The variety of marbles depicted on the cover represents the new discoveries CCR scientists have made to further appreciate and understand the heterogeneous nature of tumors and individual cells.

Credit: iStock

CONTRIBUTORS
Brenda Boersma-Maland
Chia-Chi Charlie Chang
Veronica Falconieri Hays
Kelly Haskins
Li Gwatkin
Abbie Harrison
Allen Kane
Leslie Kossoff
Joseph Meyer
Jennifer Michalowski
Mike Miller
Melissa Pandika
Lianne Priede
The **MISSION** of CCR is to improve the lives of cancer patients by solving important, challenging and neglected problems in cancer research, prevention and patient care through:

- A world-leading basic, translational and clinical research and patient-care program
- An institutional focus on high-risk and long-term projects, unmet needs and pursuit of unexplored ideas
- Leadership and coordination of national disease networks and development of technology resources for the cancer community
- Partnerships with academic institutions, commercial entities and patient advocacy groups
- Training of the next generation of the biomedical workforce.
<table>
<thead>
<tr>
<th>Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>26</td>
</tr>
<tr>
<td>02</td>
</tr>
<tr>
<td>14</td>
</tr>
<tr>
<td>29</td>
</tr>
<tr>
<td>04</td>
</tr>
<tr>
<td>16</td>
</tr>
<tr>
<td>31</td>
</tr>
<tr>
<td>06</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>08</td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>22</td>
</tr>
</tbody>
</table>
The stated mission of the NCI Center for Cancer Research (CCR) is to improve the lives of cancer patients by solving important, challenging and neglected problems in cancer research and patient care. One of the clearest indicators of our impact is the number of new treatments we bring to patients. We are pleased that in the past year, no fewer than four new clinical approaches developed by CCR physician-scientists were designated as breakthrough therapies by the U.S. Food and Drug Administration (FDA), and since 2018, three additional novel therapies were formally approved by the FDA.

The development of these innovative therapeutic strategies is fueled by our broad research program that spans the basic-translational-clinical spectrum as well as by our stable funding. As a result, every year produces a remarkable number of discoveries.

This issue of Milestones features some of the most impactful science conducted in the past year in CCR. These advances include new insights into how genomes are organized and how DNA and RNA function in cells, how cellular processes and signaling events function in healthy cells and how they are affected in cancer. Other major discoveries this year include how cancers become metastatic and what drives the proliferation of cancer cells.

As highlighted on the cover, this year has also deepened our appreciation of the extraordinarily heterogeneous nature of tumors and of individual cells. We have developed important new tools, including artificial intelligence approaches for diagnosis, clever chemical probes to investigate the metabolic changes in cancer and new clinical approaches to help fill unmet needs of patients who have had very limited treatment options.

The breadth of scientific areas covered by these milestone discoveries reflects the vibrant and diverse research program in CCR and highlights our strengths in many of the key areas of modern cancer research. We are well positioned to continue making groundbreaking discoveries and inventing new ways to treat patients. Our goal is to help patients; our research makes it possible.

Tom Misteli
Director
NCI Center for Cancer Research
ADVANCING AGAINST MULTIPLE MYELOMA
An immunotherapy treatment strategy for advanced multiple myeloma shows promise in the clinic.

In multiple myeloma, white blood cells known as plasma cells divide uncontrollably in the bone marrow. Patients with the disease require multiple treatments to try to slow the division but even with therapy, most of them eventually relapse, and only about half survive for five years after diagnosis.

Now, a multicenter phase I clinical trial of a chimeric antigen receptor (CAR) T-cell immunotherapy has shown promise in patients with advanced multiple myeloma. Researchers led by James N. Kochenderfer, M.D., reported their findings in the New England Journal of Medicine.

CAR T-cell therapy involves collecting disease-fighting white blood cells, known as T cells, from patients and engineering them in the laboratory to express a protein that targets the cancer cells. These modified T cells are then multiplied exponentially and infused back into patients where they further expand their numbers, building a vast army poised to destroy cancer cells that express the protein target. CAR T cells were first developed in the 1990s and refined in the 2000s. In 2017, the FDA approved the first CAR T-cell therapy, Kymriah, for some adults and children with advanced leukemia and shortly thereafter approved Yescarta—initially developed at CCR—for some adults whose large B-cell lymphoma has relapsed or no longer responds to treatment.

The type of CAR T-cell therapy used in this trial targets the B-cell maturation antigen (BCMA), a protein expressed by multiple myeloma cells but not healthy cells. Kochenderfer’s lab developed the first anti-BCMA CAR T-cell therapy in 2013 and conducted the earliest clinical trial of anti-BCMA CAR T cells.

Kochenderfer and his team enrolled 33 patients whose multiple myeloma had relapsed or persisted after at least three prior lines of therapy. In the first part of the trial, patients received an increasing number of CAR T cells until the team determined the maximum dose patients could tolerate. In the second part, this dose was evaluated for safety, tolerability and activity.

Nearly a year after receiving treatment, 85 percent of the patients’ tumors had shrunk, including 15 patients who had no sign of disease. The median progression-free survival across all patients was 11.8 months.

