

NewYork-Presbyterian Oncology

2017 Report on Clinical and Scientific Innovations



Weill Cornell
Medicine

**NewYork-
Presbyterian**



COLUMBIA UNIVERSITY
MEDICAL CENTER



New York's #1 Hospital
17 Years in a Row

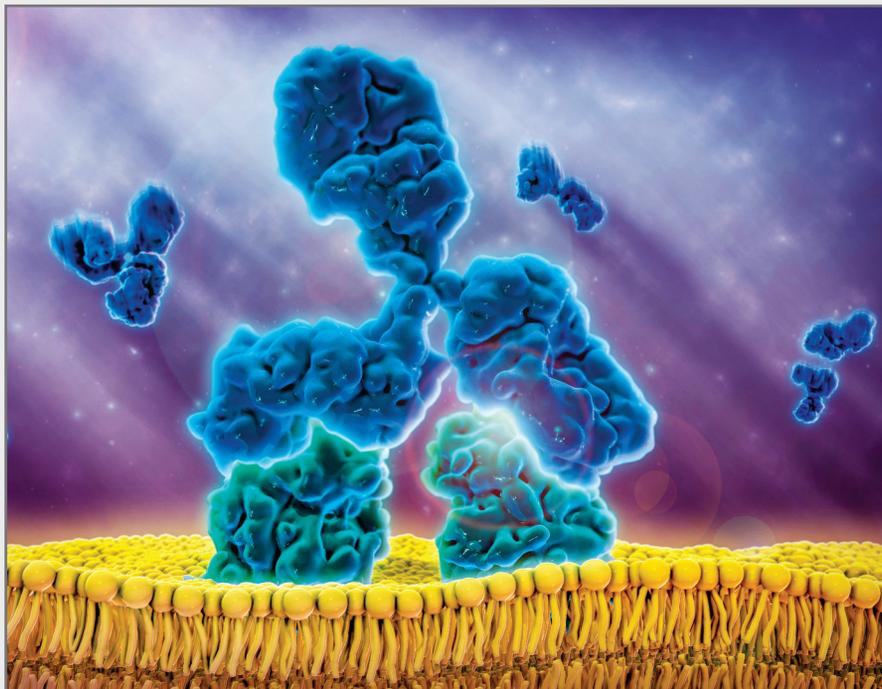


Illustration of monoclonal antibodies bonding to antigens located on the surface of a cancer cell

NewYork-Presbyterian Oncology 2017 Report on Clinical and Scientific Innovations

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For More Information
nyp.org/amazingadvances

Welcome

Dear Colleague:

We are pleased to bring you our *2017 Report on Clinical and Scientific Innovations in Oncology*. The strength of our oncology programs is derived from the exceptional clinical, scientific, and educational resources made possible by the partnership of NewYork-Presbyterian, Columbia University Medical Center, and Weill Cornell Medicine. At the foundation of these programs are two major cancer centers: the National Cancer Institute-designated Herbert Irving Comprehensive Cancer Center at Columbia and the Sandra and Edward Meyer Cancer Center at Weill Cornell.

These centers are home to preeminent clinicians and scientists whose efforts span virtually every type of cancer with a goal of someday finding a cure. Their progress continues to garner attention, from innovative research in organoids for brain cancer to N-of-1 trials for breast metastases to drug development that is changing the prognosis for patients with challenging lung and hematological cancers.

Our patients benefit from collaborations among medical, radiation, and surgical oncologists who look beyond standard-of-care to the unique molecular characteristics of each patient to formulate a personalized therapeutic plan that optimizes the opportunity for a positive outcome. Our oncology healthcare teams are compassionate and committed to providing cohesive and seamless care that supports patients and their families throughout their journey.

At the writing of this report, we are so pleased to announce an unprecedented gift of \$700 million to Columbia University and NewYork-Presbyterian that will support cancer research and patient care. This historic bequest by Florence Irving and her late husband, Herbert Irving, will have a profound impact on all aspects of our work in cancer across multiple clinical and scientific disciplines and ultimately change the landscape of cancer care the world over.

Sincerely,



Steven J. Corwin, MD
*President and
Chief Executive Officer
NewYork-Presbyterian*



Lee Goldman, MD
*Executive Vice President, Dean of
the Faculties of Health Sciences
and Medicine, and Chief Executive
Columbia University Medical Center*



Augustine M.K. Choi, MD
*Stephen and Suzanne Weiss Dean
Weill Cornell Medicine*



Dr. Steven J. Corwin



Dr. Lee Goldman



Dr. Augustine M.K. Choi

Welcome



Dr. Cory Abate-Shen



Dr. Lewis C. Cantley



Dr. David M. Nanus



Dr. Gary K. Schwartz

Dear Colleague:

There is great excitement in the field of oncology today. Scientific discoveries and new therapies are helping a greater number of patients with advanced disease. At NewYork-Presbyterian, Columbia University Medical Center, and Weill Cornell Medicine, our clinicians and scientists continue to reveal the underlying mechanisms of cancer development that may ultimately inform the newest generation of therapeutics. At the same time, many challenges continue to confront us the more we delve deeper into the vast complexities of hematological and solid tumor cancers.

In our *2017 Report on Clinical and Scientific Innovations in Oncology*, we highlight recent advances and novel initiatives that we believe are bringing us closer to offering therapies that benefit a broader range of patients. These include our work in patient-derived organoids, combination therapies, and new models of care.

The efforts of our faculty are bolstered with funding by major grants from the National Institutes of Health and other organizations and the support of individuals who place their confidence in the promise of our endeavors. This includes, most recently, the awarding of a SPORE grant in prostate cancer and an extraordinary bequest from Florence Irving and her late husband, Herbert Irving.

We are proud of our high-caliber clinical and scientific faculty and grateful for the resources and facilities that enable them to continue to pursue their groundbreaking efforts on behalf of patients and families facing a cancer diagnosis.

Sincerely,

Cory Abate-Shen, PhD

Interim Director
Herbert Irving Comprehensive Cancer Center
NewYork-Presbyterian/
Columbia University Medical Center

David M. Nanus, MD

Chief, Hematology and Medical Oncology
NewYork-Presbyterian/Weill Cornell Medical Center
Associate Director for Clinical Services
Sandra and Edward Meyer Cancer Center at
Weill Cornell Medicine/Ronald P. Stanton
Clinical Cancer Program at NewYork-Presbyterian

Lewis C. Cantley, PhD

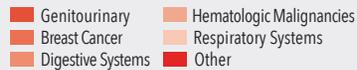
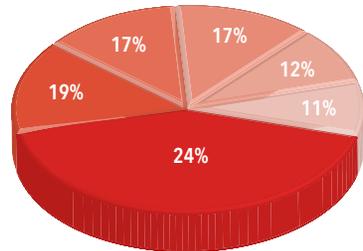
Meyer Director, Sandra and Edward Meyer
Cancer Center at Weill Cornell Medicine/
Ronald P. Stanton Clinical Cancer Program at
NewYork-Presbyterian

Gary K. Schwartz, MD

Chief, Hematology and Oncology
Deputy Director
Herbert Irving Comprehensive Cancer Center
NewYork-Presbyterian/
Columbia University Medical Center

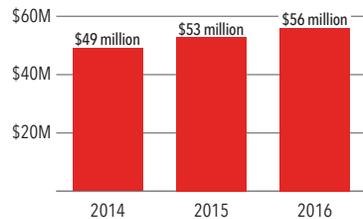
Measures of Distinction

New Cancer Cases 2016



Source: NewYork-Presbyterian Tumor Registry Cases

NCI Funding 2016



NCI funding for oncology research at NewYork-Presbyterian has increased by 16% over the past three years.

Source: NewYork-Presbyterian

CLINICAL CARE

Clinicians and Research Scientists
544

Patient Discharges
8,600

Dedicated
Oncology Beds
137

Infusion
Chairs
148

Infusions
83,000

Gamma Knife
Procedures
250

Radiation Therapy
Treatments
38,000

Bone Marrow
Transplants
240

Multidisciplinary Programs
54

Source: NewYork-Presbyterian 2016

REACH

In 2016, NewYork-Presbyterian oncology services treated patients from **30** states and **17** countries

RECOGNITION

- New York-Presbyterian is **1 of 49** National Cancer Institute-designated **Comprehensive Cancer Centers** in the country
- NewYork-Presbyterian is rated as **Best** in **Survival, Advanced Technology, and Nurse Staffing** by *U.S. News & World Report*

RESEARCH

- Received over **\$145 million** from the **National Institutes of Health** and other sponsoring organizations in 2016, including **147** awards from the **National Cancer Institute**
- More than **4,700** patients participated in **800+** research studies, including **130** phase 1 and phase 2 trials

GRADUATE MEDICAL EDUCATION

- **237** residents participated in our hematology and oncology residency programs
- **39** fellows participated in fellowship programs that include:
 - Adult Bone Marrow Transplant
 - Gynecologic Oncology
 - Colorectal Surgery
 - Hematology/Medical Oncology
 - Cytopathology
 - Urologic Oncology

\$11.3
MILLION

The five-year, \$11.3 million SPORE grant will further advance investigations that span basic, clinical, and translational research in prostate cancer.



Dr. Himisha Beltran

Prestigious SPORE Grant to Advance Prostate Cancer Research

Weill Cornell Medicine has been awarded a five-year, \$11.3 million Specialized Programs of Research Excellence (SPORE) grant from the National Cancer Institute to improve the detection and treatment of aggressive prostate cancer (PCa). Established in 1992, SPORE grants serve as the cornerstone of the NCI's efforts to promote collaborative, interdisciplinary translational cancer research.

This SPORE grant – the first ever awarded to Weill Cornell Medicine – will expand an already vibrant basic and translational research program in prostate cancer at Weill Cornell Medicine's Sandra and Edward Meyer Cancer Center and Caryl and Israel Englander Institute for Precision Medicine (IPM). In addition, the grant provides yearly funding to support new high-risk and high-reward studies led by Weill Cornell Medicine researchers, as well as a career enhancement program for junior investigators who seek to enter into the field of prostate cancer research.

The Weill Cornell Medicine SPORE grant has four major objectives:

- Develop accurate biomarkers to assess the risk of PCa disease progression
- Develop new therapeutic approaches for clinically localized and castrate-resistant prostate cancer

that are hypothesis-driven, based on newly acquired knowledge of PCa biology and genomics, and represent a paradigm shift in treatment

- Leverage existing and expand new infrastructure for the successful translation of preclinical studies into the clinic
- Train the next generation of PCa investigators

Himisha Beltran, MD, Associate Professor of Medicine at Weill Cornell and Director of Clinical Activities, IPM, serves as a co-leader of this important research endeavor that supports four innovative research projects focused on highly translational areas relevant to the detection and treatment of aggressive prostate cancer. A basic scientist and translational clinical investigator will lead each of the following projects.

