NIH NATIONAL CANCER INSTITUTE

CENTER FOR CANCER RESEARCH

MILESTONES

Cancer Research with a Purpose

HIGHLIGHTS
2024–2025

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

CENTER FOR CANCER RESEARCH

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

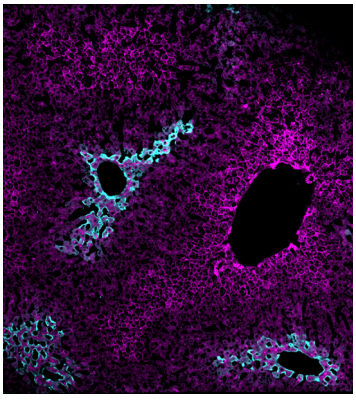
The CCR is home to an extraordinary group of scientists and clinicians exploring the cutting edge of cancer and HIV/AIDS research. Our scientists work on a wide spectrum of biological and biomedical problems that range from visualizing and understanding the structure of individual genes and proteins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

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

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

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

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



Immunofluorescence staining in this liver section shows liver cells near veins and arteries that bring blood into the liver (magenta) and cells near veins that carry blood away from the liver (cyan). Nearly a century ago, scientists saw that liver cells differed in appearance under a microscope. Now, using advanced imaging and mass spectrometry, CCR researchers have discovered that the nutrient-sensing ability of hepatocytes partly shapes this diversity. Studying these fundamental elements of biology improves our understanding of human health and will ultimately guide disease treatment.

Credit: Lauryn Brown, CCR, NCI, NIH

CONTRIBUTORS

Brenda Boersma-Maland
Li Gwatkin
Michelle Hampson
Allen Kane
Julia Langer
Jasmine Lee
Joseph Meyer
Jennifer Michalowski
Mike Miller
Gabrielle Stearns

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

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

Contents

Directors' Note

Whether it is at a desk, in a lab or at a bedside, everyone at the NCI's Center for Cancer Research is committed to our mission to improve the lives of all cancer patients.

The image of liver cells on this year's cover reveals cellular relationships and microscopic details of the inner workings of the liver. At the same time, the varied arrangement of the clustered cells evokes space, discovery and the great unknown. This reminds us that to fully understand human health and disease, we must investigate on multiple levels—from molecular mechanisms to whole patient experiences—and consider the broader context of the communities in which molecules, cells and people interact.

Each *Milestones* story in this issue shares a discovery from CCR researchers that will likely change the way we understand, detect and treat cancer. From pinpointing a protein's role in cellular development to designing new ways to target therapies to cancer cells and running clinical trials to test novel treatments, our studies build on past research and pave the way for new advances. We are honored to feature three patients in this magazine who bring home the impact of our research and represent the culmination of years of work as well as new beginnings.

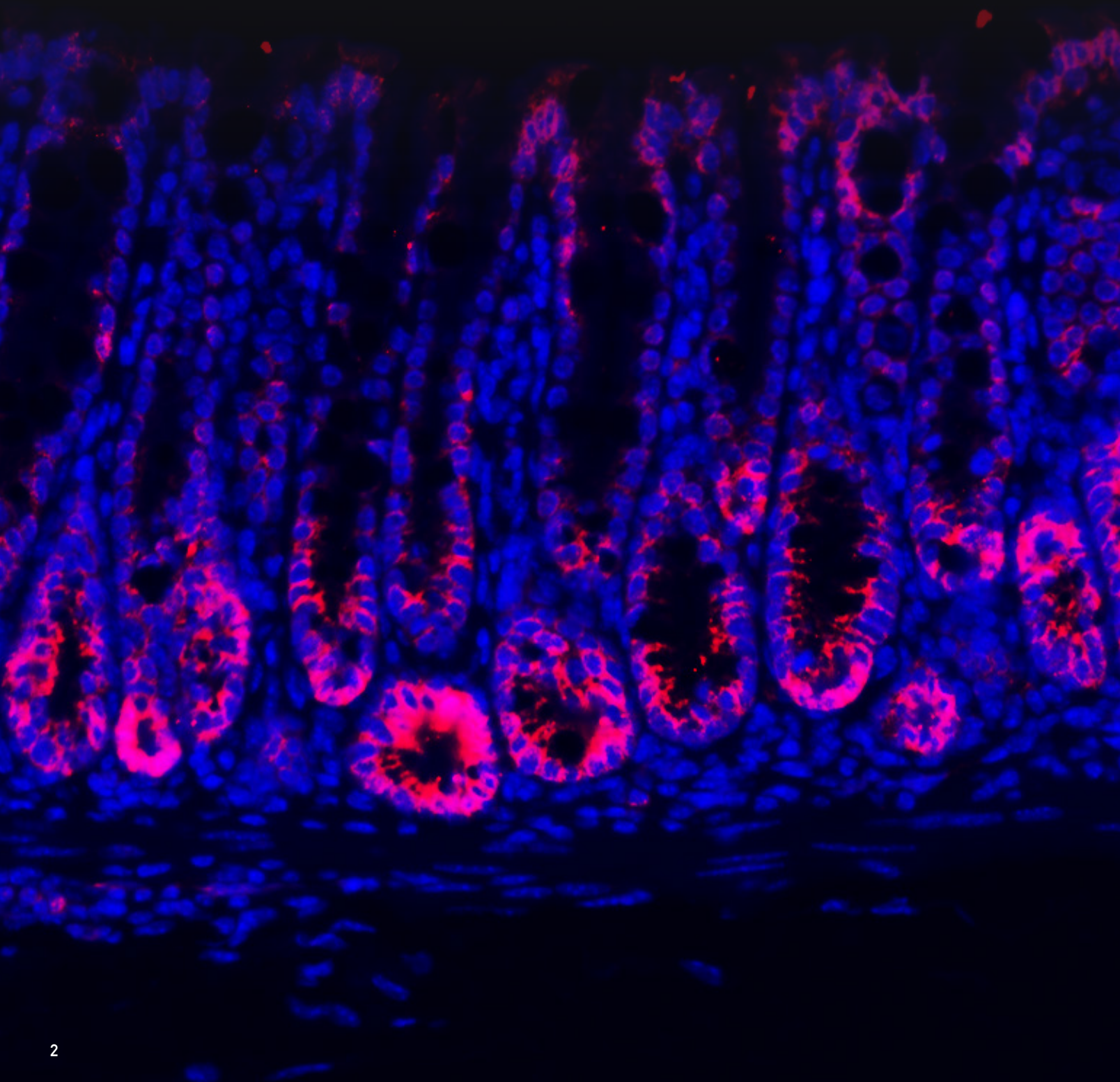
As acting co-directors, we are here to steward CCR through a period of transition. But what never wavers is our dedication to the mission and commitment to the patients we serve and who inspire us on to new frontiers.

James and Carol

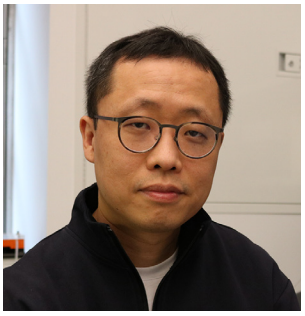
James L. Gulley, M.D., Ph.D.
Acting Co-Director
NCI Center for Cancer Research

Carol J. Thiele, Ph.D.
Acting Co-Director
NCI Center for Cancer Research

A HEALTHY GUT
STEMS FROM THE LIVER



Researchers pinpoint a critical protein in the liver that controls gut health and repair.



Chuan Wu, M.D., Ph.D.
Senior Investigator
Experimental Immunology Branch

The lining of the intestine is constantly exposed to a wide variety of microbes and food particles that can trigger immune responses and inflammatory bowel disease (IBD), a condition prevalent throughout the Western world.

Researchers have long known that activity between the liver and intestine is strongly interconnected, but knowledge about this phenomenon—called the gut-liver axis—has remained superficial for decades. This past year, CCR researchers dug deeper and detailed one element of this complex connection in unprecedented detail.

They identified an important protein in the liver that helps keep intestinal stem cell division in check, influencing health in the gut. The results, published in *Cell*, hold important implications for intestinal conditions, like IBD, and potentially for cancer.

Stem cells are precursor cells that can turn into various types of cells as needed. If the lining of the gut is damaged from inflammation, stem cells in the area can start dividing and replacing damaged cells. However, too much cell division can be associated with cancer.

As Senior Investigator **Chuan Wu, M.D., Ph.D.**, was studying the livers of mice to better understand the organ's role in maintaining gut health, he observed an unexpectedly dramatic result. Removing part of the liver caused a significant spike in the production of stem cells in the intestines.

"It was the most striking result you can observe after you perform such an experiment, so we became interested in studying these stem cells in greater detail," explains Wu.

Through a series of intricate experiments in healthy mice and mice with gut disease, the team showed how a protein called pigment epithelium-derived factor (PEDF) is released from the liver and controls stem cell division in the gut, ensuring that stem cells do not proliferate excessively. When PEDF production is reduced, these stem cells start to multiply. This is why removing part of the liver—and thus PEDF—caused such a spike in intestinal stem cell production.

The connection between the gut and liver is like a two-way street, the researchers found. Damaged intestines will release danger signals to the liver, repressing production of PEDF via a protein called PPAR-alpha. This, in turn, releases the hold on stem cell expansion in the gut, allowing the stem cells to grow and heal the inflamed tissue.

Sure enough, in mice with inflamed guts, the researchers found that inhibiting PEDF could alleviate their symptoms. "These results may actually give us an idea of how vital liver function is for IBD patients," Wu emphasizes.

The research team also looked at data from people, which suggests that similar mechanisms are at play within our bodies. In fact, the findings of this study may explain why a cholesterol drug called fenofibrate, which activates PPAR-alpha, has been associated with intestinal inflammation in humans.

Given that intestinal stem cells are important for both inflammation and tumor development, the research by Wu and his colleagues may also help shed light on how PEDF influences colon cancer on a molecular level.

Kim, G., et al. *Cell*. 2024 Feb 15;187(4):914-930.e20.

This image depicts intestinal tissues stained for PEDF protein (pink) from healthy mice. The liver produces PEDF, which binds to stem cells in the intestine and stops them from over-proliferating. When the intestines are damaged, they release signals that block PEDF production, liberating stem cell expansion to heal the gut. Credit: Kim, G., et al.

STRENGTH IN DIFFERENCE

Having more diverse *HLA* genes is better for immune control of HIV.

Mary N. Carrington, Ph.D.
Senior Investigator
Laboratory of Integrative Cancer Immunology

More than 39 million people around the world live with HIV. While antiretroviral therapy can control the disease, not everyone can access these lifesaving treatments, and new advances are needed to end the ongoing AIDS pandemic. To develop new methods of both prevention and treatment, it is essential to understand how the immune system responds to HIV on its own. At CCR, scientists led by Senior Investigator **Mary Carrington, Ph.D.**, have a newly detailed grasp of why some people's immune systems do a better job of controlling the virus than others.

