New England Journal of Medicine*, identified genetic pathways that are commonly disrupted in subgroups of papillary renal cell carcinomas and suggested strategies for developing targeted therapies.

The analysis, which compared the genetic sequences of tumors to those of healthy kidney tissue, analyzed patterns of gene activity and surveyed the proteins and RNA molecules present in tumor cells. It confirmed that the two clinical subtypes of papillary renal cell carcinoma are genetically distinct.

Type 1 tumors, the researchers found, may be characterized by disruptions to a signaling pathway involving the MET gene. Patients with these tumors might benefit from drugs that target this pathway. Changes to MET signaling are known to drive the growth and spread of cancer cells and spur the development of blood vessels that supply tumors with oxygen. Several inhibitors of the MET pathway are already being evaluated in clinical trials for the treatment of various cancers, including papillary renal cell carcinoma.

Among the Type 2 tumors, the researchers identified a subgroup characterized by high levels of DNA methylation, a chemical modification that dampens the activity of affected genes. Tumors in this subgroup were associated with the least-favorable clinical outcomes. Loss of the tumor suppressor gene CDKN2A, which affected about 25 percent of Type 2 tumors, was also associated with a poor prognosis.

These findings are the latest chapter of work completed by CCR scientists that have led to a more sophisticated system of classifying kidney cancers and allowed patients and their doctors to make more informed treatment decisions.

Linehan WM, et al. *N Engl J Med*. 2016 Jan 14;374(2):135-45.

Stained kidney tissue. The kidney is an essential organ responsible for disposing wastes from the body and for maintaining healthy ion levels in the blood. It works like a purifier by pulling breakdown products of metabolism, such as urea and ammonium, from the blood stream for excretion in urine.

Credit: *Tom Deerinck and Mark Ellisman, National Center for Microscopy and Imaging Research*

EXPLAINING
ACCELERATED AGING

The identification of a cellular pathway involved in a rare premature aging syndrome suggests a strategy for treating the disorder and offers insight into the normal aging process.

Aging is a major risk factor for most types of cancers. However, it remains unclear exactly how aging contributes to cancer development, especially because it is difficult to study the aging process in humans. To investigate the processes that drive human aging, Nard Kubben, a postdoctoral fellow in the laboratory of CCR Director Tom Misteli, Ph.D., has focused his attention on an exceedingly rare premature aging syndrome, the genetic disorder Hutchinson-Gilford Progeria Syndrome (HGPS).

HGPS causes many signs of premature aging, including stiff joints, hair loss and aged-looking skin, and patients usually die of heart attacks or stroke at a young age. Surprisingly, patients with HGPS seem to be protected from cancer, and Misteli's lab and others are investigating why.

It has been known for more than a decade that HGPS is caused by a mutation in the gene for lamin A, a structural protein of the cell nucleus. The genetic mutation causes cells to produce a dysfunctional form of lamin A that scientists have named progerin. This protein disrupts a number of cellular features and compromises the integrity of the nucleus and the genetic material it contains, but researchers did not know how it caused such cellular havoc.

Kubben and Misteli used an imaging-based screening approach to identify genes whose inhibition restored normal function to the cells despite the presence of progerin. As they report in the journal *Cell*, their experiments led them to a signaling pathway controlling the longevity-promoting factor NRF2, which normally defends cells against the damaging effects of free radicals. The researchers found evidence that progerin traps the NRF2 protein, preventing it from accessing and switching on the antioxidant genes needed for the cell's free radical response. Consequently, free radicals persist and cause various forms of damage that underlie the defects seen in the cells of patients with HGPS.

Misteli's team discovered that they could alleviate those problems by treating progerin-producing cells with chemical activators of NRF2, including the FDA-approved drug Oltipraz. Reactivating NRF2 reversed progerin-evoked defects in various cell types the scientists tested, including HGPS patient-derived stem cells in an animal model.

The finding suggests that restoring NRF2 function might prevent premature aging in children with HGPS and could revolutionize treatment of this rare disorder. Because small amounts of progerin are also produced in healthy individuals and the disruptive protein tends to accumulate as people get older, the discovery also brings researchers closer to understanding the normal aging process at a molecular level and developing therapeutic strategies to slow its effects. Notably, the research also points toward a connection between the antioxidant pathway and aging's effects on tumor development, as changes in the NRF2 pathway have been implicated in several types of cancer.

Kubben N, et al. *Cell*. 2016 Jun 2;165(6):1361-74.

Beandri, a young girl living in South Africa, has participated in many progeria clinical trials.

Credit: *Progeria Research Foundation*

FAULTY **REPAIR SYSTEMS**

Cancer cells find ways to survive damage they cannot fix.

Damage to DNA is unavoidable. Chemicals, sunlight and routine cellular activities distort the genetic code by modifying its components and severing DNA strands. Most of the time, such damage has no harmful consequences because cells' sophisticated DNA repair systems rush to replace the errors and mend the breaks. In some individuals, however, these repair systems are impaired by inherited genetic mutations and unrepaired damage accumulates, which increases the risk of tumors.

Mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 predispose individuals to cancer. They also impair cells' ability to sense and respond to DNA damage, a limitation that plays an important role in cancer therapy.

Patients whose cancers carry mutations in BRCA1 or BRCA2 almost always develop resistance to DNA-damaging chemotherapies. It has widely been assumed that this resistance develops as cells lacking functional BRCA1 or BRCA2 evolve new ways to repair their damaged DNA, but new work from CCR scientists shows that cancer cells lacking these repair factors can find other ways to thrive.

In a 2016 study reported in the journal *Nature*, scientists led by André Nussenzweig, Ph.D., Chief of CCR's Laboratory of Genome Integrity, discovered that cells with BRCA deficiencies can also become chemo-resistant by acquiring additional mutations that protect damaged DNA strands.

DNA double-strand breaks, which are caused by many chemotherapeutic agents and are the primary type of damage targeted by BRCA1 and BRCA2, normally stall the enzymes that copy DNA in preparation for cell division. This delay gives cells time to repair the damage. But in cells without BRCA2, the lesions go unrepaired, and DNA at the stall sites is degraded. Too many unrepaired lesions can ultimately lead to cell death. Nussenzweig and his colleagues found that when BRCA-deficient cells contain additional mutations that interfere with the DNA-degrading enzyme MRE11's ability to find stall sites, they are able to survive double-strand breaks and become resistant to chemotherapeutic agents, such as cisplatin, that cause them.

In complementary work, a team led by Shyam Sharan, Ph.D., Deputy Director of CCR's Mouse Cancer Genetics Program, found another challenge in treating BRCA-deficient cancer cells. Sharan and his colleagues investigated the effects of the cancer drug olaparib, which induces DNA damage and is toxic to BRCA-deficient cancer cells. However, when Sharan's team tested the drug on cells with BRCA mutations that had not become cancerous, they found the opposite effect: Cells were able to keep growing despite their reduced ability to repair damaged DNA.