- Non-Invasive Clinical Assay for Early Detection of Treatment Resistance in Patients with Metastatic Prostate Cancer
- Targeting N-Myc and EZH2-Driven Castrate-Resistant Prostate Cancer
- Toward Understanding Prostate Cancer Heterogeneity
- Targeting Genomic Instability in Distinct Subclasses of Prostate Cancer

Historic Gift for Cancer Care and Research

In November 2017, Columbia University and NewYork-Presbyterian announced that Florence Irving and her late husband, Herbert Irving, have given \$700 million to the two institutions to dramatically advance research and clinical programs for the treatment of cancer. The Irvings' historic gift will have a profound impact on research and clinical care.

The Irvings' extraordinary philanthropy will be felt across a wide range of scientific disciplines, including cancer genomics, immunology, computational biology, pathology, and biomedical engineering. A key focus will be to further advance cancer research and clinical care in Columbia's Precision Medicine Initiative, which, in partnership with NewYork-Presbyterian, is exploring the genetic and genomic basis of cancer and other life-altering diseases.

The Irvings' historic gift will have a profound impact on research and clinical care at a time when new scientific tools and techniques are enabling researchers and clinicians to better understand how cancer begins and grows and how to fight its spread.

Physical Sciences Oncology Network Supports Innovative Research

The National Cancer Institute's Physical Sciences in Oncology Network, comprised of 10 centers, funds research projects that bring together cancer biologists and oncologists with scientists from the fields of physics, mathematics, chemistry, and engineering to address some of the major questions and barriers in cancer research. Each center, among them Weill Cornell Medicine and Columbia University Medical Center, investigate complex and challenging questions in cancer research.

Researchers at Weill Cornell are interrogating the biological and physical mechanisms regulating tumor metabolism and function. Columbia researchers are undertaking projects in modeling tumor evolution.

New York State Department of Health Funds Clinical Researchers

In 2017, the New York State Department of Health granted \$13.8 million through its Empire Clinical Research Investigator Program (ECRIP) to 26 academic medical institutions, including NewYork-Presbyterian/Columbia University Medical Center and NewYork-Presbyterian/Weill Cornell Medical Center, to train physician researchers. The two-year awards fund research teams focused on a specific topic and enhance the ability of hospitals to seek additional funding from the federal government to advance their work.

At NewYork-Presbyterian, the two projects funded by ECRIP are *Optimization and Application of Precision Medicine Oncology in Cancer Care* at Columbia, led by Dr. Gary K. Schwartz, and *Improving Population Health Through Data Analytics: Identifying High Cost, High Need Patients Who Would Benefit from Care Coordination* at Weill Cornell, led by Rainu Kaushal, MD, Chair, Healthcare Policy and Research, Weill Cornell Medicine.

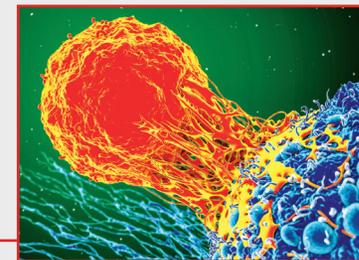
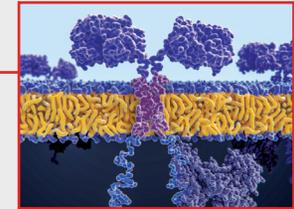
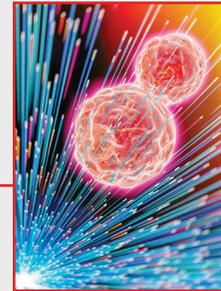
Dream Team Stands Up 2 Colorectal Cancer

Weill Cornell Medicine and NewYork-Presbyterian have been named to the Stand Up 2 Cancer (SU2C) Colorectal Dream Team to drive new advances in colorectal cancer research and treatment. The interdisciplinary team, funded by a grant of up to \$12 million, brings together researchers from four institutions who will focus on three complementary areas of research that have the potential to affect all stages of colorectal cancer, from premalignant lesion to patients diagnosed with metastatic disease. Dr. Lewis C. Cantley serves as co-leader of the SU2C Colorectal Dream Team.

Weill Cornell researchers will develop clinical trials in an effort to validate a 2015 discovery that a subset of colorectal cancers is sensitive to vitamin C therapy. About half of diagnosed cases of colorectal cancer each year harbor mutations in the KRAS and BRAF genes; these forms of the disease are more aggressive and do not respond well to current therapies. In a 2015 study, Weill Cornell researchers found in preclinical models that high doses of vitamin C impaired the growth of KRAS and BRAF mutant colorectal tumors. The SU2C grant will now enable the investigators to confirm their findings in human trials.

Innovations at a Glance

- Leading first-in-human administration phase 1 clinical trial of a CAR T-cell therapy for acute myeloid leukemia
- Determined how genes belonging to the human leukocyte antigen (HLA) system can play a role in the response to treatment with immune checkpoint inhibitors
- At the forefront of research demonstrating that local radiotherapy can contribute to immune rejection of cancer and defining the best application of ionizing radiation to stimulate the immune system
- Selected as one of only 16 clinical study sites in the U.S. and Canada, and the only one in New York, for the I-SPY trial program designed to accelerate the development and availability of new agents for patients with breast cancer
- Accelerating the identification of potential therapies for several cancer types through the development of patient-derived organoids
- Established a quantitative prediction initiative, which uses sophisticated algorithms to analyze genomic data and identify patterns and trends that may predict patients' future risk of developing cancer and other diseases, as well as potential outcomes
- Serving as international principal investigators of a phase 3 trial comparing PD-L1/CTLA-4 blockade to chemotherapy in advanced non-small cell lung cancer
- Initiated the first clinical trial in the United States evaluating a small molecule to treat men with progressive prostate cancer that has spread and is no longer responding to hormonal therapy
- Created a Good Manufacturing Practices cell production lab, one of the few available in the country with the capacity to grow and manipulate T-cells
- Engaging in investigations with the potential to develop therapeutic options for pancreatic cancer using genetically engineered mouse models, *ex vivo* organoid co-culture systems, and patient-derived organoid transplantation models



The mutation profile of a patient's cancer will not always predict whether or not it will respond to a specific drug. Additionally, clinical trials frequently are developed based on testing of cell lines in preclinical models, and often trials fail because cell lines in mice may not recapitulate what is occurring in a patient.

To reconcile these two challenges, researchers at Columbia University Medical Center and Weill Cornell Medicine are incorporating more clinically relevant model systems to test drugs that could reap more targeted benefits for patients. Specifically, they are growing organoids from patient tumors and adjacent normal tissue, which greatly narrow the field of drug testing and response for an individual patient with a particular tumor. Their work is taking cancer research in an extraordinary direction, and providing scientists and clinicians with the power to ask questions that they have never been able to ask before.

A Sea Change in Treatment Approach

With an organoid, you can try a thousand different drugs, which multiplies information about clinical response in a way that you can't do in a typical patient. Weill Cornell scientists in the Englander Institute for Precision Medicine seek to establish, using a very large number of organoids, connections between the presence of a mutation or other molecular alteration and a response to that particular molecule across tumor types that will fundamentally change routines when identifying better treatment options for patients. They will then be able to determine whether a particular alteration correlates with a response to a particular drug even in the absence of an obvious mechanistic connection.

Organoids and Genetics: A Powerful Combination

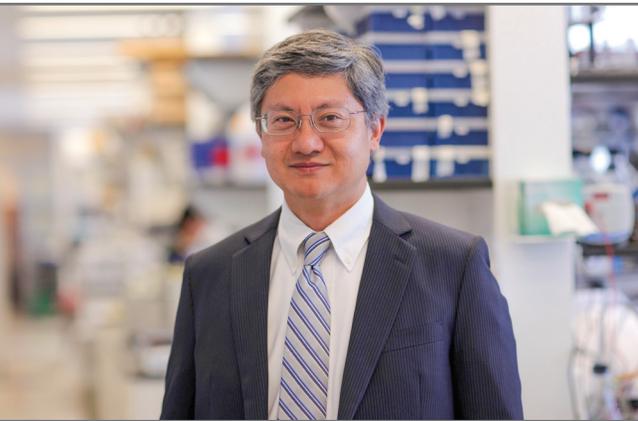
A study led by Weill Cornell investigators has shown that combining genetic information from a patient's tumor cells with three-dimensional cell cultures – tumor-derived organoids grown from these tumors – markedly accelerates the identification of potential therapies compared with current approaches. Published in the March 22, 2017, issue of *Cancer Discovery*, the study demonstrates the capability of growing a wide variety of tumors outside of the body, allowing researchers to not only obtain full exome and RNA sequencing data, but also to test a panel of approved drugs on the same tumor that is growing in the patient. Combining genome sequencing with rapid drug screening makes it possible to nominate new therapies for patients that could not have been predicted from the genomics alone.

ORGANOIDS IN DEMAND

Over the past several years, organoid models have grown in popularity for a number of reasons. These include the advantage of having a combined *in vitro* and *in vivo* system able to mimic much of the architecture of patient tissue in a histopathologically accurate manner, thereby overcoming some of the limitations associated with preclinical models.

In addition:

- the methodology allows for basic research to be pursued in terms of stem cell developmental biology as these are cell cultures that recapitulate much of the normal tissue architecture
- they enable researchers to grow cells in a dish from a patient tumor that captures many of the aspects of that tumor and reproduces the genomic alterations specific to that patient
- the platform supports the growth of not just malignant cancer cells from primary patient and mouse material, but it also supports the indefinite propagation of normal ductal epithelial cells
- the models allow scientists to potentially start thinking about applications in regenerative medicine, particularly if rare cell types that may be important in a given tissue can be recreated
- although similar in concept to patient-derived xenografts, patient-derived organoids are much easier to work with, and drug responses can be tested on a much larger scale and more economically
- with the ability to grow cells in an extracellular matrix that is reminiscent of what is present within the tumor, Weill Cornell and Columbia researchers are hopeful that the data over the next five to 10 years will be more physiologically relevant and useful in the development of therapies



Dr. Michael M. Shen

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“The real promise of approaches such as patient-derived organoids is that the organoids essentially are avatars of the patient tumor. If you want to pursue precision medicine, then having a system such as an organoid-based model greatly facilitates your ability to realize these concepts in a very practical sense.”

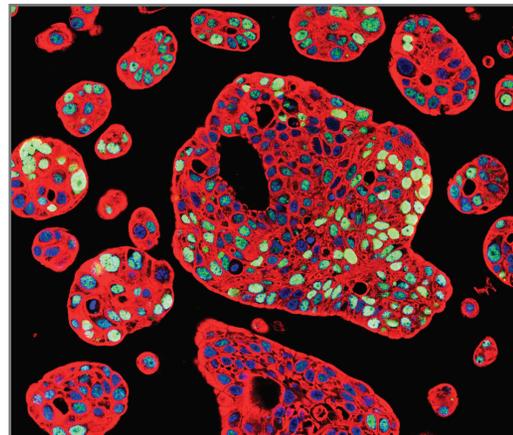
— Dr. Michael M. Shen

Current Models of Patient-Derived Organoids

Bladder Cancer For the past two years, scientists at Columbia have been generating organoid models of bladder cancer from human patient samples in collaboration with colleagues in the Department of Urology, applying approaches and concepts from stem cell and developmental biology to a translational problem. Modifying methodology that they developed for mouse prostate organoids, they have been able to grow human bladder organoids, recapitulating human bladder cancer at both the histological and molecular spectrums. To date, they have established 20 independent lines from patients with noninvasive and muscle-invasive bladder cancer that capture both common and rare mutational events.

