



OUR COVID-19 EFFORTS

Read about NYU Langone Health's response to the challenges of the COVID-19 pandemic.
See insert.



Perlmutter Cancer Center

2020 HIGHLIGHTS

Clinical Trial Growth Continues More Than 100 Trials Activated in 2020

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Three-Dimensional Genetic Structure Regulates Disease Progression in Leukemia

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Survival of Pancreatic Tumor Cells Depends on Exploiting Metabolism

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BENJAMIN G. NEEL, MD, PHD

Professor of Medicine
Director, Laura and Isaac Perlmutter
Cancer Center



MESSAGE FROM THE DIRECTOR

2020 has been a year like no other in our collective memory. As the true scope of the coronavirus disease (COVID-19) pandemic became evident, members of Perlmutter Cancer Center at all levels have shown nothing but resilience, persistence, equanimity, and most of all, dedication to our shared mission to reduce the burden of cancer now and move toward eliminating it in the future.

In 2020, we made advances in our understanding of the molecular mechanisms that drive cancer metastasis and enable pancreas tumor cells to evade the immune system. Our Lung Cancer Program expanded its footprint. We maintained an active portfolio of clinical trials, one of which resulted in approval of a new lung cancer agent by the U.S. Food and Drug Administration. And, we uncovered the role of a 3D genetic structure in T cell acute lymphoblastic leukemia.

As the virus continues to circulate through our community, it is imperative that we stay vigilant so we all can stay safe and focus our efforts on advancing cancer care in 2021.

I invite you to reach out to me directly at benjamin.neel@nyulangone.org should you like any further information about the initiatives outlined in this report, or seek a second opinion from our team.



Top 20

CANCER CENTER
IN THE COUNTRY



NCI-DESIGNATED
COMPREHENSIVE
CANCER CENTER

100+

NEW CLINICAL
TRIALS ACTIVATED



▲
Arjun V. Balar, MD

Portfolio of Clinical Trials Continues to Grow

Despite the challenges brought with the COVID-19 pandemic, 2020 was another year of growth for Perlmutter Cancer Center's clinical trials program with more than 100 new trials activated.

COMBINING CHEMORADIATION WITH IMMUNOTHERAPY FOR MUSCLE INVASIVE BLADDER CANCER

Arjun V. Balar, MD, associate professor of medicine, director of the Genitourinary Medical Oncology Program and medical director of the Clinical Trials Office at Perlmutter Cancer Center, leads a randomized Phase 3 clinical trial testing the combination of chemoradiation and pembrolizumab to treat people with muscle invasive bladder cancer (MIBC).

About 1 out of 4 people who get bladder cancer in the United States have MIBC. Chemoradiation is the standard of care for patients who are not candidates for surgery or who do not want to undergo radical cystectomy. The Phase 3 study expands on an early phase trial Dr. Balar designed that tested the combination of chemoradiation and pembrolizumab as an alternative to cystectomy. That trial treated about 54 patients, and the preliminary findings were very promising, Dr. Balar says. Patients have done well, and the vast majority have effectively treated their bladder cancer while avoiding surgical removal of the bladder.

The new Phase 3 trial tests chemoradiation alone versus chemoradiation plus immunotherapy to determine if the combination definitively improves cure rates for MIBC. Perlmutter Cancer Center will be the lead site in the United States, with other sites planned to open around the world.

"Findings from this study, if positive, will establish a new standard of care for patients with muscle invasive bladder cancer," says Dr. Balar, who chairs the scientific advisory committee for the trial.

NEW TREATMENTS FOR NON-SMALL CELL LUNG CANCER

The U.S. Food and Drug Administration recently approved Retevmo™ (selpercatinib) as the first drug for the treatment of people with non-small cell lung cancer (NSCLC) whose tumors have alterations in the RET gene. Results from a Phase 1/2 clinical trial of Retevmo™, a selective and potent RET kinase inhibitor, were published in the August 27 *New England Journal*

Clinical Trials Program Advances at NYU Langone Hospital—Long Island

The completion of NYU Langone Health's full-asset merger with NYU Winthrop Hospital (now called NYU Langone Hospital—Long Island) in August 2019 expanded Perlmutter Cancer Center's clinical trials program into Long Island.

Janice Mehnert, MD, who joined NYU Langone in July 2020 as a member of the faculty in the Department of Medicine and associate director for clinical research at Perlmutter Cancer Center, oversees the expansion of early-phase trial activity in collaboration with the cancer center's network sites in Brooklyn and Long Island, with the aim of further developing a strong culture of clinical and translational investigation that cuts across campuses.