The survival mechanism Sharan's team uncovered is similar to the drug-resistance strategy discovered by Nussenzweig's group. They found that olaparib prevents the DNA-degrading enzyme MRE11 from accessing DNA sites where replication has stalled due to damage. This promotes cell survival and permits damaged DNA to be passed on to future generations of cells, which increases the risk of new tumors.

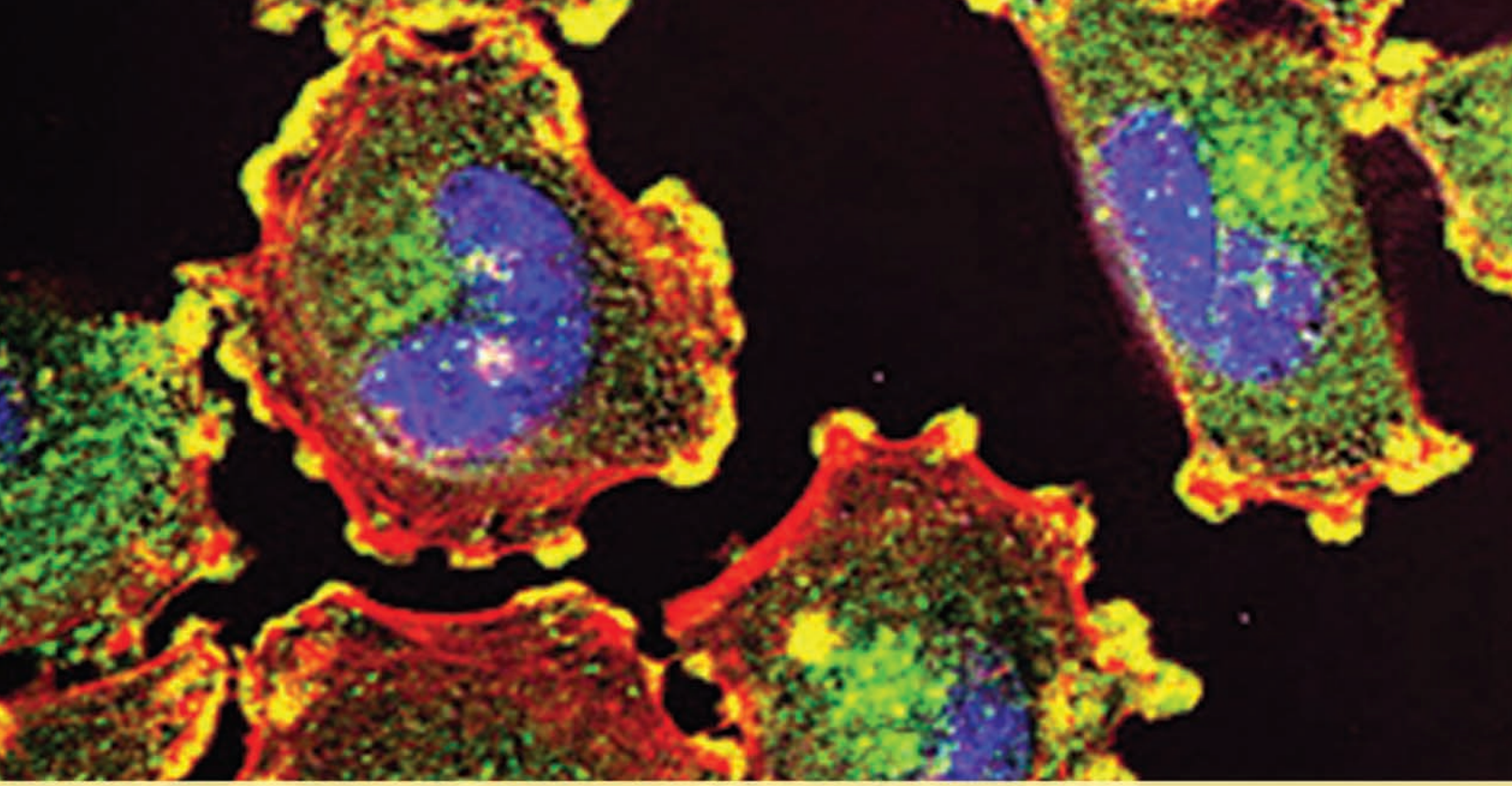
Sharan's investigations of these basic cellular mechanisms, reported in the journal *Nature Communications*, have important implications for the clinical use of olaparib and related drugs because they suggest that when these inhibitors are used to eliminate cancer cells in patients with inherited BRCA2 mutations, they may also increase the risk that new tumors will develop.

Chaudhuri AR, et al. *Nature*. 2016 Jul 20;535(7612):382-7.

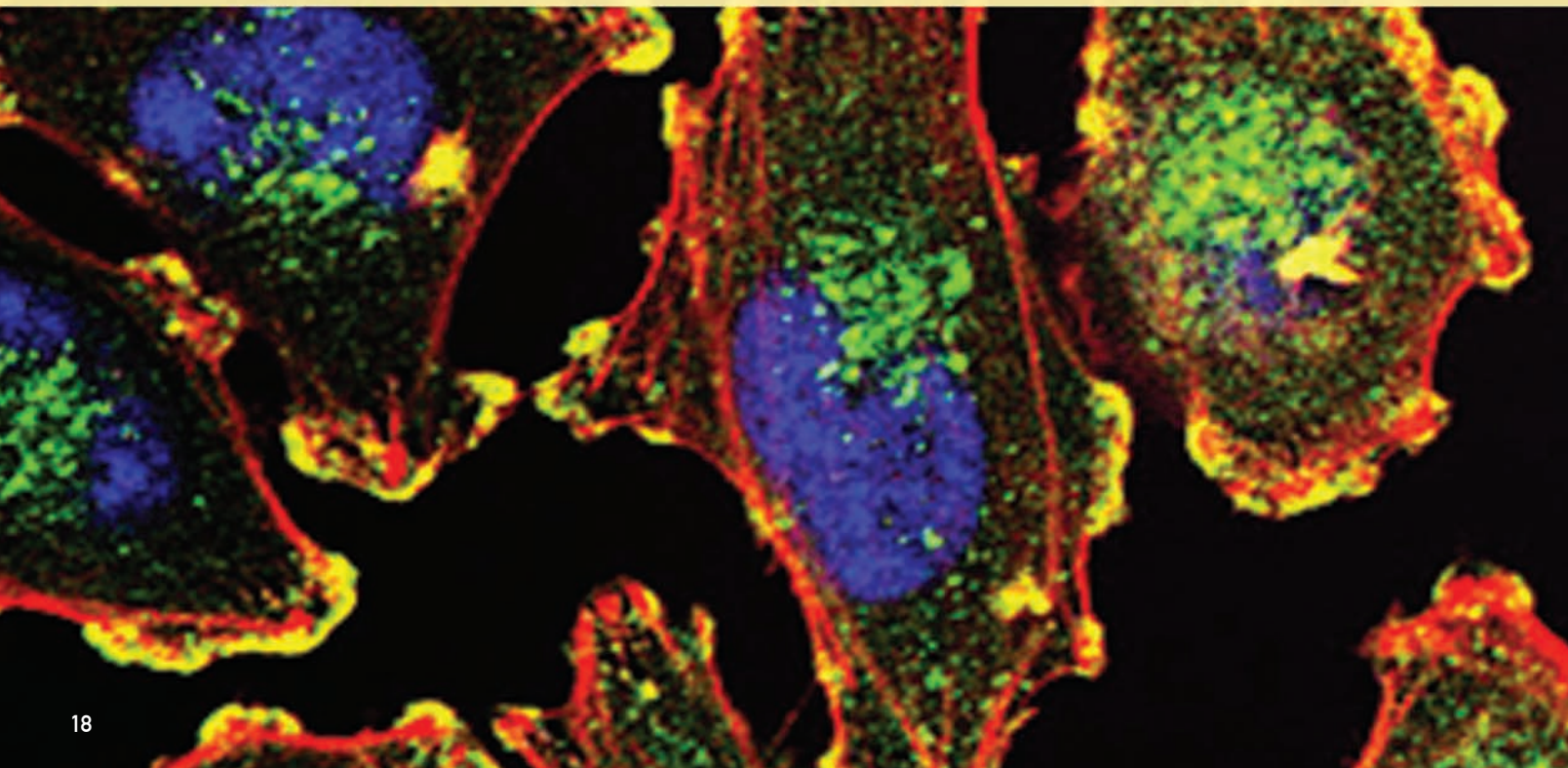
Ding X, et al. *Nat Commun*. 2016 Aug 8;7:12425.

