

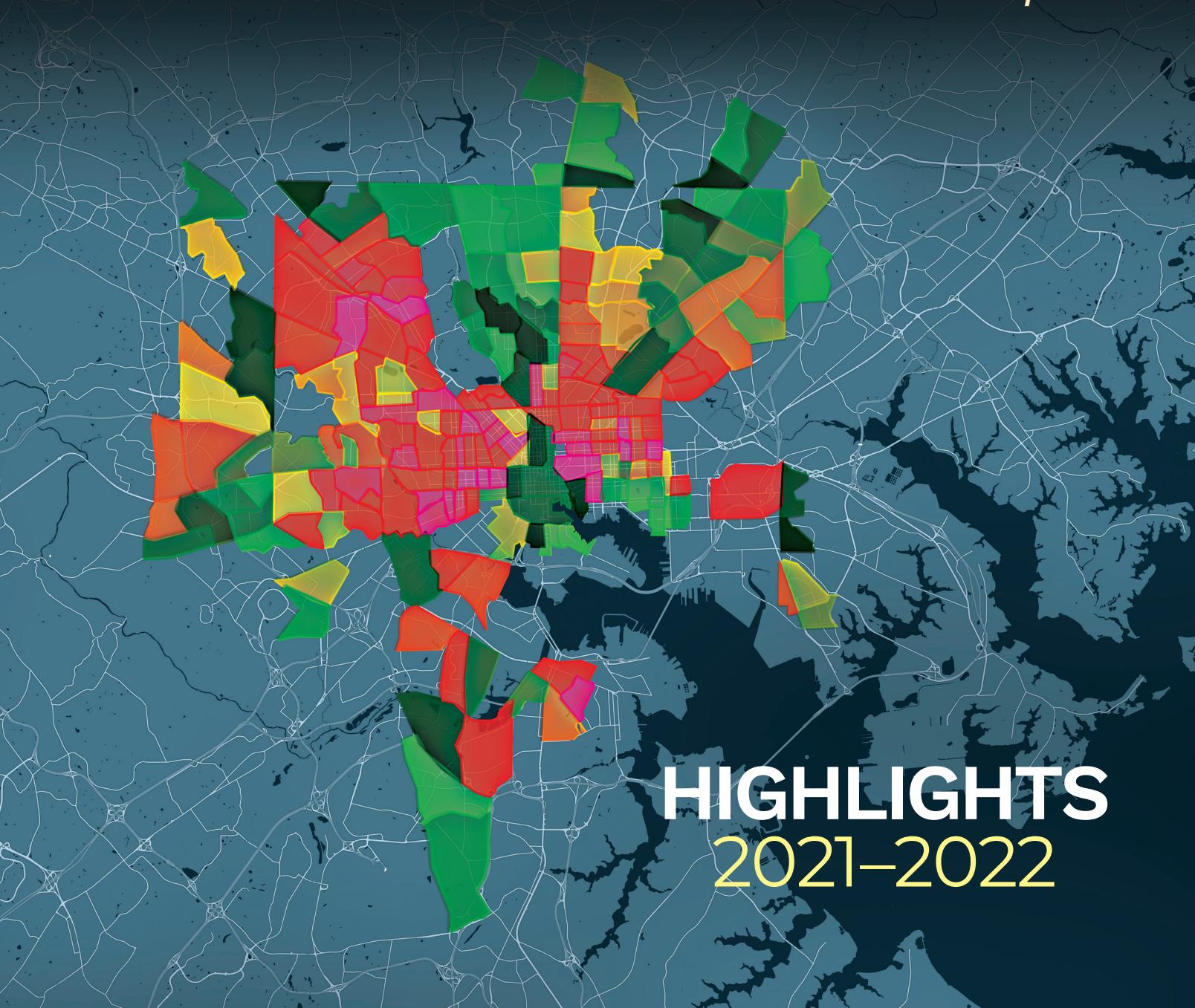


NATIONAL CANCER INSTITUTE

CENTER FOR CANCER RESEARCH

# MILESTONES

*Cancer Research with a Purpose*



**HIGHLIGHTS**  
2021–2022



# CENTER FOR CANCER RESEARCH

## The Nation's Cancer Center

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.

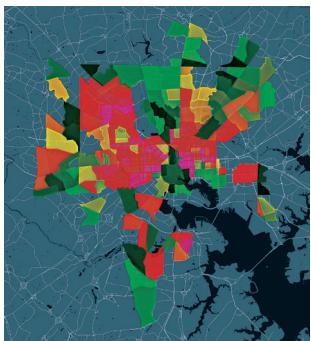
The CCR is home to an extraordinary group of scientists and clinicians exploring the cutting edge of cancer and HIV/AIDS research. Our scientists work on a wide spectrum of biological and biomedical problems that range from visualizing and understanding the structure of individual genes and proteins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

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](http://ccr.cancer.gov).



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*The colors of the map highlight levels of social vulnerability in the Baltimore area by neighborhood and reflect on social injustice and existing disparities in health experienced by communities of color. Areas in green have a lower social vulnerability score than areas in red. This index indicates a community's resilience when confronted with a natural disaster, health issue or other stressors. The cover map was inspired by the "Not Even Past: Social Vulnerability and the Legacy of Redlining" project, which was created in partnership with the University of Richmond's Digital Scholarship Lab and the National Community Reinvestment Coalition. "Not Even Past" used the Center for Disease Control's Social Vulnerability Index. Changes were made to the original image. Design credit: Allen Kane, Scientific Publications, Graphics and Media, Frederick National Laboratory, NCI, NIH*

### CONTRIBUTORS

Pamela Beltowski  
Brenda Boersma-Maland  
Chabelis Byamana  
Colleen Curran  
Li Gwatkin  
Veronica Falconieri Hays  
Michelle Hampson  
Kelly Haskins  
Allen Kane  
Jasmine Lee  
Joseph Meyer  
Jennifer Michalowski  
Mike Miller



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 of the next generation of a diverse and inclusive biomedical workforce

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# Director's Note



Just as explorers have used maps for centuries, cancer researchers rely on them daily. We use gene maps to identify new cancer drivers, chart cancer pathways and visualize complex gene expression profiles. We also create three-dimensional maps of tumors to target them with radiation, and we increasingly map the complex spatial and functional heterogeneity of tumors at the single-cell level.

The cover of this issue of *Milestones* stands symbolically for the many uses of various types of maps in cancer research. But it is more than a symbol. This map of Baltimore records differences in geographical distributions of social vulnerability, which includes cancer. It dramatically highlights the pressing issue of health disparities. Differences in cancer outcomes vary widely in local and global populations based on complicated socioeconomic factors, race/ethnicity and geographic location. While access to care is a primary cause for health disparities in cancer outcomes, scientists are discovering that other factors, including the environment and disease predispositions, contribute as well. Eliminating disparities in cancer treatment and care is a major goal in CCR.

One example of our recent efforts in this area is a study into the molecular foundation of health disparities in prostate cancer featured in this issue of *Milestones*, which every year highlights some of the most creative, innovative and impactful work of CCR researchers.

Despite the challenges of an ongoing global viral pandemic, activities at CCR have continued unabated. Our advances in the past year cover a broad range of cutting-edge topics in cancer research, including progress in basic studies on how genomes protect themselves from damage and new insights into how tumor growth is affected by the host tissue, by the bacterial microbiome of a patient and the age of a patient. We have also made major progress in precision medicine by inventing new ways to accurately diagnose cancers, optimize therapy options for patients and predict treatment responses.

Our ultimate goal remains the development of new treatment options for patients and expanding the representation of patients in our clinical trials. These efforts culminated in the past year in the approval by the U.S. Food and Drug Administration of no fewer than four new drugs developed by CCR researchers. In addition, clever new clinical and surgical technology and new ways to harness the immune system for cancer therapy bring new options and hope to patients.

Maps help guide and chart our discoveries in cancer research, but even the best maps cannot predict what is ahead. Discovery inherently contains an element of serendipity and adventure. At CCR, we fully embrace the challenges and the opportunities of the unknown as we continue to explore paths towards ending cancer as we know it.

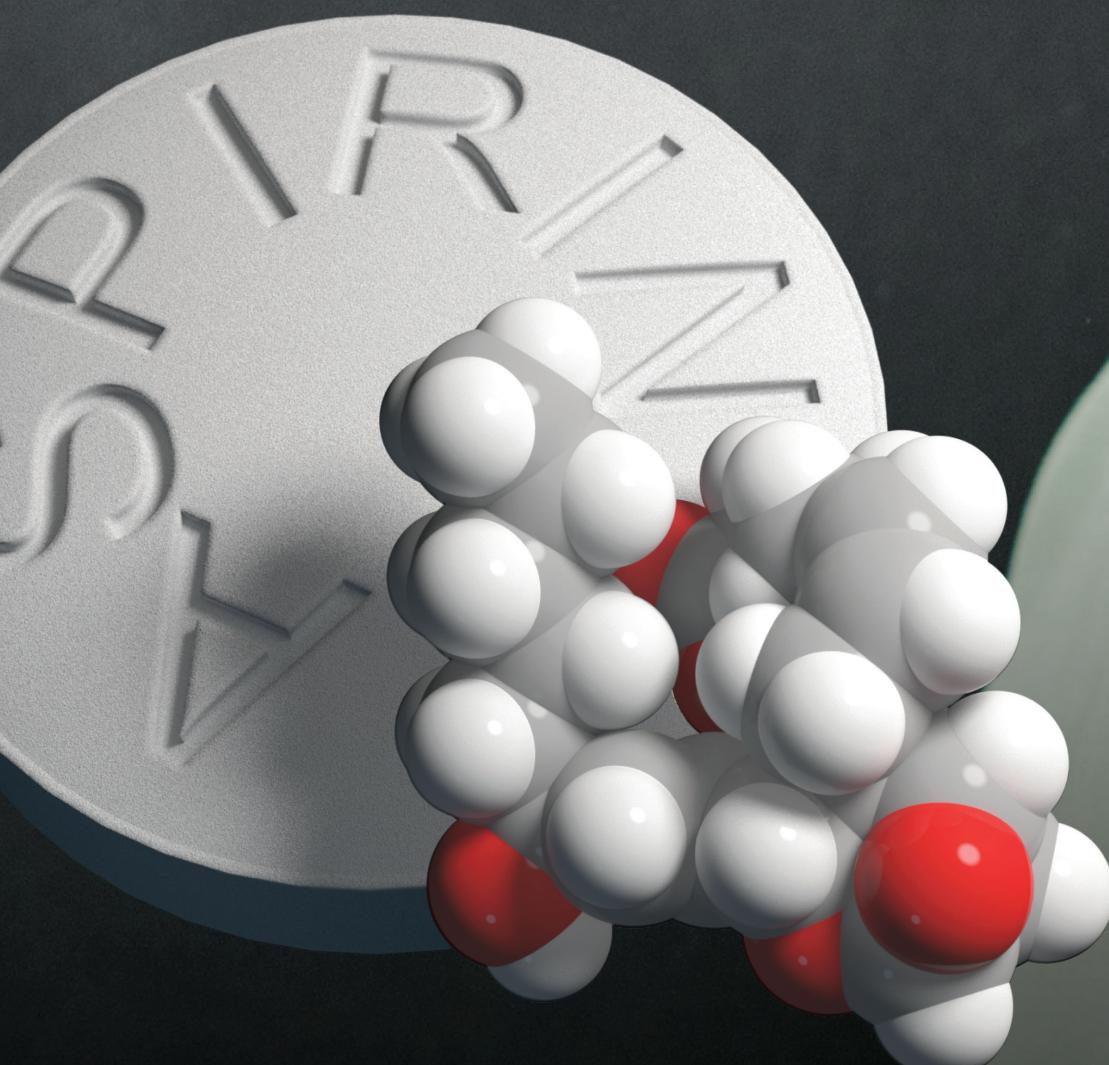
## **Tom Misteli**

Director

NCI Center for Cancer Research

# A NEW APPLICATION

FOR AN  
**OLD MEDICINE**



# Regular aspirin use may limit prostate cancer metastasis in African American men.



**Stefan Ambs, Ph.D., M.P.H.**

**Senior Investigator**

Laboratory of Human  
Carcinogenesis

For thousands of years, a substance derived from willow tree bark has been used to treat pain. Today we know it as aspirin. Now, CCR researchers have uncovered how in African American men with prostate cancer, aspirin could also improve outcomes for the disease.

This research, led by Senior Investigator **Stefan Ambs, Ph.D., M.P.H.**, and published in the *Journal of the National Cancer Institute*, increases our understanding of how regular aspirin use may benefit African American men by potentially reducing their risk of developing aggressive prostate cancer and dying from the disease. The findings are especially important given that, compared to white men, African American men are more likely to develop prostate cancer and are twice as likely to die from it.