The researchers also interconvert the organoids and patient-derived xenografts (PDX). For example, to validate drug responses observed in a dish, they convert the organoids into xenografts to determine if the same result is achieved in a mouse.

Their next step is to pursue co-clinical trials with physicians in which organoids will be created from patients enrolled in the clinical trial. Both the patient and the organoid will be treated with the same drug to answer whether the responses observed with the organoids in the laboratory resemble the patient responses to the same drug. This type of co-clinical trial could be extremely informative and necessary in order to make treatment predictions based upon work on organoids. In the case of bladder cancer, the organoids can be tested with a panel of compounds already FDA approved.



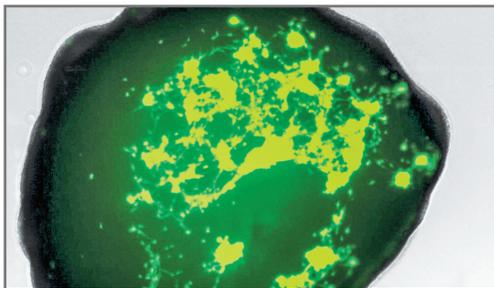
Immunostaining for p53 (green) and cytokeratin 8 (red) with nuclear counterstain (blue) in patient-derived human bladder tumor organoids (Courtesy of Dr. Michael M. Shen)

Colon Cancer A research team at Weill Cornell has developed the first stem-cell-based large intestine tissue system for modeling human colon disease for drug testing. Through a variety of steps, including genomic DNA sequencing and gene expression profiling, the investigators were able to grow large intestine cells with two different FAP mutations, FAP8 and FAP9. They also determined that the gene, APC, which, when mutated, allows FAP cells to grow out of control, was inactivated. For comparison, the team created colonic organoids using stem cells derived from a person without FAP.

When the researchers tested the colonic organoids with drugs to measure response, they found that XAV939 and rapamycin significantly curbed cell proliferation, but they also had the potential to harm healthy colon tissue. A third drug, geneticin, successfully restored normal growth in the FAP9 organoids, yet had no impact on the FAP8 or healthy control organoids. Their results demonstrate that this platform can be used to model colon cancer and identify precision medicines that may work to target specific genetic mutations driving the disease.

Gliomas For decades scientists have tried to model malignant brain cancers using patient-derived tumor cell lines cultured in lab dishes or human tumor cells implanted into the brains of mice. These traditional approaches have not been sufficiently representative of clinical disease, a major reason for the lack of success therapeutically. To address this, Weill Cornell researchers are using advanced stem cell techniques to grow cerebral organoids – large clusters of functional and interconnected human brain cells – in the laboratory.

With cerebral organoids, the research team is able to observe the physical networks of microtube structures that connect the individual tumor cells of some gliomas. The networks appear to have a profound impact on the ability of these tumors to resist chemotherapy and radiation. In October 2017, renowned neuro-oncologist Howard A. Fine, MD, Director of the Brain Tumor Center at NewYork-Presbyterian/Weill Cornell Medical Center, was awarded a five-year, \$6 million National Institutes of Health Director’s Pioneer Award for brain cancer research. With this support, Dr. Fine and his Weill Cornell colleagues are now working on enhancing the realism of their organoid models by adding two vital components: blood vessels with key properties of cerebral vessels and immune cells that normally reside in or can enter the brain.



A brain organoid infiltrated by glioblastoma cells (green) from a patient (Courtesy of Starr Foundation Cerebral Organoid Translational Core at Weill Cornell Medicine)



Dr. Howard A. Fine

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“We’ve found, for example, that if we co-culture glioma stem cells from patients with these organoid mini-brains, the glioma stem cells burrow into the mini-brains and begin to grow in a pattern that looks 100 percent like what happens in the patient’s own brain.”

— Dr. Howard A. Fine

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“We created a facility we call the ‘mouse hospital,’ which is used to study drug mechanisms and efficacy in pancreatic cancer. Ultimately, the idea is that the drugs graduate from the mouse hospital and go into the human hospital.”

— Dr. Kenneth P. Olive

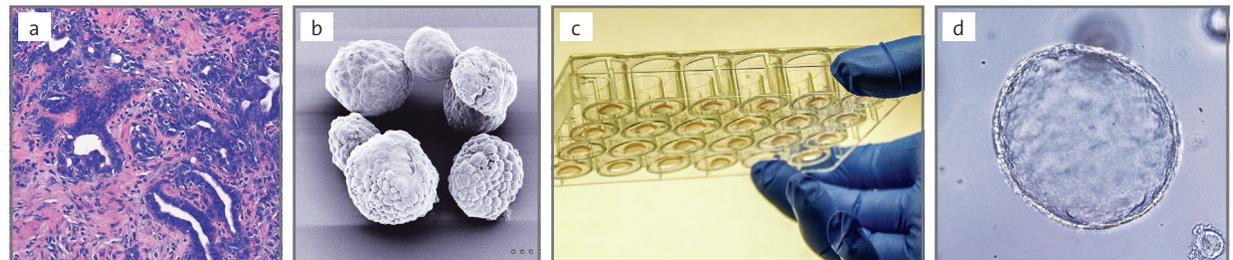
Pancreatic Cancer Targeting therapeutics for pancreatic ductal adenocarcinoma is particularly challenging because 80 to 90 percent of the tumor mass is fibrous tissue, making it very difficult to study the biology of the cancer cells. There is ample evidence in the literature that an organoid culture system supports the proliferation of normal and malignant primary pancreatic ductal cells of both mouse and human origins.

Columbia scientists have established a pancreatic cancer research laboratory pursuing translational therapeutics with a laser focus on pancreatic ductal adenocarcinoma (PDA). R01-funded investigations include studies in genetically engineered mouse models to determine the efficacy of drugs and their mechanisms of action in pancreatic cancer and building a related clinical trials program at the phase 1 and phase 2 levels.

In collaboration with computational biologists, the researchers are developing datasets for pancreatic cancer that have not existed in the public sphere and which are already beginning to inform nearly every aspect of their experiments. Their goal is to deploy a precision medicine framework for the treatment of PDA incorporating patient-derived organoids.

Comprehensive analysis of murine pancreatic organoids has revealed genes and pathways that have been altered during the progression of pancreatic cancer. Many of these protein changes have been confirmed in human tissues, demonstrating that organoids provide a practical system for examining the molecular and cellular properties of neoplastic progression in mice and humans. The underlying chemical dynamics of pancreatic cancer have already been uncovered in research conducted by Christine Chio, PhD, a Columbia scientist, during her postdoctoral research fellowship in the Tuveson Lab of Cold Spring Harbor Laboratory.

Columbia researchers are currently engaged in a number of investigations with the potential to develop therapeutic options for this lethal disease using genetically engineered mouse models, *ex vivo* organoid co-culture systems, and patient-derived organoid transplantation models. They will use these models to establish a discovery pipeline and *in vivo* validation platforms that will facilitate the design of integrated intervention strategies for pancreatic cancer and address the complex interactions between the tumor and the stroma.



a) H&E staining of pancreatic tumor b) Electron microscopy of organoid c) Organoids plated as Matrigel domes in 24 well plate d) Bright field image of organoid in culture (Courtesy of Dr. Christine Chio)

NCI-MATCH Trial

NewYork-Presbyterian participates in the National Cancer Institute-based MATCH trial and is represented on the program's Executive Committee. A nationwide effort to sequence 7,000 patients with different types of cancer across the country, MATCH is a precision medicine cancer treatment clinical trial in which patients are assigned to receive treatment based on the genetic changes found in their tumors through genomic sequencing and other tests. Now near completion, the MATCH trial has identified 30 different drugs correlated to the different genes of patients, making it possible for patients anywhere in the country to have access to treatment specific to the genetic makeup of their tumor.

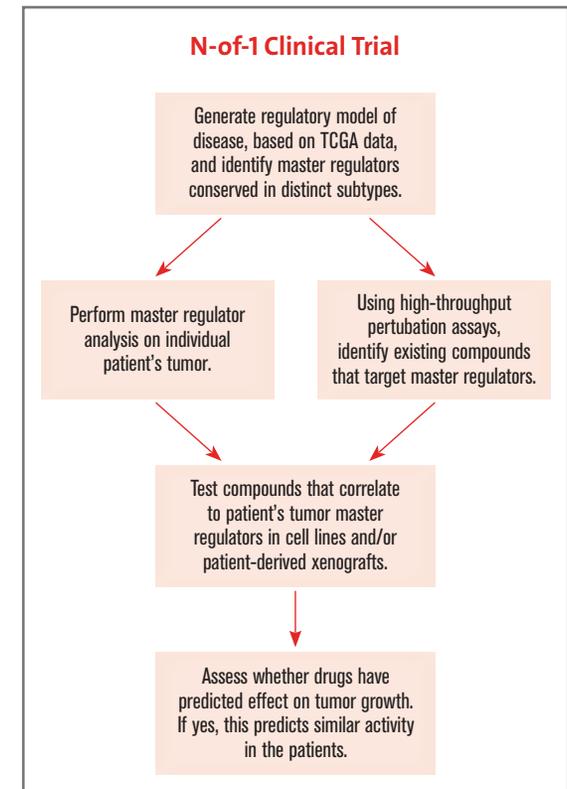
The NCI-COG Pediatric MATCH launched in July 2017 with two of the eight treatment arms of the program led by Columbia physicians.

Building on Mutation-Based Therapy

With the keen awareness that mutation-based therapy does not yet have a widespread application to cancer care, the need for a more comprehensive strategy in cancer treatment has emerged throughout the field. Researchers at Columbia are now exploring RNA-based, systems biology approaches that significantly complement the strength of therapeutic programs and collaborations at Columbia based both on mutational analysis – with its focus on whole-genome DNA sequencing – and on immuno-oncology.

Their work builds on the increasing success of their N-of-1 trial program in which FDA-approved and other clinically relevant investigational compounds are being prioritized based on their effectiveness in blocking master regulator proteins responsible for tumor state maintenance. Conducted in individual patients, who are progressing after multiple lines of standard-of-care therapy, these clinical trials have been exploratory in nature to determine the specific genetic and molecular factors that are essential for a cancer's growth in a single patient.