After patients undergo CAR T-cell therapy, they often do not need any treatment for many months, a major advantage over currently available multiple myeloma therapies, which often require chemotherapy and medication every other week. In Kochenderfer’s trial, CAR T-cell therapy allowed most patients to take a prolonged break from these often toxic treatments with some patients still not requiring any further therapy.

A phase II trial called KarMMA is underway to test the efficacy of the therapy and has already accrued patients in the United States, Canada and Europe. If shown to be active in clinical trials, anti-BCMA CAR T-cell therapy could offer an effective option for patients with advanced multiple myeloma.

CHARTING THE CHEMISTRY OF
HEREDITARY KIDNEY CANCER
In their quest to grow and divide, tumor cells process nutrients differently from healthy cells. This process of metabolism often creates an accumulation of cancer-promoting molecules, known as oncometabolites, that drive tumor formation. However, the mechanisms by which they do so have remained unclear.

To unravel these mechanisms, CCR scientists looked at hereditary leiomyomatosis and renal cell carcinoma (HLRCC), a hereditary cancer disorder driven by the oncometabolite fumarate. Using a novel chemical mapping approach, CCR scientists have identified more than 100 proteins that are modified by fumarate, which accumulates in HLRCC. Their findings, published in *Nature Chemical Biology*, may shed light on how metabolic changes contribute to cancer and hint at new approaches to targeting tumor cells.

Jordan Meier, Ph.D., and W. Marston Linehan, M.D., used a technology developed by collaborator Eranthie Weerapana, Ph.D., of Boston College, to rapidly map how fumarate affects cysteine reactivity, a fundamental chemical property important for protein function. In total, they identified 105 proteins that interact with fumarate and were altered in HLRCC, many of them involved in key tumor signaling pathways.

One of these modified proteins is part of the SWI-SNF protein complex, which binds to DNA and remodels the genome inside of cells. Meier and colleagues had previously found this complex to be dysfunctional in cancer cells in which fumarate accumulated. Interestingly, studies by other researchers had shown that a class of drugs known as EZH2 inhibitors, which target a different DNA-binding complex, were lethal to cells with disruptions in the SWI-SNF complex, pointing to them as a possible therapeutic option for kidney cancer.

The researchers also discovered that fumarate is especially reactive in the acidic environments found in cancer cells. Unlike healthy cells, cancer cells rely primarily on a metabolic process that produces lactic acid, thus creating the perfect storm for the accumulated fumarate to react with its target proteins. Clinicians could one day use the modified proteins as biomarkers to detect the disease, Meier says.

The findings by Meier and Linehan’s team may have relevance for other types of cancer beyond HLRCC, namely those in which fumarate accumulation has also been identified, such as non-hereditary kidney cancer, neuroblastoma, colorectal cancer and adrenal gland tumors.


Mapping of metabolic changes reveals the proteins that are altered in kidney cancers, offering clues for how the disorder emerges.

*The radar and cell depict the new technology developed by the study authors to map how the oncometabolite fumarate interacts with proteins in the cell and influences tumor formation.*

**Credit:** Joseph Meyer, Scientific Publications, Graphics and Media, Frederick National Laboratory, NCI, NIH
ONE GENOME
MULTIPLE SHAPES
AND FUNCTIONS
In a tumor, not all cells are the same. Even two neighboring cells can demonstrate vast differences in behavior. Some evidence suggests that this heterogeneity can help tumors adapt to their environment and develop resistance to therapy. CCR investigators have now uncovered how genomes are organized and how they function varies greatly between individual cells.

In a study published in Cell, and expanded on in Science, researchers led by Tom Misteli, Ph.D., showed that the three-dimensional organization of the genome differs vastly from one cell to the next. Meanwhile, Daniel R. Larson, Ph.D., and colleagues found that genes undergo rapid cycles of activity and inactivity and that these bursts of gene activity are not coordinated among individual cells. They reported their findings in a separate study, which appeared in Cell.

Misteli and his team investigated how the genome is folded in individual cells. To do so, they harnessed deep-imaging methods to measure how often more than 100 chromatin regions within individual skin cells are physically associated with each other. Interestingly, they found that genome regions interacted only rarely, revealing remarkable heterogeneity in the configuration of the genome between cells. Most intriguingly, even the two copies of the same gene present in every cell nucleus behaved independently of each other.

The Larson laboratory used advanced microscopy technology to visualize the synthesis of single RNA molecules in living cells. Based primarily on their observations of an estrogen-responsive gene in human breast cancer cells, the researchers found that similar genes that control RNA synthesis have periods of inactivity that can last anywhere from minutes to days. This randomness could explain why the expression of a single gene can vary between cells.

They also found that when the genes that control RNA synthesis are activated by signals like estrogen, a change in genome conformation occurs, which is consistent with the observation by the Misteli team that the organization of the genome can differ in individual cells. In other words, the randomness of RNA synthesis may be related to the extensive variability in the 3D organization of the genome from one cell to the next.

It is likely that variability in genome organization and activity underlie physiological processes. For instance, differences in periods of activity and inactivity of key genes may result in distinct responses of individual cells to drugs or immunological challenges. Uncovering the molecular differences in the organization and behavior of individual cells will be key to understanding how the heterogeneous nature of tumors contributes to their growth.


