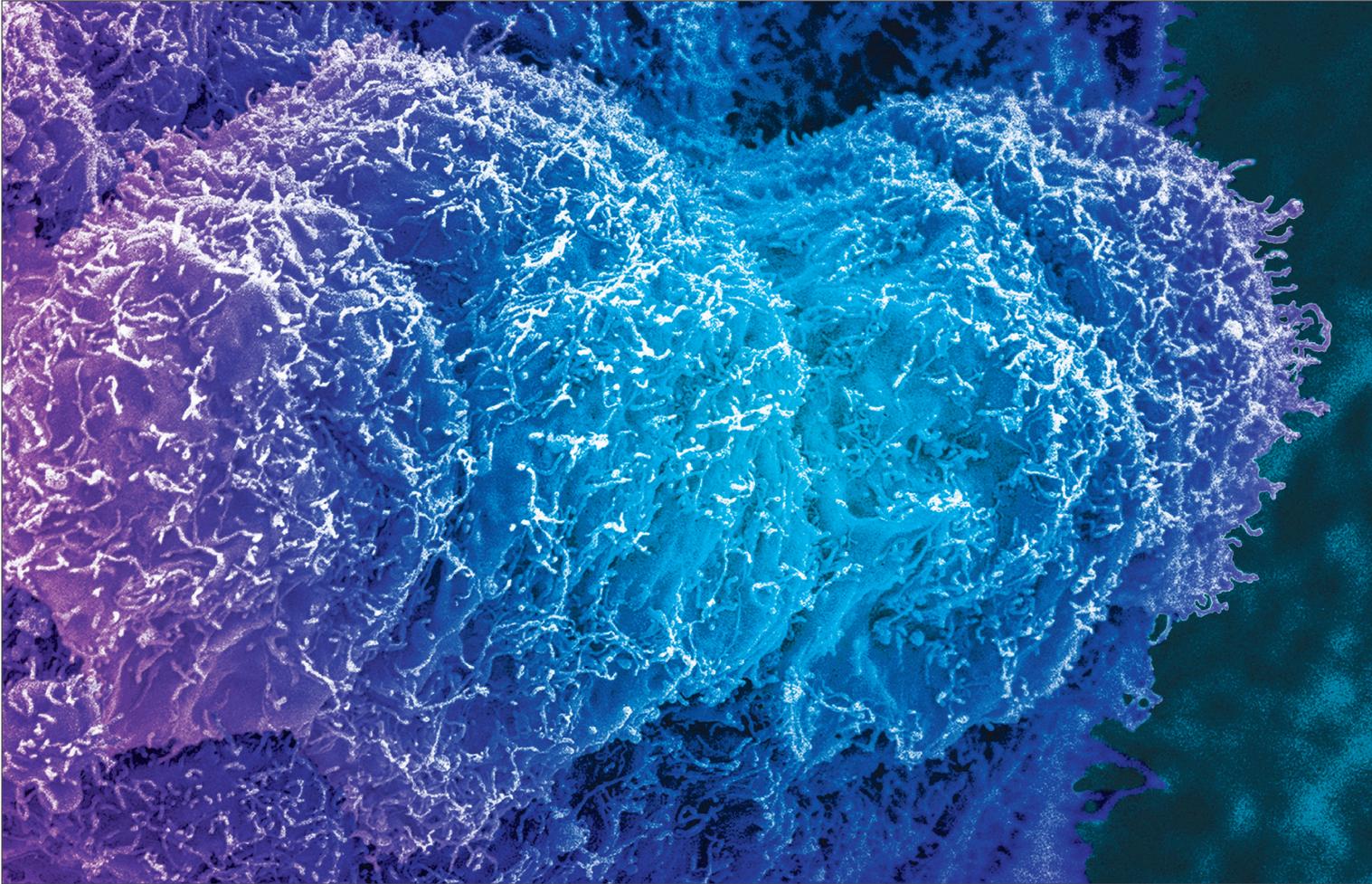




NewYork-Presbyterian Oncology

2019 Report on Clinical and Scientific Innovations



**Weill Cornell
Medicine**

**NewYork-
Presbyterian**



COLUMBIA

Leadership



Anil K. Rustgi, MD
Director
 Herbert Irving Comprehensive
 Cancer Center
Chief, Cancer Service
 NewYork-Presbyterian/
 Columbia University
 Irving Medical Center



Gary K. Schwartz, MD
Chief
 Hematology and Oncology
 NewYork-Presbyterian/
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 Irving Medical Center