N-of-1 trials currently underway or in development at Columbia target 14 adult human malignancies, from metastatic prostate, ovarian and breast cancers to glioblastoma and anaplastic meningioma, and are being extended to pediatric tumors, starting with sarcomas. Critically, the two technologies they developed to support these studies, OncoTarget and OncoTreat, recently received New York State Department of Health CLIA certification and are available for clinical studies through the Columbia Department of Pathology and Cell Biology.



(Courtesy of the Califano Lab)



Dr. Andrea Califano

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“To make real progress, we need to complement current data-driven methodologies that are focused primarily on genetic mutations with mechanism-based models that will help us exploit cryptic faults in the computer-like logic of the cancer cell.”

— Dr. Andrea Califano

To address a particular hurdle in these trials in which patients are referred at an advanced stage of their disease, generally following failure of several other therapies, the researchers are now collaborating with clinicians specializing in ovarian and breast cancer to use the algorithm in the neoadjuvant phase when the tumor is still very vulnerable. Another challenge is getting access to specific drugs prioritized by the study. To address this issue, the researchers are now looking at the N-of-1 study as a potential pre-selection phase for enrollment into a second, more traditional clinical trial where the patient will be able to receive the specific drug.

At this point in time, the Columbia researchers note that there are only 24 master regulator modules (dubbed tumor checkpoints) that cover key dependencies of about 20,000 patients whose samples have been collected by The Cancer Genome Atlas (TCGA), for which RNA and DNA profiles are already available. Buoyed by this information, an enormous amount of progress has been made in the clinic. For example, in the N-of-1 trials 34 drugs were predicted by two algorithms developed at Columbia – OncoTarget™ and OncoTreat™ – for patients who had failed from three to seven lines of therapy and were considered terminal. When the drugs were tested in direct mouse transplants of the human tumor, 20 of the 34 drugs induced an objective response, resulting in either stable or reduced tumor volume. Of four patients who could receive one of the drugs predicted by the analysis, three had a clinical response.

OncoTarget

This core, New York State Department of Health CLIA certified test systematically assesses whether any of more than 100 proteins for which a targeted drug already exists are aberrantly activated in a patient-specific tumor sample independent of the tumor’s DNA mutational state.

OncoTreat

This core, New York State Department of Health CLIA certified test systematically prioritizes FDA-approved drugs and investigational agents for a patient-specific tumor. This is accomplished by aligning their tumor-specific activity against the full repertoire of master regulator proteins that represent the “engine room” (tumor checkpoint) of a patient-specific tumor. OncoTreat is currently being deployed in clinical trials at leading cancer research centers.

Application to Pediatrics The pediatric oncology program at NewYork-Presbyterian/Columbia is one of the front-runners nationally instituting and implementing real-time precision oncology for patients, including the establishment in 2014 of a precision in pediatric sequencing program called the PIPseq Cancer Program. Through PIPseq, every child with a high-risk cancer that comes to Columbia undergoes whole-exome sequencing; the patient's tumor also undergoes RNA-seq analysis. In 2016, the Columbia program received funding from the Sohn Conference Foundation to provide this clinical testing to any child with a high-risk cancer in the New York, New Jersey, Connecticut area.

The comprehensive platform includes an assessment of the genes that code for proteins in both a patient's tumor and normal tissue. Tumor-specific genomic alterations can be identified, providing clinicians with information on cancer variance, cancer-specific mutations, copy number variations, translocations and fusions, and gene expression data, as well as a window into inherited cancer predisposition should families choose to learn this information. In 2018, the program will start integrating the OncoTarget and OncoTreat methodologies originally developed for the adult N-of-1 program. Columbia is among only a handful of institutions nationwide providing this type of platform for pediatric patients.

As of spring 2017, 250 patients have been tested. Potential targets were found in about 40 percent of patients; information of diagnostic significance in about 15 percent of patients; and a germline predisposition in about 14 percent of patients. Overall, the testing revealed something that was clinically impactful in about two of every three patients.

Under Columbia's Developmental Therapeutics Program for Pediatrics, 20 to 30 phase 1 and 2 clinical trials are enrolling patients at any one time to provide access to the drugs identified as relevant.

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“Through NewYork-Presbyterian/Columbia's pediatric sequencing program, every child with a high-risk cancer that comes to Columbia undergoes whole-exome sequencing; the patient's tumor also undergoes RNA-seq analysis. Half of the clinically applicable findings have come from the expression data; applying OncoTarget and OncoTreat will add validity and depth to the analysis.”

— Dr. Julia L. Glade-Bender



Dr. Bishoy M. Faltas

Evolution of Urothelial Carcinoma

Researchers at Weill Cornell have identified how selective pressure from chemotherapy directs the evolution of urothelial carcinoma and shapes its clonal architecture – a key biological question with clinical implications. Their whole-exome sequencing analysis of the clonality of 72 urothelial carcinoma samples, including 16 matched sets of primary and advanced tumors that were prospectively collected before and after chemotherapy, provided the following insights:

- chemotherapy-treated urothelial carcinoma is characterized by intra-patient mutational heterogeneity, and the majority of mutations are not shared
- branching evolution and metastatic spread are very early events in the natural history of urothelial carcinoma
- chemotherapy-treated urothelial carcinoma is enriched with clonal mutations involving the L1-cell adhesion molecule and integrin signaling pathways
- APOBEC-induced mutagenesis is clonally enriched in chemotherapy-treated urothelial carcinoma and continues to shape the evolution of urothelial carcinoma throughout its lifetime

Their findings demonstrate that advanced, chemotherapy-treated urothelial carcinoma undergoes extensive and dynamic clonal evolution throughout the lifetime of the tumor, with significant genetic editing that continues during and after chemotherapy. This information provides a foundation for an evolutionary understanding of advanced, chemotherapy-treated urothelial carcinoma with opportunities for advancing cancer precision medicine.

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“We demonstrated that a complex and dynamic interplay between mutagenic mechanisms and extrinsic selective pressures constantly shapes the clonal evolution of urothelial carcinoma.”

— Dr. Bishoy M. Faltas

Columbia Combined Cancer Panel

The Columbia Combined Cancer Panel (CCCP), which is approved by the New York State Department of Health, is one of the few such clinical oncology panels in the New York area. A sequencing-only test, the CCCP was designed in collaboration with Columbia oncologists and is conducted within Columbia University Medical Center's Personalized Genomic Medicine CLIA-certified clinical genomics laboratory.

This panel queries 467 cancer-related genes and is a critical assay for our mission to deliver the highest quality of cancer care to our patients. By routinely profiling the tumors of patients with advanced malignancies, we more completely understand the unique biology of each tumor and have the ability to tailor care appropriately. Through our Experimental Therapeutics Clinic, we have access to approved and investigational targeted therapies that would be predicted to be effective for our patients based upon the molecular profile of their disease, and thus we are now truly able to deliver precision oncologic care to our patients.

Single-Cell Omics

At Weill Cornell, researchers have integrated genome sequencing into the care of cancer patients. They are now pursuing a better understanding of cancer through the behavior of single cells and integrating single cell transcriptomics in their precision medicine workflow. Their work involves leveraging new technologies to analyze clinical samples and visualize various diseased tissues at single-cell resolution and to isolate and sequence the genes that are expressed within individual cells across thousands of tumor and non-tumor cells.

By dissecting the complexity of the immune cells and different types of immune cell populations within tumors and determining how they interact with tumor cells, the researchers can rapidly diagnose patients and predict which treatments might work. These include treatments that may use the immune system to kill cancer cells, which treatments may encounter resistance, and how the disease is likely to progress.

The researchers are also developing new precision medicine technologies that examine DNA and cells from a blood draw or urine sample from one patient, predict his or her future risk for developing a specific type of cancer, or reveal presence of a hidden tumor.



The CCCP uses the Illumina HiSeq2500 platform, a sequencing-only test, to query 467 cancer-related genes.



Dr. Olivier Elemento

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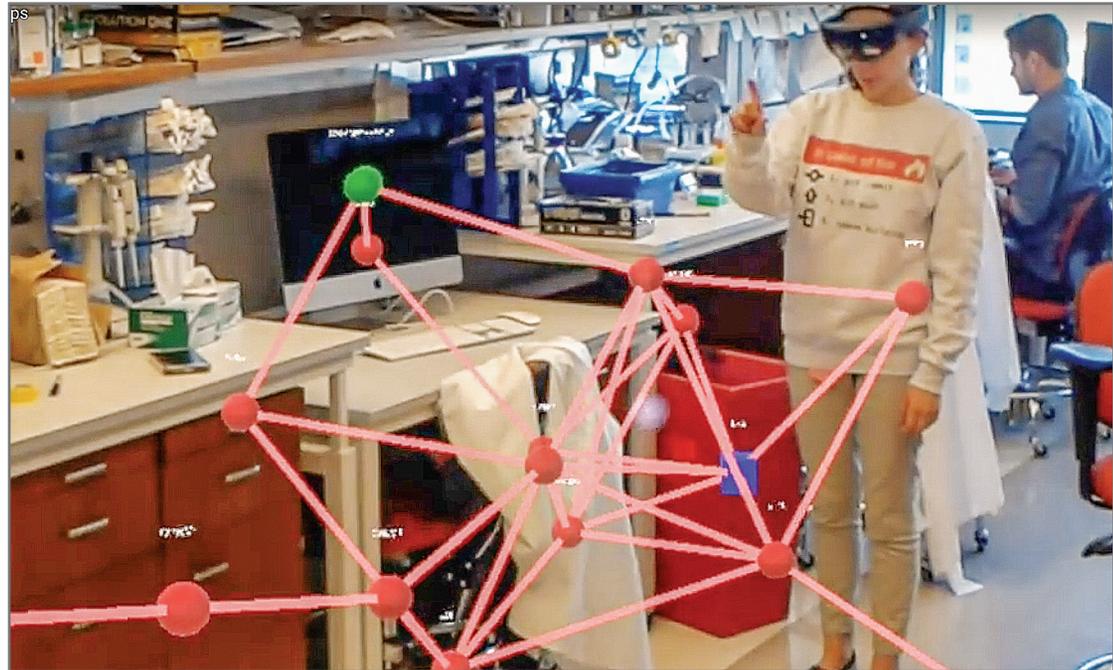
“To me, cancer genomics is a way to understand and get a complete picture of what is happening in a tumor at a given time point. Systems biology essentially is an attempt at building mechanistic models to predict how the system will behave when, for example, exposed to a particular treatment or a particular combination of drugs.”

— Dr. Olivier Elemento

Exploring Complex Datasets

In the world of cancer genomics and systems biology, it is very difficult to visualize what is being measured. Artificial intelligence can be used as a way to make connections between genomics, single-cell measurements, and responses to therapy. By combining and integrating all of the different types of information, you can then make an accurate prediction.