Although each of the objects shown in this photo is a marble, each vastly differs in its appearance. In much the same way, although every cell contains the same genomes, its appearance—that is, its 3D configuration—varies greatly from one cell to the next.

Credit: iStock
A MOSAIC OF LIVER TUMOR CELLS
Cellular diversity may enable some liver tumors to reprogram their microenvironments and render immunotherapy less effective.

Tumors are complex communities of cells. Cancerous cells intermingle with noncancerous cells, and additional diversity arises as a tumor’s cancer cells divide and acquire new genetic mutations. Now, CCR scientists have discovered that the extent of cellular diversity within a tumor may shape its response to immune checkpoint inhibitors in patients with liver cancer. According to a new analysis, patients who responded best to these experimental immunotherapies in clinical trials had tumors less cellularly diverse than those for whom the treatment was ineffective.

Liver cancer has been on the rise in the United States for most of this century, and the prognosis for patients with advanced disease remains poor. To develop new treatments that effectively target liver cancers, a better understanding of the tumors’ cellular compositions is much needed, says Xin Wei Wang, Ph.D.

In research reported in Cancer Cell, Wang and his colleagues set out to characterize cellular diversity in samples of liver tumors from 19 patients who had received immune checkpoint inhibitors through clinical trials at the NIH Clinical Center. A small percentage of patients in the trials, which were led by Tim Greten, M.D., had seen their cancer go into remission for years in response to the treatment.

Wang’s team used single-cell sequencing to profile the RNA molecules present in thousands of individual cells from the tumor biopsies, then used their findings to assess the cell-to-cell variation in individual tumors. That approach led them to discover that all of the samples in their study with low cellular diversity came from patients whose cancers had responded well to immunotherapy.

An expanded analysis, which used RNA data to assess cellular diversity in hundreds of additional liver tumors, yielded similar results. Patients whose tumors had a low level of cellular diversity tended to have better clinical outcomes than those whose tumors had higher levels of cellular diversity.

The team also found that tumor microenvironments differed in ways that correlated with the level of cellular diversity of a tumor. For instance, T cells in low-diversity tumors were in a much more active state—and thus potentially capable of killing cancer cells—than those found in other tumors. Wang says the distinct differences between microenvironments in the two groups of tumors suggest that high-diversity tumors may actively reprogram nearby cells, creating more hospitable conditions for their own survival.

Wang hopes that by understanding the impact of cellular diversity within liver tumors, researchers will be better positioned to devise treatments for patients whose cancer is unlikely to respond to checkpoint inhibitors alone. This study hints that one factor that may influence tumors’ response to immunotherapy is a protein called vascular endothelial growth factor (VEGF), which they found in greater abundance in high-diversity tumors than in low-diversity tumors. He says combining checkpoint inhibitors with drugs that block VEGF—a strategy already being tested in clinical trials and showing very promising results—might enable a better treatment response by interfering with tumors’ effects on their microenvironments.

SUPERCHARGING MESSENGER RNA
RNA plays a variety of roles inside cells, but its main role is to serve as a template for translating the genetic information encoded in DNA into proteins. Scientists are increasingly recognizing that the way RNA molecules do their work can shift when they are modified by the addition or removal of small chemical groups. These changes are similar to chemical modifications on DNA that help determine when or where genes are switched on. Those that occur on the subset of RNA known as messenger RNA are collectively called the epitranscriptome.

The laboratory of Shalini Oberdoerffer, Ph.D., has now uncovered a new chemical tag on RNA that boosts the efficiency with which specific proteins are manufactured. The modification, which Oberdoerffer’s team found on thousands of different messenger RNA molecules inside human cells, is carried out by an enzyme called N-acetyltransferase 10 (Nat10), which is disrupted in some cancers.

There are more than one hundred ways an RNA molecule can be modified after it is synthesized. Scientists around the world are working to map these changes and understand their functional consequences, even as they explore how disruptions to the epitranscriptome contribute to cancer and other diseases. The discovery by Oberdoerffer’s team, reported in Cell, reveals a type of modification not previously known to occur on messenger RNA. What makes this modification of the addition of an acetyl group to RNA special is that it is the first RNA modification found to increase protein production.

Oberdoerffer’s team discovered that when a messenger RNA is acetylated by Nat10, it becomes more stable, meaning it persists longer within the cell and can be used repeatedly to generate more copies of the encoded protein. Furthermore, the change enables the cell’s protein-making machinery to translate the information encoded by the RNA more efficiently, further enhancing production of that particular protein.

The Oberdoerffer lab found that the modification particularly impacts messenger RNAs that, prior to modification, are translated into proteins less efficiently than others. That inherent inefficiency creates an opportunity to fine-tune gene expression as the needs of a cell change, Oberdoerffer says. Nat10 likely acts quickly to acetylate target-messenger RNA molecules when demand increases for the proteins they encode, perhaps due to environmental cues. This is an especially powerful strategy for responding to change because acetylation is reversible; when it is time for protein production to be dialed back down, acetylation marks can be removed.