Before antiretroviral therapy was available, some patients developed AIDS soon after they became infected with HIV. Others lived for years with low levels of the virus in their blood. These disparities can be explained in part by differences in proteins called human leukocyte antigens (HLAs), which infected cells use to alert the immune system to the threat. HLAs sit on the surface of cells and display bits of the virus called peptides for surveilling immune cells to recognize as foreign.

When people inherit identical copies of an *HLA* gene from each parent, their immune system is less equipped to fight HIV than if their *HLA* genes were different. That is likely because having only one version limits which fragments of the virus can be displayed on the surface of an infected cell. With different HLA proteins, infected cells can present more diverse pieces of the virus, giving the immune system more ways to recognize the infected cells as targets.

The genes that encode HLAs are the most diverse genes in the human genome. While it is uncommon to have two copies that are an exact match, some mismatched pairs are more alike than others. Carrington wanted to know just how different *HLA* genes must be to improve viral control.

In work reported in *Science*, Carrington's team cataloged how different pairs of *HLA* genes complement or overlap one another in displaying peptides to the immune system. "We're asking, 'How similar are you? Do you bind primarily the same peptides with just slight differences? Or are you way over on the other end of the spectrum, where you're really recognizing completely separate types of peptides?'" Carrington explains. Using data from researchers at the Dana Farber Cancer Institute who had tested this peptide binding, her group came up with a measure of functional divergence for every possible pair of *HLA* genes.

Then they compared this functional divergence to clinical data. They looked for relationships between *HLA* diversity and patients' viral load or the time it took untreated patients to develop AIDS after they became infected.

They found a clear association: People whose two *HLA* genes enabled their immune system to recognize very different fragments of viral proteins were better able to control the virus than people whose *HLAs* were very similar.

Carrington says she suspects HLA functional diversity probably affects individuals' ability to control many kinds of infections, not just HIV. It may even influence patients' response to vaccines and cancer immunotherapies. Her team's measures of functional divergence will help researchers investigate these relationships, which could one day inform personalized treatment or prevention strategies for many diseases, including cancer.

Viard, M., et al. *Science*. 2024 Jan 19;383(6680):319-325.

When you have a variety of screwdriver heads in different sizes and shapes, you are more likely to find a precise match for a certain screw. Similarly, when you inherit different HLA genes from your parents, you are more likely to be able to display different viral proteins for your immune system to recognize. Having more ways to identify viruses makes the immune system more likely to mount a robust attack and keep viral loads in check in diseases such as HIV. Credit: SPGM, FNL, NCI, NIH; iStock

ViPOR STRIKES LYMPHOMA HARD

A novel drug combination likely cured more than a third of study participants of their lymphoma.

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

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

A clinical trial evaluating a novel drug combination has yielded dramatic results for people with forms of aggressive lymphoma, with more than a third of patients seeing their lymphoma disappear completely and not return. The results were so beneficial that the research group behind the discovery is seeking to establish this drug combination—called ViPOR—as a standard treatment for some lymphoma subtypes.

The advance, described in the *New England Journal of Medicine*, is part of a multi-decade translational science endeavor by Senior Investigators **Wyndham Wilson, M.D., Ph.D.**, and **Louis Staudt, M.D., Ph.D.**, who led the clinical and laboratory work, respectively. The duo has been working together for years to identify lymphoma subtypes and test targeted therapies for each one.

Inspired by the way that different chemotherapy drugs are combined to launch a strong attack against cancer, the researchers sought to create a drug cocktail that targets specific pathways malignant lymphoma cells use for survival. They came up with the ViPOR regimen (venetoclax, ibrutinib, prednisone, obinutuzumab and lenalidomide) based on the hypothesis that targeting multiple critical survival pathways was necessary to achieve a cure.

When Staudt studied the effects of ViPOR on lymphoma cells in the laboratory, he observed the cancer cells dying in a matter of hours. "These cancer cells were quickly dead as a doornail," he notes. "This was such a robust finding that I thought it would translate into clinical responses."

Wilson and Staudt then partnered with Associate Research Physician Christopher Melani, M.D., and Senior Clinician Mark Roschewski, M.D., to lead a clinical trial investigating the effects of ViPOR in lymphoma patients whose cancer had persisted despite standard treatment.

A total of 50 patients with diffuse large B-cell lymphoma (DLBCL) were given ViPOR in a phase 1/2 trial. More than half of the study participants responded to therapy, with 38 percent showing no trace of lymphoma after just a few brief cycles of treatment with ViPOR. Notably, ViPOR was also effective in patients who had received CAR T-cell therapy for refractory lymphoma after treatment with chemotherapy. Melani notes that aggressive lymphomas often recur quickly if treatment proves ineffective, yet many patients in this study have been lymphoma-free for several years since being treated in the trial. "The patients who are still in remission after five or six years are very likely cured of their lymphoma," he says, noting that seeing these results is very gratifying. While the drug combination involved some side effects, such as reduced white blood cell counts, they generally were not severe or worse than standard lymphoma therapies.

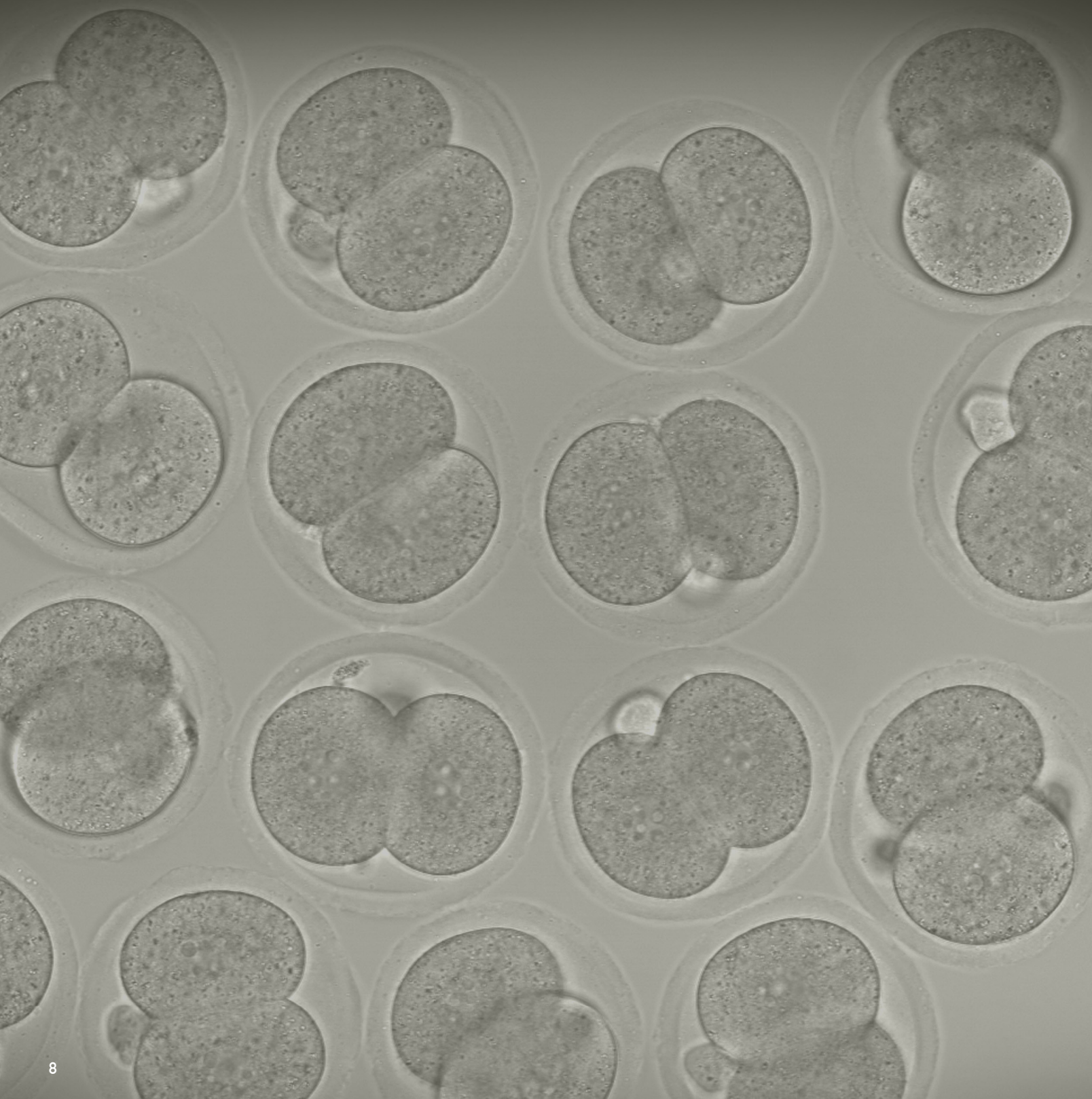
Most of the patients who experienced full remissions had certain molecularly defined lymphoma subtypes, specifically non-germinal center B-cell DLBCL or high-grade B-cell lymphoma with genetic rearrangements of the *MYC* and *BCL2* genes. A larger follow-up clinical trial is now underway in multiple centers nationally to test ViPOR in more patients, as part of NCI-funded research.

Staudt emphasizes that this research could not have been done without long-term support from CCR and close collaborations where he could make discoveries in the lab and partner quickly with colleagues to test those findings in the clinic. "That's really remarkable and doesn't happen at a lot of other places," Staudt says.

Melani, C., et al. *N Engl J Med*. 2024 June 20;390(23):2143-2155.

Lynda Flom had received standard treatments twice for lymphoma, starting in 2009, yet her cancer kept recurring. In 2017, she was in an exercise class in her hometown of Pittsburgh when she happened to strike up a conversation with an NIH researcher visiting from out of town. The new relationship prompted Lynda to seek treatment at NIH. When her lymphoma became very aggressive in 2018, NIH offered her the chance to participate in the ViPOR trial. "I was willing to give it a try, and I'm glad I did," Lynda says. Although she had a bad reaction to the first dose of the ViPOR regimen, she says the tumor "melted like crazy" shortly after starting treatment. It has been just over six years since Lynda received the novel drug combination, and her lymphoma hasn't returned. "It's very nice to see those clean scans when I come back to NIH for checkups," she says, noting that ViPOR offers another option for patients who don't respond to standard therapy. The colorful backdrop is a plot of responses to different doublet combinations of the ViPOR drugs in DLBCL cell lines. Creating the ViPOR treatment would not have been possible without close collaboration between researchers in CCR labs and clinical teams. Credit: Photo courtesy of Lynda Flom; Melani, C., et al.; SPGM, FNL, NCI, NIH

KICKSTARTING MULTICELLULAR LIFE



Researchers identify a gene critical for embryonic development.