Researchers at Weill Cornell have begun to embrace the concept of augmented reality, using tools that allow them to position complex medical objects in the real world that provide a perspective that cannot be accomplished by projecting information on a screen. The technology is designed to help scientists explore how to better visualize very complex datasets about cancer tumors and synthesize and present this information in a way that can facilitate the development of relevant hypotheses and ideas about data.



Augmented reality glasses enable researchers to navigate very complex datasets, including cancer drug networks and cancer mutations on protein structures. These 3-D images behave the same way real objects do, causing the digital images to blend in seamlessly with the real world.

While several immune checkpoint blockers have achieved unprecedented clinical success and been approved for the treatment of a growing number of malignancies, it has become increasingly evident that immunotherapy has its limitations in treating the greater population of patients with cancer. This has led to a shift in focus from single arm immune-based therapies to the development of combination treatment regimens.

Clinician-researchers at Columbia and Weill Cornell continue to make headway in understanding the role of the immune system in tumor immunogenicity, pursuing research to better understand the processes that promote tumor growth and exploiting the influence of the immune system to recognize and eradicate cancer cells. Clearly, immune checkpoint inhibitors can restore the immune system's recognition of cancer cells and have led to dramatic responses in a number of cancer types. Our researchers are now seeking a better understanding of why and when the responses are less than satisfactory and exploring approaches that can further advance the application of immunotherapeutics.

Clearly, immune checkpoint inhibitors have led to dramatic responses in a number of cancer types. Our researchers are now seeking a better understanding of why and when the responses are less than satisfactory.

Tumor Genetics Dictate Immunotherapy Response

NSCLC: Identifying the Source of Sensitivity and Resistance With the observation that tumor types that responded to immunotherapy were those expected to have the most DNA damage, such as tobacco carcinogen-related lung cancer and UV light damage-related skin cancers, Columbia scientists postulated that these tumors have a significant burden of foreign proteins that were not being recognized.

They further postulated that restoring T-cell responses with immunotherapy would activate tumor rejection. Sequencing the exomes of tumors from patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab, the researchers showed those with a higher nonsynonymous mutation burden exhibited improved durable clinical benefit. They also were the first to demonstrate a CD8+ T-cell response to a predicted neoantigen in peripheral blood that paralleled response to anti-PD-1 therapy and contributed to immunotherapy resistance (*Science* 2015).

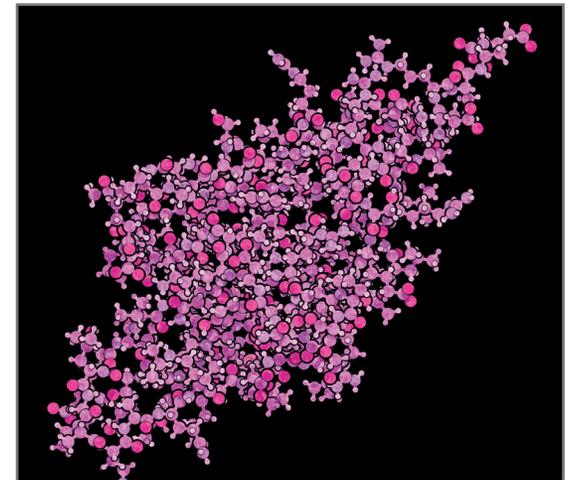


Illustration of programmed cell death 1 (PD-1) receptor protein, a major cancer drug target



The HLA Role in Tumor Response Given the important role of somatic mutation landscape in response to immunotherapy has now been well-established, investigators at Columbia, in collaboration with Memorial Sloan Kettering Cancer Center investigators, recently studied the impact of a patient’s HLA genotype on response to immunotherapy.

Major histocompatibility complex (MHC) class I and class II proteins play a pivotal role in the adaptive branch of the immune system. The human MHC is also called the HLA (human leukocyte antigen) complex. Both classes of proteins share the task of presenting peptides on the cell surface for recognition by T-cells. The main function of the MHC gene is clearing infection and thereby survival of species. HLA class I genotype has been repeatedly associated with modulating the immune response during bacterial or viral infection, inflammatory conditions, and autoimmune diseases. A population with diverse alleles of HLA classes I and II leads to resistance to infection and a survival advantage.

Prior to this study, there has been very little understanding of the relationship between an individual’s HLA composition and response to checkpoint inhibitors. The study looked at 1,535 cancer patients treated with checkpoint inhibitors and found that patients who had greater heterozygosity of HLA class I genes responded better to immune checkpoint inhibitor therapy. Patients with greater HLA class I homozygosity and low tumor mutation burden do not respond as well with immune checkpoint inhibitors as compared to patients with greater HLA heterozygosity and high tumor mutation burden. Finally, certain HLA “supertypes” or “supermotifs” affected survival as well, as observed in patients with certain autoimmune diseases (*Science* 2017).

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“We first demonstrated tumor somatic mutation burden dictated response to immunotherapy. We more recently demonstrated that patients who had a greater diversity of HLA genes responded better to immunotherapy. We are assembling multiple pieces of a genetic puzzle to create a precise framework that we can use to determine why patients do and do not respond to immunotherapy.”

— Dr. Naiyer A. Rizvi

Ionizing Radiation: Making the Tumor Its Own Worst Enemy

Researchers in the Department of Radiation Oncology at Weill Cornell are at the forefront of investigations demonstrating that local radiotherapy can contribute to immune rejection of cancer. Through a mechanism called the abscopal effect, some patients with metastatic tumors who receive radiation to one metastatic site and immunotherapy can reject other metastases that were not irradiated. The effects are superior to that of immunotherapy alone.

The researchers were the first to introduce the idea to use ionizing radiation during immunotherapy to convert the tumor to an *in situ* vaccine, individualized and capable of immunizing the patient against micrometastases or established metastases.

An important research finding that has emerged in the last six months at Weill Cornell is the convergence of the DNA damage response with the immune system, particularly in tumors treated with DNA-damaging agents such as radiotherapy or platinum compounds.

Building on concurrent laboratory work, the research team is refining how to enhance the abscopal effect by studying the immunological effects of radiotherapy.

Four investigator-initiated clinical trials are open and three others will soon be evaluating the combination of ionizing radiation and immunotherapy for specific tumor sites.

This work is making important strides in defining an additional role for ionizing radiation in cancer therapy – one in which it enhances the clinical benefit of current immunotherapy agents.



Dr. Silvia C. Formenti

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“With immunotherapy acquiring an important role in the management of most cancer patients, it is very exciting to be able to converge radiotherapy as a powerful adjuvant to this approach.”

— Dr. Silvia C. Formenti



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“Our goal is two-fold: first – to develop novel immunotherapy and targeted combinations in the laboratory, and second – to translate these findings into clinical trials for pancreas cancer patients with a goal of enrolling a majority of patients seen at Columbia onto these trials.”

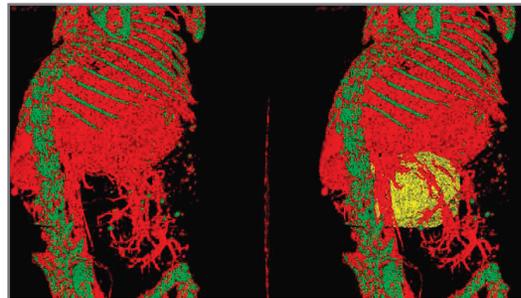
— Dr. Gulam A. Manji

Pancreatic Cancer: Pathways to Progress

Columbia researchers are conducting preclinical combination immunotherapy studies on genetically engineered mice with pancreatic cancer, which unlike other cancers, in most cases does not respond to mono-immunotherapy. It is thought that the highly immunosuppressive tumor microenvironment within pancreas cancer does not allow immunotherapy to be effective as a single agent.

Their goal is to better understand the mechanisms underlying this strong immunosuppressive tumor microenvironment in the pancreas, and identify unique pancreatic ductal adenocarcinoma (PDAC) subtypes, which may allow immunotherapy to produce a therapeutic benefit. Additionally, by identifying distinct immunosuppressive pathways, personalized combination therapies targeting these pathways could make immunotherapy more effective.

In the first phase of a large seven-arm immunotherapy combination study in mice, the researchers identified an immunotherapy combination that resulted in decreasing the rate of tumor growth and allowed the mice to live longer. This new promising combination is being considered for testing in human pancreas cancer patients in a new clinical trial.



Utilizing the PerkinElmer Quantum FX micro-CT, researchers have many imaging options, enabling them to see, for example, the entire vascular system of a mouse abdomen. In this image, an abdominal tumor is revealed (yellow) that left a void in the abdominal vasculature.

A Novel Clinical Trial Platform In mid-2017, Columbia became the first site internationally to open and enroll patients onto a new clinical trial design (MORPHEUS), which tests different immunotherapy combinations in pancreatic cancer. The multicenter trial involves testing experimental combinations with an adaptive design platform by F. Hoffmann-La Roche. The approach facilitates the investigation of distinct immunotherapy combinations based on the current understanding of pancreatic cancer biology and immunotherapy. The researchers are hopeful that the study will bring the benefits of cancer immunotherapy to bear on pancreatic cancer and allow for rapid testing of multiple combinations within a single clinical trial.

Early Stage Lung Cancer: A Tripartite Treatment Approach

In an effort to increase response rates to immunotherapy with single agent immune checkpoint blockade, the emerging trend is to combine two immunotherapy drugs, each blocking a different checkpoint. This combinatorial strategy, though scientifically valid, has been associated with an increase in the side effect profile. Therefore, there is a need to investigate alternative methods that enhance the effects of immunotherapy without a significant increase in side effects. One such approach, currently under investigation by Weill Cornell researchers, is to combine immune checkpoint blockers with low dose radiation – not to kill cancer cells, but rather to reprogram the immune cells within the tumor and produce a more vigorous anti-tumor response.

To this end, they are currently conducting an investigator-initiated, window-of-opportunity clinical trial in patients with early stage lung cancers who would ordinarily be treated with surgery or chemotherapy followed by surgery. In this trial, prior to surgery patients are given a very small dose of radiation combined with the immune checkpoint blockade. Following surgery to remove the tumor, treatment with the immune checkpoint alone is continued for one year. Having access to the tissues before and after surgery makes it possible to examine the tumor for evidence of a cancer-killing immune response and to discover biomarkers that would be useful in future refinements of this approach.

The researchers are cautiously optimistic about the results shown in both animal models and patients with lung cancer. The approach has the potential to be practice changing – since it utilizes radiation at much lower doses than is common practice with much lower frequency of side effects. Their hope is that this will redefine the role of standard anti-cancer treatments such as high-dose radiation therapy used for cancer-killing to low dose immune-modulating radiation. Weill Cornell researchers will also investigate serial measurements of circulating tumor DNA as a real-time marker of response to treatment.