The discovery reveals a new layer of information embedded in a cell’s messenger RNA. It also suggests a potential strategy for future drug development. With a deep understanding of the epitranscriptome, it may one day be possible to manipulate it in order to adjust the levels of disease-associated proteins, Oberdoerffer says.

*A newly discovered chemical modification to RNA allows cells to rapidly ramp up production of certain proteins.*

![Credit: Veronica Falconieri Hays, Falconieri Visuals](image)
TRACKING CANCER CELLS IN TRANSPARENT FISH
Zebrafish offer unique insights into how cancer spreads to distant organs.

In CCR’s Laboratory of Cell Biology, Kandice Tanner, Ph.D., and her team are watching human cancer cells travel through the bodies of small, translucent fish. As the cells make their way through the animals’ circulatory systems, the researchers are learning how cells migrate through the body and embed themselves in distant organs.

Metastasis, the spread of cancer from a primary tumor to new locations in the body, is an unpredictable and lethal process. When cancer cells migrate from their original location, new tumors tend to occur in other particular sites—metastatic breast cancer, for example, most often makes its way to patients’ bones, brain, liver or lungs. Why a particular cancer type spreads to only certain organs is not known.

Tanner wants to understand the physical factors that influence where metastatic cancer cells travel and why they settle where they do. She and her team are looking for answers in zebrafish because when the fish are very young, their bodies are almost completely transparent; therefore, Tanner can track the cancer cells’ entire journey as they make their way through the animal.

To explore whether they could use this unconventional model system to help reveal the forces that drive metastasis, Tanner’s team began by injecting human cancer cells into the circulatory systems of developing zebrafish when the animals were just a few millimeters long. Over the subsequent five days, the scientists monitored the cells as they moved through the animals’ circulatory systems, and some made their way into either the brain or a larval structure called the caudal vascular plexus (CVP), a small web of blood vessels. The researchers found that both the physical architecture of a tissue and cancer cells’ molecular compatibility with their microenvironment are important for determining where metastatic cells end up.

Physically, Tanner says, blood vessels in the brain are different from those in the CVP. In the fish’s brain, tumor cells travel through straight and narrow vessels, whereas in the CVP, they follow a more twisted path. Migrating tumor cells were more likely to stop their journey amidst the twists and turns of the CVP than in the brain.

Once stalled, some tumor cells managed to work their way out of the blood vessels into surrounding tissue—a process that is essential for metastatic tumor cells to colonize an organ. Tanner and her colleagues showed that this step was dependent not only on the architecture of the blood vessels but also on the molecular makeup of cells. Some were inherently better suited to invade the CVP, whereas others established themselves more readily in the brain. By genetically manipulating the cells, the researchers could alter these tendencies.

These findings, reported in Cell Systems, demonstrate the power of zebrafish for teasing out how migrating cancer cells sense and respond to physical cues in their environment and what allows metastatic cells to survive and grow in new surroundings. Ultimately, Tanner says, a deep understanding of the early events in metastasis might one day make it possible to redirect circulating tumor cells in patients so that new tumors, if they arise, will more likely occur in sites where they will be less harmful or easier to treat.

New insights into the regulatory mechanisms of cilia formation could help explain their abnormalities in cancer.

Cilia, the Latin term for eyelashes, are slender, hair-like protrusions found on the surface of many cell types. Cilia are assembled by centrioles, cylindrical structures that are also important for proper cell division during mitosis. Although they may look delicate, cilia are involved in a number of crucial cellular functions, including sensing changes in the environment, the movement of cells, and sending and receiving molecular signals. Defects in the assembly and function of centrioles and cilia have been linked to several genetic diseases and cancers.

CCR investigators have now uncovered new regulatory mechanisms for cilia assembly. In a study in *Developmental Cell*, Christopher J. Westlake, Ph.D., and his team showed that the Akt protein regulates a key step in initiating cilia formation. Meanwhile, researchers led by Jadranka Loncarek, Ph.D., in an article in *Nature Communications*, characterized the ultrastructure and dynamics of centriole distal appendages, structures localized on the tip of centrioles that mediate cilia formation.

Previously, Westlake and his team discovered that a protein called Rab11 shuttles another protein, Rabin8, on membrane vesicles to the centriole, spurring cilia to form. In the *Developmental Cell* study, they demonstrated in various healthy human cells that Akt, a protein involved in cellular signaling, blocks these interactions and cilia formation.

The Loncarek laboratory used advanced microscopy techniques to precisely map the position of distal appendage proteins to understand when and how they assemble on the centriole. They also demonstrated that distal appendages undergo dramatic remodeling prior to cell division, challenging the view that they remain unchanged throughout the cell cycle.

These two new studies on centriole and cilia assembly mechanisms unearth how these critical processes occur in healthy cells and could help explain how they go awry in human disease.

This image depicts the spatial arrangement of four distal appendage proteins as visualized by correlative stochastics optical reconstruction microscopy (STORM) and electron microscopy (EM). The STORM signal of each protein was pseudo-colored and combined to create the colors seen here.