Sergio Ruiz Macias, Ph.D.
Stadtman Investigator
Laboratory of Genome Integrity

The first two cells that arise from a fertilized egg are totipotent, meaning they are able to become any type of cell in the body or in the structures required to support an embryo's development, such as the placenta. For successful development to continue, these two cells must divide to make pluripotent cells which are then capable of making any cell in the body, but not in the placenta or other supporting structures. Pluripotent cells continue to divide and specialize as the embryo matures. Mammals from mice to humans are estimated to produce 200 to 300 types of cells that perform specific functions.

Cancer cells are notorious for being able to hijack genetic pathways that regulate cell development and specialization. By using genes in these pathways, they can revert to an earlier, more flexible stage that allows them to divide, mutate and adapt to new environments more easily, while evading cancer therapies. Understanding the regulatory pathways cancer cells use to reprogram to these earlier states could lead to new treatment approaches.

For years, researchers have known that the *Dux* family of genes is responsible for regulating the expression of totipotent genes in mice, with similar genes identified in humans. However, these genes must be expressed only briefly before being turned off during the transition toward pluripotency. Any missteps in the process can lead to developmental issues or failure to form an embryo. In an important advance, published in *Nature Genetics*, researchers studying mice have identified a gene called *Duxbl* that acts as an off switch for *Dux*-induced genes, paving the way for healthy embryonic development.

"There was nothing known about *Duxbl*, and it turns out that it is essential," explains Stadtman Tenure-Track Investigator **Sergio Ruiz Macias, Ph.D.**, who led the research. "Without this gene, there is no organism."

Ruiz Macias and Maria Vega-Sendino, Ph.D., a postdoctoral fellow in his lab, were curious to study the function of *Duxbl* given how it belongs to a family of genes activated during embryonic development and yet its specific function remained unknown.

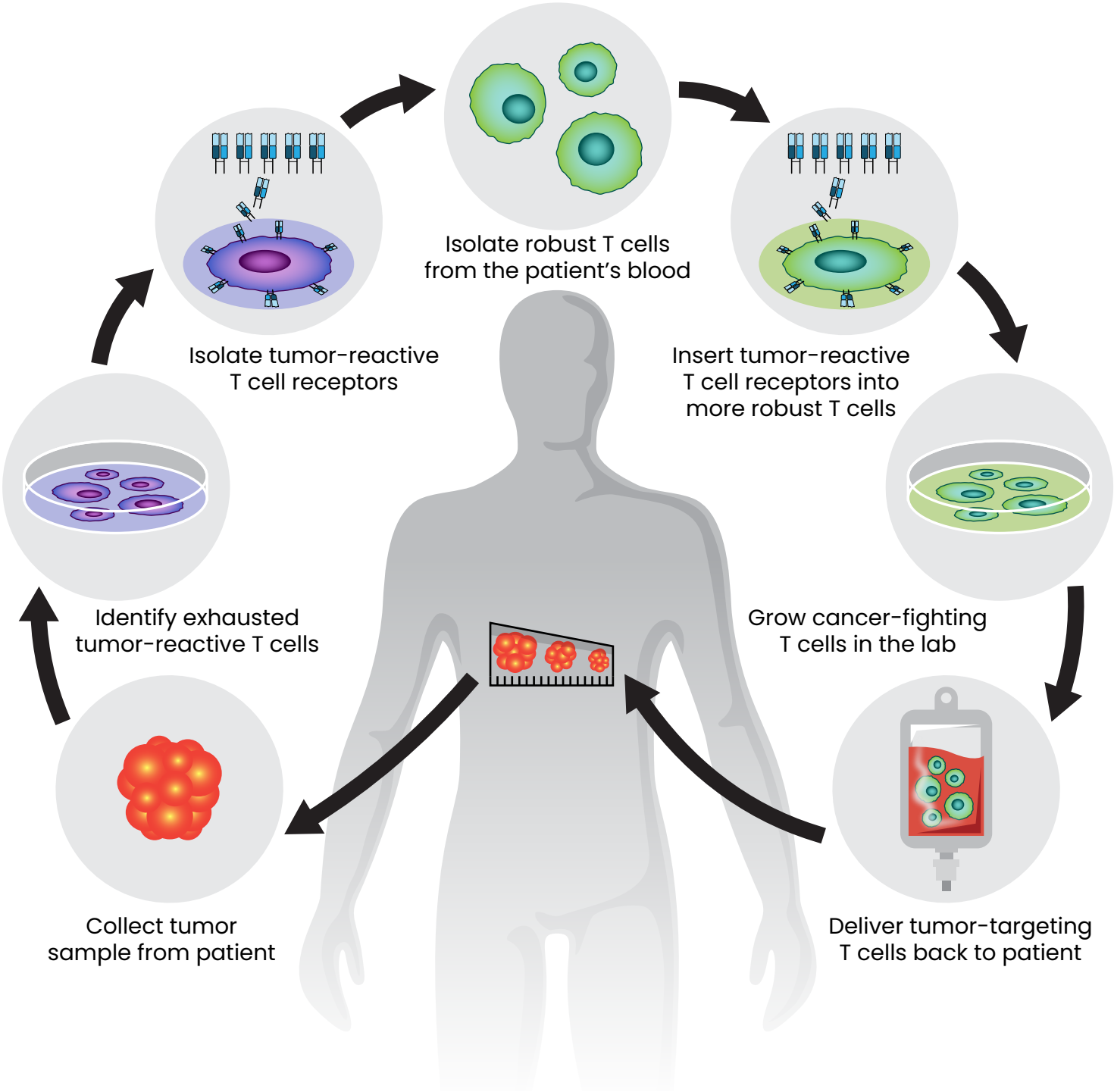
They used microscopy, mass spectrometry and genomics to study embryonic stem cells and fertilized mouse eggs lacking the *Duxbl* gene. Ruiz Macias emphasizes that the work was highly technical and was facilitated through CCR's intramural collaborations and investment in resources. In collaboration with Felipe F. Lüttmann and Johnny Kim, Ph.D., at the Max Planck Institute for Heart and Lung Research in Germany, as well as colleagues at the NIH's National Institute of Environmental Health Sciences in North Carolina, they showed that *Dux*-induced genes, including *Duxbl*, are triggered once fertilization takes place. But without *Duxbl*, these genes remain activated and actually block healthy embryonic development, revealing a repressive role for the protein produced by *Duxbl* on these genes. The effect is so strong that embryonic cells lacking DUXBL protein could not divide more than twice, making the embryo nonviable.

Ruiz Macias and his colleagues also identified two protein repressors, TRIM24 and TRIM33, that interact with the DUXBL protein. In future work, the researchers plan to study the repressive mechanisms of *Duxbl* in greater detail, digging deeper into the inner mechanisms behind this silencing gene.

Vega-Sendino, M., et al. *Nat. Genet*. 2024 Apr;56(4):697-709.

This image shows a collection of mouse embryos at the 2-cell stage similar to the ones used in this work. Changes in gene expression at this point are critical for the continued development of the embryos. Credit: Paula Stein, NIEHS, NIH; SPGM, FNL, NCI, NIH; iStock

EMPOWERING IMMUNE SYSTEMS



A personalized approach to cellular immunotherapy helps shrink solid tumors.

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

More than twenty years ago, scientists showed that it is possible to reprogram patients' own immune cells to fight their cancer. Cellular immunotherapies are now important tools for fighting cancer, and CCR scientists are working to extend their reach.

While cellular immunotherapies are effective against many blood cancers and melanomas, other kinds of solid tumors have been mostly unresponsive to this type of treatment. But in an ongoing clinical trial led by **Steven Rosenberg, M.D., Ph.D.**, researchers have found that with a new approach, patients' immune cells can be programmed to shrink metastatic colon cancer, too.

"The methodology that we've developed works," says Rosenberg, whose group at NCI has pioneered these innovative types of treatments for decades. "We're concentrating now on solid epithelial cancers—common cancers that occur in the solid organs of the body. Ninety percent of everyone who dies of cancer dies of these. This is the beginning of a new way to use immunotherapy."

The success, reported in *Nature Medicine*, comes from a phase 2 clinical trial in which Rosenberg and colleagues are reprogramming healthy T cells from patients' blood to recognize and attack their cancer cells. They are using an approach that Rosenberg says can be used to generate personalized tumor-reactive T cells for many cancer types. The trial is open to patients with metastatic solid cancers including gastrointestinal, breast, lung and endocrine cancers.

Rosenberg's group has found that most patients with cancer already have naturally occurring T cells that can recognize mutations that distinguish their tumor cells from healthy cells. However, once these T cells infiltrate tumors, they encounter a hostile, immune-suppressing environment. As a result, most of the T cells found inside tumors are too exhausted to destroy their targets or rally additional immune defenses.

To address this issue, Rosenberg's team, led by Staff Scientist Maria Parkhurst, Ph.D., collected T cells from inside the tumors of each patient in their clinical trial, then isolated the receptors that those cells used to recognize the cancer.

Parkhurst then introduced those tumor-targeting receptors onto more robust T cells from the same patient's blood. The reprogrammed cells were grown in the lab, generating enormous numbers of healthy, cancer-fighting cells to deliver back to the patient.

This approach differs from CAR T-cell therapy, which uses engineered receptors to direct T cells to their targets and was first reported in patients by Rosenberg's group in 2010. CAR T-cell therapy is used to treat certain kinds of blood cancer by targeting normal molecules overexpressed on the cancer and shared across patients. A more personalized approach is needed for solid cancers, where the tumor-specific mutations that activate the immune system are much more diverse and are largely patient specific.