Ambs and colleagues initially sought to explore whether the biology of the disease may contribute to these disparities. Through the long-standing NCI-Maryland prostate cancer case-control study, they had access to an ideal pool of patient information. Over many years, the study has recruited men diagnosed with prostate cancer for long-term monitoring to understand what contributes to the excessive burden of disease among African American men.

Initial data from the study showed that many prostate tumors found in African American men harbor a distinct immune-inflammation signature that coincides with greater disease severity. Additional research revealed that this signature also occurs systemically. Moreover, a subgroup of African American men with prostate cancer has exhibited elevated levels of the metabolite thromboxane A2 (TXA2), which is primarily produced by the cyclooxygenase (COX) enzyme located in blood platelets.

Ambs made a connection to aspirin because of its ability to inhibit the COX pathway. Early evidence suggested that regular aspirin use may protect against lethal prostate cancer

in African American men. This prompted Ambs' team to explore the role of TXA2, aspirin and disease severity and mortality in more detail.

Their retrospective study showed that pro-metastatic TXA2 is often higher in African American men with prostate cancer, but not in European American patients, and that high levels of the metabolite more than doubled the chances of developing metastases. Strikingly, African American men in the study who self-reported taking aspirin regularly had lower TXA2 levels and decreased risk of mortality.

"It's exciting and satisfying that we have discovered a mechanism that appears to have a significant effect and could potentially contribute to metastatic and lethal disease in this high-risk population for prostate cancer," says postdoctoral fellow Maeve Bailey-Whyte, Ph.D., M.P.H., who worked on this study as part of her NCI Cancer Prevention Fellowship.

Both Ambs and Bailey-Whyte agree that the NCI-Maryland prostate cancer study, for which recruitment has concluded but long-term data collection continues, is a unique and invaluable resource for studying prostate cancer in an underrepresented population. But they note some difficulties in moving forward with a prospective study, particularly because many minority groups are underrepresented in these studies and clinical trials, including African American men. This challenge is compounded by the fact that prostate cancer typically progresses slowly, requiring long-term data collection.

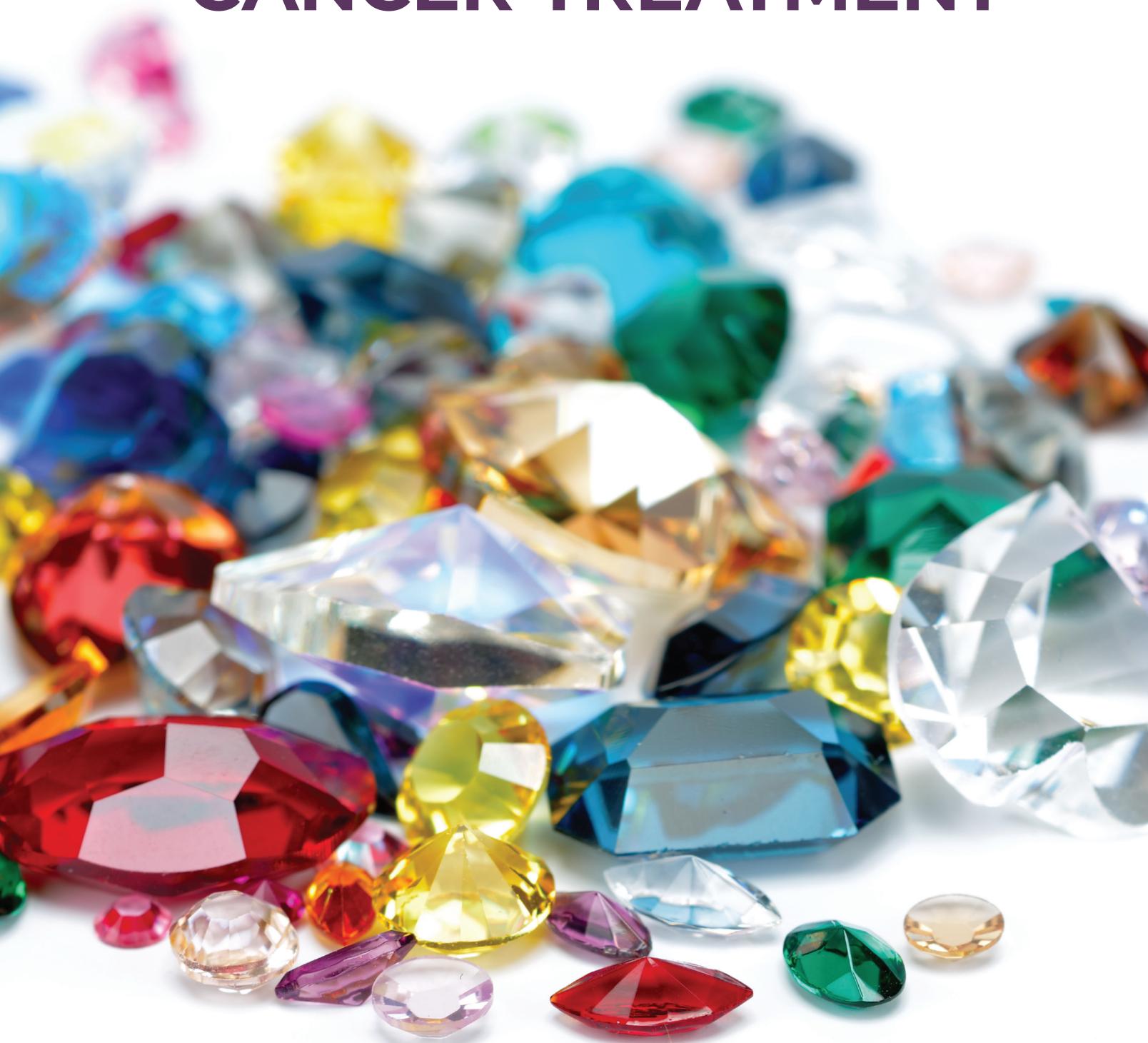
"Without long-term studies, we will be unable to assess associations between cancer risk factors and survival outcomes, which may lead to prevention strategies in the future," says Bailey-Whyte. "It reinforces the importance of including more diverse populations in future trials."

Kiely M, et al. *J Natl Cancer Inst.* 2021 Jul 15:djab129.

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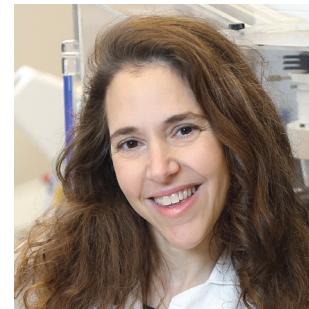
*Regular use of aspirin (shown here in pill and molecule form) may benefit Black men by reducing their risk both of developing aggressive prostate cancer and of dying from the disease. This image represents a participant in this study, most of whom came from the greater Baltimore area, including patients from both the Baltimore Veterans Affairs Medical Center and the University of Maryland Medical Center. A map of Baltimore is depicted on the front cover in a pattern that informs cancer researchers and the public about inequalities in health. Credit: Alan Hooing, NIH Medical Arts; iStock*

# A REAL GEMY OF A CANCER TREATMENT



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# A novel therapy could prevent cancer from spreading.



**Rosandra N. Kaplan, M.D.**  
Senior Investigator  
Pediatric Oncology Branch

While treatment advances have greatly benefited patients with cancers diagnosed in early stages, cancers that have metastasized — spread to other parts of the body — still present a major treatment challenge and remain the leading cause of cancer deaths. Understanding how cancers spread, and how to prevent them from doing so, is a high priority in cancer research.

In 2005, when still a research fellow at Weill Cornell Medical College and Memorial Sloan Kettering Cancer Center, now Senior Investigator **Rosandra Kaplan, M.D.**, discovered that cancer cells, in addition to manipulating their local micro-environment to survive, can also prime distant areas in the body to promote future metastasis. The areas are known as “pre-metastatic niches,” and research in her lab focuses on better understanding the microenvironmental changes that promote metastasis and disrupt this priming process.

This past year, a team led by Kaplan made a major step forward in this research. The results, described in *Cell*, could potentially yield a novel therapy for patients at high risk of cancer progression and related death.

Kaplan and colleagues discovered that cancer cells can hide by causing the immune system to treat a tumor as a wound to be healed. Myeloid cells, which are a part of the immune system’s first line of defense, can either summon T cells, a type of white blood cell, to attack harmful agents like bacteria, viruses and cancer cells, or they can message T cells to stand down, to promote healing. Cancer cells are able to secrete signaling molecules that program myeloid cells into treating the cancer as a wound to be healed, thus encouraging tumor growth.

Kaplan, postdoctoral fellows Sabina Kaczanowska, Ph.D., and Daniel Beury, Ph.D., made the important observation that cancer cells disperse signaling molecules to attract myeloid cells to distant pre-metastatic sites in the body that can help cancer spread, specifically to the lungs. Based on this information, the team created genetically engineered myeloid cells (GEMys) that promote an immune attack against cancer cells. The GEMys release a protein called interleukin-12, which recruits T cells to help fight cancer at early metastatic sites.

The team tested the GEMys in mice with rhabdomyosarcoma, an aggressive human form of cancer that often spreads to the lungs. Mice treated with the novel therapy, along with a dose of chemotherapy, experienced a complete remission of their tumors. The tumors did not come back over the course of the 250-day study. “When we took these cured mice and tried to implant them with a new tumor, they were resistant to the tumor,” Kaplan says.

Although this therapy was initially designed to treat cancer metastasis, Kaplan says that the original tumors in mice also responded to the treatment. Her team will continue to study GEMys as a possible therapy for advanced cancer before exploring its potential for treating early-stage disease.

“I hope, even in a small way, we can make things better for patients with a high risk for metastasis or recurrent disease,” Kaplan says.

Kaczanowska S, Beury DW, et al. *Cell*. 2021 Apr 15;184(8):2033-2052.e21.

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*Tumor metastasis is an area of cancer research that is both a challenge and a high priority. Researchers previously discovered that cancer cells can prime distant locations in the body to enable metastasis. In this study, researchers created genetically engineered myeloid cells (GEMys) to promote immune responses in these primed locations. This unique “gem” of an approach, symbolized by the gemstones in this image, provides a novel method to stop cancer from spreading. Credit: iStock*

# DECades IN THE MAKING



# New drug proves effective at shrinking von Hippel-Lindau-associated tumors.



Ramaprasad Srinivasan,

M.D., Ph.D.

Investigator

Urologic Oncology Branch

In von Hippel-Lindau (VHL) disease, patients develop many cancerous and non-cancerous tumors in the kidneys and other organs, such as the pancreas, brain and eyes. They often undergo repeated surgeries to remove their tumors as no other VHL therapy has been available. Following decades of CCR-led research on VHL that included the identification of the gene behind the disease in the 1990s, and work done in institutions around the world, a team led by Investigator **Ramaprasad Srinivasan, M.D., Ph.D.**, tested the drug belzutifan (Welireg™) for VHL. It is now the first and only U.S. Food and Drug Administration (FDA) approved systemic therapy for certain patients with the disease.

VHL disease develops when a mutation in the VHL gene occurs, making people unable to produce a protein that cells use for sensing and adapting to changes in oxygen levels. Cells respond by accumulating an excessive amount of several proteins called hypoxia-inducible factors (HIFs). Increased levels of HIFs can lead to tumor growth and the formation of new blood vessels that supply nutrients to the tumors. Scientists have been interested in targeting HIFs, particularly HIF2, to treat VHL-associated tumors. But directly targeting and inhibiting HIFs has proven difficult.

A breakthrough came when researchers at the University of Texas Southwestern Medical Center designed several small-molecule drugs that could block the activation of HIF2 through what was considered "brilliant engineering," according to Srinivasan. One of these drugs was belzutifan.

When the time came to test belzutifan in patients, Merck & Co., Inc., the company behind the drug, turned to Srinivasan and other CCR researchers with established expertise in VHL disease and patient groups. Srinivasan, in collaboration with physician Eric Jonasch, M.D., University of Texas MD Anderson Cancer Center, recruited 61 patients with VHL and tested

belzutifan in a phase II clinical trial at 11 centers in the United States, Denmark, France and the United Kingdom, including the U.S. National Cancer Institute and the NIH Clinical Center.

A few months after the first patient was treated with belzutifan, Srinivasan reviewed an imaging scan to assess the patient's response to treatment. He says he was "elated" with what he saw: dramatic tumor shrinkage. "This was a very emotional moment for all of us," says Srinivasan, who has been studying VHL disease since the early 2000s. "We were overjoyed."