**Credit:** Jadranka Loncarek, CCR, NCI, NIH


A SMALL TARGET WITH A
BIG EFFECT
The growth of most cancer cells is fueled by networks of genes, yet therapeutic strategies often target only a single gene. New research from CCR scientists suggests that people with rhabdomyosarcoma may benefit from a class of drugs known as histone deacetylase inhibitors, which slows the activity of an entire set of cancer-driving genes.

Rhabdomyosarcoma, a cancer most often diagnosed in children, develops in the body’s soft tissues and evolves most commonly from immature muscle cells. Aggressive cases of the disease are often driven by a rearrangement within the genome known as a PAX fusion, which occurs when parts of two chromosomes fuse together. This change disrupts a gene network that guides the development of fully functional muscle cells. When a PAX fusion is present, muscle-cell progenitors fail to mature properly and grow excessively instead.

Javed Khan, M.D., realized that the PAX fusion presented an exploitable vulnerability. The disrupted genes that drive the growth of these cancers are part of a core-regulatory circuit, a type of network whose genes are regulated differently than other genes. Because of this, Khan suspected there might be a way to selectively shut down the PAX-fusion-regulated circuit in rhabdomyosarcoma cells. That, he hoped, might halt their growth.

Working with CCR’s Molecular Targets Laboratory, Khan’s team screened tens of thousands of compounds, seeking any that disabled the core-regulatory circuitry of rhabdomyosarcoma cells without disturbing other genes. According to results published in *Nature Communications*, one of the drug classes that was highly potent included small molecules referred to as histone deacetylase (HDAC) inhibitors. These compounds alter cells’ ability to process and interpret acetylation, a chemical modification that occurs on the histone proteins that organize DNA.

Inhibitors of histone deacetylation are known to affect how the genome is folded inside cells. In intricate work, Khan and his team discovered that HDAC inhibitors interfered with a mode of gene regulation that requires DNA to form a loop, bringing a distant regulatory region close to its target genes. By mapping the three-dimensional shape of the genome, they showed that HDAC inhibitors prevented DNA from assuming the correct organization, thereby preventing activation of PAX-fusion-controlled genes. Importantly, this effect was not limited to a single gene but affected an entire network of genes that are misregulated in rhabdomyosarcoma. The team reported these findings in *Nature Genetics*.

Khan says this new understanding gives researchers the information they need to begin exploring whether histone deacetylase inhibitors, likely in combination with other drugs, can treat rhabdomyosarcoma in patients who do not respond well to current therapies. He is also optimistic that this strategy for targeting entire networks of genes may be an effective way to treat other types of transcription-driven cancers.


---

Studies of the pediatric cancer rhabdomyosarcoma suggest a way to exploit the complexity of gene networks to intervene in cancer growth.
SMARTER PROSTATE CANCER DIAGNOSIS
When a blood test suggests the possibility of prostate cancer, a urologist biopsies the patient's prostate to find out whether a tumor is present. Increasingly, such biopsies are guided by MRI/ultrasound fusion, a CCR-developed imaging technique that allows a urologist to precisely place biopsy needles into suspicious areas of the tissue, rather than using the older approach of sampling the tissue in a systematic but untargeted way, guided only by ultrasound.

This approach can improve the detection of clinically significant prostate cancers, but using it effectively requires a great deal of expertise. A team of CCR researchers, led by Peter Choyke, M.D., F.A.C.R., and Baris Turkbey, M.D., have now enhanced the usability of this cutting-edge diagnostic method by developing artificial intelligence (AI) tools that enable users to more easily detect tumors.

Making sense of an MRI of the prostate is inherently challenging. The gland is located deep within the pelvis, crowded among other organs and a distracting array of blood vessels. Cancer-associated changes in this region can be difficult to detect, even for a trained radiologist.

Choyke and Turkbey want the MRI/ultrasound fusion technology they developed to be as useful as possible, even to clinicians who are not experts in its use. Thus, they have turned to AI to support radiologists as they interpret the complex images at the heart of the technique. The tools they have developed are based on the same kinds of computer-vision algorithms used to analyze satellite imagery and guide self-driving cars, fine-tuned to differentiate between healthy prostate tissue and potentially problematic areas.

To ensure their algorithms will perform well even on complex or ambiguous images, the team trained the program with data from hundreds of MRI scans, incorporating variations in quality and an assortment of complicating factors. CCR experts carefully analyzed each scan, identifying potentially cancerous areas and scoring their severity so they could teach the computer what to look for.

The result, the researchers say, is a set of AI tools that will act like a deeply trained expert offering guidance to radiologists. The tools were tested this year by radiologists at multiple institutions with varying levels of experience who read MRIs from more than 200 patients. Based on their findings, the group reported in Oncotarget that the tools have the potential to improve the detection of cancers that, because of their location within the prostate, are particularly difficult to detect.

AI is already poised to significantly impact how prostate cancer is diagnosed, but Turkbey and Choyke say the new tools are only a first step toward a more ambitious goal. Ultimately, the two scientists would like to see AI offer patients and their doctors more useful diagnoses than are available today. They say tools that integrate information from images, biopsy samples and genomic data could one day help to determine not just where in the prostate a tumor is located but how likely it is to progress. Such an advance would allow patients to begin receiving individualized treatments for their cancer as soon as possible.