Bladder Cancer: A Bold New World

For some 30 years, there had not been any drugs beyond chemotherapy approved for second-line treatment of bladder cancer. In the last two years, the FDA has approved five immuno-therapeutic agents, yet the challenge to treat bladder cancer remains. Among patients treated with any of these five new drugs, only one out of five will respond. Bringing together experts in precision medicine, immunology, and genitourinary oncology, Weill Cornell's world-class bladder cancer research program encompasses a multidisciplinary team of physician-scientists who span the basic, translational, and clinical research arenas. The cornerstone of the program is a basic science laboratory, one of the few in the country dedicated to bladder cancer research. It is supported, in part, by a prestigious grant awarded to Bishoy M. Faltas, MD, from the Department of Defense's Congressionally Directed Medical Research Program, which for the first time has added bladder cancer to its list of fundable areas.

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“This trial, if early results are confirmed, has the potential to redefine the role of standard cancer therapy from cancer-killing to immune modulation.”

— Dr. Nasser K. Altorki

Dr. Faltas is an oncologist in the Genitourinary Oncology Program in the Division of Hematology and Medical Oncology at Weill Cornell. The work of the laboratory focuses on understanding the biology of the disease as the key to progress in identifying the next generation of therapeutic advances for patients with bladder cancer.

One of the research initiatives is focusing on the biology of the APOBEC3 family of proteins. A pattern of mutations ascribed to these proteins was found to be enriched in bladder cancer patients who have had chemotherapy and could be driving resistance to chemotherapy in the advanced stages of bladder cancer. Dr. Faltas is now testing whether these proteins play a role in editing the DNA of bladder cancer cells to cause mutations that drive chemotherapy resistance over time.

The hypothesis is that chemotherapy drugs cause breaks to form in double-stranded DNA, exposing single strands of DNA during the repair process. These exposed strands are then bound and mutated by the APOBEC3 proteins in bladder cancer cells. Ongoing studies in the new bladder cancer research program will dissect the mechanisms that drive the evolution of bladder cancer and resistance to therapy with the ultimate goal of translating these results to new treatments for patients.

CAR T-Cell Therapy: Genetically Engineering Attack Cells

Columbia and Weill Cornell researchers have conducted significant foundational work in T-cell-based cancer treatments in the lab and with patients, with the goal of bringing T-cell therapies to patients with a wide range of cancers. Chimeric antigen receptor (CAR) T-cell therapy is one such approach, engaging an individual's own immune cells to treat cancer, and, in particular, hematological malignancies. In CAR T-cell therapy, T-cells are obtained from the patient and with genetic engineering, these cells are trained to identify, attack, and kill cancer cells. With the first ever FDA approval for a CAR T-cell therapy, (CTL019), in August 2017 for children and young adults with relapsed or refractory β -cell acute lymphoblastic leukemia, interest in this first-in-class therapy has intensified.

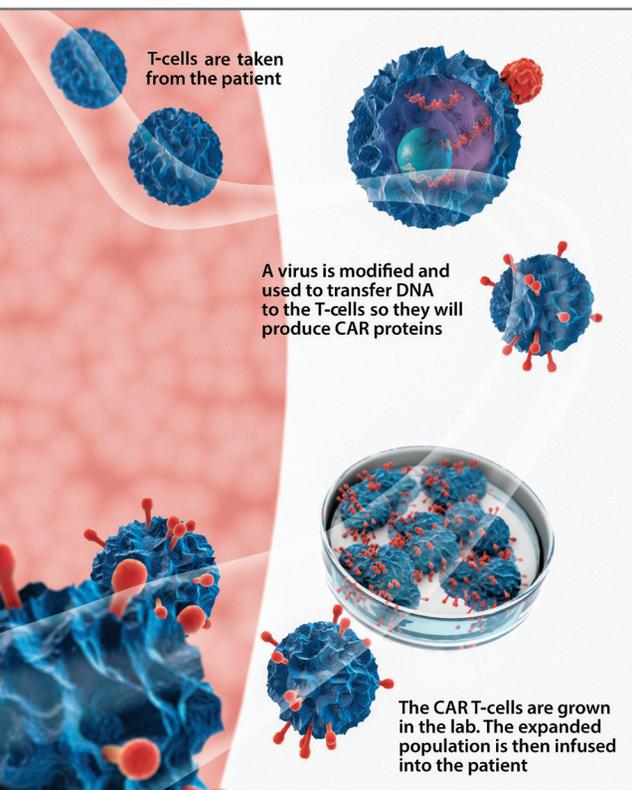


Illustration of the stages involved in CAR (chimeric antigen receptor) T-cell immunotherapy

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“NewYork-Presbyterian/Columbia is among the medical centers selected to offer the recently approved CAR T-cell therapy to children and young adults, and several physicians have been trained in understanding the risks associated with infusion of CAR T-cells and how to appropriately manage them.”

— Dr. Prakash Satwani

Targeting AML The first-in-human administration of UCART123 in acute myeloid leukemia (AML) is underway in a phase 1 clinical trial at Weill Cornell Medicine. This marks the first allogeneic, “off-the-shelf” gene-edited CAR T-cell product candidate targeting CD123 to be investigated in clinical trials. The clinical trial will investigate the safety and efficacy of UCART123 in patients with AML, a devastating clonal hematopoietic stem cell neoplasm characterized by uncontrolled proliferation and accumulation of leukemic blasts in bone marrow, peripheral blood and, occasionally, in other tissues. These cells disrupt normal hematopoiesis and rapidly cause bone marrow failure.

While complete response rates can be as high as 80 percent in younger patients who undergo initial induction cytotoxic chemotherapy, the majority of AML patients relapse and die from the disease. AML patients with high-risk genetic features have an especially urgent unmet medical need, as their outcomes are dismal with all existing treatment modalities. Weill Cornell researchers are hopeful that this novel immunotherapy modality will prove to be a significant and effective weapon against AML.

Potential for Advanced Thyroid Cancer In the first demonstration of the potential for CAR T-cell immunotherapy for previously untreatable anaplastic thyroid cancers (ATC), researchers at Weill Cornell were able to eliminate cancerous cells in cultures and mice. Investigators are now hoping to validate their findings in human trials in 2018. Targeting the intercellular adhesion molecule-1 (ICAM-1), which has an increased expression in ATC tumors, Irene M. Min, PhD, Assistant Professor of Molecular Biology Research in Surgery, harvested T-cells from human patients and encoded the cells to seek out ICAM-1 to attack the tumor (*Clinical Cancer Research* 2017). The researchers found that a single dose on thyroid cancer cells in a mouse model mediated significant tumor killing with a 100-fold reduction in primary tumor burden compared to pre-treatment.

The ICAM-1 CAR T-cells were also injected into mice engrafted with human tumor samples. The tumors were in most cases completely eliminated and the mice thrived, with no significant toxicity, presenting an opportunity for patients with advanced thyroid cancer who have no other options. The researchers noted that high expression of ICAM-1 has also been observed in many other cancers, and linked to metastasis, so the implications of the study could be far reaching. In collaboration with Moonsoo Jin, PhD, Associate Professor in the Department of Radiology, a lower affinity of CAR T-cells to ICAM-1 were developed to make them more selective to cancer cells with limited off-target toxicity (*Scientific Reports* 2017). The researchers teamed up with Thomas J. Fahey, III, MD, Director of the Endocrine Oncology Program at Weill Cornell, along with hematologists, radiologists, and other clinicians to develop a phase 1 clinical trial.



Dr. Gail J. Roboz

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“The CAR-modified T-cells are engineered in the laboratory and then infused into a patient. These enhanced cells are designed to recognize and attack stem cells harboring the CD123 antigen, which is present on AML blast and stem cells.”

— Dr. Gail J. Roboz



Dr. Manish A. Shah

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“It often takes decades for cancer to emerge, so there is a long window in which to intervene; understanding the role the bacteria may play could help us devise new prevention and treatment strategies.”

— Dr. Manish A. Shah

Confronting Solid Tumors

Vitamin C Takes on the KRAS Gene About 40 to 50 percent of colon cancers have a mutation in the RAS pathway, which includes the KRAS, NRAS, and BRAF genes. A mutation in this pathway makes the disease more aggressive and less likely to respond to current therapies. With support from Stand Up 2 Cancer, Weill Cornell researchers have begun a clinical trial to validate their earlier lab findings in cell culture and in mouse *in vivo* studies that showed that high doses of vitamin C impaired the growth of KRAS mutant and BRAF mutant colorectal tumors. In fact, by taking advantage of the metabolic derangements caused by their specific cancer mutations, high doses of vitamin C were specifically lethal to KRAS mutant or BRAF mutant colon cancer models.

The phase 2 pilot study evaluates high dose intravenous vitamin C in two cohorts. The first cohort is of patients with resectable solid tumor malignancies likely to harbor mutations in KRAS or BRAF – for example, colon, pancreatic, and lung cancers – about to undergo surgery. Tumor samples collected during their surgery will undergo extensive genetic sequencing and molecular characterization, including development of organoid models. The organoids will be treated with vitamin C *ex vivo* to see if the response replicates the patient response and to determine, by manipulating the organoids, if they can overcome resistance as well.

Patients with metastatic refractory KRAS or BRAF mutant tumors make up the second cohort. They receive the same infusion of vitamin C for up to six months, with a three-month check to evaluate disease response. Information from both cohorts will be used to determine how patients with KRAS and BRAF mutations responded to treatment compared to those without those mutations. If a clinical benefit is indicated, additional trials will be designed to determine optimal efficacy and dosage, and to compare therapeutic results against other treatments, such as current chemotherapy-based standard-of-care or combination therapy.

A Microbiome Context Weill Cornell researchers are pursuing a better understanding of the gastrointestinal microbiota, evaluating the relationships among microbiome composition, host immune response, and genomic characterization. Using whole-genome sequencing of endoscopic biopsy samples from 87 people, they compared the bacterial makeup of those with a history of *H. pylori* infection – including those who were treated, those with active infection, and those who developed gastric cancer – and those with no history of infection. They found that those with active *H. pylori* infections had less bacterial diversity, but a higher abundance of *H. pylori* itself. Other patients without *H. pylori* had more bacterial diversity. And in the cases of those with gastric cancer, most of the bacteria were found not in the tumor, but in the area immediately surrounding it. The researchers will now test 200 patients, retesting infected patients a few months after treatment with antibiotics, as well as cancer patients who have undergone immunotherapy treatments such as PD-1 inhibitors, to see how the microbiome composition changes and how it may influence therapy. They are also analyzing immunological data they were able to collect using the mucosal biopsies, which has shown a possible association with activation of T-cells. They hope to uncover the link between the microbiome and cancer, as well as causal immunity and tumorigenesis.

Multiple Perspectives on Breast Cancer

The p53 Gene The p53 gene – a well-studied marker in breast cancer – is an essential pathway for tumor suppression, and mutations in the tumor suppressor gene p53 are present in up to 25 percent of primary breast carcinomas. With the knowledge that p53 mutations are the most common genetic lesions associated with human cancer, a major objective of molecular oncology researchers at Columbia is to elucidate the mechanisms by which p53 is regulated, identify the regulators for p53, and determine how to inactivate the negative regulators. The researchers have identified most of the molecules and pathways that regulate p53 activity, and current research focuses on uncovering novel strategies to target this critical pathway therapeutically, including dissecting the roles of cell metabolism in tumor suppression.