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



Manuel Hidalgo, MD
Chief
 Hematology and
 Medical Oncology
 NewYork-Presbyterian/
 Weill Cornell Medical Center

Herbert Irving Comprehensive Cancer Center

NewYork-Presbyterian/Columbia University Irving Medical Center

Sandra and Edward Meyer Cancer Center

NewYork-Presbyterian/Weill Cornell Medical Center



NewYork-Presbyterian
A Top 5 Hospital in the Nation



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

NewYork-Presbyterian Oncology

2019 Report on Clinical and Scientific Innovations

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Welcome

Dear Colleague:

We are proud to bring you our *2019 Report on Clinical and Scientific Innovations in Oncology*. At NewYork-Presbyterian and our distinguished medical schools – Columbia University Vagelos College of Physicians and Surgeons and Weill Cornell Medicine – innovators in medicine and science are accelerating the discovery and development of novel diagnostic and therapeutic advances in cancer that are enabling us to achieve the best possible outcomes for patients.

Central to their endeavors 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 Medicine. Here, our cancer specialists collaborate on strategies for early detection and optimal diagnosis, develop groundbreaking therapies, and apply the latest technology and techniques to translate discoveries from the lab directly into the clinic.

In 2019, we were pleased to welcome two renowned gastrointestinal physician-scientists to lead cancer care and research programs at NewYork-Presbyterian. Anil K. Rustgi, MD, a global leader in GI cancers, has been appointed Director of the Herbert Irving Comprehensive Cancer Center and Chief of the Cancer Service at NewYork-Presbyterian/Columbia University Irving Medical Center. Manuel Hidalgo, MD, PhD, a pioneer in pancreatic cancer, has joined NewYork-Presbyterian/Weill Cornell Medical Center and Weill Cornell Medicine as Chief of the Division of Hematology and Medical Oncology. Dr. Rustgi and Dr. Hidalgo bring a wealth of experience and expertise that will help us advance our mission to provide the highest quality and most innovative cancer care for our patients.

In this report, we will share with you just some of the recent research developments in lung and genitourinary cancers, mantle cell lymphoma, myeloma, and glioblastoma. We believe that the efforts of our clinicians and scientists will have a profound impact in ultimately changing the landscape of cancer care for years to come.

Sincerely,



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



Lee Goldman, MD
*Dean of the Faculties of
Health Sciences and Medicine
and Chief Executive
Columbia University
Irving 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

Measures of Distinction

Clinical Care

372

Clinicians and Research Scientists

7,630

Adult Discharges

105

Oncology Beds

34

BMT Beds

101

Infusion Chairs

88,073

Infusion Treatments

39,528

Radiation Therapy Treatments

597

Gamma Knife Procedures

256

Bone Marrow Transplants

Research

>\$164 million

received in 2018 from the National Institutes of Health, including the National Cancer Institute and other major funding sources

>8,900 patients

enrolled in nearly 1,375 research studies, including 440 phase 1 and phase 2 clinical trials

Graduate Medical Education

273

internal medicine residents who rotate through hematology/oncology programs

12 residents

in radiation oncology programs

43 fellows

in fellowship programs that include:

- Colon and Rectal Surgery
- Cytopathology
- Gynecological Oncology
- Hematology/Oncology

6 fellows

in hematology/oncology received 2019 Young Investigator Awards from the Conquer Cancer Foundation

Innovations at a Glance

- Conducting a phase 2 clinical trial for resectable non-small cell lung cancer comparing immunotherapy alone to immunotherapy with radiation therapy in the neoadjuvant setting



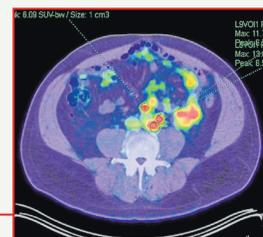
- Tested PTC596, an experimental compound, in combination with gemcitabine in mice with an aggressive pancreatic cancer, extending survival three times longer than with a single standard agent



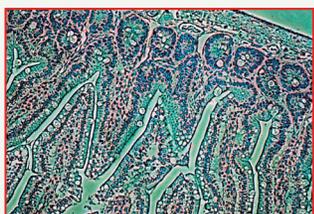
- Led a phase 2 clinical trial treating patients with advanced, metastatic esophageal cancer with pembrolizumab, an immune-system boosting drug, resulting in regression of tumors in some patients

- Developed a closed implantable convection-enhanced delivery system to facilitate chronic infusion of topotecan with gadolinium to target glioma cells