RETHINKING PREVENTION OF

GRAFT vs. HOST DISEASE
A drug routinely used to prevent the adverse effects of bone marrow transplantation works differently than widely thought.

Many patients with advanced blood or bone marrow cancers have no choice but to undergo treatment with a bone marrow transplant. However, the procedure carries the risk of graft-versus-host disease (GVHD), a potentially fatal condition in which the immune cells in the transplant view the recipient’s body as foreign and mount an attack against it.

To prevent GVHD, transplant recipients can be treated early after transplant with a drug called cyclophosphamide. This commonly used drug has long been thought to work by eliminating the disease-fighting T cells that turn against the recipient’s body. Research led by Christopher G. Kanakry, M.D., and published in the Journal of Clinical Investigation, challenges this theory, suggesting that cyclophosphamide impairs the function of these T cells rather than eliminating them.

In the 1990s, studies in skin grafts in mice reported that cyclophosphamide eliminated the T cells that respond to the transplant. Since then, this has been the accepted mechanism for how the drug prevents GVHD in bone marrow transplant patients. However, this model does not square with clinical observations. Up to 80 percent of patients experience low-to-intermediate grade acute GVHD, despite undergoing cyclophosphamide treatment, which should not occur if the drug eliminates the T cells that cause GVHD.

Kanakry and his team investigated the effects of the drug in mice that had undergone bone marrow transplantation. They found that the percentages of T cells reactive to the recipient were roughly equal to or greater in cyclophosphamide-treated mice than in untreated mice. They also saw that these recipient-reactive donor T cells isolated from mice treated with cyclophosphamide had a dampened immune response when cultured with host cells. In addition, when they were infused into new recipient mice, the result was lower-grade GVHD than with donor T cells isolated from untreated mice.

The results suggest that the drug does not eliminate T cells but impairs them enough to prevent them from causing severe GVHD while still potentially allowing them to trigger lower-grade acute GVHD, consistent with clinical observations. Now, the Kanakry laboratory is investigating the specifics of how the drug impairs the T cells. He thinks that understanding how cyclophosphamide prevents GVHD will potentially allow for the rational development of new strategies that could later improve outcomes for patients undergoing bone marrow transplantation and could have relevance for other types of tissue transplants as well as autoimmune diseases.

Kanakry notes that the protective environment of CCR, which nurtures high-risk research, was critical to being able to steadily pursue these studies that challenge a widely accepted theory.

Sridhar Hannenhalli, Ph.D.
Sridhar Hannenhalli, Ph.D., has joined the Cancer Data Science Laboratory as a Senior Investigator. His lab harnesses a variety of high-throughput omics data to address fundamental biological questions as they pertain to both normal organismal functions and diseases with a special emphasis on cancer.

Peng Jiang, Ph.D.
Peng Jiang, Ph.D., has joined the Cancer Data Science Laboratory as its first Stadtman Tenure Track Investigator. His research focuses on developing integrative frameworks that leverage big-data resources in public domains to identify regulators of cancer therapy resistance.

Mary Kearney, Ph.D.
Mary Kearney, Ph.D., has been appointed as a Senior Scientist in the Host-Virus Interaction Branch of the HIV Dynamics Replication Program. She conducts research on the emergence of HIV drug resistance, the persistence of HIV during antiretroviral treatment (ART) and the sources of rebound viremia after stopping ART.

Laurie Krug, Ph.D.
Laurie Krug, Ph.D., has joined the HIV and AIDS Malignancies Branch as a Stadtman Tenure Track Investigator. She applies novel molecular approaches to define the gammaherpesvirus proteins and host signaling networks that are required for different stages of chronic infection.

Ashish Lal, Ph.D.
Ashish Lal, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Genetics Branch. Dr. Lal is an expert on noncoding RNAs and cancer. He has extensively studied miRNAs in the p53 pathway and in the regulation of differentiation in colorectal cancer.

Daniel Larson, Ph.D.
Daniel Larson, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Receptor Biology and Gene Expression. Dr. Larson’s research focuses on understanding gene expression in eukaryotic cells, starting from the mechanistic behavior of individual macromolecules and proceeding to their regulation in cells and tissue.

Vanja Lazarevic, Ph.D.
Vanja Lazarevic, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Experimental Immunology Branch. She researches how transcription factors regulate differentiation and effector function of CD4+ T helper cells in the context of autoimmune disorders with an emphasis on experimental autoimmune encephalomyelitis, a model for multiple sclerosis.
Amy LeBlanc, D.V.M.

Amy LeBlanc, D.V.M., has been appointed as a Senior Scientist in the Molecular Imaging Program. As Director of the Comparative Oncology Program, Dr. LeBlanc has a strong interest in animal modeling for development of new cancer drugs and imaging agents and identification of imaging biomarkers, development and optimization of PET imaging hardware and imaging protocols.

Ji Luo, Ph.D.

Ji Luo, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Cancer Biology and Genetics. His laboratory investigates how mutant KRAS promotes tumor initiation, maintenance and metastasis.