BRCA1 and BRCA2 Genes While it is well-established that mutations in the BRCA1 or BRCA2 genes can lead to breast or ovarian cancer, researchers are just beginning to decipher the mechanisms that control this process. Several studies conducted over the two decades since these genes were identified have focused on characterizing their function, including the maintenance of genome stability. Recent studies have described the role of BRCA1 and BRCA2 in promoting the stability of replication forks, structures through which the replication of the genome occurs, suggesting that a deficiency in this function can lead to chromosomal aberrations that can ultimately incite cancer development.

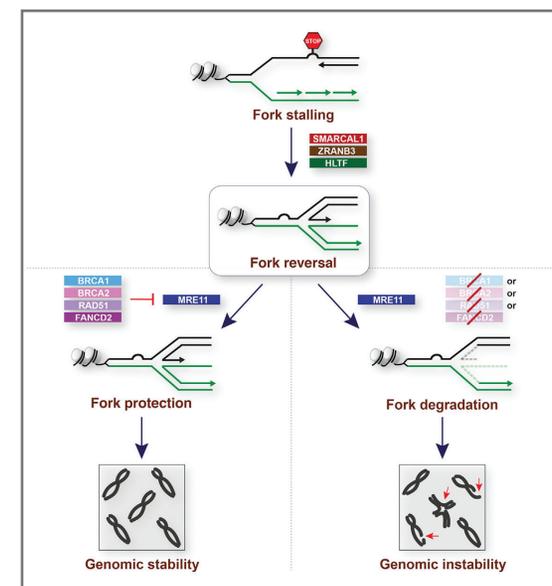
Studies by Columbia researchers raise the possibility that inhibition of factors that cause fork instability could reduce the occurrence of breast and ovarian cancer in BRCA1/2 mutation carriers. The Columbia research team is interested in understanding the pathways through which BRCA1 and BRCA2 protect the replication fork from degradation and avoid genomic instability. To this end, they have discovered a line of three newly characterized genes – SMARCAL1, ZRANB3, and HLF – that cause the degradation of forks in cells with mutated BRCA1. Depletion of these factors restores fork integrity and reduces genome instability in BRCA1/2-deficient cells, thus suppressing potentially damaging DNA lesions and therefore possibly causing less of a propensity to develop breast and ovarian cancer. The team also has shown that inhibition of SMARCAL1 in BRCA1-deficient breast cancer cells caused resistance to chemotherapy, identifying a new chemoresistance mechanism in this form of breast cancer.

Beyond BRCA For many years, scientists focused on the role of the BRCA1 and BRCA2 genes in breast cancer risk, but today some 30 to 40 additional genes are being tested for cancer susceptibility. As the field of cancer genetics has evolved, our researchers are expanding investigations in hereditary breast cancer genes utilizing next generation sequencing to identify germline mutations that will help clarify future cancer risk. As information on genetic mutations becomes more available, our clinicians are helping their patients and family members manage their cancer risk.

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“Our studies raise the possibility that inhibition of factors that cause fork instability could reduce the occurrence of breast and ovarian cancer in BRCA1/2 mutation carriers.”

— Dr. Alberto Ciccia



(Tagliatalata et al., 2017, *Molecular Cell*)

Clinical and Research Highlights



Dr. Katherine D. Crew

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“We know that family history is an important risk factor in breast cancer. Now, with personalized medicine and next generation sequencing, we are rapidly expanding knowledge of hereditary breast cancer genes beyond BRCA1 and BRCA2.”

— Dr. Katherine D. Crew

Mitochondrial DNA Triple-negative breast cancer (TNBC) is aggressive and therapeutically challenging. Researchers at Columbia are exploring genetic ancestry testing through mitochondrial DNA (mtDNA), which is distinct from nuclear DNA as it is maternally inherited and allows for origin determination. This is one of the first studies of self-described African American, White, and Hispanic patients with TNBC to identify mtDNA patterns. The study, which included 92 patients with TNBC, indicated discordance between self-reported ethnicity and mtDNA analysis in 13 percent of patients. The highest discordance (26 percent) was noted in self-described Hispanic patients. The investigators concluded that the identification of mtDNA patterns with a predisposition toward TNBC may allow for risk stratification. Further studies that identify the impact of variation in mtDNA and its association with TNBC would assist in personalizing risk assessment, allowing for the potential development of ethnically tailored therapeutic interventions.

Novel Clinical Trials As an I-SPY 2 clinical trial site, NewYork-Presbyterian/Columbia is participating in a multi-center trial for women with newly diagnosed operable breast cancer. The study is designed to test promising new treatments and identify whether these novel therapies are most effective in patients with early-stage breast cancer.

In collaboration with researchers in the Department of Systems Biology and the JP Sulzberger Columbia Genome Center, clinical researchers are conducting a pilot study to investigate genomic factors that are important for tumor growth with the ultimate goal of reducing the risk of breast cancer recurrence after surgery by targeting treatment of tumors according to their molecular dependencies. The study includes patients scheduled to undergo surgery for breast cancer after receiving chemotherapy treatment and who continue to have evidence of residual breast cancer. The investigators are using the N-of-1 clinical trial model to identify the tumor vulnerabilities that represent the Achilles' heel of the tumor growth in that specific patient's cancer from the analysis of its RNA rather than DNA. Initial results suggest that this type of N-of-1 study may enable a more precise therapeutic selection and identify treatments that are more universal than mutation-based personalized therapy.

Predicting Treatment Response Patients with breast cancer who have a pathologic response to neoadjuvant chemotherapy have been shown to do better than those with a significant amount of cancer after treatment. In an observational study of 40 women with stage 2 to 3 breast cancer who received standard neoadjuvant chemotherapy, researchers used diffuse optical tomography (DOT) – a novel imaging modality that uses near-infrared light to assess hemoglobin concentrations within breast tumors – to determine its value in predicting response. The results showed that the two-week percent change in DOT-measured hemoglobin concentrations was associated with the pathologic response after five months of neoadjuvant chemotherapy. The ultimate hope is that DOT may help guide neoadjuvant therapy in the future.

A Role for Exercise Patients undergoing neoadjuvant chemotherapy are traditionally directed to rest during treatment. A Columbia University researcher hypothesized that since breast cancer is linked to obesity, perhaps losing weight and exercising might have a positive impact on tumor biology. In a pilot study of 10 patients with stage 2-3, estrogen and progesterone receptor positive, with BMI >25, five patients were randomized to standard neoadjuvant chemotherapy plus a supervised intensive exercise regimen – “bootcamp” – and five received chemotherapy alone. While there were no initial differences between groups regarding tumor size, the mean Ki-67 for neoadjuvant chemotherapy plus exercise was 7 percent versus 29 percent with chemotherapy alone.

Addressing Treatment Toxicity Oncologists at NewYork-Presbyterian/Columbia are designing a new clinical study focusing on ways to improve cardiovascular health in breast cancer survivors. The researchers are collaborating with experts in lipids, behavioral cardiology, and cardiovascular risk factor assessment as they seek to design interventions or studies to improve the global health of breast cancer patients. They are also working with neurologists on studies that are examining chemotherapy-related neurotoxicity.

Enhancing Surgical Results In a refinement of nipple-sparing mastectomy, Columbia breast surgeons are employing a minimally invasive endoscopic video-assisted approach to better visualize the planes between the breast and muscle and between the breast and skin. This technique offers a less noticeable scar, excellent cosmetic outcomes, and high patient satisfaction.

Novel Treatments for Prostate Cancer

New Targeted Molecular Therapy In January 2017, Weill Cornell researchers began the first clinical trial in the United States that uses a radiolabeled small molecule to treat men with progressive prostate cancer that has spread beyond the prostate and is no longer responding to hormonal therapy. The researchers are using the radioactive particle lutetium-177 (¹⁷⁷Lu) linked to the small molecule PSMA-617 to target prostate-specific membrane antigen (PSMA), a protein that is abundantly expressed in 85 to 90 percent of metastasized prostate cancers. The small molecule binds to PSMA and delivers precise radiation therapy intended to shrink the cancer – even in cases in which cells have yet to form a visible tumor on a bone or CT scan.

The trial primarily seeks to determine the highest dose level of the drug that can be given without significant side effects. Once the optimal dose is found, the trial will be expanded to other centers to test efficacy. PSMA-targeted therapy is thought to be one of the most promising approaches in treating metastasized prostate cancer. While this trial is the first of its kind in the United States, this same approach to treat metastatic prostate cancer has gained traction in recent years in Germany. German physicians have published anecdotes where ¹⁷⁷Lu-PSMA-617 can reduce the volume of tumors in the body and lead to remission of the cancer. Weill Cornell researchers have been at the forefront of PSMA-targeted radionuclide (including ¹⁷⁷Lu) therapy for more than a decade, developing the first monoclonal antibodies that could bind to PSMA in viable prostate cancer cells.



Dr. Roshni Rao

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“Exercise in the neoadjuvant setting for patients with breast cancer may be a potentially useful tool for impacting tumor biology in addition to the known quality-of-life improvements.”

— Dr. Roshni Rao

Clinical and Research Highlights



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“This trial is the first of its kind in the U.S. and one of the few in the world to test this type of targeted treatment in a formal research setting with the goal of benefitting both the participants as well as future patients.”

— Dr. Scott T. Tagawa

As a result, PSMA has become recognized as the best-known prostate-cancer specific cell surface molecular target. The lead antibody they developed, J591 – available nowhere else – was shown to be able to target virtually all prostate cancers in patients while also avoiding healthy tissue and normal organs, producing better responses with fewer side effects. In another trial that began in October 2017 with support from the Weill Cornell prostate cancer SPORE, the researchers are testing the effects of the more potent alpha-emitter actinium-225 (^{225}Ac) linked to J591 in patients with prostate cancer to find the highest dose that can be administered without causing severe side effects. Weill Cornell received a \$1 million Prostate Cancer Foundation Challenge Award to expand these clinical trials in several centers nationwide to test the efficacy of these highly promising new PSMA-targeted radiation-emitting treatments.

High-Intensity Focused Ultrasound NewYork-Presbyterian/Weill Cornell urologists are offering high-intensity focused ultrasound (HIFU) for the treatment of localized prostate cancer. This approach – which is in its early stages of use in the U.S. – aims to preserve noncancerous prostate tissue and minimize damage to surrounding healthy tissue or organs, providing the potential for better functional outcomes. The procedure, which uses an ultrasound-guided transducer to ablate the cancerous tissue, is radiation-free and offers significantly lower risk of side effects than radiation therapy. Focally treating areas of prostate cancer can delay surgical or whole-gland irradiation, which have greater risks of erectile dysfunction and urinary incontinence.