Nussenzweig and Sharan demonstrated how the replication fork is protected from predators. The image depicts MRE11 nuclease as a shark chewing up newly synthesized DNA at a replication fork, thus resulting in genome instability.

***Credit:** Alan Hoofring, NIH*



OVERCOMING
THE ELEMENTS



Studies of some of the body's simplest chemical components suggest new strategies for empowering the immune system.

The immune system is continuously on the lookout for foreign objects. Most often these are viruses, bacteria or parasites, but the immune system also looks for tumors. For cancer to survive and spread, it must evade the body's natural defenses.

Cancer cells find many ways to avoid being attacked by the immune system, but CCR investigators are learning enough about their tactics to begin to counter them. New research from Nicholas Restifo, M.D., a Senior Investigator in CCR's Surgery Branch, has demonstrated how two elements that are common in the body, oxygen and potassium, suppress immune activity and create opportunities for tumors to grow. In animal studies, Restifo and his colleagues have shown that it is possible to engineer antitumor immune cells to be less sensitive to the effects of potassium or oxygen, which makes them more effective in places where cancer cells might otherwise grow unopposed.

Researchers have long known that many cancers spread to the lungs. Restifo and his colleagues were investigating the effects of oxygen on tumor immunity when they began to suspect that the abundant oxygen in the lungs might foster an environment where migrating cancer cells can settle and grow undisturbed. Indeed, they found that T cells, important components of the immune system's anticancer defense, are less likely to trigger an attack when oxygen levels are high. This restraint can prevent overactive immune responses to the dust, pollen and other particles that are commonly inhaled into the lungs, but when cancer cells infiltrate, sluggish T cells can be dangerous. Restifo and his colleagues reported these findings in the journal *Cell*.

In a second study, published in *Nature*, Restifo's team determined that potassium can also inhibit T cells' ability to fight cancer. The body's potassium is usually contained inside cells, but when tumor cells die, their contents leak into the space that surrounds them. In tumors with a lot of dead cells, or necrosis, extracellular potassium levels can rise sufficiently to impair T-cell responses.

Both findings hold promise for designing more effective cancer immunotherapies. Restifo's team has already shown that introducing a potassium channel into T cells or disrupting the cells' oxygen-sensing machinery enhances their function in mice. It may be possible to empower patients' immune cells with the same modifications using drugs or genetic manipulation.

Restifo's team plans to use their new knowledge to develop better treatments for patients with cancer. Their next step, he says, is to develop clinical trials based on the findings.

Clever D, et al. *Cell*. 2016 Aug 25;166(5):1117-1131.e14.
Eil R, et al. *Nature*. 2016 Sep 14;537(7621):539-543.

The ability of cancer cells to move and spread depends on actin-rich core structures such as the podosomes (yellow) shown here in melanoma cells. Cell nuclei (blue), actin (red), and an actin regulator (green) are also shown.

***Credit:** Julio C. Valencia, CCR, NCI, NIH*

BETTING ON BRD4

A newly revealed target for a protein that drives cancer growth may lead to better treatment options.

After promising results in laboratory experiments, an experimental class of anticancer drugs known as BET inhibitors is now being evaluated in early clinical trials. The drugs target a group of gene-regulating proteins called BETs, which boost gene activity according to chemical marks that they read on the DNA-protein complex known as chromatin. The inhibitors affect the binding of BET proteins to genes that control the growth of cancer cells, and there is hope that BET inhibitors will be effective treatments for a wide range of cancers.

The best-studied BET protein is BRD4, whose activities appear to help drive the growth of many types of cancer cells. This year, research in the laboratory of Dinah Singer, Ph.D., Senior Investigator in CCR's Experimental Immunology Branch, revealed a new way in which BRD4 regulates gene activity. The discovery suggests a path for designing therapies that modulate gene activity more precisely than the BET inhibitors currently in development.

Like other BET proteins, BRD4 recognizes chemical marks on histone proteins, the major protein component of chromatin. Specifically, BRD4 recognizes and responds to acetylation, which is associated with increased gene activity. BRD4 mediates this boost in activity in two ways. Once it has latched onto chromatin near the start of a gene, it attracts other factors that interact with the DNA to turn the gene on. Secondly, it stimulates the activity of the RNA polymerase, the cellular machinery that reads the gene.

Singer and her team found that BRD4 not only reads patterns of histone acetylation along the DNA, but it also modifies chromatin by attaching more acetyl groups of its own. The researchers found that placing an acetyl group on a specific histone site weakens the chromatin fiber and leads to the eviction of histones, unpacking the DNA and making genes in the area more likely to be read. BRD4 adds acetyl groups to sites throughout the genome. Several growth-promoting genes, including the oncogenes Myc and Fos, are among those whose activity is enhanced.