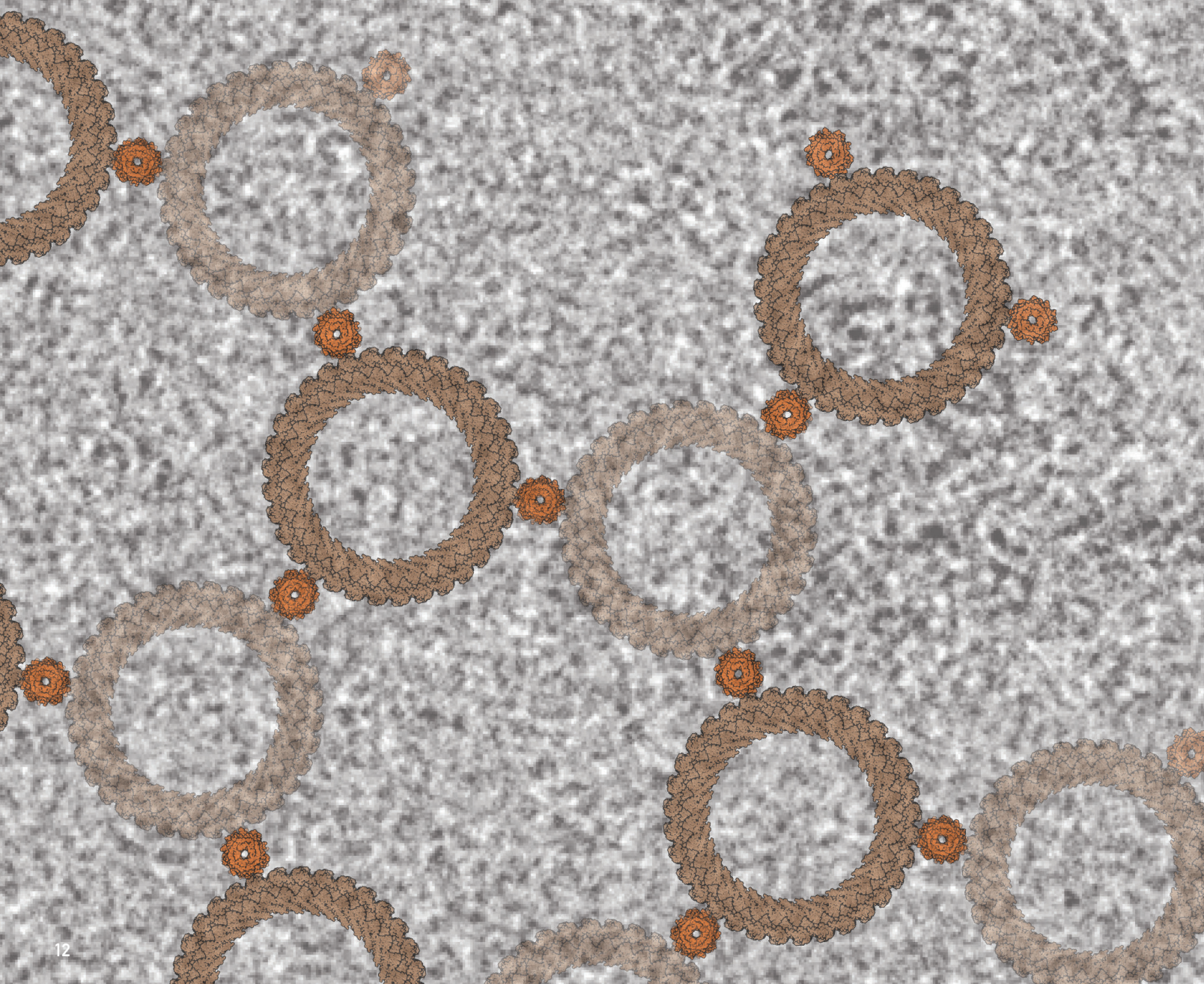
The early results of the clinical study focused on seven participants with metastatic colon cancer. All had undergone multiple cancer treatments prior to entering the study, and their cancers had continued to grow. After the experimental immunotherapy, tumors shrank for three of the patients, and regrowth was kept at bay for four to seven months.

Although the trial is ongoing and the results are preliminary, they are encouraging. "Cancer immunotherapy is already having an important impact," Rosenberg says. "I think it represents the most exciting area of research that has the potential to develop effective treatments for patients with metastatic cancer."

Parkhurst, M., et al. *Nat Med*. 2024 Sep;30(9):2586-2595.

A new approach to cellular immunotherapy, outlined here, holds promise for patients with solid epithelial cancers. The treatment is highly personalized. It combines T-cell receptors that can identify the specific mutations of the patient's tumor with robust T cells from the patient's blood to attack the cancer. Credit: SPGM, FNL, NCI, NIH

SWITCHING DIRECTION



Images of a bacterial motor show how it can reverse direction with the flip of a biological switch.

Susan M. Lea, D.Phil., F.Med.Sci., F.R.S.
Chief
Center for Structural Biology

Many bacteria, including pathogenic ones, propel themselves with whip-like appendages called flagella. Rotations of the flagella keep a bacterium moving steadily forward—sometimes toward food, sometimes away from toxins. With the flip of a biological switch, the rotary motor that powers a flagellum can be reversed, setting the microbe off in a new direction—potentially toward a more hospitable environment.

Striking new images of the motor that powers this movement, captured in the lab of Senior Investigator **Susan Lea, D.Phil.**, and published in *Nature Microbiology*, show how the motor reconfigures itself to change direction. "The changes that we see between the states which go in one direction and the states which go in the other direction are huge, huge conformational changes—much bigger than we might have predicted would be possible without tearing an object apart," Lea says. That physical transformation enables the motor to turn both clockwise and counterclockwise.

Scientists have struggled to explain this directional shift, because flagella are powered by the flow of ions across the cell membrane, which typically move in only one direction. And it is hard to get a close look at the system to learn how it works. The flagellar motor, which is made up of dozens of proteins, is fragile, dynamic and, as biological complexes go, massive in size. These features make it difficult for structural biologists to visualize the complex at a molecular level.

Steven Johnson, D.Phil., and Justin Deme, Ph.D., Staff Scientists in Lea's lab, solved the problem using a high-resolution imaging method called cryo-electron microscopy. They captured about 85,000 images of the bacterial motor, viewing it from every angle and in both of its forms: positioned to move clockwise or counterclockwise. Lea points out that her team needed the vast computing power of the Frederick Research Computing Environment, made available through NCI, to assemble the data into complete three-dimensional structures.

In their final models, the ion-powered motor and a smaller adaptor that links the motor to the flagellum appear as a pair of cogs that fit together in two dramatically different ways. In one configuration, the smaller cog rotates along the outer edge of the larger cog. In the other, a change in the shape of one of the proteins in the complex moves the small cog inside the larger cog. This rearrangement means that while the motor that drives the movement always rotates in the same direction, the flagellum-turning cog can move in either direction, depending on where it sits.

"If you compared the two states, that little piece literally flipped 180 degrees over. That's a rare thing for a protein to do," Lea says. "It's a pleasingly simple answer, but it was incredibly complex to get there."

Lea says her team's discovery not only shows that proteins are capable of extreme conformational change, it also exposes a fundamental aspect of microbial biology that might one day inform the design of new kinds of antibiotics. Because the core components of bacterial flagella are very similar across species, what they have learned is expected to apply to many types of bacteria. "A lot of cancer patients die of bacterial infections, so we think it is really important for cancer," she says.

Johnson, S. et al. *Nat Microbiol.* 2024 May;9(5):1282-1292.

The background shows a field of view from a cryo-electron microscopy-generated micrograph with a single Salmonella flagellar basal body—the flagellar motor—visible in the top right (darker gray). Overlayed on the image is a lattice created from atomic models of the C-ring (larger ring in tan) and the stator (smaller ring in orange), which are responsible for driving the rotation of bacterial flagella. Credit: Steven Johnson, CCR, NCI, NIH

AN UNEXPECTED TEAM

New insights reveal how bone marrow cells impact the survival of plasma cells and their antibodies.

Avinash Bhandoola, M.B.B.S., Ph.D.
Senior Investigator
Laboratory of Genome Integrity

When a dentistry researcher encountered a curious protein produced by teeth and other bone-related cells, he approached CCR researchers to help him dig deeper to understand its function. Their unusual partnership led to the discovery that bone marrow cells play a critical role in regulating the immune system's long-term memory via plasma cells.

Plasma cells are specialized immune cells that secrete antibodies, which are the immune proteins that recognize and attack harmful viruses and bacteria. A subset of plasma cells live longer than others, retaining valuable long-term memories of these pathogens after initial exposure. They live in the supportive microenvironment of the bone marrow, but how that environment impacts their lifespan has been poorly understood.

In 2007, Masaki Ishikawa, D.D.S., Ph.D., was at the NIH's National Institute of Dental and Craniofacial Research where he studied a protein, called pannexin-3, which was highly expressed in teeth and in bone-related cells, but not other organs. Over time, he began to suspect it could influence the immune system.

Later, while at Tohoku University in Japan, Ishikawa reached out to Senior Investigator **Avinash Bhandoola, M.B.B.S., Ph.D.**, who studies immune cell development. They then recruited David Allman, Ph.D., an expert on plasma cells at the University of Pennsylvania.

The researchers found that mice lacking the gene needed to produce pannexin-3 had reduced plasma cell numbers in bone marrow, as well as reduced antibody levels. Notably, pannexin-3 forms a channel in a cell's surface membrane that allows it to release ATP, an energy molecule.

This prompted the team to explore whether pannexin-3 in bone cells was helping to supply life-sustaining signals in the form of ATP to plasma cells, which they confirmed. They also identified the P2RX4 receptor on plasma cells as responsible for sensing the ATP after it had been released through pannexin-3. Blocking P2RX4 in mice caused a significant decrease in bone marrow plasma cells and antibodies, including long-lived plasma cells, similar to eliminating pannexin-3.

This discovery, published in *Nature*, shows a novel and essential way in which bone marrow supports healthy sustenance of plasma cells, with clinical implications.

"We're thinking this new knowledge should be useful for autoimmunity caused by antibodies," Bhandoola explains.

Autoimmune diseases occur when a person's immune system produces antibodies that mistakenly bind to their own tissues, called autoantibodies. In mice modelling the autoimmune disease lupus, the researchers found that blocking the P2RX4 channel on plasma cells decreased the animals' autoantibody levels and lessened some of their lupus symptoms.

Along with implications for autoimmune disorders, Bhandoola believes these findings could provide new insights into the antibody protection gained from vaccines, eventually boosting their efficacy.

In addition, Bhandoola and Allman are now working with CCR colleagues to see if already existing drugs that inhibit P2RX4 can be valuable in treating multiple myeloma, a type of cancer that begins in plasma cells.

Bhandoola adds that this research—where Ishikawa was able to approach him and they were able to pursue a scientific curiosity without writing a grant—was made possible at CCR. "Masaki was able to follow an intuition," he says. "I think it would have been very difficult to do anywhere else."

Ishikawa, M., et al. *Nature*. 2024 Feb;626(8001):1102-1107.

A team of researchers discovered an unexpected way that bone marrow cells and plasma cells are connected. This image illustrates the general findings: bone marrow cells (pink) release the energy molecule ATP (yellow), and a protein on the surface of plasma cells (purple) allows the cells, including long-lived plasma cells, to pick up and respond to the ATP. Credit: SPGM, FNL, NCI, NIH

CLEARING THE AIRWAYS

A novel gene therapy helps eliminate recurring respiratory growths in patients—and the frequent surgeries they required.