According to the results, published in the *New England Journal of Medicine*, most patients in the trial experienced tumor shrinkage in their kidneys, with about half of patients experiencing tumor shrinkage of 30 percent or more.

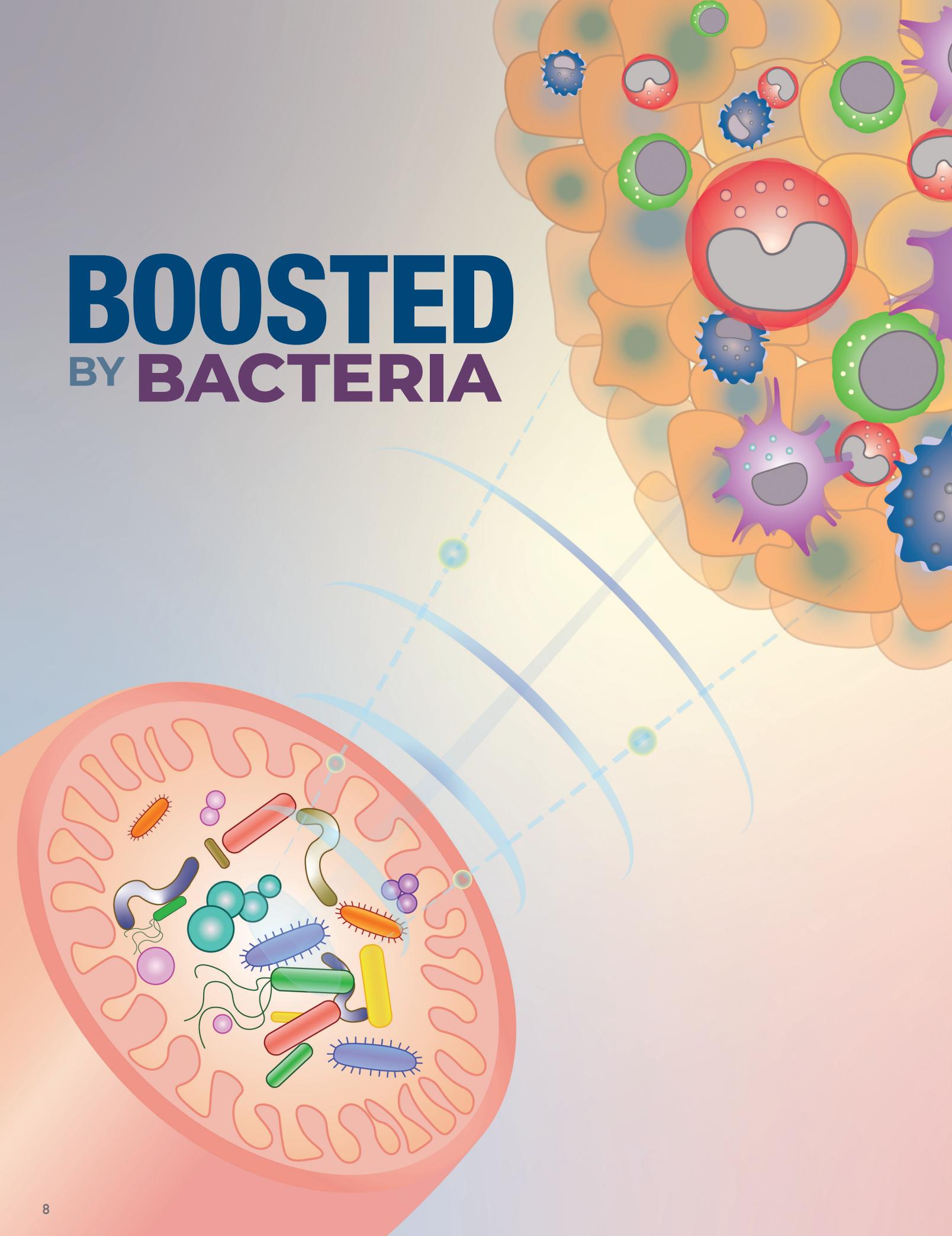
Moreover, belzutifan was able to shrink or stop the progression of tumors in organs such as the pancreas, brain, spinal cord and eyes to an extent that has not been seen with other drugs tested for VHL disease. Srinivasan notes that the vast majority of patients remain enrolled in the trial and continue taking belzutifan because of its benefits and relatively few side effects.

As a result of this research, the FDA approved belzutifan in 2021 for patients who require therapy but not immediate surgery and have VHL disease-associated renal cell carcinoma, pancreatic tumors or central nervous system hemangioblastomas. "In every respect you can imagine, we found this drug to be a big, big step in the right direction. It's effective, it's well-tolerated — everything that we could ask for in the first study of this agent in VHL," says Srinivasan. "We now have a reasonable alternative to surgery for some patients."

Jonasch E, et al. *N Engl J Med*. 2021 Nov 25;385(22):2036-2046.

*Kimber Hall first came to the NIH Clinical Center in 2008 for laparoscopic surgery to remove a von Hippel-Lindau (VHL) disease-associated kidney tumor. After the surgery, she made regular trips from her home in Washington state to NIH to monitor the size of her other tumors. During this time, she developed a pancreatic neuroendocrine tumor. About four years ago, Kimber learned about a trial using belzutifan for VHL-associated renal cell carcinoma. "I wanted to avoid surgery as much as possible, so I joined the trial at NIH," she says. Since then, her kidney lesions have remained stable or decreased in size. "My favorite outcome is that my pancreatic tumor shrank so much they can't see it," she says. "I'm glad I joined this trial, and I feel so happy that it's gone this well. It was an honor to be a part of it." Kimber hopes that this now FDA-approved drug will someday help others like her, including her family members who have VHL syndrome. Credit: Chris Hall*

# BOOSTED BY BACTERIA



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# Gut bacteria promote anti-cancer immunity by activating a key innate immune signaling pathway.



**Romina Goldszmid, Ph.D.**

**Stadtman Investigator**

Laboratory of Integrative  
Cancer Immunology

A tumor's fate depends not just on the tumor alone. An entire community of cells influences how cancer grows, spreads and responds to treatment. Amazingly, that includes microbes that live in our guts. It has become clear that some gut bacteria can help the immune system keep tumor growth in check — and CCR scientists have now figured out one way bacteria do it.

Stadtman Investigator **Romina Goldszmid, Ph.D.**, and her team are studying how gut microbes affect tumors by looking at an important aspect of anti-tumor immunity: the white blood cells of the innate immune system. The innate immune system provides a first-line defense against cancer and invading pathogens. Its cells are usually well represented at tumor sites, where they both attack the threat directly and summon other immune cells to the fight.

Goldszmid's team has shown in animal studies that having a community of microbes in the gut is important for the innate immune system's ability to defend the body against tumors. In mice raised in a sterile environment, whose guts remain microbe-free, innate immune cells are still present at tumor sites. But when Goldszmid's team analyzed those immune cells, they found that the mix of cell types was different from the mix found at the tumor sites of mice with gut microbes. The tumors of microbe-free mice even contained innate immune cells that had been programmed to support tumor cells' growth, rather than destroy them.

In work reported in *Cell*, graduate student Khiem Lam and postdoctoral fellow Romina Araya, Ph.D., traced these differences to the absence of molecular signals produced by

bacteria that activate an immune-stimulating pathway called STING. They found that when a normal mix of bacteria is present in the gut, some of those bacteria produce molecules that enter immune cells called monocytes; the molecules activate the STING protein to induce production of the immune mediator type I interferon (IFN). Type I IFN then triggers changes that help the innate immune system rally an anti-tumor defense.

Goldszmid and her colleagues have reason to believe gut microbes may use the same signals to modulate anti-tumor immunity in patients. Other researchers have noted that the microbial communities in the guts of patients successfully treated with cancer immunotherapy are comprised differently from those of patients who do not respond to this treatment. And when Goldszmid's team transferred the gut microbes of patients responsive to therapy to microbe-free mice, they saw a similar shift toward anti-tumor immunity, activated again by the STING pathway. Through analysis of published datasets, the researchers found an enhancement of the same innate immune signatures and type I IFN in the tumors of patients that responded to treatment.

In their animal experiments, Goldszmid's team identified several ways to boost gut microbes' anti-tumorigenic immune signals, including a simple shift to a high-fiber diet. Goldszmid hopes that figuring out how microbes manipulate the innate immune system will lead to new ways to use the microbes in a patient's gut to their benefit.

Lam KC, Araya RE, et al. *Cell*. 2021 Oct 14;184(21):5338-5356.e21.

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*Gut microbiota can influence the response to cancer therapy, and CCR researchers are beginning to understand how. This diagram illustrates how gut bacteria, depicted as different colored shapes in the bottom left-hand pink structure (the intestines) send signals (blue waves) to reprogram innate immune cells inside tumors (top right-hand side) and shape the anti-cancer immune microenvironment. Credit: Romina Goldszmid and Romina E. Araya, CCR, NCI, NIH*



# ONE-TWO PUNCH FOR CANCER

# A new algorithm to SELECT the best therapy helps advance precision oncology.



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

**Chief**

Cancer Data Science Laboratory

**Kenneth Aldape, M.D.**

**Chief**

Laboratory of Pathology

Identifying a pathway mutation in a patient's tumor and using it to guide cancer treatment has become a standard approach to designing personalized cancer treatments. Identifying two pathways that work synergistically may be even better.

A team of computational researchers at CCR have developed a new algorithm, called SELECT, to predict the best treatment strategies for multiple tumor types.<sup>1</sup> SELECT uses the powerful concept of synthetic lethality — where the combination of mutations in two pathways packs a one-two punch that results in cell death whereas a mutation in only one pathway alone does not.

The team, led by Senior Investigators **Eytan Ruppin, M.D., Ph.D.**, and **Kenneth Aldape, M.D.**, is using SELECT to identify such pathway pairs and partner them with drugs that can disable a pathway in a cancer cell that already contains a mutation in another. Importantly, SELECT complements current precision oncology approaches that rely on genomic data by analyzing tumor transcriptome information, which represents the complete set of RNA molecules present in a cell and better reflects the cell's functional status.

The algorithm, described in *Cell*, also leverages another type of interaction called synthetic rescue, where a pathway mutation reduces the cell's viability, but a mutation in a different pathway rescues the cell from death. The team is using this information to predict whether checkpoint therapy — a type of immunotherapy — might benefit a patient.

To test SELECT, the researchers used numerous publicly available datasets from targeted, chemotherapy and immu-

notherapy clinical trials and found that it can predict the efficacy of therapies in individual patients with 80 percent accuracy, outperforming existing prediction models.

Ruppin has been developing prediction algorithms since 2013, and SELECT is his fourth such model. He says that the SELECT algorithm is among the most comprehensive current predictive approaches in oncology but underscores the need for more data to improve the algorithm. "Conceptually, what we are trying to do is actually quite simple. It is the details that are complicated, and sorting them out requires more work and patient data," he emphasizes.

To obtain enough data for the latest version of SELECT, Ruppin partnered with Aldape with whom he shares a vision of using additional molecular information, such as tumor methylation, proteomics and liquid biopsies, to develop better treatment strategies.

Going forward, with the support of CCR leadership and in collaboration with many clinical colleagues at the NIH Clinical Center, Aldape and Ruppin hope that their tool will stimulate the development of precision oncology-based trials. These trials would prospectively test SELECT's ability to improve patient treatment and collect more data that could in turn lead to improvements in the underlying SELECT prediction algorithms. Plans are underway to conduct studies in brain, breast, bladder and kidney cancers, among others.

Lee JS, et al. *Cell*. 2021 Apr 29;184(9):2487-2502.e13.

<sup>1</sup>SELECT stands for SynthEtic LEthality and rescue-mediated precision onCology via the Transcriptome.

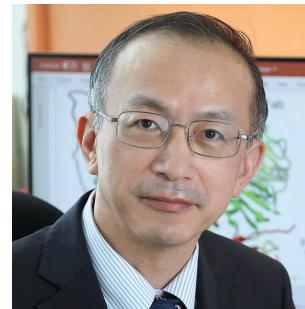
*Normal cells can have two pathways for certain essential biological functions in case one fails. In this study, researchers developed a computer algorithm to identify cancer cells that have disabled such backup pathways. By finding cells that already have a mutation in one pathway, the researchers can knock out the second pathway to cause cell death via a "one-two punch."*  
Credit: Natalie Runnerstrom



# CAR T CELLS FOR SOLID TUMORS

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## CAR T-cell therapy homes in on a new target: neuroblastoma.



**Mitchell Ho, Ph.D.**  
Deputy Chief  
Laboratory of Molecular Biology

The emergence of chimeric antigen receptor (CAR) T-cell therapy has provided renewed hope for many patients with blood cancers who have not benefited from traditional therapies. However, ways to use this therapy for many other cancers have remained elusive — until now. Senior Investigator **Mitchell Ho, Ph.D.**, and colleagues have discovered a way to target solid tumors through CAR T-cell therapy.