"We have engaged our faculty partners at NYU Langone Hospital—Long Island to be part of the process and really have a seat at the table, from initiating clinical trials to helping us write study concepts," she says.

Across New York City and Long Island, Perlmutter Cancer Center network sites serve a large, diverse population of patients, each with different needs that are essential to the cancer center's mission, Dr. Mehnert says. A strategic initiative has been launched to identify the patient populations that are currently served at NYU Langone Hospital—Long Island and match clinical research offerings to those populations. Plans are also underway to establish an early phase clinical trials program that will collaborate closely with the early phase program at Perlmutter Cancer Center in Manhattan.

"A cancer diagnosis is stressful enough for people without adding the need to travel for care," Dr. Mehnert says. "A lot of high-quality care can be delivered without traveling. We are trying to identify the niches that can be met close to home and the niches that require travel to our main campus in Manhattan so we can better serve the population that our health system sees."

of Medicine. Study co-author Vamsidhar Velcheti, MD, associate professor of medicine and director of the Thoracic Medical Oncology Program, led the study at Perlmutter Cancer Center, one of 84 sites around the world that participated in the trial.

In the first 105 consecutively enrolled patients with RET-positive NSCLC who had previously received at least platinum-based chemotherapy, the percentage with a measurable response was 64 percent. Among 39 previously untreated patients, the percentage with an objective response was 85 percent, with 90 percent of the responses ongoing at six months. Among 11 patients with measurable central nervous system metastasis at enrollment, the percentage with an objective intracranial response was 91 percent.

"The most exciting thing about this agent is that it can cross the blood-brain barrier, so we can actually use it to treat lung cancer that has metastasized to the brain," says Dr. Velcheti.

Dr. Velcheti is currently conducting a Phase 1/2 trial of MRTX849 in combination with TNO155 in patients with advanced solid tumors that have a KRAS G12C mutation. Conducted in collaboration with Mirati Pharmaceuticals, the trial is testing the hypothesis that combining the KRAS inhibitor MRTX849 with TNO155, an inhibitor of the protein tyrosine phosphatase SHP2, can overcome resistance in patients with KRAS G12-positive lung cancer.

The trial is based on preclinical work from the lab of Benjamin G. Neel, MD, PhD, professor of medicine and director of Perlmutter Cancer Center, that demonstrated inhibiting SHP2 with KRAS signaling can augment responses to selective KRAS inhibitors.

"This is still an early Phase 1 clinical trial, but the science behind it is absolutely fascinating, and we are very excited about it," Dr. Velcheti says. "My hope is that if we demonstrate safety and if we have early signs of efficacy, this trial would expand to a larger Phase 2 trial."

TESTING ANTIBODY-DRUG CONJUGATE IN WOMEN WITH METASTATIC BREAST CANCER

Yelena Novik, MD, associate professor of medicine, is lead investigator of a Phase 3 clinical trial of the antibody-drug conjugate Immu-132, also known as sacituzumab govitecan-hziy, in women with hormone receptor-positive, HER2-negative metastatic breast cancer that has progressed after endocrine therapy as well as two lines of chemotherapy.

In April 2020, the U.S. Food and Drug Administration approved Immu-132 for the treatment of metastatic triple-negative breast cancer (TNBC). Because Immu-132 has been effective in treating TNBC, the current Phase 3 trial, part of a multi-site, international study, is testing the hypothesis that this drug might also be effective in breast cancers that used to be sensitive to hormonal therapy, Dr. Novik says.

Immu-132 combines the cancer drug SN-38 with a Trop2 antibody, which drags it specifically to an antigen frequently seen on cancer cells. Coupling SN-38, a topoisomerase inhibitor, with Trop2 enables targeted delivery of the chemotherapy with potentially fewer side effects.

"By using smarter drug delivery with potentially more effective delivery of the chemotherapy molecule to the tumor, we hope to improve the chances that a woman with metastatic breast cancer can live longer," Dr. Novik says.