Clint T. Allen, M.D.
Senior Investigator
Surgical Oncology Program

For people with a condition called recurrent respiratory papillomatosis (RRP), surgery is an all-too-familiar ordeal. The disease, which affects more than 20,000 adults in the United States, is caused by certain forms of human papillomavirus (HPV) and causes growths to develop in the upper airways, where they can interfere with a person's voice and make it harder to breathe. In rare cases, the growths can become cancerous. Surgery to remove the growths is a temporary fix, because surgery does not address the underlying cause of the disease and growths almost always come back, but for decades has been the only option for managing RRP.

Many patients with RRP need hundreds of surgeries in their lifetime—but an NCI-led clinical trial suggests that a new experimental gene therapy could change that. The treatment, called PRGN-2012, developed with the cell and gene therapy company Precigen, is designed to direct patients' immune systems to destroy cells infected by the HPV that causes RRP. In the clinical trials evaluating PRGN-2012, nearly all participants (86%) needed fewer surgeries to manage their disease in the year following treatment than they had in the previous year. More than half needed no surgery at all during the first year of follow-up.

"RRP has always been difficult to treat," says Senior Investigator **Clint Allen, M.D.**, who, with Associate Research Physician Scott Norberg, D.O., co-led a phase 1/2 trial evaluating PRGN-2012 at the NIH Clinical Center. Allen explains that surgeries to remove RRP-related growths often leave scar tissue that causes many of the same problems as the growths themselves. "If you ask RRP patients what they care about, it's not having procedures to remove their disease," he says.

PRGN-2012 helps the immune system eliminate RRP by training T cells to kill cells that have been infected by RRP-associated types of HPV viruses (HPV6 and HPV11). It was inspired by immunotherapies being developed and tested at NCI for the treatment of HPV-related cancers.

Allen says the NIH Clinical Center's unique resources and expertise in treating RRP patients were vital for completing PRGN-2012 clinical trials in an expedient manner for this major unmet need. After treating 15 patients with PRGN-2012 in a phase 1 clinical trial, Allen and colleagues analyzed participants' blood and found that 93 percent of patients now had T cells that could recognize HPV-infected cells. For six people, those T cells completely curbed the disease, eliminating the need for surgery in the following year.

Phase 1 results were reported in *Science Translational Medicine*. Results from the phase 2 portion of the pivotal trial, which demonstrated similar success in a larger group, were subsequently published in *Lancet Respiratory Medicine* and confirmed the efficacy of the treatment. The treatment was well tolerated by patients and no serious side effects were reported.

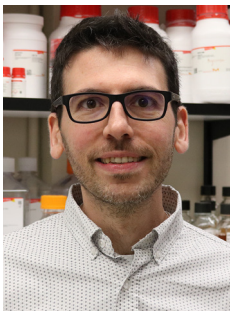
Because of its potential impact for patients, PRGN-2012 has been granted Breakthrough Therapy designation and Precigen's biologics license application (BLA) has been granted priority review by the U.S. FDA. The BLA is currently in review by the FDA and if successful, RRP patients may finally have an FDA-approved therapy that addresses the underlying cause of RRP.

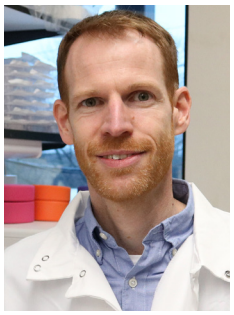
Norberg, S.M., et al. *Sci. Transl Med*. 2023 Oct 25;15(719):eadj0740.
Norberg, S.M., et al. *Lancet Respir Med*. 2025 Apr;13(4):318-326.

Kim McClellan was diagnosed with RRP when she was just 5 years old. Since then, she has had more than 250 surgeries to manage the condition. Each one has caused anxiety and worry, and has taken time away from the rest of her life. "Even one surgery is too many," she says. As President of the Recurrent Respiratory Papillomatosis Foundation, Kim is a vocal advocate for patients with the rare disorder. For too long, medical and research communities accepted surgery as the only option for managing RRP. Now, with the development of PRGN-2012 and Dr. Allen's clinical trials in collaboration with Dr. Norberg, things are finally changing. "I talk to patients daily, and they tell me how it's changed their lives," she says. "They talk about being able to make plans, their voice coming back stronger, and just the improvement to their quality of life. That's the end game for us: It's 'Has your life been improved?' And it has." This showed in Kim's smile throughout her son's wedding weekend in 2023, where this photo was taken. Credit: Photo courtesy of Kim McClellan; SPGM, FNL, NCI, NIH; Adobe Firefly

SPLICING MATTERS

A genome-wide screen drills down to gene segments called exons to find out what really matters for cell fitness.





Thomas Gonatopoulos-Pournatzis, Ph.D.
Stadtman Investigator
RNA Biology Laboratory

Michael Aregger, Ph.D
Stadtman Investigator
Molecular Targets Program

Humans have about 20,000 genes that spell out the instructions for how to produce proteins. But our cells don't have to use these genes the same way every time. Every gene's protein-coding sequence lies in segments of DNA called exons, which can be assembled in different ways. This gives cells flexibility to produce the vast array of proteins they need to keep the body healthy. However, it also introduces opportunities for error.

To produce a particular protein, cells first make an RNA copy of a gene. Non-coding sequences called introns are snipped out of the RNA and some or all of the exons are pieced back together in a process called splicing. When splicing is disrupted, as it often is in cancerous cells, exons can be left out from where they are needed or included when they should be skipped. The consequences of these missteps vary, but sometimes generate abnormal proteins that contribute to cancer's growth or spread.

"It is very well established that splicing is messed up in cancer cells," says Stadtman Tenure-Track Investigator **Thomas Gonatopoulos-Pournatzis, Ph.D.** "The cancer cells take advantage to find what will help them grow better, evade treatments and metastasize. But despite this knowledge, we still don't know which are the most critical splicing events to exploit therapeutically."

In fact, Gonatopoulos-Pournatzis says, little is known about how most individual exons impact function. Thus, it's hard to predict whether omitting an exon will have significant consequences on cells' ability to survive and multiply, which is known as cell fitness.

In research published in *Molecular Cell*, Gonatopoulos-Pournatzis collaborated with Stadtman Tenure-Track Investigator **Michael Aregger, Ph.D.**, to assess how exons throughout the human genome affect cell fitness. While similarly comprehensive screens have tested how individual genes impact cell function, Gonatopoulos-Pournatzis and Aregger are the first to do it at the exon level.

The researchers used a CRISPR-based gene editing tool they had developed to snip more than 12,000 exons out of the genomes of lab-grown human cells, one at a time. Then they assessed how well cells grew when they were missing any given exon. In this way, they identified more than 2,000 exons that promote cell fitness. They also found 171 fitness-suppressing exons.

Gonatopoulos-Pournatzis says the findings help clarify what makes certain exons important for cell survival and proper proliferation. Beyond that, the new catalog of fitness-promoting exons is a roadmap for further study, particularly for cancer and other diseases where splicing is dysregulated.

"I think it's a very useful resource," Aregger says. "For the first time, we systematically categorized thousands of different exons to pinpoint which ones may be most interesting for functional follow-up studies, because we see they're linked to a phenotype that is important for health and disease."

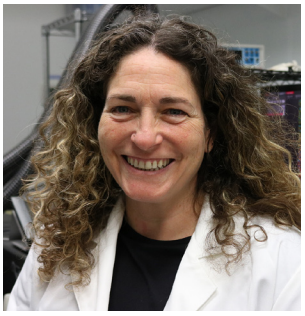
Gonatopoulos-Pournatzis' team has already followed up on one exon on their list—exon 8 from a gene called TAF5. They found that its exclusion prevents a regulator of gene activity from assembling, which leads to dramatic changes in how genes are expressed. As their teams and others continue to investigate exons' functional impacts, they will learn which splicing changes are most consequential for health and why—which could ultimately inform the design of new cancer therapeutics.

Xiao, M.S., et al. *Mol Cel*. 2024 Jul 11;84(13):2553-2572.e19.

Although no hands, scissors or tweezers are involved, a process called RNA splicing acts like a molecular editor, cutting and pasting gene segments, called exons, into different combinations. This allows a single gene to produce multiple proteins, but also introduces new opportunities for errors, which frequently occur in cancer cells. Now, CCR researchers have analyzed how individual exons influence a cell's ability to survive and multiply on an unprecedented scale, taking the first step toward identifying exons that could serve as targets for new cancer therapies. Credit: SPGM, FNL, NCI, NIH; iStock

METABOLIC MULTITASKING

Liver cells divvy up metabolic tasks to take advantage of available nutrients.



Natalie Porat-Shliom, Ph.D.
Stadtman Investigator
Thoracic and GI
Malignancies Branch

The liver is a multitasking organ, responsible for clearing toxins from the blood, breaking down nutrients, generating energy, storing fats and hundreds of other functions. Every cell has a job to do and is equipped with specialized tools to do it. Stadtman Tenure-Track Investigator **Natalie Porat-Shliom, Ph.D.**, is examining how and why liver cells adopt their particular features and functions. She wants to understand this cellular diversity in healthy livers so she and others can make sense of changes that occur during disease.

Porat-Shliom explains that a quarter of adults in the developed world are affected by a progressive spectrum of diseases related to fat buildup in the liver. As the prevalence of these diseases increases, they are becoming a leading cause of liver cancer. One hallmark of this type of liver disease is changes to structures inside liver cells called mitochondria. To understand the significance of these changes, Porat-Shliom and her team think it is important to first fully appreciate natural variations in mitochondria's form and function inside the liver.

The liver is organized into thousands of working units known as lobules. Some of the cells that make up each lobule have mitochondria that appear large and round under a microscope, whereas others are elongated like noodles. In the livers of healthy, well-fed mice, the round mitochondria appear at the edges of each lobule, where nutrient-rich blood enters. In the center of the lobules, where blood exits to a central vein, mitochondria adopt their skinnier form.

In a study reported in *Nature Communications*, Porat-Shliom and her team analyzed mitochondria isolated from these different locations in the liver and uncovered new details on the relationship between mitochondria function, structure and position.

They found that the round and skinny mitochondria housed different sets of proteins, suggesting that they perform different functions and hinting at the mechanisms they use to become specialized.

With a series of experiments assessing energy production and storage, the researchers confirmed that at the edges of a liver lobule, where blood arrives rich with nutrients, cells use their mitochondria to convert some of those nutrients to energy. Nearer to the center of the lobule, mitochondria focus instead on equipping cells to synthesize fatty molecules called lipids that can be stored for later use.

The researchers also found that if they blocked liver cells' ability to sense how many nutrients were available, they could shift the function of the mitochondria in those cells. That suggests liver cells can adjust their metabolic activities to manage critical resources.