In CAR T-cell therapy, physicians program a patient's immune cells to recognize unique proteins on the surface of cancer cells to help them better target and kill the cancer. The key to success, however, is to target a protein that is found *only* on the cancer cells, not on healthy ones. While CAR T cells can safely target and destroy lymphoma and leukemia blood cells without harming other organs in the body, researchers have struggled to identify tumor-specific proteins that can be used in CAR T-cell therapy to target solid cancers without harming healthy organs in the process.

Ho is in a unique position to solve this problem because he studies proteins that are only expressed in cancers. In 2014, Ho and postdoctoral fellow Nan Li, Ph.D., began to investigate one such protein, called GPC2. Early evidence showed that it is expressed in neuroblastoma, an extremely rare and notoriously difficult-to-treat form of cancer that mainly affects children.

As Li studied GPC2 and investigated its prevalence in healthy human tissues, she found that almost all the tissues were GPC2-negative, which made GPC2 an ideal candidate for CAR T-cell therapy with the potential to treat neuroblastoma. The team reported their finding in *Proceedings of the National Academy of Sciences*.

As a next step, the researchers sought to engineer a new type of CAR T cell capable of targeting GPC2. They identified an antibody called CT3, which is a protein that can bind to GPC2 but not to other targets. The researchers then modified T cells to express CT3, which helps the immune cells better target, bind to and kill GPC2-expressing cancer cells. When it came time to test their CAR T cells, their efforts proved fruitful.

"With only a single CAR T-cell treatment, we could see a dramatic effect," says Ho. "In all preclinical models we looked at, our CAR T cells showed activity against neuroblastoma, leading to complete remission of tumors in mice." The results were described in *Cell Reports Medicine*.

As a next step, the team is partnering with the Pediatric Oncology Branch to test this therapy in a first-in-human clinical trial led by Rosa Nguyen, M.D., Ph.D., a Physician-Scientist Early Investigator, with funding from the NCI Cancer Moonshot<sup>SM</sup> program. "If this therapy proves beneficial for patients, it would be a remarkable achievement in a short timeline," Ho says, noting that the full spectrum of research on GPC2 CART cells — from basic science to a clinical trial — will be done by CCR.

Ho, Li and Nguyen believe that this new therapy could improve outcomes for patients with neuroblastoma and may even apply to other solid tumors.

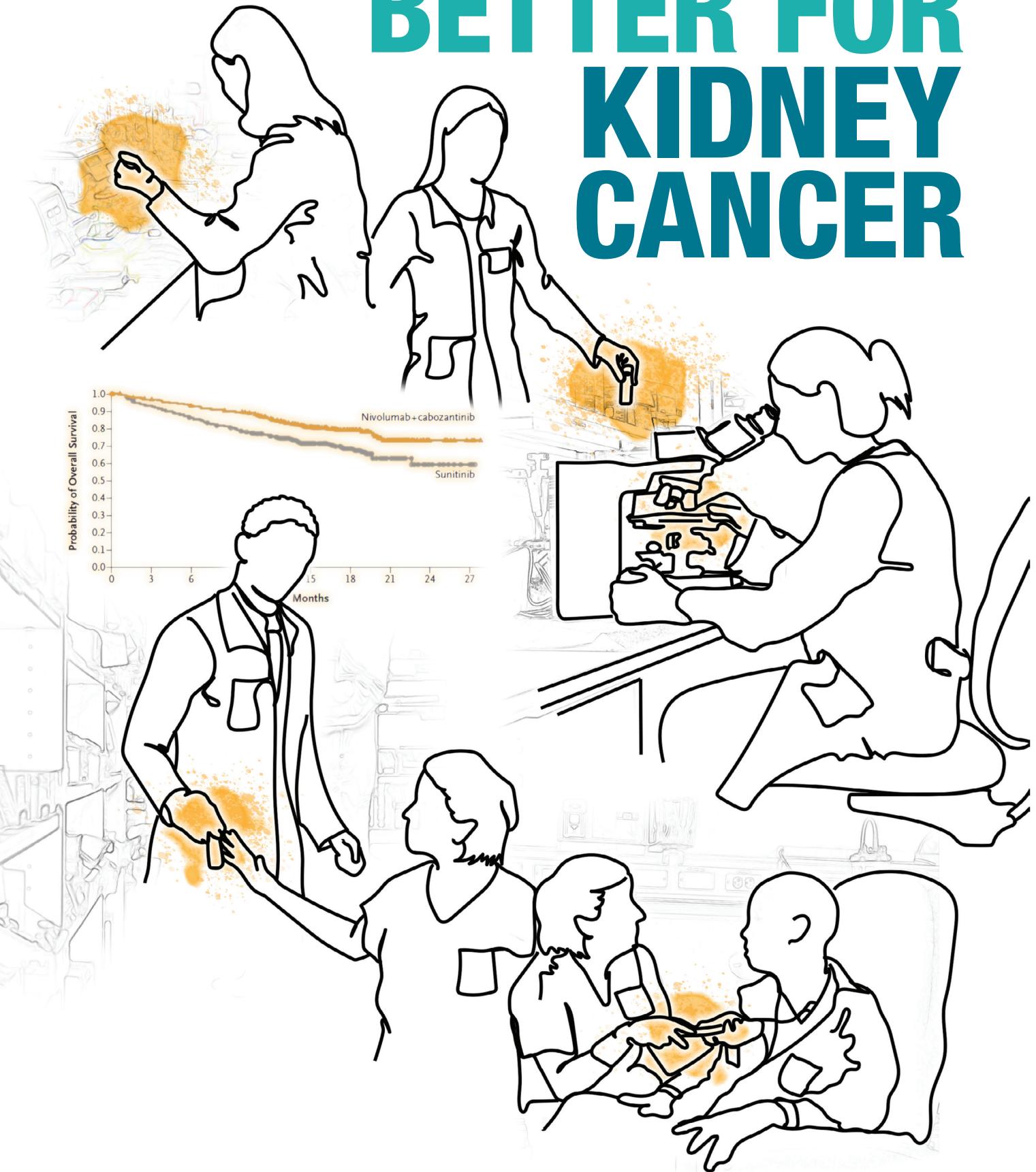
Li N, et al. *Proc Natl Acad Sci U S A*. 2017 Aug 8;114(32):E6623-E6631.

Li N, et al. *Cell Rep Med*. 2021 Jun 1;2(6):100297.

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*In this scanning electron microscopy image, CAR T cells attack a lung cancer cell, colored in blue at the center of the image. CAR T cells are immune cells that are artificially programmed to recognize unique proteins on the surface of cancer cells. Researchers discovered that CAR T cells can be programmed to fight neuroblastoma, an extremely rare and aggressive form of cancer that mainly affects children. Credit: Steve Gschmeissner/Science Photo Library*

# GOOD FOR BLADDER CANCER, BETTER FOR KIDNEY CANCER



# A novel drug combination becomes the standard of care for kidney cancer.



**Andrea B. Apolo, M.D.**

Senior Investigator  
Genitourinary Malignancies  
Branch

Some discoveries lead you in unexpected directions. When Senior Investigator **Andrea Apolo, M.D.**, sought to explore a new combination of drugs for treating bladder cancer, the results yielded impressive benefits in another tumor type. Apolo had enrolled patients with bladder cancer as well as several patients with other genitourinary tumors including renal cell carcinoma (RCC), the most common form of kidney cancer, in a phase I clinical trial to evaluate drug safety. While the bladder cancer patients benefited from the drug combination, the patients with kidney cancer did even better and were twice as likely to experience an overall response. Their tumors shrank more than 30 percent from their original size.

These initial results prompted Apolo and her colleagues, oncologists Toni Choueiri, M.D., Dana-Farber Cancer Institute, and Robert Motzer, M.D., Memorial Sloan Kettering Cancer Center, to study the novel drug combination in a larger clinical trial, specifically in patients with RCC. The positive results from this phase III trial, reported in the *New England Journal of Medicine*, led to U.S. Food and Drug Administration (FDA) approval of cabozantinib (Cabometyx<sup>®</sup>) combined with nivolumab (Opdivo<sup>®</sup>) for RCC in 2021. The combination is now considered a first-line therapy for patients with the disease.

Cabozantinib works by inhibiting the activity of multiple protein receptors in cancer cells that are associated with tumor growth, thereby limiting the formation of new blood vessels that supply the tumor with nutrients and stopping the spread of cancer. Apolo initially studied cabozantinib with collaborators in the lab, and as she began to study the drug in patients, she realized that it was not only able to affect protein receptors in cancer cells, but it also interfered with the ability of cancer cells to manipulate the immune system for survival.

This finding provided the rationale to pair cabozantinib with nivolumab for treating patients with RCC. Nivolumab is a

checkpoint inhibitor that works by boosting the immune system's ability to kill cancer cells.

In the phase III trial, participants were given either the combination of cabozantinib and nivolumab or the drug sunitinib (Sutent<sup>®</sup>) alone, which is a standard therapy for kidney cancer that blocks a key enzyme needed for cancer growth. Although patients who received the novel drug combination experienced more adverse side effects, they had a longer progression-free survival period of 16.6 months, compared to 8.3 months for patients given sunitinib.

"I knew this combination would be extremely effective in RCC based on the early phase I results," Apolo says. "There were no patients treated with this combination that did not have some kind of response or, at minimum, stable disease — nobody's disease progressed."

Apolo not only initiated the research of this drug combination for bladder cancer and RCC, but she guided the clinical trials that, in less than three years, led to FDA approval of the combination therapy. She notes that patients living with RCC have had few new treatment options for decades. "It feels amazing to have identified a new way to treat this cancer and to see it approved and helping patients," she says.

Apolo attributes her team's ability to move quickly from a phase I to a phase III trial to support from the Cancer Therapy Evaluation Program, which oversees national extramural clinical trials funded by the National Cancer Institute, including cooperative research and development agreements for this study with industry partners Exelixis, Bristol Myers Squibb and Pfizer. "The NIH is a wonderful place," Apolo says, "because of the basic laboratory resources and clinical trial infrastructure, which helps us conduct these kinds of trials that can eventually lead to effective cancer therapies."

Choueiri TK, et al. *N Engl J Med*. 2021 Mar 4;384(9):829-841.

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*CCR scientists discovered that a treatment being tested in bladder cancer patients was surprisingly effective in patients with kidney cancer. Upon this discovery, the treatment, represented in yellow, received FDA approval in less than three years following clinical testing. This image illustrates how abundant basic laboratory resources and robust clinical trial infrastructure at NIH can accelerate cooperative research and quickly lead to effective cancer therapies. Credit: Veronica Falconieri Hays, Falconieri Visuals, LLC*



# WHY AGE IS AN ADVANTAGE

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# Surprisingly, young immune systems may support breast cancer metastasis to the brain.



**Patricia S. Steeg, Ph.D.**  
Deputy Chief  
Women's Malignancies Branch

The risk of being diagnosed with breast cancer increases with age. Yet, the risk of a poor outcome is higher for women who are diagnosed when they are young. Although only seven percent of women diagnosed with breast cancer are 40 years of age or younger, many of those cancers are lethal. Patients in this age group usually endure intense treatment, but many find their disease recurs and spreads. Compared to patients diagnosed later in life, they are more likely to develop metastatic tumors in the brain. The tumors can be treated with radiation or surgery, but they often return.

Scientists have struggled to understand the more aggressive nature of breast cancer in young women. Now, Senior Investigator **Patricia Steeg, Ph.D.**, and her team think they have an answer. The key difference between young and old, they say, may be less about the tumor cells themselves, and more about the tumor microenvironment in which those cells travel and grow. Steeg's team has found evidence in animal studies, reported in *Clinical Cancer Research*, that a younger immune system supports breast cancer's metastasis to the brain, whereas an older immune system makes the brain less hospitable to migrating breast cancer cells.

To investigate whether identical cancer cells behave differently in young animals than they do in older ones, Steeg, Senior Investigator Lalage Wakefield, D.Phil., and postdoctoral fellow Alex Man Lai Wu, Ph.D., injected human breast cancer cells into mice of different ages and then monitored those mice for metastases. The mice in their experiments developed similar numbers of metastatic tumors in their

livers and lungs, regardless of age. But the situation was different in the brain. Steeg's team found up to four times more metastases in the brain of young animals than in older animals.

The team traced this effect to age-related differences in the immune system. They found that in young animals, the brain contains more infiltrating macrophages and microglia — immune cells that are capable of both fighting tumors and protecting them, depending on circumstances. Macrophages and microglia were not only more abundant in the brains of young animals, they also behaved differently. According to the team's experiments, in the brains of young animals, these immune cells promote the survival of metastatic cancer cells.