ADJUVANT STUDY TARGETS RESECTED MELANOMA

More than 20 active trials are underway investigating treatments for melanoma and skin cancers, says Jeffrey S. Weber, MD, PhD, the Laura and Isaac Perlmutter Professor of Oncology in the Department of Medicine and deputy director of Perlmutter Cancer Center. With significant philanthropic support from Brian C. and Mary Jo Rogers, Dr. Weber conducts the only adjuvant study in Manhattan for resected stage II and stage III melanoma. ■



For more information on Perlmutter Cancer Center's clinical trials, email cancertrials@nyumc.org



Three-Dimensional Genetic Structure Regulates Disease Progression in Leukemia

The new work, published online March 23 in the journal *Nature Genetics* builds on the discovery that DNA chains exist in organized “neighborhoods” called topologically associating domains, or TADs. Specifically, enhancers are known to regulate the expression of genes, but normally only those housed in their own TADs. Within TAD boundaries, DNA is free to fold back on itself in three-dimensional (3D) loops, bringing together enhancers and other elements, such

as promoter DNA, that interact to read a specific DNA sequence and produce RNA that eventually is translated into protein.

The new study shows that key TAD boundaries are lost in T-ALL, enabling parts of DNA to interact with enhancers from the wrong neighborhoods, activating the genes that promote cancer growth and spread. Researchers say their findings suggest that these 3D changes in chromosome structure

are as important as mutations that alter specific proteins, with both mechanisms promoting cancer onset and evolution.

T-ALL is largely driven by mutations that occur on the NOTCH1 gene, leading to the high expression of the oncogene MYC. Drug therapies designed to block NOTCH1 (and thus MYC) have been affected by toxicities and acquired resistance leading to eventual relapse. The research team tested such therapies targeting NOTCH1 and found that part of the explanation for relapse may reside in the failure of single-drug therapies to correct the 3D chromosomal changes that come with the disease.

Indeed, experiments with a drug that successfully blocks NOTCH1 activity showed that it did not effectively block access to the exposed MYC gene neighborhood or completely shut down MYC expression, which could explain why NOTCH1 inhibitors do not work for most patients, says study co-senior investigator Iannis Aifantis, PhD, the Hermann M. Biggs Professor and chair of NYU Langone’s Department of Pathology and a researcher at Perlmutter Cancer Center.

However, a second experimental drug that targets epigenetic changes in these DNA neighborhoods effectively restored DNA looping in the MYC neighborhood, restoring normal chromosomal structure and gene regulation, and dramatically decreasing MYC action and cancer progression.

“Overall, our study underscores the need for further investigation of factors that maintain or rewire 3D chromosomal interactions, especially during cellular transformation, as they could be potential targets for small-molecule drug development,” says co-senior investigator Aristotelis Tsiganos, PhD, professor in the Department of Pathology and a researcher at Perlmutter Cancer Center. ■



Learn more about Perlmutter Cancer Center’s Leukemia care at nyulangone.org/leukemia

Blood Cancer Program Grows at Perlmutter Cancer Center

A number of appointments in key research areas and infrastructure expansion has cemented Perlmutter Cancer Center’s position as a nexus for blood cancer research and care.

Bolstered by a \$75 million anonymous gift in 2019, Perlmutter Cancer Center is moving forward with the establishment of a Center for Blood Cancers. Last year, nationally renowned hematology experts Gareth J. Morgan, MD, PhD, and Faith E. Davies, MD, joined Perlmutter to lead its Multiple Myeloma Program. Dr. Morgan, the center’s director of multiple myeloma research, focuses on developing new targeted treatments for high-risk variants of the disease. Dr. Davies, who serves as director of the center’s Clinical Myeloma Program, focuses on the genetic, biological, and radiological theranostic markers to improve myeloma patient outcomes.

This year, Benedetto Bruno, MD, PhD, joined Perlmutter Cancer Center from the University of Torino, where he was director of its transplant program. Dr. Bruno’s clinical activities center around bone marrow transplantation and cell therapies. He has a particular interest in the role of allogeneic stem cell transplantation and innovative T cell therapies in the treatment of hematological malignancies.

The anonymous gift also supports construction of a new outpatient clinic for the Blood and Marrow Transplant Program, directed by Samer Al-Homsi, MD, MBA, clinical professor in the Department of Medicine. Projected to open in late spring 2021, the new clinic will be home to physician practices, examination rooms, an infusion center, and an apheresis center. The clinic will also house a new stem cell processing laboratory and, for the first time, enable Perlmutter Cancer Center hematologists to perform allogeneic transplants on an outpatient basis.

Lung Cancer Center Targets Expanded Screening for Earlier Detection and Enhanced Care

Dedicated Screening Programs Identify
At-Risk Patients, as Center Works to Connect
Diagnosed Patients With Clinical Trials

To bring the proven benefits of routine screening to more patients at risk of lung cancer, the Lung Cancer Center at Perlmutter Cancer Center has expanded its National Cancer Institute-affiliated lung cancer screening program in a New York City community inordinately impacted by the disease. The effort is one element of an initiative aimed at earlier intervention—and improved patient access to a growing clinical trials portfolio—for better outcomes.