- Conducted a study showing how high-fructose corn syrup fuels the growth of colon tumors in mice and demonstrated a potential strategy to block excess tumor growth



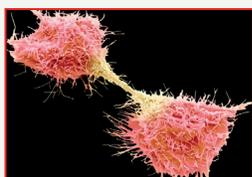
- Launched a phase 1b/2 trial to test whether nivolumab, with or without anti-IL-8 therapy, combined with a short course of ADT, promotes anti-tumor immune responses that prolong time to disease relapse for castration-sensitive prostate cancer



- Developing a vaccine in preclinical studies that could effectively train the immune system to recognize and attack cancer cells with mutations common in Lynch syndrome

- Demonstrated in a mouse model of lymphoma a novel engineered system to deliver immunotherapy from bacteria, leading not only to complete regression, but could also treat distant tumors

- Developed a powerful set of scientific tools in collaboration with the New York Genome Center to track the molecular evolution of cancer



- Exploring the use of APX005M, an antibody targeting CD40, in combination with standard chemotherapy to stimulate an immune response in sarcoma

Lung Cancer

Forging Therapeutic Alliances



Dr. Nasser K. Altorki and Dr. Silvia C. Formenti

Does combining sub-ablative doses of radiation with immune checkpoint inhibitors in patients with resectable non-small cell lung cancer have immunomodulating properties that produce potent local and systemic anti-tumor immune responses?

This is the fundamental question **Nasser K. Altorki, MD**, Chief of Thoracic Surgery, and Director, Neuberger Berman Lung Cancer Research Center, and **Silvia C. Formenti, MD**, Chair, Radiation Oncology, NewYork-Presbyterian/Weill Cornell Medical Center, are seeking to resolve through their collaborative research. At the September 2019 world-wide conference of the International Association for the Study of Lung Cancer, Dr. Altorki and Dr. Formenti presented preliminary results of their ongoing phase 2 clinical trial for patients with resectable non-small cell lung cancer to compare neoadjuvant therapy with the immunotherapy cancer drug durvalumab alone to sub-ablative stereotactic therapy (SBRT) with durvalumab. Both groups then receive adjuvant durvalumab for 12 months.

“It takes a lot of collaboration with the surgical department to recruit patients for a trial like this,” says Dr. Formenti. “These patients traditionally undergo surgery as the first-line therapy. It is challenging to recruit patients when discussing the risk of delaying surgery versus the potential benefit of a longer impact in terms of being free of disease after the surgery compared to surgery alone. Dr. Altorki is a very

enlightened surgeon who understands basic science and has a track record of tapping into our discoveries in the lab and bringing them to fruition with our patients.”

“Our departments meet almost every week for our tumor conference with strong participation from radiation oncology, surgery, and medical oncology,” says Dr. Altorki. “Within a short period of two years, we have enrolled 45 patients for this trial, which is an amazing recruitment rate. Our primary objective is to determine whether preoperative anti-PDL-1 therapy with or without radiation leads to improvement in disease-free survival from a historical control rate of 75 percent at two years to 88 percent. Our preliminary results show that the response rate is far above what you would expect from other regimens using immune checkpoint inhibitors. More importantly, patients enrolled in this trial go to the operating room within six weeks, while patients who undergo immunotherapy with chemotherapy will not go to surgery for 12 weeks. We are very excited about this protocol.”

The clinical protocol developed by Dr. Altorki and Dr. Formenti focuses on patients newly diagnosed with early resectable lung cancer – clinical stages I, II, and IIIA. “These are patients who are potentially curable by surgery,” says Dr. Formenti. “Instead of performing surgery first followed by immunotherapy, we are doing immunotherapy first – plus or minus radiation – then taking them to surgery. The results of adding radiation are quite promising, with data suggesting that radiation significantly increases the response rate. We know this because all of these patients undergo surgery, so we can assess the response in the specimen analyzed after surgery.”

Both Dr. Altorki and Dr. Formenti believe this study will pave the way for similar trials whereby immunotherapy with or without radiation is tested prior to surgery. “This trial could become a model and proof of principle study that demonstrates you can use the tumor to immunize the patient against his or her original disease,” says Dr. Formenti. “When you go to the OR there is no tumor left having already recruited the immune system of the patient to fight the same tumor.”

“My hope is to create a consortium to conduct preoperative treatment trials investigating various immunotherapy strategies where you obtain tissue before and after surgery and during treatment to better understand the biology of how the treatment works,” says Dr. Altorki. “Wouldn’t this be terrific?”