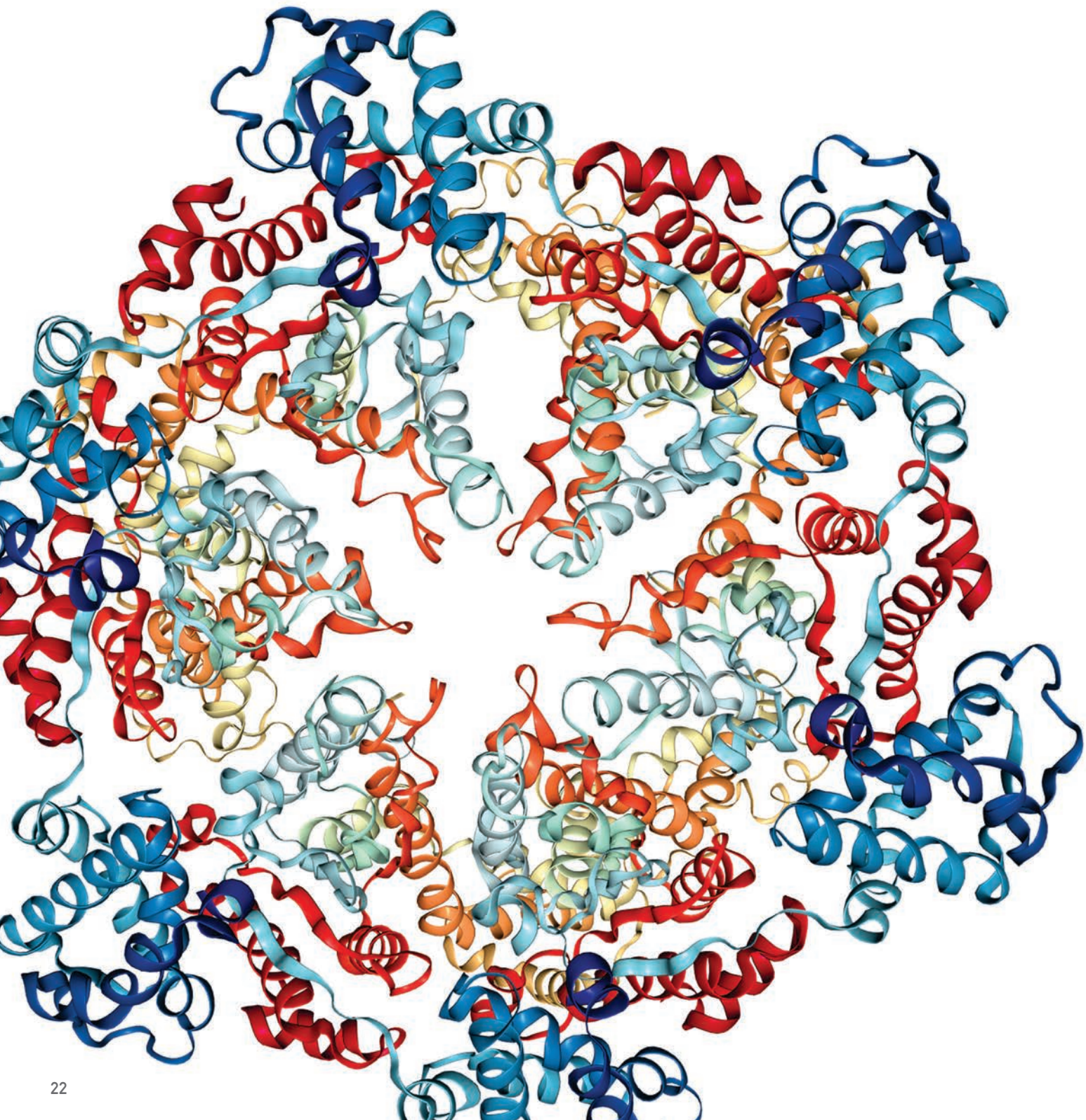
This discovery, reported in the journal *Nature Structural & Molecular Biology*, should enable researchers to develop better BET inhibitors. Based on these findings, it may become possible to specifically target BRD4's enzymatic activities while sparing its other functions and leaving other members of the BET family fully functional, Singer explains. Drugs that work in this way might effectively treat cancers with fewer side effects than treatments that inhibit BET proteins more broadly.

Devaiah BN, et al. *Nat Struct Mol Biol*. 2016 Jun;23(6):540-8.

This scanning electron microscope image shows dendritic cells, pseudo-colored in green, interacting with T cells, pseudo-colored in pink. The dendritic cells internalize the particles, process the antigens, and present peptides to T cells to direct immune responses.

Credit: *Victor Segura Ibarra and Rita Serda, NCI, NIH*

MARKED FOR DESTRUCTION



Proteasomes use a previously unknown method to recognize and process proteins that need to be destroyed.

For cells, disposing of proteins at the right time is as critical as producing essential proteins in the first place. Proteins that linger too long can be disruptive, as can those that are damaged or defective. Cells devote a lot of resources to identifying and destroying these unwanted proteins. The process is so essential that errors in the system have been linked to a range of diseases, including developmental disorders, neurodegenerative diseases, immune disorders and cancer.

The cellular machine that disintegrates unwanted proteins is called the proteasome, a large, barrel-shaped complex with protein-degrading enzymes in its internal core. A large fleet of enzymes patrols cells and marks proteins to be destroyed with a chemical tag that is recognized by the proteasome. This label ensures that proteasomes only destroy proteins that are faulty or unsuitable for a cell's current conditions.

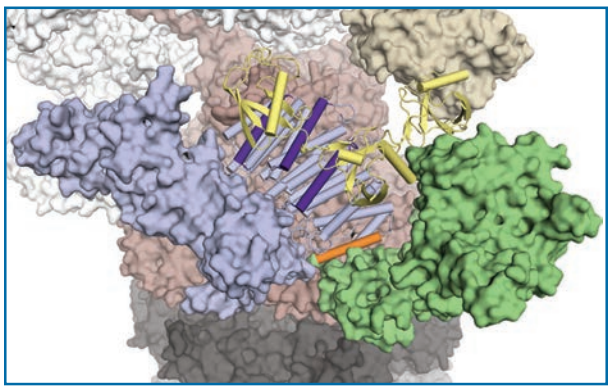
Kylie Walters, Ph.D., a Senior Investigator in CCR's Structural Biophysics Laboratory, studies this regulated protein-disposal pathway. Her work has helped scientists develop a detailed understanding of how proteasomes recognize and degrade target proteins. This is important for cancer because proteasomes are thought to work overtime in tumor cells, which generate more unwanted proteins than normal cells. A cancer cell's reliance on proteasomes to get rid of the excess proteins makes it more vulnerable to drugs that block this function. Since they were introduced in 2003, proteasome inhibitors, such as bortezomib (Velcade) and ixazomib (Ninlaro), have dramatically improved survival for patients with certain blood cancers. Researchers hope to extend this approach to treat other types of cancer.

In a study published in *Science*, Walters and her collaborators, Daniel Finley, Ph.D., from Harvard Medical School and John Engen, Ph.D., from Northeastern University, focused on how proteasomes recognize the chemical tag that marks proteins destined for degradation, a small molecule called ubiquitin. This recognition takes place at the cap of the proteasome, which processes target proteins and ensures only properly tagged molecules enter the core of the proteasome.