HIFU was FDA-approved for ablation of prostate gland tissue in 2015, but not for a prostate cancer indication, citing there was not enough long-term evidence for efficacy or patient benefit. In fact, a review of studies undertaken by Weill Cornell researchers supports this concern. The investigators reported that early evidence suggests that partial gland ablation is a safe treatment option for men with localized disease. However, longer-term studies are needed to evaluate its efficacy and functional outcomes, to be able to identify optimal candidates for this therapy, and to provide data that will allow for better comparison between studies and among treatment modalities.

Cryotherapy: An Alternative Focal Therapy NewYork-Presbyterian/Weill Cornell physicians have performed the first in-office MRI-ultrasound fusion-guided cryotherapy in New York City and the northeast. Building upon the technology that allows more accurate detection of prostate cancer during biopsy, they use cryotherapy to destroy areas of biopsy-identified prostate cancer with MRI guidance. A benefit compared to HIFU is the real-time monitoring of the area that is being thermally ablated and no limitation in terms of the prostate size.

PSMA PET/CT Scanning NewYork-Presbyterian is among the few institutions in the world to offer PSMA PET/CT imaging, a relatively new imaging technology that greatly assists in localizing the extent of prostate cancer, as well as cancer in the lymph glands and bones. PSMA PET/CT scanning offers high sensitivity and specificity and is much more accurate than other scanning methods described to date. As a result, therapy can be targeted more appropriately.

New Models of Care

Comprehensive Programs Address Brain and CNS Metastases

NewYork-Presbyterian has developed brain metastases programs that provide patients with the latest diagnostic and treatment modalities and access to resources to help address the consequences of metastases and side effects of therapy.

The Central Nervous System Metastases Clinic (CNSMets), established by NewYork-Presbyterian/Columbia's Division of Neuro-Oncology, coordinates the treatment of patients with brain, leptomeningeal, skull base, and spine metastases. CNSMets grew out of the need to organize the complex array of specialist expertise – neurosurgery, neurology, radiation oncology, medical oncology, neuroradiology, and complementary and alternative medicine among others – to address the many and varied challenges that can accompany a diagnosis of brain metastases.

The Brain Metastases Clinic at the Weill Cornell Brain and Spine Center provides comprehensive care to patients diagnosed with metastatic brain tumors and leptomeningeal disease. The program includes neurosurgery, radiation oncology and medical oncology, as well as psycho-oncology and palliative care. In addition, the clinic incorporates an integrated health program that offers acupuncture, yoga, and integrative therapies. Research efforts include investigations in reducing neurotoxicity from radiation therapy and minimizing complications from neuro-cognitive decline.

The CMS Oncology Care Model

The Centers for Medicare & Medicaid Services (CMS) has selected the hematology and oncology programs of NewYork-Presbyterian to participate in a care delivery model that supports and encourages higher quality, more coordinated cancer care. Our physicians join nearly 200 physician group practices and 17 health insurance companies participating in the Medicare arm of the Oncology Care Model, which includes more than 3,200 oncologists and will cover approximately 155,000 Medicare beneficiaries nationwide. The person-centered approach promotes coordination among patient services and encourages practices to lower costs through episode- and performance-based payments that reward high quality care. The Oncology Care Model is one of the first CMS physician-led specialty care models.

NCI's Community Oncology Research Program

Through the National Cancer Institute's Community Oncology Research Program (NCORP), NewYork-Presbyterian/Columbia is further able to provide local residents access to the latest cancer prevention programs and clinical trials. NCORP is part of a \$93 million initiative launched by the NIH to ensure that all population groups are represented in cancer research and will facilitate services to meet minority needs. Cancer is the leading cause of reduced lifespan for members of the Washington Heights Community served by NewYork-Presbyterian/Columbia, one of only 12 NCORP programs in the country. The neighborhood is 71 percent Hispanic and 14 percent black, with nearly one-third living below the poverty level.

NewYork-Presbyterian Brings Breakthrough Radiation Therapy to New York

The new David H. Koch Center at NewYork-Presbyterian/Weill Cornell Medical Center – an innovative ambulatory care facility equipped with the most sophisticated clinical technologies – includes an outpatient radiation oncology suite offering the first MRI-guided linear accelerator available in the northeast. This leading edge technology propels radiation therapy into a new generation, allowing physicians to image and treat cancer patients simultaneously (real time), enhancing the capacity to see the extent of the tumor, providing accurate information needed to verify and adjust treatment plans in real time, and controlling for intra-fraction motion with unprecedented precision. Because of these characteristics of precision, the treatment can be delivered in a few larger dose fractions, reducing drastically the number of visits.



The MRI-guided linear accelerator for precision radiation treatment is delivered to the new David H. Koch Center.

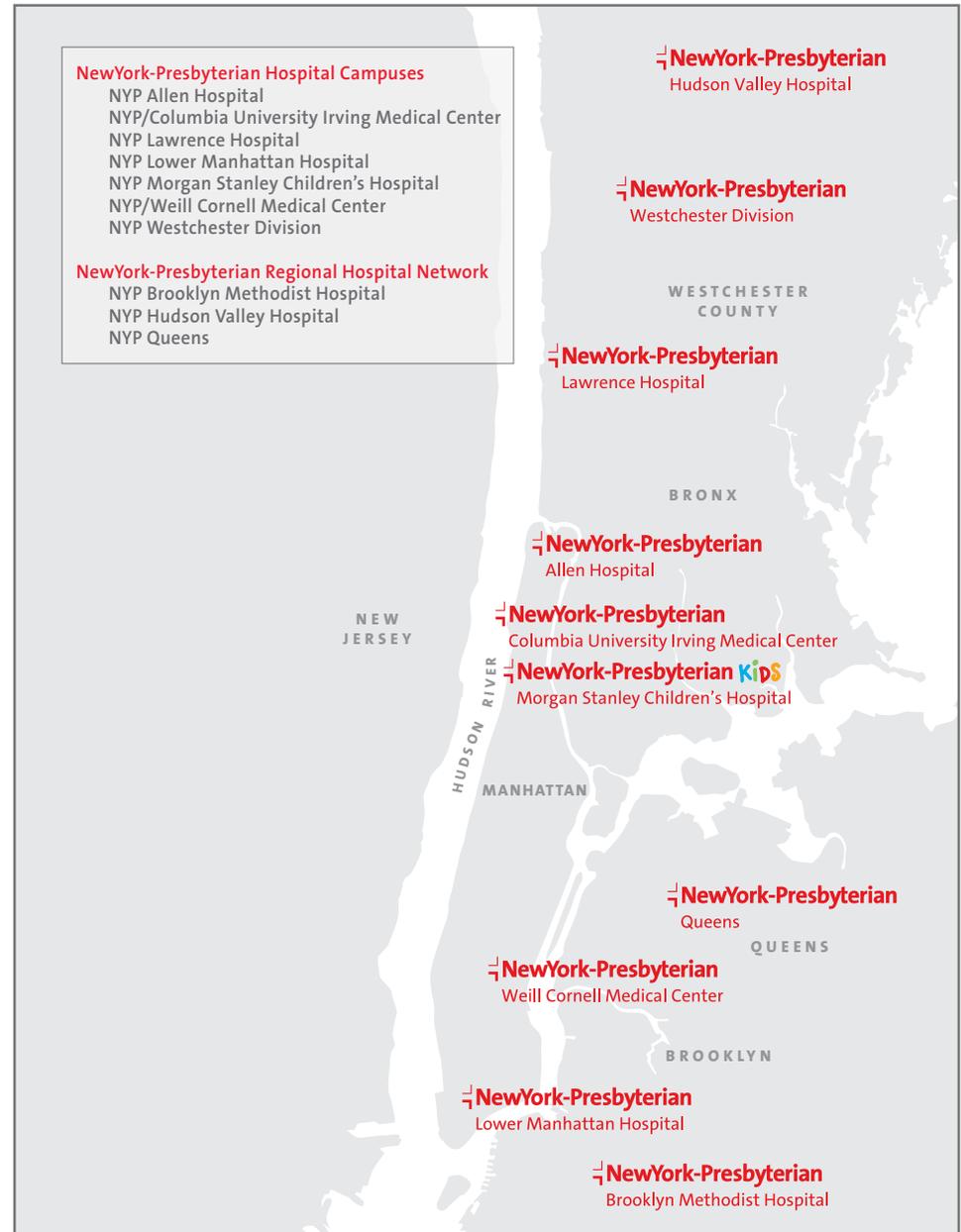


Two decades ago, on January 1, 1998, The New York Hospital announced its full-asset merger with The Presbyterian Hospital to create NewYork-Presbyterian Hospital. In this unprecedented event, two world-class academic healthcare institutions combined to become one of the highest quality medical, teaching, and research institutions in the country. Each hospital shared illustrious histories as providers of exemplary healthcare services, having made innumerable contributions to the field of medicine. The merger resulted in an improved quality of healthcare provided to patients, enhanced availability of clinical services to an expanded population, and lowered costs of services through improved efficiencies.

Today, NewYork-Presbyterian is one of the nation's most comprehensive, integrated academic healthcare delivery systems dedicated to providing the highest quality, most compassionate care and service to patients in the New York metropolitan area, nationally, and throughout the globe. In collaboration with two renowned medical schools, Weill Cornell Medicine and Columbia University Medical Center, NewYork-Presbyterian is consistently recognized as a leader in medical education, groundbreaking research, and innovative, patient-centered clinical care.

NewYork-Presbyterian has four major divisions:

- NewYork-Presbyterian Hospital is ranked #1 in the New York metropolitan area by *U.S. News and World Report* and repeatedly named to the Honor Roll of "America's Best Hospitals."
- NewYork-Presbyterian Regional Hospital Network comprises hospitals and other facilities in the New York metropolitan region.
- NewYork-Presbyterian Physician Services connects medical experts with patients in their communities. It includes the NewYork-Presbyterian Medical Groups in Westchester, Queens, and Brooklyn, which increase access to primary care in collaboration with Weill Cornell Medicine Physicians and ColumbiaDoctors, which deliver specialty care.
- NewYork-Presbyterian Community and Population Health encompasses ambulatory care network sites and community healthcare initiatives, including NewYork Quality Care, the Accountable Care Organization jointly established by NewYork-Presbyterian Hospital, Weill Cornell Medicine, and Columbia University Medical Center.





Only one hospital outperforms all six
government measures on survival rates:
NewYork-Presbyterian.

NewYork-Presbyterian is the only hospital in the nation with statistically better mortality rates in all six of the Centers for Medicare and Medicaid Services (CMS) 30-day mortality measures: heart failure, pneumonia, COPD, heart attack, stroke and coronary artery bypass graft.

While these statistics are only for Medicare patients, they tell a compelling story: a combination of clinical excellence, dedicated patient care, and the experience and resources of two great medical schools.

We invite you to learn why so many doctors trust us for their most challenging conditions and difficult procedures at nyp.org/amazingadvances



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