▲
Catherine Concert, NP, and Abraham Chachoua, MD

PRIORITIZING SCREENING TO INCREASE LUNG CANCER SURVIVABILITY

In spite of studies demonstrating that routinely screening people between the ages of 55 and 80 who have a 30 pack-year smoking history can detect lung cancer early and enhance survival, the practice remains underutilized by primary care physicians and patients, says Abraham Chachoua, MD, the Jay and Isabel Fine Professor of Oncology and director of the Lung Cancer Center.

“The use of screening for early detection of lung cancer is limited by poor patient awareness and a relatively high false-positive rate at 30 percent, which potentially exposes people to unnecessary procedures and radiation,” notes Dr. Chachoua.

At NYU Langone, a lung cancer screening program based at NYU Langone’s general pulmonary practice originally took root through a 15-year, National Cancer Institute (NCI)-funded research project, the NYU Langone Lung Cancer Biomarker Program. Directed by Daniel H. Serman, MD, the Thomas and Suzanne Murphy Professor of Pulmonary and Critical Care Medicine, the initiative is now part of the NCI’s Early Detection Research Network. In parallel, NYU Langone Hospital—Long Island (formerly NYU Winthrop Hospital) maintains a successful, long-standing lung cancer screening program with more than 700 patients enrolled.

EXPANDING SCREENING THROUGH COMMUNITY POINTS OF CARE

Lung cancer impacts more patients in Brooklyn, home to several immigrant populations with a history of heavy smoking, than in any other New York City borough—making it the logical hub for the Lung Cancer Center’s initial phase of expanded screening outreach. In August 2020, a pilot screening program was launched at Sunset Park Family Health Center at NYU Langone—Second Avenue, one of the largest Federally Qualified Health Center networks in the nation. The community-based program provides high-quality primary and preventive outpatient care to adults and children, regardless of their ability to pay or health insurance status—expanding care to underserved populations.

The pilot screening program produced 26 patient referrals for screening by early October, based on best practice alerts in the patients’ electronic health records related to their smoking history. Among these referrals, 52 people were found eligible for screening, ten of which required follow-up pulmonary appointments. In November, a second screening program was launched at a multi-specialty practice with a large population of Russian patients, typically heavy smokers. There are plans to continue expanding to all Family Health Centers and faculty group practice sites across Brooklyn in an effort to reach as many eligible patients as possible.

At the same time, the center is working to increase awareness of screening and prevention in the community as part of its Stamp Out Cancer Brooklyn (SOCB) initiative. Supported in part by a generous gift from Lauren Sands and James Ryan III, SOCB aims to reduce the disproportionate burden of cancer in the borough through education, screening, and supportive resources.

Targeting Lung Cancer at the Molecular Level

New research from the laboratories of Benjamin G. Neel, MD, PhD, director of Perlmutter Cancer Center, and Kwok-Kin Wong, MD, PhD, the Anne Murnick Cogan and David H. Cogan Professor of Oncology and director of the Division of Hematology and Medical Oncology, holds promise for treating patients with solid tumors that express KRAS, the most commonly mutated form of the RAS family of oncogenes.

The study, published online October 8 in the *Journal of Experimental Medicine*, shows that combining inhibitors of a mutant form of the RAS oncogene and SHP2, a molecule that promotes activation of RAS, promotes favorable changes in the immune microenvironment of pancreatic and non-small cell lung cancers in mice. The researchers further showed that adding an immune checkpoint inhibitor that blocks PD-1 or PD-L1 increases the efficacy of the RAS and SHP2 inhibitor combinations.

Until recently, it was thought that the KRAS protein was not druggable because its structure made it difficult to inhibit with a small molecule. Newly developed molecules that inhibit a specific KRAS mutant, called KRAS-G12C, bind to the mutant protein in its inactive state and irreversibly react with the mutated G12C residue.

Dr. Neel’s lab discovered SHP2, which helps a molecule called SOS promote the inactive form of RAS to the active form, in the 1990s. Since then, several drugs have also been developed to block the action of SHP2.

In the new study, the Perlmutter Cancer Center researchers found that combining a KRAS-G12C inhibitor with a SHP2 inhibitor prevents KRAS from switching to the active state, thereby increasing the ability of the KRAS inhibitor to inactivate the mutant protein. This combination is currently being tested in patients in a clinical trial at Perlmutter Cancer Center.