Walters and her colleagues discovered recognition sites for ubiquitin and structurally related molecules on a component of the proteasome cap called Rpn1. One of these sites can bind both to ubiquitin tags as well as a shuttle protein that escorts certain tagged proteins to proteasomes, while a second site binds to an enzyme that can remove ubiquitin tags. The tags must be trimmed away from a target protein before it can enter the interior of the proteasome, where it is degraded. According to the team's findings, Rpn1 coordinates the proteasome's recognition of target proteins with this deubiquitination step.

The work suggests a previously unknown way in which proteasomes recognize and process their protein targets. Understanding Rpn1's role in this process should help researchers develop anticancer therapies that target the proteasome differently than existing inhibitors, which block enzymes in the interior of the proteasome. Walters says such drugs might be effective in patients whose cancers have become resistant to the existing drugs and might act synergistically when used in combination.

Shi Y, et al. *Science*. 2016 Feb 19;351(6275).



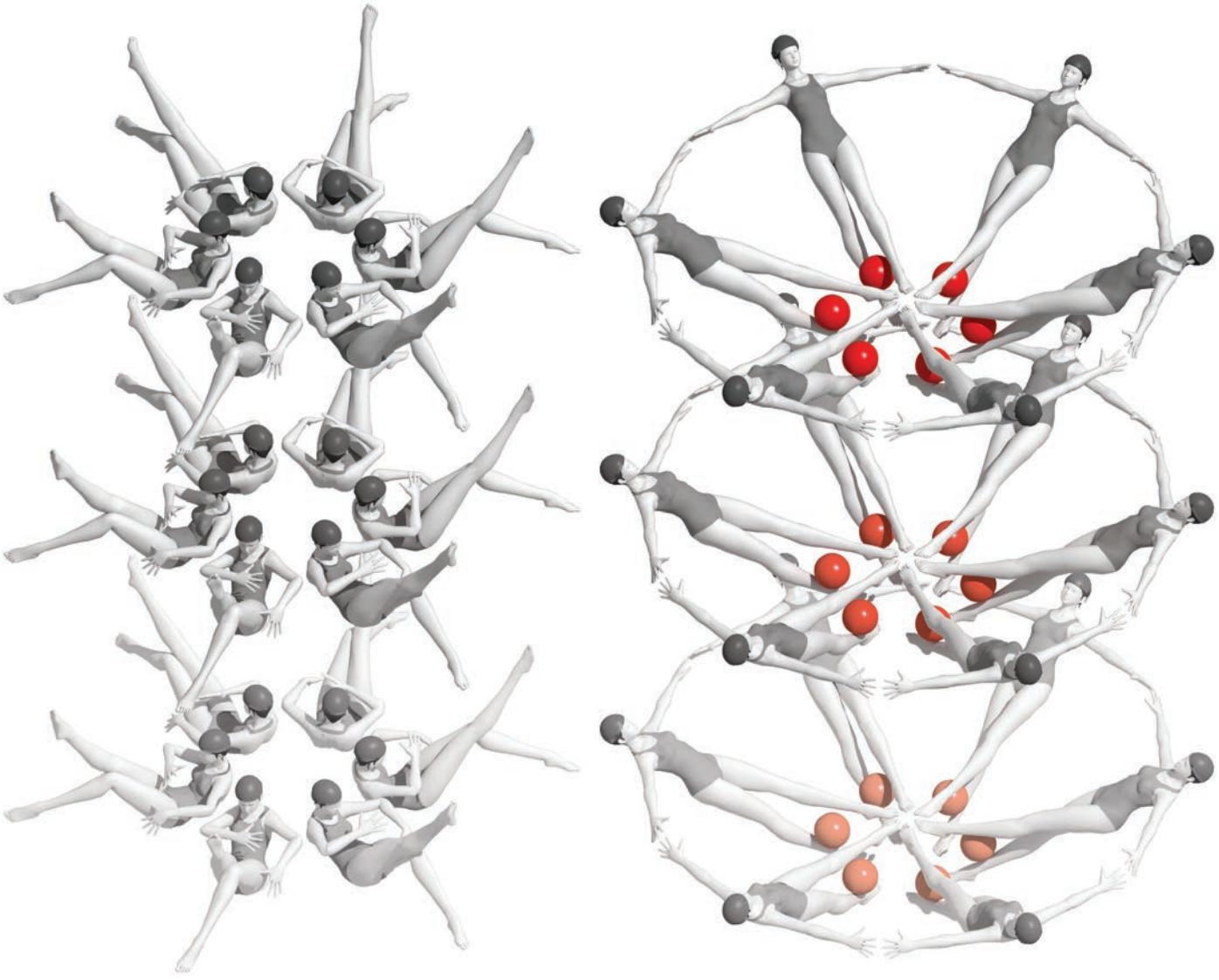
A proteasome is the cellular machine that disintegrates unwanted proteins. It's a large, barrel-shaped complex with protein-degrading enzymes in its internal core.

Credit: *Protein Data Bank ID: 1DO2*

A newly identified ligand-binding hotspot in the proteasome for assembling substrates and cofactors.

Credit: *Xiang Chen, CCR, NCI, NIH*

MOLECULAR FREEZE FRAME



The capture of a molecular arrangement that exists for a fraction of a second may improve drug design.

For more than half a century, researchers have used a method called X-ray crystallography to visualize exactly how atoms are arranged within proteins and other biological molecules. The technique produces remarkably detailed images that can help reveal how molecules function and how their activity might be manipulated with drugs to treat disease. Structures obtained in this way have been instrumental in developing and improving targeted therapies for cancer.

X-ray crystallography generates static snapshots of molecules. This year, a team of scientists led by Yun-Xing Wang, a Senior Investigator in CCR's Structural Biophysics Laboratory, took advantage of groundbreaking new technology to capture the dynamics of a gene-regulating RNA structure at an atomic level. Their image shows a structure called a riboswitch in the process of reorganizing itself to regulate protein production.

Riboswitches are elements at the ends of some messenger RNA molecules that reconfigure themselves in the presence of particular small molecules to alter gene expression. Based on prior work in his laboratory, Wang had speculated that the riboswitch molecule they were studying goes through a transient form that lasts only a few milliseconds after its small molecule binds.