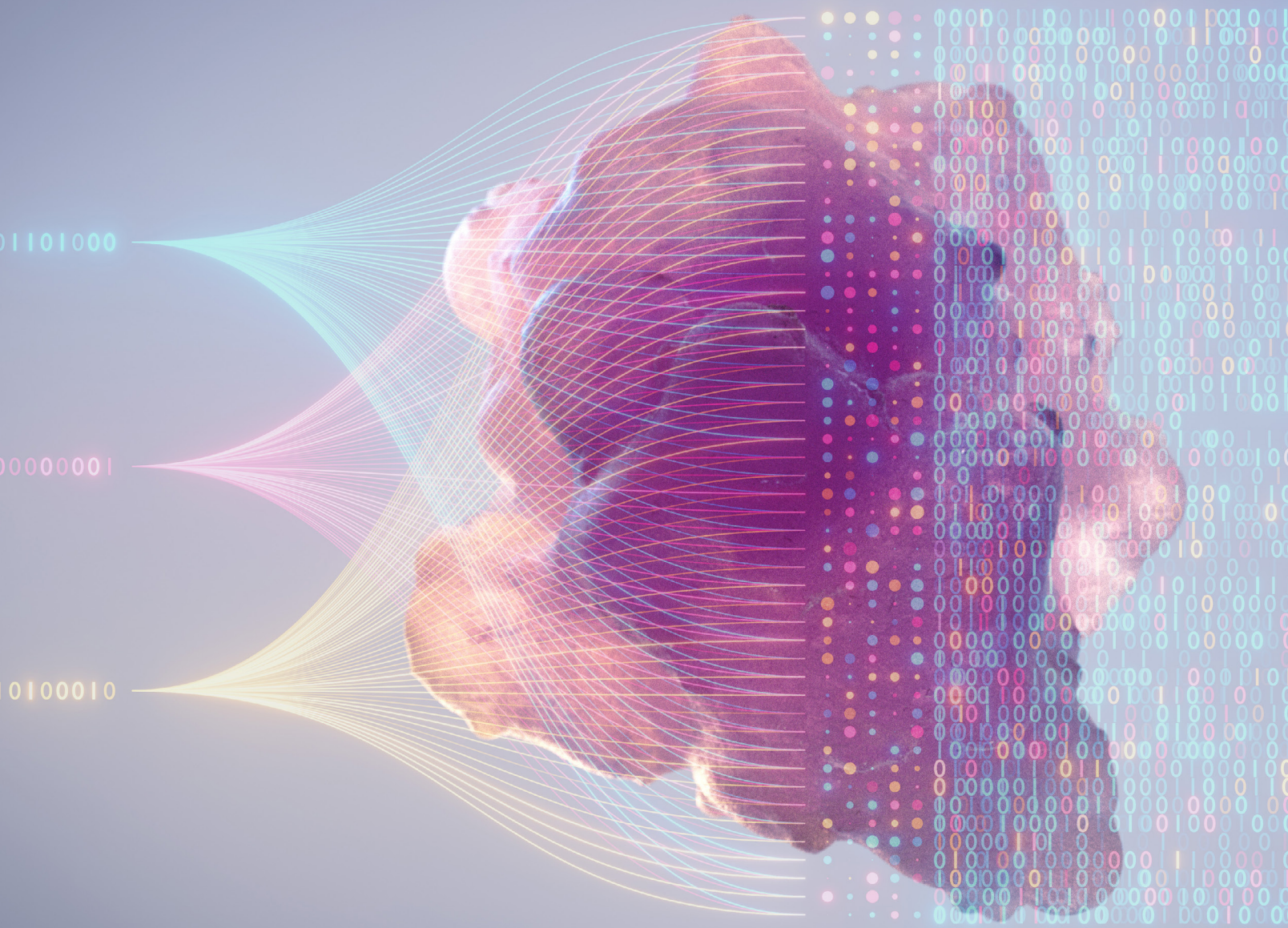
"When you have enough nutrients, your liver can multitask," Porat-Shliom says. "You can afford to make lipids and send them for storage for times when food becomes unavailable."

Porat-Shliom says her team has seen the same spatial variations in mitochondrial architecture within samples of healthy human liver tissue, and understanding this diversity is critical for shedding light on metabolic diseases that place the liver at a greater risk for cancer. "The liver is just a remarkable organ, and we have the technology now to really look at this in an unprecedented resolution," she says.

Kang, S.W.S., et al. *Nat Commun*. 2024 Feb 28;15(1):1799.

At the top of this image is a depiction of mitochondria from liver cells at the edges of liver lobules. These mitochondria typically have access to nutrient-rich blood and convert some of these nutrients to energy. At the bottom is a depiction of mitochondria from liver cells closer to the center of liver lobules. These mitochondria focus on equipping cells to synthesize lipid molecules for later use. CCR researchers have uncovered new details on the relationship between mitochondria function, structure and position in the liver, with implications for human health and disease. Credit: Adam Harned and Kedar Narayan, CCR, NCI, NIH; SPGM, FNL, NCI, NIH

A NEW PERCEPTION OF DRUG RESISTANCE



An AI tool predicts tumor response to targeted therapy using single-cell datasets.

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

A new artificial intelligence (AI) tool called PERCEPTION analyzes single-cell RNA sequencing (scRNA-seq) data from tumors and predicts whether a patient will respond to a specific targeted treatment. PERCEPTION also identifies when patients' tumors are likely to develop resistance to treatment—and even provides drug recommendations to combat it.

Different cancer treatments target different elements of tumor biology, and not every treatment will work against each tumor. In response to this challenge, Senior Investigator **Eytan Ruppin, M.D., Ph.D.**, develops AI programs that analyze tumor data to match patients with treatments that will be most effective. A postdoctoral fellow in his lab, Sanju Sinha, Ph.D., who is now an Assistant Professor at Sanford Burnham Prebys in La Jolla, CA, was interested in applying this approach to scRNA-seq data from tumors.

Single-cell RNA sequencing generates a molecular profile for each cell in a sample, and can shed light on tumor heterogeneity, or the fact that not all cells in a tumor are the same. Cells in one area of a tumor may have a different molecular profile than cells elsewhere in the tumor. This makes choosing anti-cancer therapy difficult because it may only be effective against some, but not all, of the cancer cells in a tumor, and the surviving cells could allow the tumor to grow and spread.

Because it is looking at tens of thousands of individual cells, scRNA-seq creates large volumes of complex data that is challenging to interpret. However, AI can help interpret this data all at once and connect it to clinical outcomes. "That's why we wanted to use AI to see if we can use tumor single-cell RNA sequencing to predict therapy response, as well as track resistance," explains Sinha.

To this end, the researchers developed an AI method, PERCEPTION (**PER**sonalized Single-**C**ell **E**xpression-Based **P**lanning for **T**reatments **I**n **ON**cology), and used it to analyze scRNA-seq datasets of patients' multiple myeloma, breast and lung cancer tumors. Importantly, some of the data contained scRNA-seq data before and after treatment, showing how different cells within tumors responded to therapy.

In a study in *Nature Cancer*, they show how PERCEPTION helps to predict which anti-cancer drugs are most effective for individual patients. What's more, it was able to track the evolution of drug resistance over the course of a patient's disease—which Sinha notes is the first time a tool has demonstrated such capabilities—and outperform all other existing predictive tools for matching patients and treatments.

PERCEPTION can be applied to other cancer types where scRNA-seq data and matching clinical outcome data exists. Although scRNA-seq is expensive and future studies are needed to verify PERCEPTION's abilities, the initial findings suggest that the tool could open new avenues for precision oncology.

"Treatment of patients would be more adaptive, in terms of taking more measurements, looking at how the tumor is changing over time, and changing the treatment accordingly," explains Alejandro Schäffer, Ph.D., a Staff Scientist in Ruppin's lab who helped develop PERCEPTION.

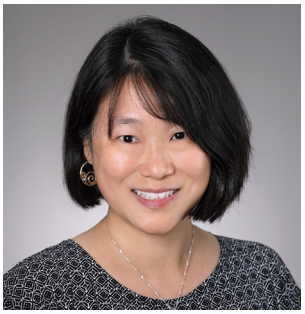
Sinha adds that this work was possible because of his mentors and the environment at CCR. "I really thank Eytan, Alejandro and CCR for providing a space where, as a young scientist, I was able to be bold and creative," he says.

Sinha, S., et al. *Nat Cancer.* 2024 Jun 5(6):938-952.

Artificial intelligence can take vast amounts of data and process it into something that researchers can use. CCR researchers have developed a new AI model, called PERCEPTION, to analyze RNA sequencing data from individual tumor cells and predict if the tumor will respond to a broad array of cancer targeted therapies. This new precision oncology approach offers exciting new ways to match cancer patients to the best possible therapies in a more accurate manner. Credit: Donny Bliss, NIH Medical Arts; SPGM, FNL, NCI, NIH; Adobe Firefly

RESTORING CRITICAL GENES

A novel gene therapy approach proves safe and effective for children with Wiskott-Aldrich syndrome.



Sung-Yun Pai, M.D.
Chief
Immune Deficiency Cellular Therapy Program

Wiskott-Aldrich syndrome (WAS) is a rare genetic disorder in which a mutation in the *WAS* gene hinders production of the WAS protein. This protein is critical for healthy white blood cell and platelet function, so people with WAS are at high risk of bleeding, eczema, infections, autoimmunity and lymphoma. Few patients live beyond the age of 15 without treatment.

WAS mainly affects boys because the gene is found on the X chromosome. Males only have one copy of the X chromosome, while females have two, and this second copy often compensates for the mutation on the other.

For decades, the standard treatment for WAS has been stem cell transplant from healthy tissue-type matched donors. However, immune-related complications and a lack of well-matched donors limit the success of this standard therapy.

Now, a clinical trial investigating a novel gene therapy for treating WAS shows that it is safe and can dramatically improve symptoms. Senior Investigator **Sung-Yun Pai, M.D.**, launched and led the phase 1/2 clinical trial in five children with WAS while in her previous position at Boston Children's Hospital, with her final analysis completed at CCR.

The therapy aims to add a functioning copy of the gene to the children's own blood cells, avoiding immune complications from using a donor. A virus is used to insert the *WAS* gene into stem cells extracted from the patient, which are then reinfused back into the patient. With the gene added to their stem cells, patients were able to produce WAS protein in their white blood cells and platelets. Despite having below average levels of the protein after gene therapy, the significant reduction of symptoms in the patients suggests that enough WAS protein was being produced to be beneficial. The children had fewer infections and improved eczema, and there were no serious adverse events caused by the gene therapy itself. The results of the study were reported in *Blood*.