The study also found that while the overall effects of the inhibitor combination in the models of lung cancer and pancreatic cancer are similar, the details are different. For example, in pancreatic cancer, the SHP2 inhibitor has anti-angiogenic effects and helped cut off the blood supply to pancreas tumors, which contributed to the efficacy of the combination. In the lung cancer model, however, SHP2 promoted blood vessel formation.

“Our study shows the importance of analyzing the effects of drug combinations—both on the tumor and its microenvironment, and also on the specific tumor type and its particular microenvironment,” says Dr. Neel.

LEADING SCREENED PATIENTS TO CLINICAL TRIALS AND ENHANCED CARE

The Lung Cancer Center is also working to enhance clinical research and care as the number of lung cancer patients rises with expanded screening. In a partnership with Delfi Diagnostics, the center team is comparing circulating tumor DNA with low-dose CT findings both in high-risk patients identified through the Lung Cancer Screening Program and in never-smoking Asian women. The goal is to accrue 1,000 participants in each population over the next two to three years.

Additionally, researchers are working to improve patients’ navigation to the Perlmutter Cancer Center’s 21 active and 15 pending trials for lung cancer. Through a partnership with Foundation Medicine, the Lung Cancer Center has streamlined the process for referring patients

with somatic mutations to targeted therapy trials, and established a process for genetic counseling referrals to evaluate potential germline mutations. As a result of these focused efforts, the center accrued 60 patients to lung cancer trials through the fall of 2020—an increase from 28 within the same timeframe in 2019—making Perlmutter the leading site in accruals to some clinical trials. ■



Learn more about the Lung Cancer Center and reach Dr. Chachoua by visiting

nyulangone.org/lungcancer



Eva M. Hernando-Monge, PhD

Improving Understanding of Cancer Metastasis

Researchers at NYU Langone Health's Perlmutter Cancer Center are developing a better understanding of the molecular mechanisms that drive cancer metastasis, focusing on the role of a recently discovered form of RNA in melanoma metastasis and how nutrient availability and altered metabolism cooperate to promote tumor evolution and metastasis in the brain.

ABSENCE OF CIRCULAR RNA PROMOTES MELANOMA PROGRESSION

While genetic alterations that affect cellular signaling pathways have been extensively studied in melanoma, they alone are insufficient to explain the metastatic behavior of these tumors. For example, tumors with the same mutations in those pathways can be very aggressive and metastasize rapidly or can have a more indolent course and be cured surgically. Work in the laboratory of Eva M. Hernando-Monge, PhD, professor in the Department of Pathology at NYU Grossman School of Medicine, is aimed at understanding the mechanisms that lead to melanoma metastasis. Dr. Hernando-Monge and her colleagues are investigating the contribution of so-called non-coding RNAs, such as recently discovered circular RNAs (circRNAs) and long non-coding RNAs (LINC RNAs), as well as the epigenome (how genes are packaged and regulated in the nucleus) in promoting metastatic behavior.

Dr. Hernando-Monge's lab recently found that the loss of a particular circRNA called CDR1as promotes metastasis in melanoma. CDR1as sequesters IGF2BP3, an RNA-binding protein that controls the stability of messenger RNAs involved in invasion and metastasis. In the absence of CDR1as, IGF2BP3 is released and stabilizes pro-metastatic targets, thereby promoting melanoma progression. Analysis of human melanoma tissues also linked higher CDR1as levels to increased patient survival. This is the first study to expose a circRNA as a suppressor of metastasis.

The study also identified LINC00632, a long noncoding RNA, as the source of CDR1as in cells. Experiments further revealed that an epigenetic mechanism in melanoma cells—histone methylation—silences the LINC00632 gene, which halts CDR1as production.

"CDR1as silencing could represent a mechanism that helps cells migrate during normal fetal development but drives metastasis when it is turned on in tumors," Dr. Hernando-Monge says.

CANCER CELLS METASTASIZE BY ADAPTING TO THE BRAIN'S ENVIRONMENT

For treating a subset of brain metastases, stereotactic radiosurgery techniques such as Gamma Knife® radiosurgery are highly effective with good outcomes, yet patients inevitably return for follow-up treatments as brain metastases recur. Although there are known genetic drivers of tumors, there are few genes known to specifically enable brain metastases.

Michael E. Pacold, MD, PhD, assistant professor in the Department of Radiation Oncology at NYU Grossman School of Medicine, and his colleagues have been exploring what is different about the brain environment that cancer metastases must adapt to in order to survive in the brain.