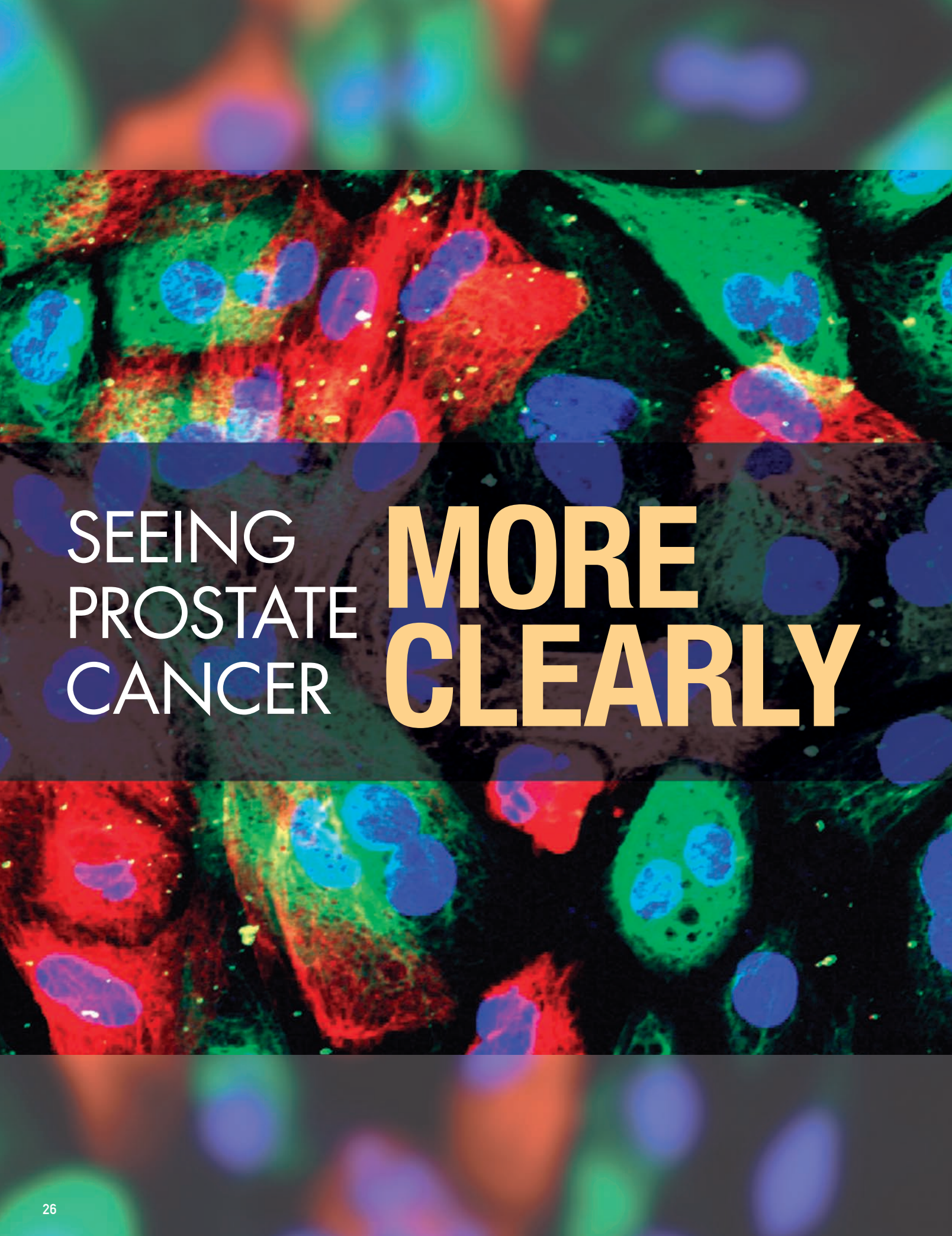
Conventional tools would not be able to capture this transient structure. Wang and his colleagues used an ultrafast, high-intensity radiation source called an X-ray free-electron laser (XFEL). XFEL generates extremely bright X-ray light in pulses lasting less time than it takes light to travel the width of a human hair. For structural biologists, such speed is equivalent to having a very fast shutter on a camera, freezing the action of even the fastest molecular transformations. For their experiments, the scientists used tiny nanocrystals of the riboswitch, which allowed the riboswitch's activating molecules to quickly diffuse through the crystals, triggering a shape change in all RNA molecules in the crystal.

The team's achievement, reported in the journal *Nature*, suggests that crystallography can now be used to capture even the most fleeting steps of biochemical reactions. A series of images captured in this way could allow researchers to watch biological processes unfold in real time with atomic-level detail. Visualizing the conformational changes that proteins, DNA and RNA undergo when they interact is critical to understanding how they function and designing drugs that modify their activities, Wang says.

Stagno JR, et al. *Nature*. 2017 Jan 12;541(7636):242-246.

After ligand binding, riboswitch RNA molecules packed into micro- and nanocrystals rearrange themselves into a new crystal form. Large conformation changes triggered by ligand binding appear to cause the molecules to transition in unison, like synchronized swimmers.

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



SEEING PROSTATE CANCER MORE CLEARLY

A new imaging method enables sensitive detection and monitoring of high-risk prostate cancers.

Early detection and treatment of prostate cancer has the potential to save lives. On the other hand, many prostate tumors never become life-threatening. For men with slow-growing prostate cancers, aggressive treatments and their serious side effects may be unnecessary. Thus, the major challenge in prostate cancer diagnosis is not in finding every tumor but in identifying those that are most likely to cause harm if left untreated.

The standard approach to biopsying prostate cancer is to use an ultrasound probe to visualize the prostate. Ultrasound images enable the physician to see where the biopsy needle enters the tissue and to safely and systematically collect tissue samples from throughout the prostate. However, ultrasound does not give a sufficiently detailed picture of the prostate for physicians to biopsy specific lesions, even when they have been detected separately by magnetic resonance imaging (MRI). Thus there is significant potential to miss clinically important tumors.

Advanced imaging technology is changing clinical practice and allowing physicians to perform much more precise prostate biopsies. The CCR's Urologic Oncology Branch Investigator, Peter Pinto, M.D., along with the Program Director of the Molecular Imaging Program, Peter Choyke, M.D., and the Director of the National Institutes of Health's Center for Interventional Oncology, Bradford Wood, M.D., are at the forefront of developing high-resolution imaging methods for prostate biopsy. Together they have pioneered the use of ultrasound combined with MRI for biopsies from the laboratory to the clinic. Images collected with the two techniques are superimposed on one another during the biopsy, which allows a urologist to directly guide the biopsy needle to areas of the prostate that appear suspicious.

In a 2015 study, the team determined that MRI-ultrasound fusion-guided procedures find more high-risk tumors, those that are most likely to grow quickly and spread, than standard biopsies. In 2016, new studies provided further evidence that fusion-guided biopsy can improve prostate cancer diagnosis.

In April, the team reported in the *Journal of the National Cancer Institute* that combining MRI and ultrasound images makes prostate cancer biopsies more efficient and requires fewer tissue samples than a standard biopsy to detect high-risk cancers. They analyzed biopsies from more than 1,000 men who received both standard and targeted biopsies as part of a clinical trial. Both biopsy methods detected a similar number of cancer cases in the group, but targeted fusion biopsies detected more high-grade cancers than the standard procedure.