Jordan Meier, Ph.D.

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

Meera Murgai, Ph.D.

Meera Murgai, Ph.D., has joined the Laboratory of Cancer Biology and Genetics as a Stadtman Tenure Track Investigator. Prior to her appointment, Dr. Murgai was a postdoctoral fellow in the Pediatric Oncology Branch. Her research centers on perivascular cell plasticity and heterogeneity in the metastatic microenvironment.

Naris Nilubol, M.D.

Naris Nilubol, M.D., has been appointed as a Physician-Scientist Early Investigator in the Surgical Oncology Program. His research focuses on identifying and utilizing the unique and specific dysregulated molecular pathways and altered multi-omics in endocrine tumors as targets for novel therapeutics and markers to predict treatment response.

Shalini Oberdoerffer, Ph.D.

Shalini Oberdoerffer, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Receptor Biology and Gene Expression. Her lab broadly examines how DNA and RNA epigenetics dynamically regulate gene expression.

Ramya Ramaswami, M.B.B.S., M.P.H.

Ramya Ramaswami, M.B.B.S., M.P.H., has been appointed as a Physician-Scientist Early Investigator in the HIV and AIDS Malignancy Branch. She focuses on Kaposi sarcoma herpesvirus-associated diseases and other HIV-associated cancers, and her clinical studies will use immunotherapy and other targeted therapies for these rare conditions.
Nitin Roper, M.D.
Nitin Roper, M.D., has been appointed as a Physician-Scientist Early Investigator in the Developmental Therapeutics Branch. His research focuses on high-grade neuroendocrine tumors, including small cell lung, bladder, prostate, pancreatic and non-small cell cancers that transform to high-grade neuroendocrine cancers.

S. Cenk Sahinalp, Ph.D.
S. Cenk Sahinalp, Ph.D., has joined the Cancer Data Science Laboratory as a Senior Investigator. His research focuses on developing algorithmic methods for managing, storing, communicating and analyzing high-throughput sequencing data, especially in the context of cancer.

John ‘Jay’ Schneekloth, Ph.D.
John ‘Jay’ Schneekloth, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Chemical Biology Laboratory. He focuses on identifying and studying small molecules that interact with structured RNA and DNA.

Nirali Shah, M.D., M.H.Sc.
Nirali Shah, M.D., M.H.Sc., has been appointed as an NIH Lasker Scholar Tenure Track Investigator in the Pediatric Oncology Branch. Her primary research interests focus on translation of immunotherapeutic approaches to treat high-risk hematologic malignancies in children, adolescents and young adults.

Shy Shorer, M.D.
Shy Shorer, M.D., has been appointed as a Senior Clinician in the Office of Sponsor and Regulatory Oversight. His office will oversee safety, clinical monitoring and quality management; provide analytic support; lead the pharmacovigilance program; and maintain high-level expertise regarding FDA regulations.

David Takeda, M.D., Ph.D.
David Takeda, M.D., Ph.D., has been appointed as an NIH Lasker Scholar Tenure Track Investigator in the Laboratory of Genitourinary Cancer Pathogenesis. His research seeks to understand the role of epigenetic reprogramming in disease progression by combining genomic and epigenomic profiling of patient samples with functional studies in model systems.

Masaki Terabe, Ph.D.
Masaki Terabe, Ph.D., has been appointed as a Tenure Track Investigator in the Neuro-Oncology Branch. He is working to elucidate the mechanisms of immune regulation of tumor immunity, in particular the roles of regulatory cells including natural killer T cells, regulatory T cells and myeloid-lineage cells.
Eugene Valkov, Ph.D.
Eugene Valkov, Ph.D., has joined the RNA Biology Laboratory as its first Stadtman Tenure Track Investigator. His research focuses on the study of molecular mechanisms of regulation and degradation of messenger RNA.

Changqing Xie, M.D., Ph.D.
Changqing Xie, M.D., Ph.D., has been appointed as a Physician-Scientist Early Investigator in the Thoracic and GI Malignancies Branch. His research focuses on exploring the potential mechanism of resistance to treatment with immune checkpoint inhibitors in gastrointestinal malignancies and dissecting the role of cancer stem cells in cholangiocarcinoma therapy resistance.

Euna Yoo, Ph.D.
Euna Yoo, Ph.D., has joined the Chemical Biology Laboratory as a Stadtman Tenure Track Investigator. She is developing new strategies to study and manipulate the human immune system.

Martha Zeiger, M.D.
Martha Zeiger, M.D., has joined the Surgical Oncology Program. She is an internationally renowned endocrine surgeon and scientist who has been a leader in developing molecular diagnostics for thyroid cancer.

Chen Zhao, M.D.
Chen Zhao, M.D., has been appointed as a Physician-Scientist Early Investigator in the Thoracic and GI Malignancies Branch. His research focuses on tumor immunology and immunotherapy in lung cancer and thymic malignancies.