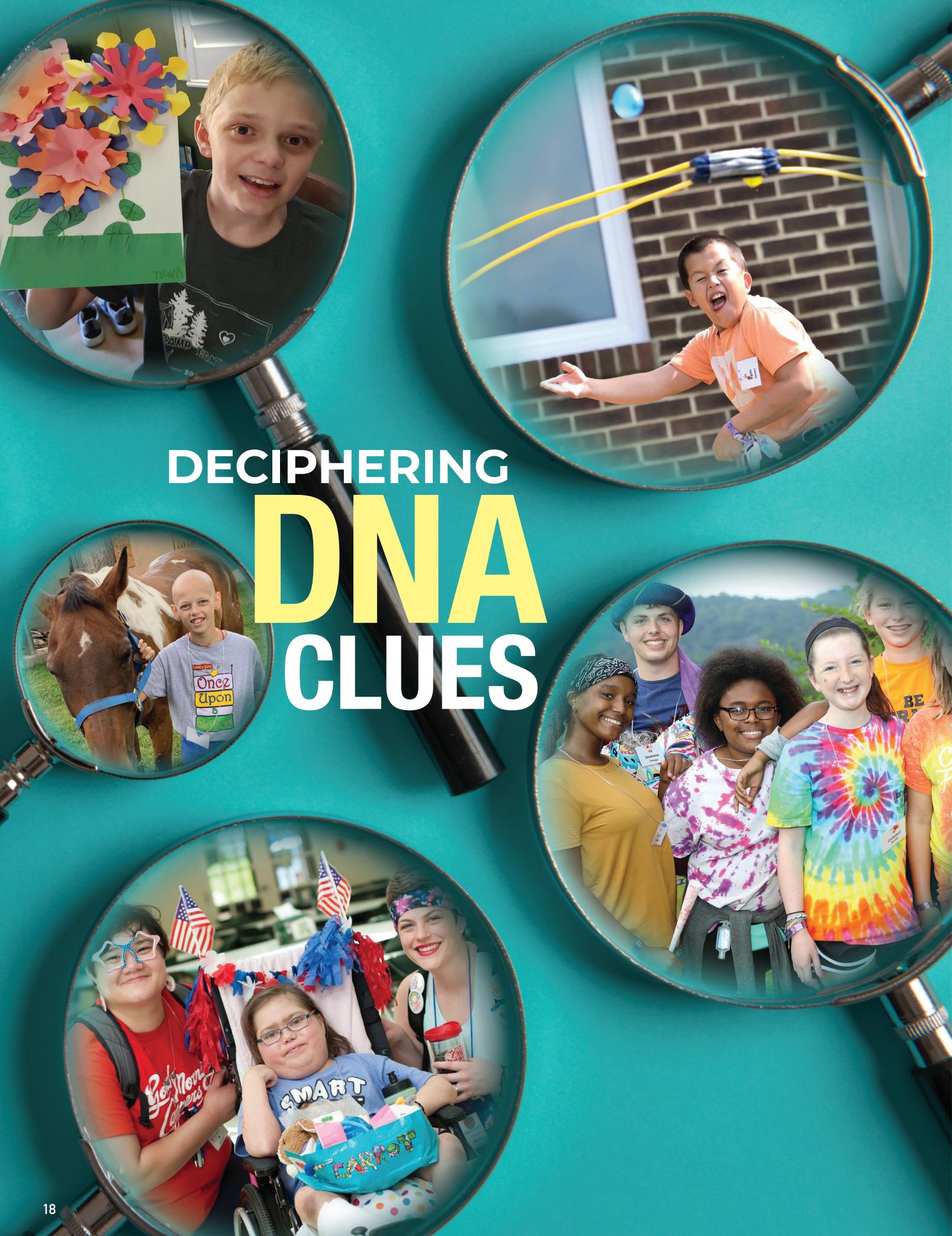
Based on her team's findings, Steeg is optimistic that modifying the immune environment might help stave off brain metastasis in young patients with breast cancer. The young mice in their experiments developed significantly fewer brain metastases when they were given a drug that reduced macrophages and microglia, making the immune environment in their brains more closely resemble that of older mice. They were able to achieve this by inhibiting an immune-system regulator called colony-stimulating factor-1 receptor. Steeg hopes a similar approach might benefit young patients with breast cancer, and she has begun investigating potential candidates for clinical studies.

Wu AML, et al. *Clin Cancer Res*. 2021 Aug 1;27(15):4422-4434.

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*CCR researchers studying mice found that a younger immune system supports the metastasis of breast cancer cells to the brain whereas an older immune system makes the brain less hospitable to breast cancer cells. On the left, an older woman's silhouette is overlaid with a scene of small metastatic tumors and a few immune cells and neurons. On the right, in a younger woman's silhouette, there are many more metastatic tumors, neurons and immune cells. In the team's experiments, they found that immune cells in a younger setting promote the survival of metastatic breast cancer cells. Credit: Veronica Falconieri Hays, Falconieri Visuals, LLC*

# DECIPHERING **DNA** CLUES



# Genetic analyses improve the detection and diagnosis of childhood cancers.



**Jack F. Shern, M.D.**

Lasker Clinical  
Research Scholar

**Javed Khan, M.D.**

Deputy Chief  
Genetics Branch  
Pediatric Oncology Branch

Genetic analyses have become a critical part of many cancer diagnoses, and CCR scientists are seeking to expand the impact of this technology. They have teamed up with colleagues around the world to pore over DNA from patient samples, looking for patterns that reveal the presence of cancer or hint at the future behavior of a tumor. Their recent discoveries could lead to more personalized treatments for patients with the childhood cancer rhabdomyosarcoma and more reliable cancer screenings for people with another childhood condition, neurofibromatosis type 1 (NF1).

Children diagnosed with rhabdomyosarcoma, a cancer that begins in the cells that give rise to muscle tissue, are usually treated with a combination of chemotherapy, radiation and surgery. Doctors use clinical features, such as the size and location of tumors, to determine how aggressive this treatment should be. These criteria are good at identifying patients whose risk of poor outcomes is particularly high or low, but most patients fall somewhere in between, where outcomes are difficult to predict.

New findings from the largest-ever international study on rhabdomyosarcoma, led by Senior Investigator **Javed Khan, M.D.**, and Lasker Clinical Research Scholar **Jack Shern, M.D.**, will help clinicians refine their diagnoses and offer patients more personalized treatment plans. The CCR team and collaborators at the Institute for Cancer Research in London, U.K., analyzed DNA from the tumors of more than 600 children with rhabdomyosarcoma, focusing on 39 genes linked to the disease.

They discovered that outcomes tended to be worse for patients whose tumors had mutations in a small handful of genes, including *TP53*, *MYOD1* or *CDKN2A*, as reported in the *Journal of Clinical Oncology*. Additionally, patients with more than one mutation that drive cancer progression fared particularly poorly. This information is now guiding the

design of clinical trials and will help in the development of new experimental therapies.

Another application that is quickly becoming useful in diagnosing and monitoring pediatric patients is the genomic profiling of circulating tumor DNA. Shern collaborated with a team at Washington University School of Medicine in St. Louis, led by assistant professors Angela Hirbe, M.D., Ph.D., and Aadel Chaudhuri, M.D., Ph.D., to analyze DNA isolated from the blood of people with NF1 in search of a better way to detect malignant tumors. NF1 is a condition that can cause large growths to develop along nerves throughout the body. Most of these remain benign, but sometimes they turn into aggressive cancers, and even with regular MRI (magnetic resonance imaging) scans, it can be difficult to spot those that do.

Shern's team focused on DNA shed by cells into the blood, which included short fragments from tumor cells. When they sequenced the circulating DNA and compared the results of patients who had benign NF1 tumors to those from patients with malignant tumors, they found several features that set them apart.

The discovery, reported in *PLOS Medicine*, suggests it may be possible to distinguish between benign and malignant tumors in patients with NF1 with a simple, non-invasive blood test. Because the amount of tumor DNA in the blood dropped when patients' malignant tumors shrank following treatment, a liquid biopsy might also be used to monitor how patients respond to therapy.

Khan and Shern are eager to see these genomic profiling tools move out of the lab to become routine for pediatric patients and help people with rhabdomyosarcoma and NF1.

Shern JF, et al. *J Clin Oncol*. 2021 Sep 10;39(26):2859-2871.

Szymanski JJ, Sundby RT, et al. *PLoS Med*. 2021 Aug 31;18(8):e1003734.

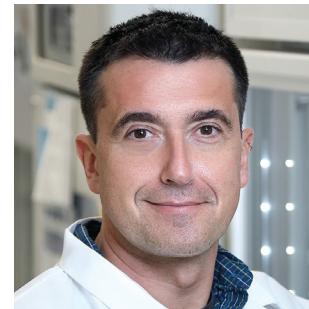
*Camp Fantastic (CF), a week-long adventure at which Dr. Jack Shern serves as lead physician, lets children with cancer and neurofibromatosis "just be kids." Since 1983, the camp has offered outdoor activities, and since COVID, virtual offerings like crafting and online science. Pictured clockwise from top left: Travis Carpenter creates paper flowers at Virtual CF 2020; Ryan Kovacs launches a water balloon at CF 2019; (from left) Taylor Caquias, Dominic Ortega, Tsadet Brannon, Campbell Brandt and Carolyn Shaffer enjoy some teen time at CF 2019; Abby Furco flanked by CF 2018 staff K School (left) and Sarah Rostock (right); and Becca Chamberlain goes horseback riding at CF 2019. CF is a partnership between the National Cancer Institute (NCI) and Special Love, Inc., a Northern Virginia charity that also provides programming and financial assistance for siblings and young adults. "It's wonderful that the NCI can provide a safe environment where patients and survivors can feel normal and connect to other kids who understand what they're going through," says Shern. Credit: Special Love, Inc.; iStock*

# PROTECTION STRATEGY



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# An unusual means of chromosome protection sheds light on cancer cell growth.



**Eros Lazzerini Denchi, Ph.D.**  
Senior Investigator  
Laboratory of Genome Integrity

Chromosome ends need special care. To a cell, the free strands of DNA at the end of chromosomes may look like pieces of broken DNA that need to be repaired. This would be detrimental because it would lead to the fusion of chromosomes. A DNA-protein complex, called a telomere, caps each chromosome end, protecting and hiding it from the DNA damage-response pathway. Telomeres gradually shorten as we age until eventually, cells lose their ability to divide because their telomeres become too short. To continue their growth, cancer cells must circumvent this limit, and understanding how telomeres work is important for finding better ways to keep cancer cells in check.

Almost all of our cells use the same strategy to guard their telomeres against inappropriate DNA repair, but researchers led by Senior Investigator **Eros Lazzerini Denchi, Ph.D.**, have discovered that embryonic stem cells — cells that arise early in development and have the potential to become virtually any of the body's specialized cells — have a unique way of dealing with this problem. Findings that the team reported in *Nature* suggest that embryonic stem cells may be able to elongate vulnerable telomeres to avoid triggering a problematic DNA damage response.

In their studies of mouse embryonic stem cells, Lazzerini Denchi and colleagues found that these cells can grow

without a protein called TRF2. This was surprising because, for most other cell types, TRF2 is an essential telomere protection protein. Without it, chromosomes usually fuse together, and cells lose their ability to divide.

Postdoctoral fellow Marta Markiewicz-Potoczny, Ph.D., found that when she eliminated TRF2, embryonic stem cells activated a set of genes that are usually only turned on in a newly fertilized egg. One of these, *ZSCAN4*, appears to be a key part of these cells' unusual strategy for protecting their chromosome ends. Notably, this gene is sometimes active in cancer cells — so the discovery may tell us something about how cancer cells grow.

Lazzerini Denchi notes that most cancer cells evade telomere-imposed growth limits by reactivating an enzyme called telomerase, which rebuilds chromosomes' shortening ends. But about 10 percent of cancers manage to extend their telomeres without telomerase — and many of these cancers are particularly aggressive. If *ZSCAN4* turns out to be important for enabling such cells to escape growth restrictions without telomerase, it might point researchers toward new targets for drug development.

Markiewicz-Potoczny M, et al. *Nature*. 2021 Jan;589(7840):110-115.