Additionally, whereas standard biopsies usually involved the removal of 12 tissue samples, the targeted procedures took an average of only five samples. This is significant because even though prostate biopsies are generally considered safe they can cause bleeding or infection, and decreasing the number of tissue samples needed to diagnose cancer can reduce the occurrence of these complications.

After further analysis of their clinical trial data, Pinto, Wood, Choyke and their colleagues determined that fusion imaging improves clinicians' ability to monitor existing prostate tumors and determine whether they have progressed. In a study reported in the *Journal of Urology*, the team analyzed data from 166 patients with low- or intermediate-risk prostate tumors that were under "active surveillance." Fusion-guided biopsies detected 26 percent more cancer progression than standard biopsies.

This groundbreaking technology is becoming increasingly available at cancer centers in the United States. The new studies suggest that, because of its ability to distinguish prostate tumors that need treatment from those that do not, it will improve the quality of life for many patients and has the potential to become the standard of care.

Siddiqui MM, et al. *J Natl Cancer Inst.* 2016 Apr 29;108(9).
Frye TP, et al. *J Urol.* 2016 Sep 6. doi:pii: S0022-5347(16)31209-5.

Wild-type human prostate cells from an organoid (a man-made construct that resembles an organ). These cells have come from a xenograft where they serve as controls for the study of primary prostate cancer tumor cells, which are also injected into mice and then extracted for characterization.

Credit: *NCI, NIH*

New Faculty

Christine Alewine, M.D., Ph.D.

Christine Alewine has been promoted to a Lasker Scholar Tenure Track Investigator in the Laboratory of Molecular Biology. Her research focuses on using novel therapies to target pancreatic cancer, with an interest in immunotoxin therapeutics and how these can be used to improve outcomes for patients.

Terri Armstrong, Ph.D.

Terri Armstrong has joined the Neuro-Oncology Branch (NOB) as a senior investigator. Dr. Armstrong's work is focused on improving the assessment of patient outcomes measures and their incorporation into clinical trials. She is also exploring the clinical phenotypes and genotypes associated with significant symptoms as well as the underlying biologic correlates of both symptoms and toxicity with the goal of developing interventions to improve patient outcomes.

Ramiro Iglesias Bartolome, Ph.D.

Ramiro Iglesias Bartolome joins the Laboratory of Cellular and Molecular Biology as a Stadtman Tenure Track Investigator. Dr. Iglesias Bartolome is an expert in G-protein-coupled receptors (GPCRs) and their regulation of signaling mechanisms that control tissue-specific stem cell differentiation and renewal. His research focuses on identifying GPCRs that are expressed in epithelial stem cells and that regulate their proliferation and differentiation; identifying and studying heterotrimeric G proteins coupled to the GPCRs; and identifying and characterizing cytoplasmic and nuclear events downstream of the GPCRs and G proteins.

Pedro Jorge Batista, Ph.D.

Pedro Jorge Batista has joined the Laboratory of Cell Biology (LCB) as a Stadtman Tenure Track Investigator. Dr. Batista's research focuses on the determination of the effect of RNA modifications on RNA biogenesis and function and the underlying mechanisms of why RNA molecules are modified or how these modifications affect RNA maturation and function.

John Brognard, Ph.D.

John Brognard is now a Stadtman Tenure Track Investigator in the Laboratory of Cell and Development Signaling. Dr. Brognard's research focuses on identifying and characterizing new protein kinases that function as drivers of human cancer, with the goal of elucidating new targets for therapeutic intervention and drug discovery. He aims to translate his findings to the clinic by developing patient-derived xenograph mouse models of the newly identified kinases and by encouraging the design of therapeutic strategies focused on these new kinase targets.

Natasha Caplen, Ph.D.

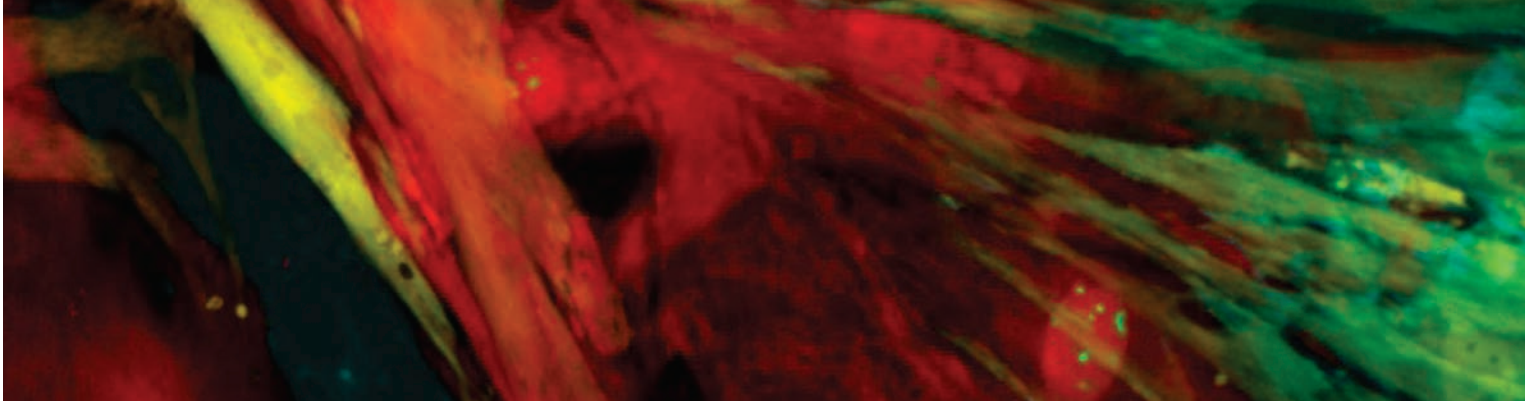
Natasha Caplen is now a Tenure Track Investigator in CCR's Genetics Branch. She joined CCR in 2004 as a senior scientist where she pioneered approaches for exploiting RNAi to investigate cancer biology and treatment and helped establish a trans-NIH facility for genome-wide RNAi screening. Her current research focuses on using functional genetic methods to interrogate specific aspects of the genetic, transcriptional and signaling alternations observed in cancers driven by fusion oncogenes.

Alex Compton, Ph.D.

Alex Compton has joined the HIV Dynamics and Replication Program (HIV-DRP) as a Tenure Track Investigator. Compton's research is broadly focused on the antiviral innate immune response against HIV-1 infection. His work combines cell biology, immunology, virology and evolutionary biology.

Chengkai Dai, Ph.D.

Chengkai Dai is a new Stadtman Tenure Track Investigator in the Mouse Cancer Genetics Program (MCGP). Dai is a pioneer in the field of proteomic stability, and his findings on the interjections of proteotoxic stress response with RAS/MAPK-MEK signaling, cell cycle regulation, protein translation and amyloidogenesis have already laid the foundation for collaborations with members of MCGP. His research focuses on the molecular mechanisms by which proteomic instability may affect genomic instability, cell invasion and autophagy - areas that hold promise to unveil new molecular pathways for targeted cancer therapy.