In a recent collaboration with Lewis Cantley, PhD, at Weill Cornell Medical Center, Dr. Pacold and his colleagues used the brain cerebrospinal fluid as an approximation of available nutrients in the brain environment and determined that the brain microenvironment is low in both serine and glycine, which are crucial for tumor growth. They also found that tumor cells that are effective in colonizing the brain are serine prototrophs, meaning that they have the ability to grow in conditions where serine and glycine concentrations are limited.

Using small molecule inhibitors of serine synthesis in a mouse model of breast cancer brain metastasis, the researchers were able to attenuate and, in some cases, prevent the colonization of the brain by these tumors. They also have preliminary evidence that when melanoma cells are placed in an environment similar to the brain and treated with inhibitors of serine synthesis, they don't grow.

Dr. Pacold says this study reflects a shift from thinking not only about the behavior of individual tumor cells, but looking at the environments they live in and targeting therapy not just to the tumor cell, but to its metabolic microenvironment.

"Going forward, we're going to be looking a lot more at cancer cells and the context in which they grow," Dr. Pacold says. "From the standpoint of drug development, we're going to have to consider how the cellular environment might alter the efficacy of the drugs themselves." ■

Survival of Pancreatic Tumor Cells Depends on Exploiting Metabolism

Scientists at Perlmutter Cancer Center are beginning to unravel some of the key mechanisms behind the development of pancreatic cancer, which may lead to improved therapies for people with the disease.

PANCREATIC TUMORS ACT AS METABOLIC SCAVENGERS

One strategy for developing new therapies for pancreatic cancer is understanding the unique metabolism of pancreatic tumors and how they use different fuel sources to grow and survive in a very austere tumor microenvironment. Alec Kimmelman, MD, PhD, professor and the Anita Steckler and Joseph Steckler Chair in the Department of Radiation Oncology, and his colleagues study metabolic adaptations in pancreatic cancer and how to potentially target them ultimately for potential therapeutic gain.

Dr. Kimmelman's research has provided a growing body of evidence that pancreatic tumors are "metabolic scavengers," with the ability to use cellular processes such as autophagy and macropinocytosis to produce needed metabolic substrates when oxygen and glucose, normally supplied by the bloodstream, are in short supply.

In a study recently published in *Cell*, experiments in cancer cells, mice, and human tissue samples showed that pancreatic tumors can use neurons to divert nutrients from the bloodstream to the more austere pancreatic tumor microenvironment. The researchers found that pancreatic cancer cells starved of the amino acid serine take advantage

of the process that translates messenger RNA into proteins. The serine-starved pancreatic cancer cells secrete nerve growth factor (NGF), which sends signals for axons instructing them to grow deeply into tumors. The researchers found further that axons secrete serine, which rescues pancreatic cancer cells from starvation and restores their growth.

The study is the first to show that axons provide metabolic support to cancer cells by secreting serine in nutrient-deprived areas.

Administering LOXO-101, a drug approved by the U.S. Food and Drug Administration for treating solid tumors with NTRK gene fusions, to mice with pancreatic tumors blocked the activation of a receptor protein on the surface of neurons that interacts with NGF, stopping the neuronal ingrowth into the tumors.