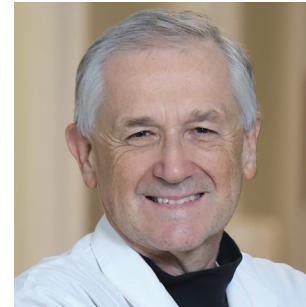
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For most cells, a protein called telomere-associated factor TRF2 is essential for protecting the ends of chromosomes. Without it, chromosomes usually fuse together, and cells lose their ability to divide. These images show the consequences of TRF2 deletion in differentiated cells, with DNA labeled in red and telomeres in green. CCR scientists have discovered that for embryonic stem cells, however, TRF2 may not be essential. This understanding may help to find better ways to keep cancer cells in check. Credit: Marta Markiewicz-Potoczny, CCR, NCI, NIH



# REINING IN ROGUE IMMUNE CELLS

# FDA approves new treatment for chronic graft-versus-host disease.



**Steven Z. Pavletic, M.D., M.S.**

**Senior Clinician**

Immune Deficiency Cellular Therapy Program

A life-saving hematopoietic stem cell transplant, which replaces cancerous cells with a healthy immune system, allows many patients diagnosed with certain blood cancers to live for years with their cancer in remission. However, the treatment is not without side effects. One complication is chronic graft-versus-host disease (GVHD), an autoimmune-like condition with a wide range of potential symptoms. Because of work by CCR investigators, patients have a new option to treat the condition. In 2021, belumosudil (Rezurock™) became the first drug developed specifically to treat chronic GVHD to be approved by the U.S. Food and Drug Administration (FDA).

Scientists at CCR have a long history of studying chronic GVHD. The disease has become more prevalent in the past few decades as increasing numbers of patients have received and recovered from stem cell transplants. Beginning in the early 2000s, Senior Clinician **Steven Pavletic, M.D., M.S.**, led colleagues across NIH in an interdisciplinary effort to develop the clinical tools and diagnostic criteria that researchers needed to study the complex disease and evaluate potential treatments.

Chronic GVHD develops when transplanted immune cells (the graft) attack a recipient's tissues. The disease can cause a myriad of incapacitating problems, including thickening of the skin, the formation of scar tissue, dry eyes and mouth, painful joint stiffness as well as liver and lung disease. Chronic GVHD is usually treated with corticosteroids, but this only works for some patients. Even for those who respond well, steroid treatment is not suitable for long-term use due to significant side effects, though for most patients, chronic GVHD persists for years.

Because the disease can affect nearly any organ in the body, Pavletic and the GVHD working group drew on expertise

from across many fields of medicine to develop consensus guidelines on how to diagnose the disease and assess its severity. That work built the foundation for clinical studies, planned and coordinated in part by Pavletic and CCR colleagues, to test the safety and efficacy of belumosudil. They reported in *Blood* that the drug can reduce symptoms of treatment-refractory chronic GVHD and improve patients' quality of life.

Belumosudil treats chronic GVHD by blocking a signaling protein called ROCK2. This both reins in the activity of rogue immune cells and prevents the buildup of scar tissue. Pavletic, transplant physician Corey S. Cutler, M.D., M.P.H., F.R.C.P.C., Dana-Farber Cancer Institute, and colleagues tested the drug in a phase II clinical trial conducted at sites around the country. The trial included 132 participants who were in remission from cancer and had received prior treatments for chronic GVHD.

Investigators on the trial relied on the guidelines established by Pavletic's group to evaluate patients' response to the treatment. Symptoms improved for three-quarters of trial participants, including many whose condition at the outset of the study was considered severe. Seven participants had a complete response, with complete resolution of symptoms in all eight of the organs that were evaluated for the study.

Based on these findings, the FDA approved belumosudil as a treatment for chronic GVHD in patients for whom at least two other treatments have failed. It is now one of only three drugs approved since 2017 for treating the condition. Ongoing research aims to identify ways of predicting which treatment is best for an individual patient.

Cutler C, et al. *Blood*. 2021 Dec 2;138(22):2278-2289.

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Stephanie Britton received an allogeneic stem cell transplant in June 2019 following a diagnosis of acute lymphoblastic leukemia. In October 2020, she was diagnosed with chronic GVHD after she noticed scaling as well as tight and itchy skin on her body, which limited her mobility and caused great discomfort. "I think it impacted about 80 percent of the skin all over my body," she says. As a mother of three small children, it affected her daily life. After trying four different therapies with few results, she joined the ROCKstar study and immediately started to feel better. She noticed that her skin wasn't as thick and itchy, tightness had been reduced, and her comfort level changed dramatically. Stephanie thanks the clinical team for her experience on the trial. "They've been so accommodating," she says. "I have felt so blessed to have access to the amazing team at NIH." Credit: Charlie Chang, NIH Events Management; Jacqueline W. Mays, NIDCR, NIH (background cells)

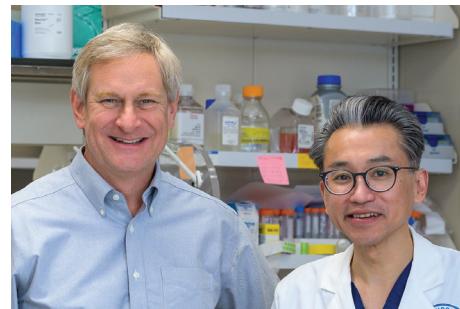


# GELLING TOGETHER

AGAINST CANCER

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# Surgeons and chemists team up to create a new hydrogel for treating mesothelioma.



**Joel P. Schneider, Ph.D.**

Chief

Chemical Biology Laboratory

**Chuong D. Hoang, M.D., F.A.C.S.**

Investigator

Thoracic Surgery Branch

Every time a surgeon removes a tumor, there is a risk that some cancer cells remain. While this risk is relatively small with certain cancers, it is very high for mesothelioma, a cancer that affects the thin membranes encasing vital organs. It is virtually impossible to remove all traces of mesothelioma via surgery. To combat this problem, an interdisciplinary team of CCR surgeon-scientists and chemists created a novel solution: a hydrogel containing microRNAs that can be applied to the surface of organs during surgery to target and kill residual mesothelioma cancer cells.

MicroRNAs are molecules that control gene expression mainly by binding with messenger RNA. Investigator **Chuong Hoang, M.D., F.A.C.S.**, had previously identified microRNAs that can disrupt the signaling of mesothelioma cells and kill them, but he needed an effective way to deliver the microRNAs to the cells.

It was not a problem that would automatically occur to chemists, but once Hoang and postdoctoral fellow Anand Singh, Ph.D., presented this clinical challenge to Senior Investigator **Joel Schneider, Ph.D.**, and former postdoctoral fellow Poulam Majumder, Ph.D., the chemists began to apply some of the rules of basic science around it.

By partnering together, the team was able to develop a hydrogel that contains miniature proteins called peptides, which can bind to microRNAs and deliver them directly into cancer cells. Hoang and Schneider attribute the highly collaborative environment at CCR as a key reason for this innovative partnership and research.

During surgery, the hydrogel can be injected or sprayed onto the affected site, such as the surface of a patient's lungs. Its highly viscous nature allows it to seep into the nooks and crannies of organs, ensuring that the microRNAs can target any residual cancer cells left behind after surgery.

The researchers tested the hydrogel in four different mouse models. They found that in even the most aggressive models of mesothelioma, mice that received the hydrogel treatment lived significantly longer than the mice that did not.

The results, which were reported in *Nature Nanotechnology*, "were quite striking," Hoang says. "Our hope is that we will be able to do something similar in humans, as most other drugs and small molecule strategies to date have not significantly improved survival in people with mesothelioma."

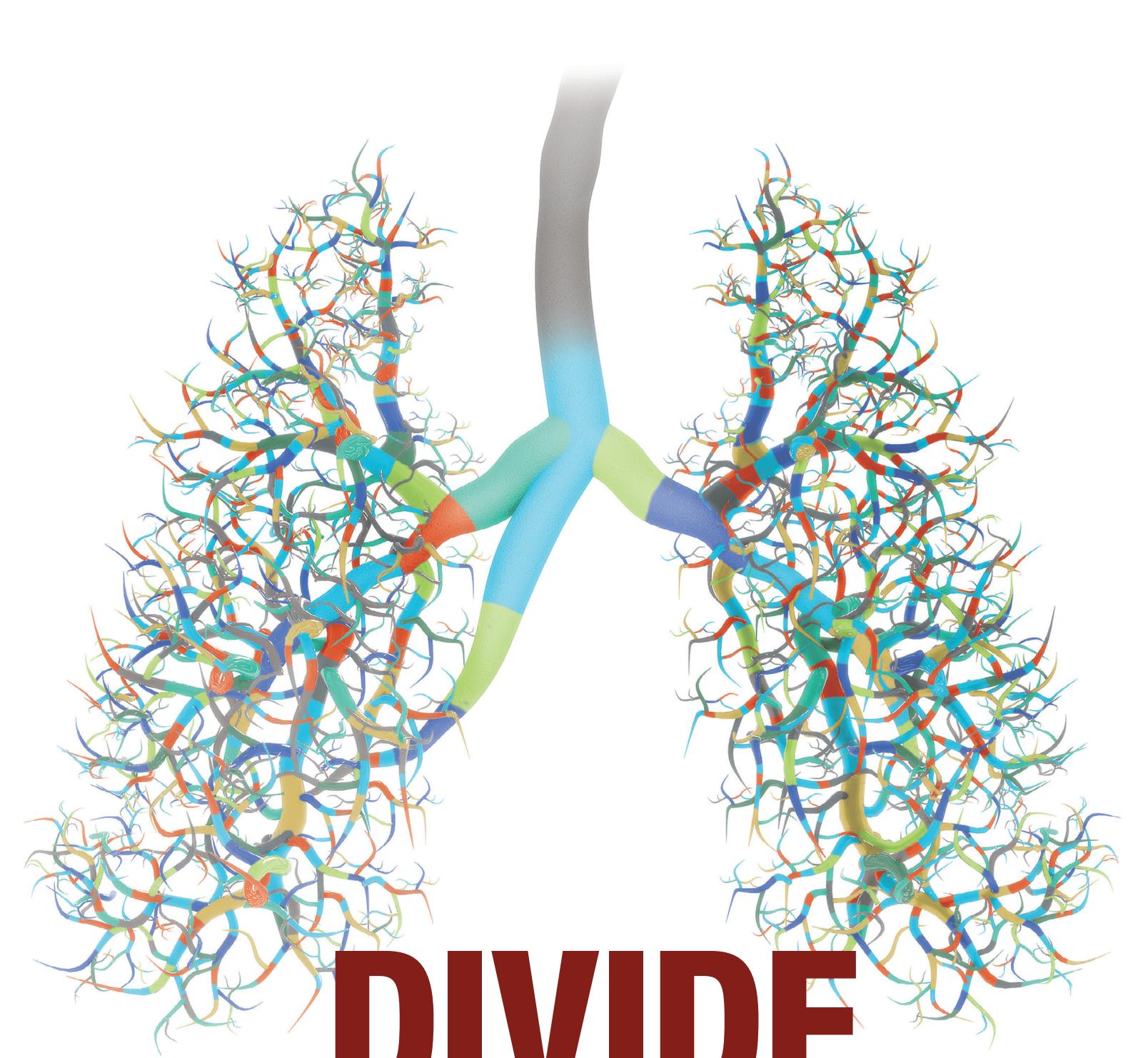
Notably, this method could also be applied to other difficult-to-treat surface tumors, such as ovarian cancer or glioma, if the right microRNAs for targeting and killing these cancers could be identified.

The researchers are considering the possibility that the hydrogel could be used as a first-line therapy, sidestepping the need for surgical resection, and they plan to explore this possibility in future studies. In such a case, the hydrogel would be sprayed directly on organs, but no tissue would need to be surgically removed. "That would be a paradigm shift," Hoang says. "It would be a big game changer for all surface cancers."

Majumder P, Singh A, et al. *Nat Nanotechnol*. 2021 Nov;16(11):1251-1259.

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CCR scientists developed a novel treatment that delivers therapeutic small RNAs (microRNAs) locally to tumors. This image illustrates the two-stage process. First, the microRNAs (seen in pink) bind to peptides (seen in blue). The paired particles are then encased in a hydrogel matrix (seen at the bottom of the image) which can be applied to tissue surfaces via a spray or syringe. The peptides help deliver the microRNAs directly into residual cancer cells to kill them. Credit: Anand Singh, CCR, NCI, NIH



**DIVIDE  
AND  
CONQUER**

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# Not all small cell lung cancers are the same.



**Anish Thomas, M.B.B.S., M.D.**  
Lasker Clinical Research Scholar  
Developmental Therapeutics Branch

About 30,000 people in the United States are diagnosed every year with small cell lung cancer (SCLC), the deadliest form of lung cancer. Patients are typically treated with a 30-year-old chemotherapy regimen and immunotherapy, which can work well initially. However, the cancer often comes roaring back, and most patients die within a year of their diagnosis. Progress toward improving that outcome has been notoriously elusive.