Jonathan Hernandez, M.D.

Jonathan Hernandez has joined the Thoracic and Gastrointestinal Oncology Branch (TGIB) as a Tenure Track Investigator. Dr. Hernandez will be developing a clinical program focused on innovative surgical management of pancreatic and hepatobiliary malignancies, including the development of novel approaches to the diagnosis and treatment of these neoplasms through his laboratory research. His service responsibilities will include surgical management of patients with GI malignancies on TGIB protocols, as well as consults from other NIH services.

Jung-Min Lee, M.D.

Jung-Min Lee is now a Lasker Scholar Tenure-Track Investigator in the Women's Malignancies Branch (WMB). Dr. Lee first joined CCR as a medical oncology clinical fellow and most recently served as an assistant clinical investigator. Her research focuses on investigating the biology of breast and ovarian cancers, developing novel therapeutic strategies and evaluating these therapeutic approaches in clinical trials. She is the principal investigator on numerous clinical trials, including two parallel phase 1 and 2 studies combining either olaparib or cediranib with an immune checkpoint anti-PDL1 inhibitor for patients with ovarian cancer and triple negative breast cancer.

Frank Lin, M.D.

Frank Lin has joined the Molecular Imaging Program (MIP) as a Lasker Clinical Research Scholar. Dr. Lin will perform pre-clinical and clinical research in the use of targeted radionuclide therapy (tRNT). He will conduct research with promising new targeted agents capable of harnessing therapeutic radioistopes as well as imaging isotopes.

Jagan Muppidi, M.D., Ph.D.

Jagan Muppidi has joined the Lymphoid Malignancies Branch (LYMB) as a Stadtman Tenure Track Investigator. Dr. Muppidi will develop an independent research program centered on mechanisms of lymphomagenesis and collaborate on clinical investigations into the treatment of lymphoma.

Ramaprasad Srinivasan, M.D., Ph.D.

Ramaprasad Srinivasan has been appointed as a Tenure Track Investigator in the Urologic Oncology Branch (UOB). Dr. Srinivasan is a recognized expert in genitourinary oncology, notably in targeted therapeutic approaches for patients with advanced forms of renal cell carcinoma. His research focuses on developing and conducting clinical trials using molecular treatment approaches targeting kidney cancer pathways and targeted therapeutic agents in patients with localized and advanced forms of kidney cancer. He is currently investigating a variety of newer targeted agents in clear cell and papillary kidney cancer, as well as hereditary kidney cancer syndromes, such as von Hippel-Lindau, hereditary leiomyomatosis and renal cell cancer and hereditary papillary renal cell cancer.

Ping Zhang, Ph.D.

Ping Zhang has joined the Structural Biophysics Laboratory (SBL) as a Stadtman Tenure Track Investigator. Dr. Zhang's expertise is in the fields of X-ray crystallography and cryo-EM for the study of multicomponent complexes relevant to cancer and human disease. Her program is expected to be synergistic with the existing program with the SBL and to expand the expertise into the rapidly developing area of cryo-EM investigation of proteins and protein-complexes.

Awards & Honors

Stephen Hughes, Ph.D., received the 2017 Distinguished Research Career Award from the Center for Retrovirus Research of Ohio State University.

Stuart Le Grice, Ph.D., was the 2015 recipient of the DHHS Career Achievement Award.

Elaine Jaffe, M.D., received the Arthur Purdy Stout Award from the Society of Surgical Pathologists.

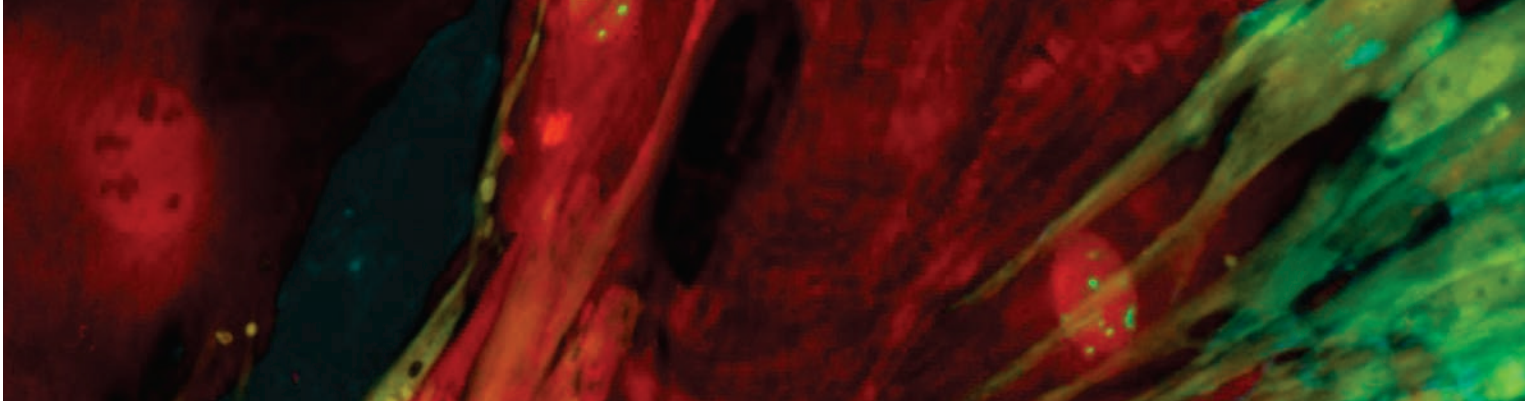
Michael Lichten, Ph.D., was elected to the American Academy of Arts and Sciences.

Marston Linehan, M.D., was selected for the 2016 Ramon Guiteras Award from the American Urological Association.

Tom Misteli, Ph.D., received the 2016 Herman Beerman Award by the Society for Investigative Dermatology.

Glenn Merlino, Ph.D., was elected as a member of the 2016 class of American Association for the Advancement of Science (AAAS) Fellows in the section on Biological Science.

Steven Rosenberg, M.D., Ph.D., was the recipient of the 2016 Novartis Prize for Clinical Immunology.



Kandice Tanner, Ph.D., received the 2016 Young Fluorescence Investigator Award from HORIBA Scientific.

Brigitte Widemann, M.D., received the 2016 Humanitarian Award from the Children's Tumor Foundation.

Howard Young, Ph.D., was chosen for the 2016 Honorary Life Membership Award of the International Cytokine and Interferon Society.

Robert Yarchoan, M.D., was elected to the Association of American Physicians.

Jeffrey Schlom, Ph.D., James Gulley, M.D., Ph.D., Claudia Palena, Ph.D., and Chris Heery, M.D., were members of the NCI team that received the 2016 Excellence in Federal Technology Transfer National Award by the National Federal Laboratory Consortium for Technology Transfer for the technology "Development of First Immunotherapy to Treat Chordoma, Rare Bone Cancer."

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