Joseph Ziegelbauer, Ph.D.
Joseph Ziegelbauer, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the HIV and AIDS Malignancies Branch. He was the first to report using pulse labeling of proteins coupled with tandem mass spectrometry to discover human targets of herpesvirus microRNAs.
Awards & Honors

Ravi A. Madan, M.D., Jenn Marte, M.D., James L. Gulley, M.D., Ph.D., Jeffrey Schlom, Ph.D., Amy Hankin, P.A., Andrea Apolo, M.D., Julius Strauss, M.D., and Myrna Rauckhorst, R.N., (retired), were the CCR members of the NIH Avelumab Team who received the HHS Hubert H. Humphrey Award for Service to America.

Nataliya P. Buxbaum, M.D., won the International Society for Magnetic Resonance in Medicine Magnetic Moments Competition.

John A. Beutler, Ph.D., was named a fellow of the American Association for the Advancement of Science.

John Brognard, Ph.D., received the Presidential Early Career Award for Scientists and Engineers.

Renee N. Donahue, Ph.D., received a Penn State Alumni Achievement Award.

William Douglas Figg, Sr., Pharm.D., received an honorary Doctor of Science from Philadelphia College of Osteopathic Medicine and was a keynote speaker at their Doctor of Pharmacy and Master of Biomedical Science commencement.

Genoveffa Franchini, M.D., was awarded an honorary Doctor of Science degree by the Medical University of Bialystok, Poland.

William L. Dahut, M.D., received the NIH Alan S. Rabson Award for Clinical Care.
Eric O. Freed, Ph.D., was named a fellow of the American Academy of Microbiology and received the Distinguished Research Award from the Ohio State University Center for Retrovirus Research.

Romina Goldszmid, Ph.D., received the Presidential Early Career Award for Scientists and Engineers.

Jonathan M. Hernandez, M.D., was selected as a Top Doctor by The Washingtonian.

Elaine S. Jaffe, M.D., received the Distinguished Pathologist Award from the United States and Canadian Academy of Pathology; was named an NIH Distinguished Investigator; an honorary fellow of the Royal College of Pathology of Australasia; and a trailblazer on The Pathologist’s Power List.

W. Marston Linehan, M.D., received the Whitmore Lecture Award from the Society of Urologic Oncology; the American Urologic Association Urology Care Foundation Distinguished Mentor Award; and was a finalist for the Partnership for Public Service’s Service to America Medals, also known as the SAMMIES.

James N. Kochenderfer, M.D., received the Foundation for the National Institutes of Health Trailblazer Prize for Clinician-Scientists.

Douglas R. Lowy, M.D., received the Association of American Cancer Institutes Distinguished Scientist Award and an honorary Doctor of Science degree from NYU.

Tom Misteli, Ph.D., was elected as a foreign fellow to The Learned Society of the Czech Republic.
Awards & Honors continued

**Thomas A. Waldmann, M.D.,** received the HHS Career Achievement Award.

**Lori Wiener, Ph.D.,** received the Dr. Nathan Davis Award for Outstanding Government Service from the American Medical Association; the American Association of Immunologists Steinman Award for Human Immunology Research; the Szent-Györgi Prize for Progress in Cancer Research; the Friends of Cancer Research Cancer Leadership Award; and the Edogawa NICHE Prize.

**Steven A. Rosenberg, M.D., Ph.D.,** was named an NYU Alumni Changemaker.

**Martha A. Zeiger, M.D.,** was elected President of the American Thyroid Association and received their Lewis E. Braverman Distinguished Award.

**Andre Nussenzweig, Ph.D.,** was elected to the National Academy of Medicine.

**Lawrence E. Samelson, M.D.,** received the Cancer Research Institute’s William B. Coley Award for Distinguished Research in Basic and Tumor Immunology.

**Louis M. Staudt, M.D., Ph.D.,** was elected as a fellow of the American Association for Cancer Research Academy.

**William G. Telford, Ph.D.,** received the International Society for the Advancement of Cytometry Distinguished Service Award.

**Anish Thomas, M.B.B.S., M.D.,** received the Presidential Early Career Award for Scientists and Engineers.

**Steven A. Rosenberg, M.D., Ph.D.,** was elected President of the American Thyroid Association and received their Lewis E. Braverman Distinguished Award.
Technology Transfer Activities

- **59** New Employee Invention Reports
- **49** Issued U.S. Patents
- **27** New Cooperative Research and Development Agreements (CRADA)
  - **13** of these are Clinical CRADAs
- **184** Active CRADAs
  - **83** of these are Clinical CRADAs
- **18** New Clinical Trial Agreements (CTAs)
- **74** Active CTAs
- **103** New Licenses for NCI Technologies
- **576** Active Licenses
- **4** FDA Breakthrough Drug Designations

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. 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 FY2019.*
For more information on CCR:

CENTER FOR CANCER RESEARCH
https://ccr.cancer.gov
240-760-6400

CCR CLINICAL TRIALS
https://ccr.cancer.gov/clinical-trials
1-888-624-1937

CCR NEWS
https://ccr.cancer.gov/news

CCR CAREERS
https://ccr.cancer.gov/careers

CCR TRAINING OPPORTUNITIES
https://ccr.cancer.gov/training

CCR MAGAZINES
https://ccr.cancer.gov/news/magazines

For more information on the topics mentioned in these stories:

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