"We followed each patient for at least five years, and they did great. All of the patients had improvements in their immune system," Pai notes. "Unhindered by their condition, they were able to act like kids again."

Notably, when scientists use viruses to insert copies of a gene into cells, sometimes only one copy of a gene makes it into the cell. In this study, patients whose cells took up two copies of the *WAS* gene had platelet counts restored to essentially normal levels, while those with only one copy of the gene continued to have low platelets. Nevertheless, all patients had a reduction in severe bleeding.

The next step for Pai is to develop a more effective gene therapy for WAS that results in better protein expression and corrects platelet counts more effectively even if only one copy of the gene is inserted.

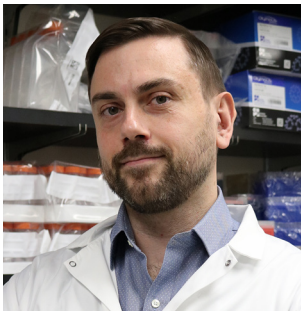
She emphasizes how important it is to continue doing research into rare diseases such as WAS, first and foremost to benefit patients. "Unless somebody takes an interest in their disease, they will never have better treatments," Pai says, noting that research into genetic disorders also provides critical insights into the unknown underpinnings of disease biology.

Labrosse, R., et al. *Blood*. 2023 Oct 12;142(15):1281-1296.

Duy Anh "Harry" Le was just 2 months old, living in southern Vietnam, when his parents first noticed strange bleeding spots developing on his body. Doctors initially thought he had Dengue fever, but mysterious symptoms continued to emerge, including eczema and numerous infections. In April 2016, after months of exploring potential causes, a genetic test finally diagnosed Harry with WAS. The family moved to northern Vietnam in search of more information and treatments. "Harry was desperate. There was no treatment for him at that time," explains Duy Le, Harry's father, noting that his son was struggling to eat due to severe lesions in his mouth and digestive tract. Duy undertook a worldwide search for solutions at that point, eventually bringing his son to the U.S. in November 2016 to participate in Dr. Pai's gene therapy clinical trial. After the trial, Harry's symptoms improved dramatically, and he is now a happy and healthy 9-year-old with a broad smile. "The clinical trial, it's like a miracle. Now Harry can have a normal life, the same as other children," says Duy. "I think it's really important for scientists to keep doing research like this, which is really, really helpful for children with rare diseases." Credit: Photo courtesy of Duy Le; SPGM, FNL, NCI, NIH; Adobe Firefly

BUILDING SUPPORT FOR CANCER IMMUNOTHERAPY

A new method makes therapeutic cancer vaccines more reliably effective in mice.



Matthew T. Wolf, Ph.D.
Stadtman Investigator
Cancer Innovation Laboratory

Cancer therapies aren't always drugs alone. Fighting cancer can involve multiple therapeutic approaches with fusions of new and existing treatments. In one such innovation, CCR researchers have developed a novel treatment that unites an existing surgical practice and tissue engineering with targeted therapeutic cancer vaccines. The combination caused tumor regression and provided a long-lasting anti-cancer immune response in mice.

Surgeons often use biomaterials to reconstruct or reinforce tissue after an operation; these materials can range from plastics to collagen. For example, when doctors remove a tumor, biomaterials can act as a scaffolding to fill the empty space left behind or support nearby structures in the body. Depending on their physical and chemical composition, these biomaterials also can initiate and regulate inflammation, a key process in how the immune system protects us from cancer.

"These biomaterials work well in a post-surgery environment, particularly because you can choose a material that facilitates healing by recruiting immune cells to repair the surgical wound," says Stadtman Tenure-Track Investigator **Matthew Wolf, Ph.D.** He was curious to know if he could take advantage of the biomaterials and the unique immune cells that they summon to create an environment additionally suited to fighting cancer cells.

Wolf came up with the idea that therapeutic cancer vaccines might help to redirect the immune response from the biomaterials towards a specific cancer. While preventive vaccines prepare the healthy immune system to protect against viruses and bacteria, therapeutic cancer vaccines train the immune system to recognize and remember cancer cells that might have been left behind or start growing again after tumor removal.

In their study, published in *Advanced Materials*, Wolf's team infused their biomaterial scaffolding with a therapeutic cancer vaccine cocktail that activates cytotoxic T lymphocytes, a type of cancer-fighting immune cell. Their design was engineered so that the scaffold would generate cancer-killing T cells in concert with the vaccine trapped within it, so the vaccine stayed at the site and did its work for longer rather than dissipating.

The result? An environment rich with immune cells, where the therapeutic cancer vaccine helps them effectively target tumor cells for longer than usual.

"Both the vaccine and the scaffold are providing unique parts of this immune response to turn into something that's greater than the sum of the two," says Wolf.

The researchers tested their therapy in mice with lymphoma tumors. The scaffold-enhanced cancer vaccine was able to stimulate the immune system to eradicate 50 to 75 percent of existing tumors. Months later, more tumors were introduced into the mice, and their immune systems successfully eradicated the new tumors too. This indicates that the treatment created a long-lasting immune memory, something Wolf and his colleagues are excited about.

"CCR's extensive preclinical facilities made it possible for us to follow the animals for nearly a year so that we could show the longevity of our treatment," says Wolf. "Our method is also convenient because it uses biomaterials that fit into normal surgical approaches to removing cancer; it may usher in an era that combines cancer immunotherapy treatment with regenerative medicine of surgical trauma."

Pal, S., et al. *Adv Mater.* 2024 Apr;36(15):e2309843.

CCR researchers developed a biocompatible, porous and degradable scaffolding—seen here imaged with a scanning electron microscope—using the cell-free extracellular matrix of small intestine tissue. The biomaterial scaffolding can be implanted in the body where it will be remodeled into, and support the growth of, new tissue to repair injury by recruiting immune cells to the site. CCR researchers leveraged these properties to create a biocompatible scaffold-assisted therapeutic cancer vaccine that enhanced vaccine efficacy and eliminated tumors in mice and generated protective anti-cancer memory. This immunotherapy-infused scaffold could one day be implanted in patients to help prevent tumors from coming back after surgery. Credit: Iris Baurceanu and Adam Harned, CCR, NCI, NIH; SPGM, FNL, NCI, NIH

Faculty News

New faculty contribute to our work of making breakthrough scientific discoveries to find cures and treatments for cancer. We also recognize current faculty who have started new roles within CCR.

Leslie N. Aldrich, Ph.D.

Leslie N. Aldrich, Ph.D., has been appointed as a Stadtman Tenure-Track Investigator in the Molecular Targets Program. Dr. Aldrich joins CCR from the University of Illinois at Chicago. Her research is focused on drug discovery, and a main interest of her lab is the autophagy pathway in the context of basic biology and human disease.

Grégoire Altan-Bonnet, Ph.D.

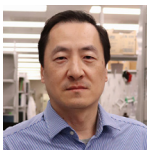
Grégoire Altan-Bonnet, Ph.D., has been appointed Deputy Chief of the Laboratory of Integrative Cancer Immunology. Dr. Altan-Bonnet develops experimentally validated quantitative models of aspects of immune systems and lymphocyte communications to advance tailored immunotherapies for cancer.

Deborah E. Citrin, M.D.

Deborah E. Citrin, M.D., has been appointed Scientific Director for Clinical Research at CCR. In this role, Dr. Citrin will oversee the vision and scientific management of CCR's clinical research program, including scientific plans and priorities, identification and implementation of new opportunities, programs and partnerships, recruitment of faculty, and the training and mentorship of early investigators.

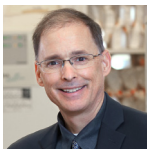
Leah M. Cook, Ph.D.

Leah M. Cook, Ph.D., has joined the Cancer Innovation Laboratory as a Senior Investigator and has been named an NIH Distinguished Scholar. She joins CCR from the University of Nebraska. Dr. Cook's research goal is to identify mechanisms associated with bone metastatic prostate cancer and the underpinnings of the immune-tumor bone environment that contribute to metastatic disease.



Chengkai Dai, Ph.D.

Chengkai Dai, Ph.D., has been awarded tenure at NIH and appointed as a Senior Investigator in the Mouse Cancer Genetics Program where he was previously a Stadtman Tenure-Track Investigator. Dr. Dai is a pioneer in the field of proteomic instability of cancer. His research focuses on the molecular mechanisms through which proteomic instability may affect genomic stability, cell invasion and autophagy.



James L. Gulley, M.D., Ph.D.

James L. Gulley, M.D., Ph.D., has been appointed Acting Co-Director of CCR. Dr. Gulley also serves as NCI Clinical Director, Co-Director of the Center for Immuno-Oncology and as a Senior Investigator. His research focuses on immunotherapies, particularly in prostate cancer.

Fatima Karzai, M.D.

Fatima Karzai, M.D., has been appointed as NCI Deputy Clinical Director. In this role, Dr. Karzai will lead institutional partnership efforts, drive expanding access and inclusion for participation in clinical trials and collaborate with the NIH Clinical Center to optimize clinical operations and ensure patient safety.

Daniel R. Larson, Ph.D.

Daniel R. Larson, Ph.D., has been appointed Chief of the Laboratory of Receptor Biology and Gene Expression. Dr. Larson studies gene expression in eukaryotic cells utilizing biophysical, molecular and genomic approaches, including single-molecule microscopy, RNA visualization in fixed and living cells, computational modeling of gene regulation and nascent RNA sequencing.

Jung-Min Lee, M.D.

Jung-Min Lee, M.D., has been awarded tenure at NIH and appointed as a Senior Investigator in the Women's Malignancies Branch where she was previously a Lasker Clinical Research Scholar and Tenure-Track Investigator. Dr. Lee's research focuses on developing targeted therapies for ovarian carcinoma and emphasizes the collection of patient samples to better understand treatment response and tumor biology in gynecologic malignancies.

Glenn Merlino, Ph.D.

Glenn Merlino, Ph.D., was appointed Acting Co-Director of CCR until his retirement in June 2024. Dr. Merlino also served as the Scientific Director for Basic Research and as a Senior Investigator in the Laboratory of Cancer Biology and Genetics. His research focused on cutaneous malignant melanoma.

Joe T. Nguyen, D.D.S., Ph.D.

Joe T. Nguyen, D.D.S., Ph.D., has joined the Surgical Oncology Program as a Physician-Scientist Early Investigator from the National Institute of Dental and Craniofacial Research. He has also been named an NIH Distinguished Scholar. Dr. Nguyen's research seeks to uncover the intricate link between metabolism and the tumor immune microenvironment, to enhance the accuracy of pre-clinical head and neck cancer models and to develop novel therapeutics to improve immune checkpoint inhibitor effectiveness.

Terren K. Niethamer, Ph.D.