Lung Cancer

Therapeutic Breakthroughs on the Horizon

Naiyer A. Rizvi, MD, has become a household name in the field of lung cancer and immunotherapy drug development. Dr. Rizvi, who serves as Director of Thoracic Oncology and Co-Director of Cancer Immunotherapy at NewYork-Presbyterian/Columbia University Irving Medical Center, played a significant role in the FDA approval path of immune checkpoint inhibitors for melanoma and lung cancer, and his pioneering research continues with a focus on tumor mutation burden and the role of neoadjuvant immunotherapy for non-small cell lung cancer.

The Benefit of Tumor Mutation Burden

In 2015, Dr. Rizvi published the first data on lung cancer and tumor mutation burden (TMB) in *Science* showing a correlation with benefit. It became one of the most cited papers in immunotherapy, with over 3,000 citations. “As more mutations accumulate, the tumor ends up subverting the immune system and turning off the immune recognition. Immunotherapies turn the immune system back on and eradicate these mutations,” says Dr. Rizvi. In a subsequent large phase 3 clinical trial, Dr. Rizvi and his colleagues were able to determine the tumor mutation burden from the plasma of patients. “This was important for two reasons. We could actually determine the tumor mutation burden from a 2mL plasma sample, and we now knew that we could use this to select high TMB patients who may benefit from combination immunotherapy.”

Next Generation Cancer Vaccines

“Beyond tumor mutation burden, we now know that there are very unique mutations that are immunologically important, and when immune checkpoint inhibitors such as nivolumab and pembrolizumab are given to patients, there are very specific T cells that expand against very specific mutations,” says Dr. Rizvi. “There are likely only to be very few of these mutations, called neoantigens, within a tumor and we are now able to predict these mutations with great accuracy, work we published in *Nature Biotechnology* in 2018. The next step is to see if we could ‘target’ these neoantigens with cancer vaccines.” However, the challenge is that neoantigens are typically patient specific so a vaccine needs to be created for each patient as a personalized immunotherapy approach. This approach has now entered the clinic with personalized vaccine treatments being conducted at NewYork-Presbyterian/Columbia.



Dr. Naiyer A. Rizvi



Dr. Catherine A. Shu

A New Take on Neoadjuvant Therapy

Dr. Rizvi is also leading a global phase 3 clinical trial with an estimated 400 patients comparing combination immunotherapy versus chemotherapy plus neoadjuvant immunotherapy in patients who have locally advanced lung cancer that is resectable. “We recently finished a phase 2 trial of 30 patients who were given neoadjuvant chemotherapy in conjunction with the immune checkpoint inhibitor atezolizumab,” says Dr. Rizvi. “About 30 percent of the patients had a complete pathologic response. If the global trial also shows positive outcomes, it too will offer a landscape-changing therapy for FDA approval.”

Catherine A. Shu, MD, Clinical Director of the Thoracic Medical Oncology Service, is Principal Investigator of the phase 2 trial. “Our work directly led to a pharmaceutical company adapting our study for the global phase 3 trial,” says Dr. Shu. “This trial has truly been a Columbia team effort. As a matter of fact, our thoracic pathologist, **Dr. Anjali Saqi**, is now serving as the phase 3 trial study pathologist given her experience with the phase 2 effort.”

“Neoadjuvant chemotherapy is an accepted treatment approach for resectable non-small cell lung cancer,” says Dr. Shu. “However, the cancer recurs in 30 to 70 percent of patients, who then ultimately succumb to the disease. Our goal is to improve upon this. Using a combination of chemotherapy and immunotherapy in this preoperative setting is novel, and we are extremely encouraged by results from our phase 2 trial.”

Mantle Cell Lymphoma

Tackling Molecular Causes of Treatment Resistance

With a five-year, \$9 million Program Project Grant (P01) from the National Cancer Institute, **Selina Chen-Kiang, PhD**, Principal Investigator, and her colleagues at Weill Cornell Medicine are moving forward to better understand why patients with an aggressive and incurable form of lymphoma

initially respond to treatment, only to relapse over time. Their findings may enable them to develop therapies that are effective, well tolerated, and tailored to individual patients with mantle cell lymphoma (MCL). This is the first P01 that is solely focused on MCL. “Currently we have approved drugs and experimental therapies for MCL, yet we don’t precisely know how they work or why patients ultimately become resistant to them,” says Dr. Chen-Kiang, who

is Professor of Pathology and Laboratory Medicine, Professor of Microbiology and Microbial Pathogenesis, and a member of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine. “We need to know how to use these drugs based on scientific principles so that we can better patients’ lives and ultimately cure their disease.”