Lasker Clinical Research Scholar **Anish Thomas, M.B.B.S., M.D.**, has long believed that patients with SCLC could benefit from a more precise approach. His vision is to find subgroups of SCLCs with genetic features that make them vulnerable to particular treatments, a strategy that has yielded success in other cancers. His team has now found some of the first molecular indicators that could be used to tailor SCLC treatments for patients.

Because lung cancer is so strongly linked to smoking, genetic risk factors and vulnerabilities for the disease have received little attention. Moreover, SCLC is typically diagnosed at an advanced stage where surgery is no longer a treatment option. For that reason, significant tissue samples that can be crucial to studying the genetic makeup of the disease are rarely obtained.

In work reported in *Science Translational Medicine*, Thomas' team identified several inherited mutations that appear to increase an individual's risk of developing SCLC. About ten percent of patients with small cell cancers were found to harbor inherited mutations in cancer-predisposing genes. Thomas and former postdoctoral fellow Camille Tlemsani, M.D., Ph.D., found that small cell cancer patients with these mutations, including patients with SCLC, responded better to standard chemotherapy and experienced a longer period of remission after treatment than patients without these mutations. Their work demonstrates that SCLC may also have an inherited predisposition and lays the groundwork for targeted therapies based on the genes involved.

Another option for some patients with SCLC may be treatment with a combination of two U.S. Food and Drug Administration-approved drugs, topotecan and berzosertib. In an early clinical trial reported in *Cancer Cell*, Thomas and colleagues found that a combination of topotecan and berzosertib, used together in an experimental compound that interferes with a cell's ability to repair damaged DNA, reduced tumors in about a third of patients with chemotherapy-resistant small cell cancers. Tumors that responded best shared a pattern of gene activity associated with extremely rapid growth and a high demand for DNA repair. This work, done in collaboration with Nobuyuki Takahashi, M.D., Ph.D., former NIH Hematology Oncology fellow, and Craig J. Thomas, Ph.D., Leader of Chemistry Technologies at the National Center for Advancing Translational Sciences at NIH, provides the first evidence that targeting replication stress offers clinical benefit in cancer patients, and the combination regimen is now being investigated in two larger trials.

Finally, research published in *Nature Communications* points to a group of patients with SCLC who may be good candidates for immunotherapy. Beyond chemotherapy, immunotherapy benefits only a small percentage of patients with SCLC. Thomas and Physician-Scientist Early Investigator Nitin Roper, M.D., M.Sc., found that SCLC tumors, in which a developmental pathway called Notch was overactive, are more likely to respond favorably to immunotherapy that uses immune checkpoint inhibiting drugs.

SCLC remains one of the most challenging cancers to treat. By identifying subgroups and defining their specific vulnerabilities, Thomas and his colleagues aim to transform the way it is treated — moving from a one-size-fits-all approach to one that is more strategic, guided by the biology of each person's disease.

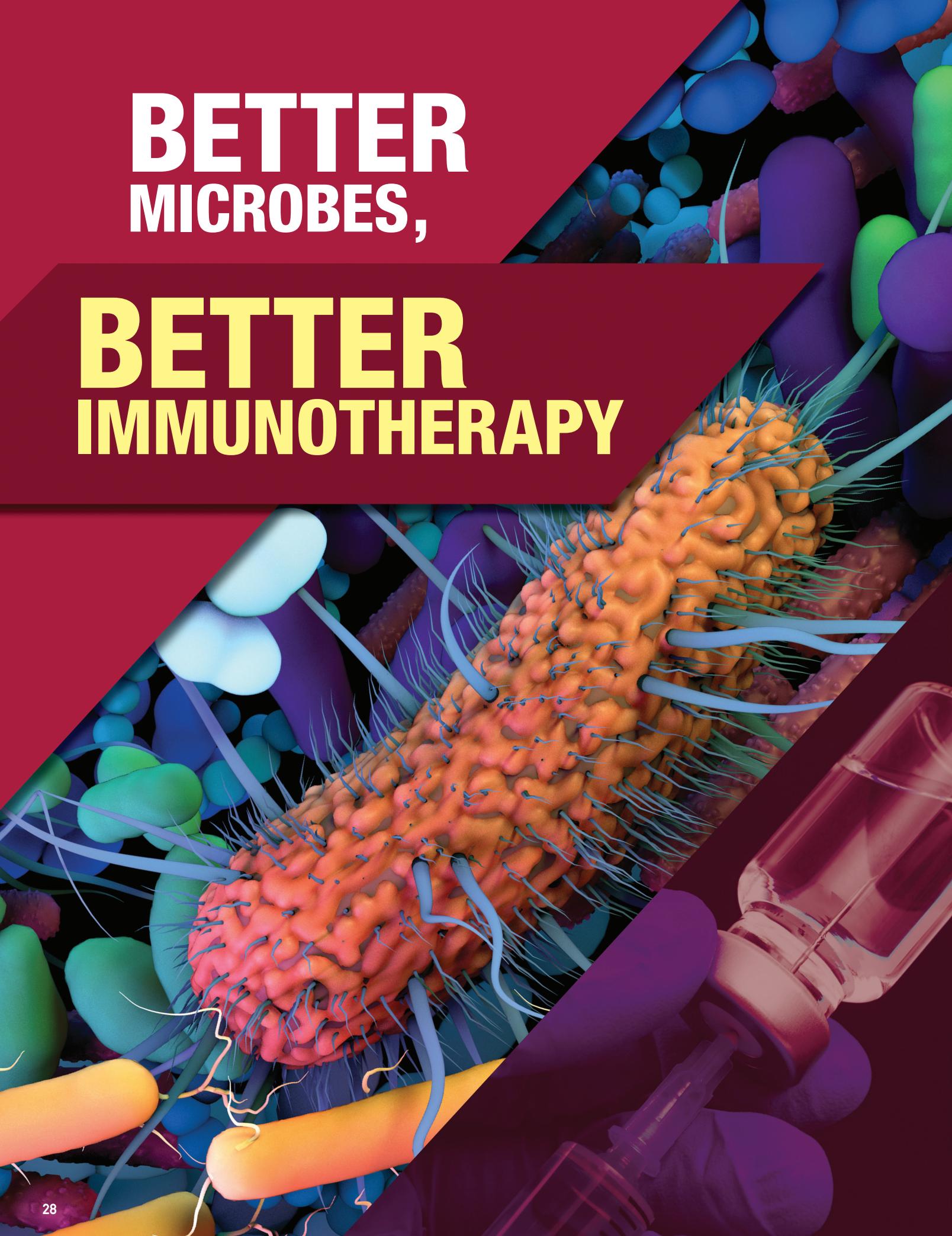
Tlemsani C, et al. *Sci Transl Med*. 2021 Jan 27;13(578):eabc7488.  
Thomas A, Takahashi N, et al. *Cancer Cell*. 2021 Apr 12;39(4):566-579.e7.  
Roper N, et al. *Nat Commun*. 2021 Jun 23;12(1):3880.

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*Identifying genetic features that make people vulnerable to small cell lung cancer can help physicians better treat patients with the disease. This image represents the genetic variations only recently found in different patients with small cell lung cancer. These newly found variations may help physicians select different treatment approaches that will work better for people with specific mutations. Credit: Pamela Beltowski, SPGM, FNL, NCI, NIH*

# BETTER MICROBES,

# BETTER IMMUNOTHERAPY



# Microbial transplants can lead to a better immunotherapy response.



**Giorgio Trinchieri, M.D.**  
**Chief**  
Laboratory of Integrative Cancer Immunology

Cancer immunotherapy can help a patient's immune system recognize and destroy tumors, but it does not work for everyone. Research increasingly supports the idea that microorganisms inside the gut play a role in whether or not someone responds to immunotherapy, so researchers are looking for ways to modify a person's microbiome to improve the odds of a successful outcome.

A team co-led by NIH Distinguished Investigator **Giorgio Trinchieri, M.D.**, has now demonstrated one strategy that can work: introducing an entire community of gut microbes donated by a patient who has responded favorably to immunotherapy to a patient for whom immunotherapy has failed. They found that such transplants improve the response to immunotherapy in some people.

The gut is home to a complex group of bacteria and other microbes, and the composition of this community varies significantly between individuals. Mounting evidence indicates that the composition of microbes affects a tumor's growth, progression and response to therapy in a variety of ways. Without knowing exactly which microbes are most beneficial, the team reasoned that the best place to find an immunotherapy-enhancing mix of microbes might be in the gut of an immunotherapy-responsive patient. They could deliver this complete mix by administering a donated stool sample to a recipient via colonoscopy — a procedure known as a fecal microbial transplant.

Trinchieri, Staff Scientist Amiran K. Dzutsev, M.D., Ph.D., and their University of Pittsburgh colleagues Hassane Zarour, M.D., and Diwakar Davar, M.D., tested this idea in a small clinical trial. Patients with advanced melanoma whose cancer had not responded to the immune checkpoint inhibitors pembrolizumab (Keytruda®) or nivolumab (Opdivo®), which

are designed to promote anti-cancer immunity by releasing a natural brake on the immune system, received transplanted fecal matter donated by individuals who had responded favorably to the same type of treatment. The transplant recipients next underwent a new round of therapy with pembrolizumab.

According to the results reported in *Science*, six of 15 trial participants had long-lasting positive responses to this treatment: their cancer stopped progressing and for some, the existing tumors shrank.

The success shows that cancer treatments that adjust the makeup of patients' microbiomes can work, Trinchieri says. He and his colleagues confirmed that after the transplant, patients who went on to respond to immunotherapy had acquired certain types of gut bacteria that are thought to be advantageous for an anti-tumor immune response. At the same time, bacterial groups suspected of hindering that response had been depleted.

Further clinical research is needed to validate this approach and to determine which patients are most likely to benefit from a fecal transplant. At the same time, researchers like Stadtman Investigator Romina Goldszmid, Ph.D., are working to better understand exactly how microbes modulate an immune response to cancer. A deeper understanding of how gut microbes interact with the immune system and which species are most influential could allow researchers to develop even better-targeted treatments. See the related story "Boosted by Bacteria" on page 8 and 9 for more information.

Davar D, Dzutsev AK, et al. *Science*. 2021 Feb 5;371(6529):595-602.

*Gut bacteria and microbes, like the ones in this illustration, can play a role in helping a patient respond well to immunotherapy treatments when microbes are transplanted from a patient who responded favorably to immunotherapy to a patient for whom immunotherapy failed. This transplant sometimes results in improved responses to immunotherapy, blocked cancer progression and even tumor shrinkage. Credit: iStock*

# New Faculty



## **Andrea B. Apolo, M.D.**

Andrea B. Apolo, M.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Genitourinary Malignancies Branch. Dr. Apolo designs and implements clinical trials to test novel agents for the treatment of urologic cancers. Her research focuses on developing targeted therapies for bladder cancer and rare genitourinary tumors.



## **Michael B. Aregger, Ph.D.**

Michael B. Aregger, Ph.D., has joined the Molecular Targets Program as a Stadtman Tenure-Track Investigator. Dr. Aregger's research focuses on metabolic plasticity in cancer cells by mapping genetic interactions and cancer dependencies using CRISPR-based genome engineering tools and functional genomics approaches.



## **Hans Elmlund, Ph.D.**

Hans Elmlund, Ph.D., has joined the Center for Structural Biology as a Senior Investigator. Dr. Elmlund pioneered the use of stochastic 3D reconstruction algorithms for analyzing images obtained with cryo-electron microscopy and graphene-liquid-cell electron microscopy. His laboratory develops novel algorithmic solutions to address the most difficult problems in fields ranging from structural biology to nanoscience.



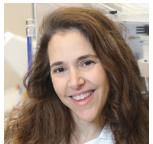
## **Freddy E. Escoria, M.D., Ph.D.**

Freddy E. Escoria, M.D., Ph.D., has been appointed as an NIH Lasker Scholar Tenure-Track Investigator in the Molecular Imaging Branch and is a member of the NIH Distinguished Scholars Program. Dr. Escoria aims to develop new agents to help treat and monitor cancer patients by harnessing systemic, targeted radiopharmaceuticals.



## **Christine M. Heske, M.D.**

Christine M. Heske, M.D., has been appointed as a Tenure-Track Investigator in the Pediatric Oncology Branch and is a member of the NIH Distinguished Scholars Program. Dr. Heske is a physician-scientist with a research focus on novel therapeutic agents for pediatric sarcomas. Her program identifies and evaluates new therapeutic targets by understanding the mechanisms behind therapeutic resistance and developing strategies to mitigate resistance through targeting tumor metabolism and DNA damage repair.