Terren K. Niethamer, Ph.D., has joined the Cancer and Developmental Biology Laboratory as a Stadtman Tenure-Track Investigator from the University of Pennsylvania. Dr. Niethamer is a cell and developmental biologist, and the goal of her research program is to understand how endothelial cells communicate with other lung cells to build complex three-dimensional structures during development and regeneration.

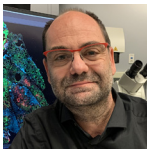
Faculty News continued

Samira M. Sadowski, M.D.

Samira M. Sadowski, M.D., has been appointed as a Lasker Clinical Research Scholar and Tenure-Track Investigator in the Surgical Oncology Program where she was previously a Physician-Scientist Early Investigator. Dr. Sadowski's research focuses on the identification of diagnostic and prognostic markers for endocrine tumors, with a particular focus on pancreatic and small bowel neuroendocrine tumors and developing new therapies for such tumors.

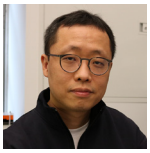
Carol J. Thiele, Ph.D.

Carol J. Thiele, Ph.D., has been appointed Acting Co-Director of CCR. Dr. Thiele also serves as Deputy Chief of the Pediatric Oncology Branch and as a Senior Investigator. Her research focuses on molecular and epigenetic regulation of neuroblastoma tumor heterogeneity.



Roberto Weigert, Ph.D.

Roberto Weigert, Ph.D., has been appointed Deputy Chief of the Laboratory of Cellular and Molecular Biology. Dr. Weigert's research focuses on the basic mechanisms that regulate how materials move in mammalian tissues, with a particular emphasis on membrane remodeling.



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

Chuan Wu, M.D., Ph.D., has been awarded tenure at NIH and appointed as a Senior Investigator in the Experimental Immunology Branch where he was previously a Stadtman Tenure-Track Investigator. Dr. Wu's laboratory studies intestinal neuroimmune interactions in health and disease to understand the cellular and molecular mechanisms of interactions between the enteric nervous system and the immune system.

Recently Retired

With appreciation for their service, we recognize these CCR Investigators who have recently retired.

Terri S. Armstrong, Ph.D., ANP-BC, FAAN, FAANP, Senior Investigator, Neuro-Oncology Branch

Jonathan D. Ashwell, M.D., Chief and Senior Investigator, Laboratory of Immune Cell Biology

Jay A. Berzofsky, M.D., Ph.D., Chief and Senior Investigator, Vaccine Branch

R. Andrew Byrd, Ph.D., Senior Investigator, Center for Structural Biology

Mark R. Gilbert, M.D., CCR Deputy, Chief and Senior Investigator, Neuro-Oncology Branch

Xinhua Ji, Ph.D., Senior Investigator, Center for Structural Biology

Jonathan R. Keller, Ph.D., Senior Investigator, Mouse Cancer Genetics Program

Glenn Merlino, Ph.D., CCR Acting Co-Director, Scientific Director for Basic Research and Senior Investigator, Laboratory of Cancer Biology and Genetics

Leonard M. Neckers, Ph.D., Senior Investigator, Urologic Oncology Branch

David D. Roberts, Ph.D., Senior Investigator, Laboratory of Pathology

Howard A. Young, Ph.D., Senior Investigator, Cancer Innovation Laboratory

In Memoriam

C. Norman Coleman, M.D., Senior Investigator, Radiation Oncology Branch

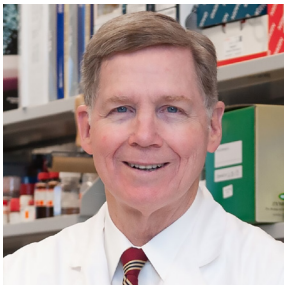
Faculty list is for calendar year 2024.

Awards & Honors

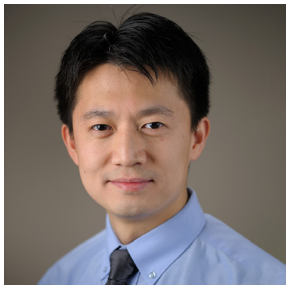
Jaydira Del Rivero, M.D., received the Women Leaders in Oncology 2023 Rising Star Award.

Elaine S. Jaffe, M.D., was elected to the Association of American Physicians.

Jung-Min Lee, M.D., was elected to the American Society for Clinical Investigation.



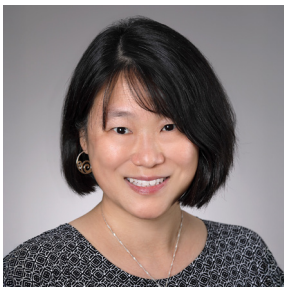
W. Marston Linehan, M.D., received the 2024 Secretary's Award for Distinguished Service from the Department of Health and Human Services (HHS).



Ji Luo, Ph.D., received the 2024 Dr. Francisco S. Sy Award for Excellence in Mentorship at HHS.

Andre Nussenzweig, Ph.D., received the 2024 Environmental Mutagenesis and Genomics Society Award and a 2024 HHS Career Achievement Award.

Ruth Nussinov, Ph.D., was elected as a member of the European Molecular Biology Organization.



Sung-Yun Pai, M.D., was appointed as a 2024 Fellow of the American Society for Transplantation and Cellular Therapy.

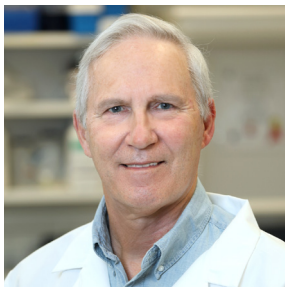
Peter A. Pinto, M.D., received the 2024 Barringer Medal from the American Association of Genitourinary Surgeons.

Yves Pommier, M.D., Ph.D., was elected to the Association of American Physicians.

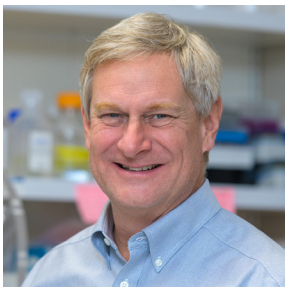
Steven A. Rosenberg, M.D., Ph.D., was elected to the National Academy of Sciences, received the 2023 Lombardy is Research Prize from Regione Lombardia, the 2023 European Society for Medical Oncology Award for Immuno-Oncology and the 2024 American Association for Cancer Research (AACR) Award for Lifetime Achievement in Cancer Research.

Dr. Rosenberg and Sanghyun (Peter) Kim, Ph.D., jointly received the 2024 *Cancer Immunology Research* Award for Outstanding Journal Article from the AACR.

Awards & Honors continued



John T. Schiller, Ph.D., was elected to the 2024 class of Fellows of the AACR Academy.



Joel P. Schneider, Ph.D., received the 2023 Murray Goodman Memorial Prize from *Biopolymers*.

Nirali N. Shah, M.D., M.H.Sc., received the 2024 Frank A. Oski Memorial Lectureship from the American Society of Pediatric Hematology/Oncology.

R. Mark Simpson, D.V.M., Ph.D., received the 2023 Dr. Daniel E. Salmon Award for Exemplary Achievement in Federal Veterinary Medicine from the National Association of Federal Veterinarians.

Giorgio Trinchieri, M.D., was elected to the National Academy of Sciences.

Brigitte C. Widemann, M.D., received the 2024 Secretary's Award for Meritorious Service from HHS.

Lori Wiener, Ph.D., DCSW, LCSW-C, received the 2024 Jimmie Holland Lifetime Achievement Award from the American Psychosocial Oncology Society.

Alexander Wlodawer, Ph.D., received the 2023 Casimir Funk Award in the Natural Sciences from the Polish Institute of Arts and Sciences of America.

Sandra L. Wolin, M.D., Ph.D., was elected to the National Academy of Sciences.

CCR Research Recognition Awards

These awards provide resources and recognition to our staff and fellows for their crucial contributions and dedication to cancer research.

CCR Excellence in Postdoctoral Research Transition Award

Recognizes exceptional CCR postdoctoral fellows and facilitates their transition to an independent research position at an academic institution:

Can Li, Ph.D., Experimental Immunology Branch

Sushant Patkar, Ph.D., Molecular Imaging Branch

CCR Outstanding Ph.D. Student Award

Recognizes outstanding Ph.D. students who conducted part or all of their thesis research at CCR:

Sooraj Achar, University of Oxford, NIH Oxford-Cambridge Scholars Program, for work performed in the Laboratory of Integrative Cancer Immunology

Khiem Lam, University of Maryland (UMD), NCI-UMD Partnership Program, for work performed in the Laboratory of Integrative Cancer Immunology

Staff Scientist/Staff Clinician Outstanding Mentor Award

For exceptional dedication and commitment to the mentoring of junior physicians:

Lucas A. Horn, Ph.D., Center for Immuno-Oncology

Binwu Tang, Ph.D., Laboratory of Cancer Biology and Genetics

CCR by the Numbers

386 Open Clinical Trials

42 New Clinical Trials

1,487 New Patients

238 Principal Investigators

5 New Faculty Recruits*

3 Newly Tenured Investigators*

321/82 Staff Scientists/ Staff Clinicians

~600 Technical Lab Staff

802/97 Postdoctoral/ Clinical Fellows

392/45 Postbaccalaureate/ Predoctoral Students

187 Summer Students

>1,000 Articles in Peer-Reviewed Journals

64 Technology Facilities and Platforms

Technology Transfer Activities

71 New Employee Invention Reports

46 Issued U.S. Patents

23 New Cooperative Research and Development Agreements (CRADAs)

176 Active CRADAs

90 Clinical CRADAs

7 Umbrella CRADAs

16 New Clinical Trial Agreements (CTAs)

118 Active CTAs

101 New Licenses for CCR Technologies

708 Active Licenses

2 FDA Approvals**

The **NCI Technology Transfer Center (TTC)** works to enable and guide collaboration, invention development and licensing to advance today's discoveries into tomorrow's medical care. The TTC supports technology development activities for NCI in therapeutics, diagnostics, research tools, vaccines, devices, 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**).

Numbers are for fiscal year 2024 unless otherwise marked.

**Numbers are for calendar year 2024.*

***Path to approval supported by CCR co-developed agents and/or collaborations.*

CCR Resources

For more information about CCR, the topics mentioned in these stories, and the featured researchers, go to:

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

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

Search CCR Principal Investigators by Research Area
https://ccr.cancer.gov/staff-directory/principal-investigators/research-areas

Search CCR Principal Investigators by Disease Focus
https://ccr.cancer.gov/staff-directory/principal-investigators/disease-focuses

NCI Center of Excellence in Immunology
https://ccrod.cancer.gov/confluence/display/COEI/Home

Center for Cancer Research

NATIONAL
CANCER
INSTITUTE