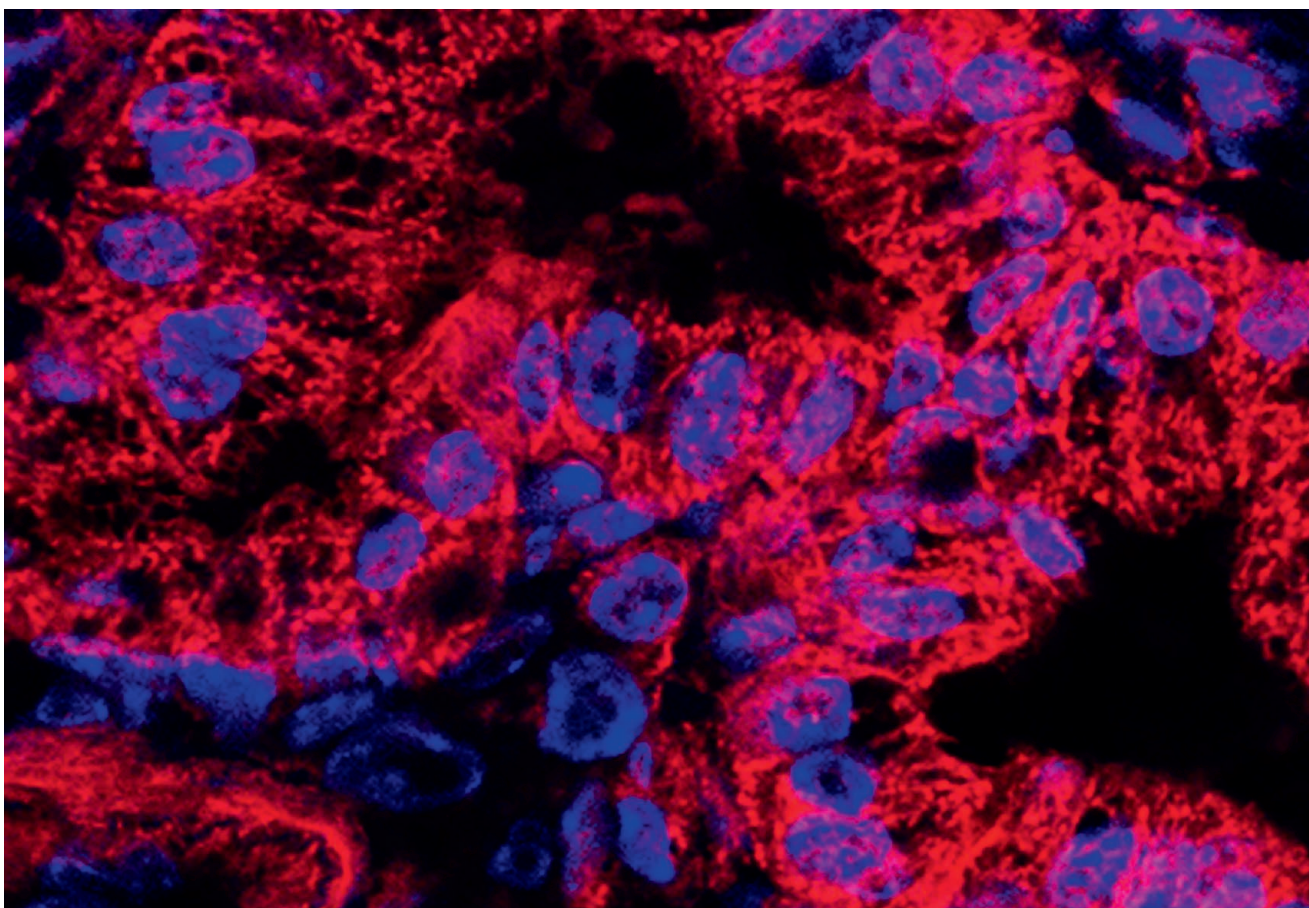
"This finding still requires more preclinical validation, but there is a potential therapeutic advance," Dr. Kimmelman says.

HIJACKING AUTOPHAGY ENABLES PANCREATIC TUMOR SURVIVAL

Dr. Kimmelman's lab has studied autophagy in pancreatic cancer cells extensively over the years. In a study published in *Nature* in 2016, Dr. Kimmelman's lab found that pancreatic tumor cells signal pancreatic stellate cells, which degrade proteins through autophagy, releasing alanine, which in turn is taken up by the tumor cells and used as fuel instead of glucose. Inhibiting autophagy in the stellate cells disrupts this metabolic crosstalk and impairs the growth of tumors.

Dr. Kimmelman's recent research on autophagy and pancreatic tumors has also provided new insights into the longstanding question of why pancreatic cancers are resistant to immunotherapies.

In a collaboration with researchers at the University of California, San Francisco, Dr. Kimmelman's team published a study in



NYU Langone researchers reveal how cancer cells avert starvation by signaling to nerves, which grow into dense tumors and secrete nutrients.
PHOTO: CALLISTA IMAGES/GETTY

World-Renowned Pancreatic Surgeon Joins Perlmutter

Christopher L. Wolfgang, MD, PhD, FACS, has been appointed as the director of the new Division of Hepatobiliary and Pancreatic Surgery at NYU Langone Health following 15 years at Johns Hopkins where he was the Chief of Surgical Oncology.



Nature in early 2020 found that in pancreatic cancer, the major histocompatibility complex class I (MHC-I) is pulled into vesicles inside the cancer cells. Once inside, MHC-I is degraded by autophagy, enabling cancer cells to avoid notice by the immune system and resist immunotherapies.