### **Rosandra N. Kaplan, M.D.**

Rosandra N. Kaplan, M.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Pediatric Oncology Branch. Dr. Kaplan, a physician-scientist, developed the concept of the pre-metastatic niche, identifying microenvironmental changes occurring early in metastatic sites that regulate metastatic progression. She has recently developed new cell therapy approaches to reprogram these microenvironments to limit cancer progression.



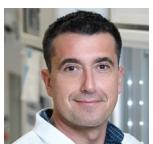
### **Nicholas D. Klemen, M.D.**

Nicholas D. Klemen, M.D., has joined the Surgery Branch as part of CCR's Physician-Scientist Early Investigator Program. Dr. Klemen is a surgical oncologist who specializes in the treatment of gastrointestinal tumors, particularly those of the colon, pancreas and liver.



### **Andra V. Krauze, M.D., F.R.C.P.C., D.A.B.R.**

Andra V. Krauze, M.D., F.R.C.P.C., D.A.B.R., has joined the Radiation Oncology Branch as part of CCR's Physician-Scientist Early Investigator Program. Dr. Krauze is a radiation oncologist with a research interest in harnessing computational analyses of large-scale data to personalize management of patients with cancer and improve oncologic outcomes.



### **Eros Lazzerini Denchi, Ph.D.**

Eros Lazzerini Denchi, Ph.D., has been awarded tenure at NIH and appointed to Senior Investigator in the Laboratory of Genome Integrity. Dr. Lazzerini Denchi's research focuses on two fundamental aspects of telomere biology: the mechanism by which functional telomeres prevent DNA damage activation and the *in vivo* consequences of telomere dysfunction.



### **Susan M. Lea, D.Phil., F.Med.Sci.**

Susan M. Lea, D.Phil., F.Med.Sci., has been appointed Chief of the Center for Structural Biology. Dr. Lea pioneered the use of mixed structural methods to study host-pathogen interactions and other medically important molecular pathways. Her laboratory uses and develops cutting-edge structural methods to define molecular mechanisms involved in health and disease states.

# New Faculty continued



## Troy A. McEachron, Ph.D.

Troy A. McEachron, Ph.D., has been appointed as a Tenure-Track Investigator in the Pediatric Oncology Branch and is a member of the NIH Distinguished Scholars Program. Dr. McEachron leads the Integrated Solid Tumor Biology Section where his team is using various molecular and cellular tools and technology platforms to dissect the metastatic osteosarcoma microenvironment and identify actionable therapeutic targets for clinical translation.



## Anandani Nellan, M.D., M.P.H.

Anandani Nellan, M.D., M.P.H., has joined the Pediatric Oncology Branch as part of CCR's Physician-Scientist Early Investigator Program and is a member of the NIH Distinguished Scholars Program. Dr. Nellan is a pediatric neuro-oncologist specializing in pediatric hematology-oncology and neuro-oncology. Her primary goal is to pioneer new immunotherapies for pediatric brain tumors.



## Rosa Nguyen, M.D., Ph.D.

Rosa Nguyen, M.D., Ph.D., has joined the Pediatric Oncology Branch as part of CCR's Physician-Scientist Early Investigator Program. Dr. Nguyen is a pediatric oncologist and physician-scientist specializing in the discovery and preclinical development of immunotherapies for the treatment of children with neuroblastoma.



## Sung-Yun Pai, M.D.

Sung-Yun Pai, M.D., has been appointed Chief of the Immune Deficiency Cellular Therapy Program and Medical Director of the NIH Transplantation and Cellular Therapy Clinical Program. Dr. Pai develops tailored cellular therapies for children, adolescents and young adults with genetic diseases of the blood and immune system.



## Drew W. Pratt, M.D.

Drew W. Pratt, M.D., has joined the Laboratory of Pathology as part of CCR's Physician-Scientist Early Investigator Program. Dr. Pratt seeks to use epigenetic and multiomic data to refine the classification of cancer and to discover novel, clinically relevant entities.



### **Padma Sheila Rajagopal, M.D., M.P.H., M.Sc.**

Padma Sheila Rajagopal, M.D., M.P.H., M.Sc., has joined the Cancer Data Science Laboratory as part of CCR's Physician-Scientist Early Investigator Program and has an adjunct appointment in the Women's Malignancies Branch. Dr. Rajagopal investigates how genomic and transcriptomic interactions between germline variants, inherited cancer syndromes and somatic development in tumors can improve clinical prediction in patients with cancer.



### **Gabriel J. Starrett, Ph.D.**

Gabriel J. Starrett, Ph.D., has joined the Laboratory of Cellular Oncology as a Stadtman Tenure-Track Investigator. Dr. Starrett studies the contributions of tumor viruses, including polyomaviruses and papillomaviruses, to the development of cancer using sequencing, bioinformatics and classical wet-bench molecular biology.



### **Ismail Baris Turkbey, M.D.**

Ismail Baris Turkbey, M.D., has been appointed to Senior Clinician in the Molecular Imaging Branch. Dr. Turkbey's research focuses on prostate cancer imaging, prostate biopsy techniques, focal therapy for prostate cancer and artificial intelligence.



### **Marielle E. Yohe, M.D., Ph.D.**

Marielle E. Yohe, M.D., Ph.D., has been appointed as an NIH Lasker Scholar Tenure-Track Investigator in the Laboratory of Cell and Developmental Signaling. Dr. Yohe studies the role of aberrant small GTPase signaling in the development of pediatric solid tumors and RASopathies, using a combination of biochemical, epigenetic, cellular and model organism approaches.

## **Newly Retired**

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

**Dhruba K. Chattoraj, Ph.D.**, Senior Investigator, Basic Research Laboratory

**George N. Pavlakis, M.D., Ph.D.**, Senior Investigator, Vaccine Branch

**Bruce A. Shapiro, Ph.D.**, Senior Investigator, RNA Biology Laboratory

**David S. Waugh, Ph.D.**, Senior Investigator, Center for Structural Biology

**Cheryl Ann Winkler, Ph.D.**, Senior Investigator, Basic Research Laboratory

**Stuart H. Yuspa, M.D.**, Co-Chief/Senior Investigator, Laboratory of Cancer Biology and Genetics, NIH Scientist Emeritus

# Awards & Honors



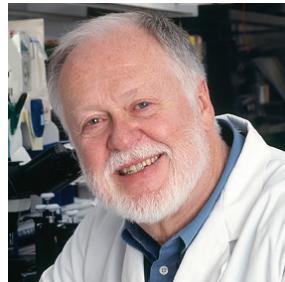
**Mary N. Carrington, Ph.D.**, was elected to the 2021 American Academy of Microbiology class of fellows.



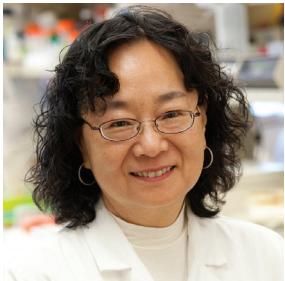
**Sheue-yann Cheng, Ph.D.**, received the 2021 Valerie Anne Galton Distinguished Lectureship Award from the American Thyroid Association.



**William Douglas Figg Sr., Pharm.D.**, received the 2021 American College of Clinical Pharmacology Distinguished Investigator Award.



**Curtis C. Harris, M.D.**, was elected to the 2021 class of fellows of the American Association for Cancer Research Academy.



**Wei-Shau Hu, Ph.D.**, was elected to the 2021 American Academy of Microbiology class of fellows and received the 2021 Distinguished Research Career Award from The Ohio State University Center for Retrovirus Research.



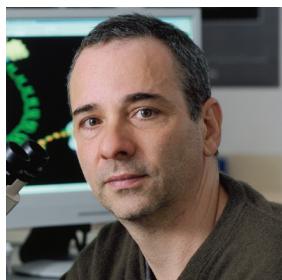
**Elaine S. Jaffe, M.D.**, received the 2022 American Society for Investigative Pathology Gold-Headed Cane Award.



**Douglas R. Lowy, M.D.**, received the 2021 American Association for Cancer Research-Margaret Foti Award for Leadership and Extraordinary Achievements in Cancer Research.



**Jordan L. Meier, Ph.D.**, received the 2020 International Chemical Biology Society Young Chemical Biologist Award.



**André Nussenzweig, Ph.D.**, received the 2021 Basser Global Prize.



**Ruth Nussinov, Ph.D.**, was elected to the 2021 class of fellows of the American Institute for Medical and Biological Engineering.



**Vinay K. Pathak, Ph.D.**, received the 2020 Proceedings of the National Academy of Sciences Cozzarelli Prize in Biomedical Science.



**Peter A. Pinto, M.D.**, was elected to the American Association of Genitourinary Surgeons and received the 2021 American Urological Association Distinguished Contribution Award.

# Awards & Honors continued



**Nitin Roper, M.D., M.Sc.**, received the 2021 Forbeck Foundation Scholar Award.



**Steven A. Rosenberg, M.D., Ph.D.**, received the 2021 Dan David Prize and the Health and Human Services Secretary's Award for Distinguished Service.



**Eytan Ruppin, M.D., Ph.D.**, was elected to the 2021 International Society for Computational Biology class of fellows.



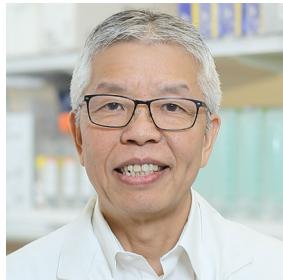
**Vassiliki Saloura, M.D., Ph.D.**, received the 2021 Career Development Award from Conquer Cancer, the American Society of Clinical Oncology Foundation.



**Joel P. Schneider, Ph.D.**, received the 2021 American Peptide Society Vincent du Vigneaud Award.



**Louis M. Staudt, M.D., Ph.D.**, received the Health and Human Services Departmental Award for Career Achievement.



**Xin Wei Wang, Ph.D.**, received the 2021 Blue Faery Award.



**Sandra L. Wolin, M.D., Ph.D.**, received the Sandra K. Masur Senior Leadership Award from the American Society for Cell Biology.



**Howard A. Young, Ph.D.**, received the 2021 International Cytokine & Interferon Society Mentorship Award.



**Brigitte C. Widemann, M.D.**, was selected as a 2021 Sammies (Samuel J. Heyman Service to America Medals) finalist in the Science and Environment category and was the NIH Director's 2021 Astute Clinician Lecturer. She received the American Association for Cancer Research-Joseph H. Burchenal Award for Outstanding Achievement in Clinical Cancer Research and was elected to the Association of American Physicians. She was also named a Top Ten Clinical Research Achievement Awardee and selected for a Distinguished Clinical Research Achievement Award by the Clinical Research Forum.

## Group Award

**James L. Gulley, M.D., Ph.D., Christian S. Hinrichs, M.D., Scott M. Norberg, D.O., Clint T. Allen, M.D., (NIDCD), Michael Pollack, Ph.D., (NCI Technology Transfer Center) and Helen Sabzevari, Ph.D., (CEO/President Precigen)** were selected by the Federal Laboratory Consortium (FLC) Mid-Atlantic Region to receive the 2021 Excellence in Technology Transfer award for "PRGN-2012, FDA Orphan Drug Designation for Recurrent Respiratory Papillomatosis."

# CCR by the Numbers



**333** Open Clinical Trials

**57** New Clinical Trials

**1,351** New Patients



**239** Principal Investigators

**8** New Faculty Recruits

**3** Newly Tenured Investigators

**303** Staff Scientists/  
Staff Clinicians

**480** Technical Lab Staff

**773** Postdoctoral/  
Clinical Fellows

**401** Postbaccalaureate/  
Predoctoral Students



**>1,100** Articles in  
Peer-Reviewed Journals



**52** Technology Facilities  
and Platforms



**>50** COVID-19 Projects

**>140** COVID-19 Publications

## Technology Transfer Activities



**63** New Employee Invention Reports

**52** Issued U.S. Patents

**21** New Cooperative Research and  
Development Agreements (CRADAs)

**9** New Clinical CRADAs

**171** Active CRADAs

**84** Clinical CRADAs

**6** Umbrella CRADAs

**24** New Clinical Trial Agreements (CTAs)

**105** Active CTAs



**102** New Licenses for CCR Technologies

**655** Active Licenses



**4** FDA Approvals

**1** FDA Orphan Drug Designation

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

*Numbers are for FY21.*

# 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>

**Cancer Immunology and Immunotherapy at CCR**

<https://ccr.cancer.gov/research/immunology-and-immunotherapy>

**NCI CCR Prostate Cancer Multidisciplinary Clinic**

<https://ccr.cancer.gov/clinical-trials/prostate-cancer-clinic>

**CCR Myeloid Malignancies Program**

<https://ccr.cancer.gov/myeloid-malignancies-program>

**CCR Office of Science and Technology Resources**

<https://ostr.ccr.cancer.gov>

## Center for Cancer Research



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