Experiments in mice with pancreatic cancer showed that blocking autophagy either with genetic approaches or with the antimalaria drug chloroquine caused an increase in MHC-I molecules on the surfaces of the tumor cells. Chloroquine and its derivative hydroxychloroquine are known to inhibit autophagy using the same mechanism. Combining chloroquine with two checkpoint inhibitors in mice significantly increased tumor responses over that achieved by the immunotherapies alone.

Hydroxychloroquine, combined with standard chemotherapy, has been found to increase a patient's response to chemotherapy. The study's findings suggest hydroxychloroquine could also improve the effectiveness of immunotherapy, though Dr. Kimmelman cautions such combinations must be studied further before they can be tested clinically.

"While pancreatic cancer is one of the most challenging cancers that we see and results are still not where we want them, there have been significant advances in the past several years," says Dr. Kimmelman, who is a senior member of Perlmutter Cancer Center. "We now have therapeutic regimens that have activity and efficacy and prolong survival, and there has been a huge growth in basic research on pancreatic cancer, which I think will lead to promising potential therapeutics." ■



Learn more about Perlmutter Cancer Center's pancreatic cancer care and research at nyulangone.org/pancreaticcancer

Early Detection and Prevention Initiative Seeks to Increase Pancreatic Cancer Survival Rate Over Next 10 Years

Diane M. Simeone, MD, the Laura and Isaac Perlmutter Professor of Surgery and professor of pathology and director of the Pancreatic Cancer Center, partnered with the American Society of Clinical Oncology to implement a new guideline that calls for all patients with pancreatic cancer to receive germline testing. "We are now learning that certain germline mutations are associated with much better therapeutic responses to certain types of drugs than others, so this information can be of direct benefit to our pancreatic cancer patients," says Dr. Simeone. "We want to increase identification of family members who are at increased risk, so that they can be enrolled in early detection programs. Studies have found that screening in high-risk individuals increases the chance of detecting a resectable lesion from 15 to 90 percent."

Under the direction of Dr. Simeone and her team, NYU Langone serves as the coordinating center for the newly formed PRECEDE (Pancreatic Cancer Early Detection) Consortium, a collaborative of 35 academic centers around the country and the world focused on early detection in familial high-risk individuals.

COVID-19–related Publications from the Perlmutter Cancer Center

NYU Langone researchers have led many efforts to better understand the impact of COVID-19 across nearly every medical specialty, with 617 publications in 2020. The Perlmutter Cancer Center contributed to this research with publications that included:

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ABOUT NYU LANGONE HEALTH

Leader in Quality

NYU Langone's emphasis on continuous improvement inspires teams to continually raise the bar on quality and safety across our growing network in Manhattan, Brooklyn, Queens, Long Island, Staten Island, and Florida. NYU Langone's Tisch Hospital, Kimmel Pavilion, NYU Langone Hospital—Brooklyn, and NYU Langone Hospital—Long Island were awarded an "A" as well as a Top Hospital award as part of the fall 2020 Leapfrog Hospital Safety Grades. NYU Langone Hospitals achieved Five Star ratings on CMS Hospital Compare effective October 2019 and is the only major academic medical center in the New York metropolitan region to attain a Five-Star Quality rating.



#9

in the Nation

Ranked ninth by *U.S. News & World Report* for Best Hospitals; and ranked fourth for Best Medical Schools (Research).



#4

in the Nation



Transforming Medical Education

As COVID-19 has added new urgency to nationwide physician shortages, debt burden, and lack of diversity, we remain committed to our accelerated pathways to the MD degree and full-tuition scholarships regardless of need or merit at the recently renamed NYU Grossman School of Medicine and the new primary-care focused NYU Long Island School of Medicine.



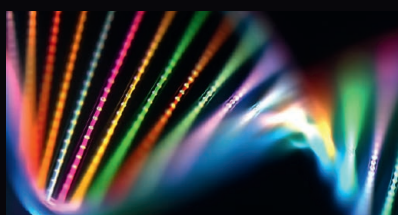
Perlmutter Cancer Center

2020 HIGHLIGHTS

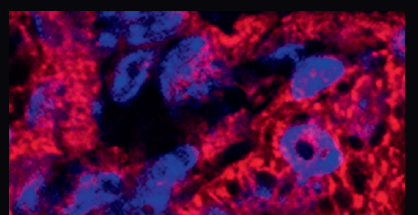


**Perlmutter
Cancer Center**

An NCI-designated
Comprehensive Cancer Center



Three-Dimensional Genetic
Structure Regulates Disease
Progression in Leukemia
See page 3.



Survival of Pancreatic
Tumor Cells Depends on
Exploiting Metabolism
See page 7.