Dr. Chen-Kiang and her team have spent the last two decades investigating how the cell cycle is regulated in normal immune function and in B-cell cancers. In previous studies, they discovered that intentionally stopping the cell cycle by inhibiting the enzyme CDK4 or CDK6, which is needed for the first growth phase, not only prevents cancer cells from dividing, but also weakens them by causing an imbalance in gene expression in mice. To replicate these findings in humans, Dr. Chen-Kiang identified a small molecule on Pfizer’s shelf that could act in the same way as the natural CDK4/6 inhibitor. “I knew I needed this molecule to understand the normal immune response and how to correct it and possibly control cancer,” says Dr. Chen-Kiang. “I also knew at that time that this particular step in the cell cycle was the key step in driving human cancer, especially MCL and breast cancer.”

In two phase 1 clinical trials, her team found that the drug, palbociclib, now approved by the FDA for breast cancer,

shrank MCL tumors and induced remission in a significant number of patients. “Our trial showed that palbociclib plus ibrutinib, an FDA-approved MCL drug, is very well tolerated,” says Dr. Chen-Kiang.

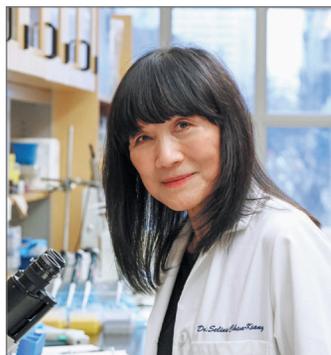
This trial, led by **Peter Martin, MD**, Director of the Lymphoma Service at Weill Cornell, revealed that palbociclib combined with ibrutinib shrank MCL tumors in 67 percent of patients. Moreover, 37 percent of the patients achieved durable complete remission for as long as 5.5 years. “This was remarkable,” says Dr. Chen-Kiang. “Patients who were treated with ibrutinib alone initially went into partial or complete remission, only to become resistant to it quickly or over time.”

The P01 grant is enabling Dr. Chen-Kiang and her team to expand on these findings with three synergistic translational studies. The team used genomic and bioinformatic approaches to discern how genes are programmed by the cell cycle in tumor cells, how palbociclib reprograms them to thwart cell division, and how to overcome resistance to palbociclib and ibrutinib. “In the past we analyzed the tumor in bulk. But now we have the ability to actually analyze and interrogate every tumor at the single cell resolution. And that’s extremely powerful,” says Dr. Chen-Kiang.

“By controlling the cell cycle, palbociclib can make the tumor cell exquisitely sensitive to other drugs.”

— Dr. Selina Chen-Kiang

In September 2018, Dr. Chen-Kiang began a multicenter phase 2 study of palbociclib-ibrutinib combination therapy to understand why this combination therapy is more effective than ibrutinib alone. “If we know how to combine the cell cycle inhibitor with a partner drug, we can increase the durability and depth of the clinical response dramatically,” she says. “We have 10 sites across the nation and we’re hoping to complete patient accrual in two and a half years. The most important thing, which is very gratifying, is that we already have 16 patients in our trial, and 15 of them have responded, so we know it’s working.”



Dr. Selina Chen-Kiang

Multiple Myeloma and Amyloidosis

One Common, One Rare, Both Challenging



Dr. Suzanne Lentzsch

“Multiple myeloma is the second most common hematologic disease. In contrast, AL amyloidosis is a very rare disease,” says **Suzanne Lentzsch, MD, PhD**, Director of the Multiple Myeloma and Amyloidosis Program at Columbia University Irving Medical Center. “We have multiple clinical trials and investigator-initiated trials for both. Our strength here at Columbia is a substantial conflation of

research that takes us from bench to bedside.”

Multiple Myeloma

“Our laboratory found a connection between the immune system and bone disease in multiple myeloma,” says Dr. Lentzsch. “We initially identified that multiple myeloma cells secrete a protein called MMP13. This protein induces osteoclast formation and leads to the development of lytic lesions, which can cause spine fractures, paraplegia, and pain...all characteristic of multiple myeloma bone disease. We then discovered that MMP13 also binds to and inhibits

T-cells, providing a link between the immune micro-environment in multiple myeloma and bone disease that has never been described before.”

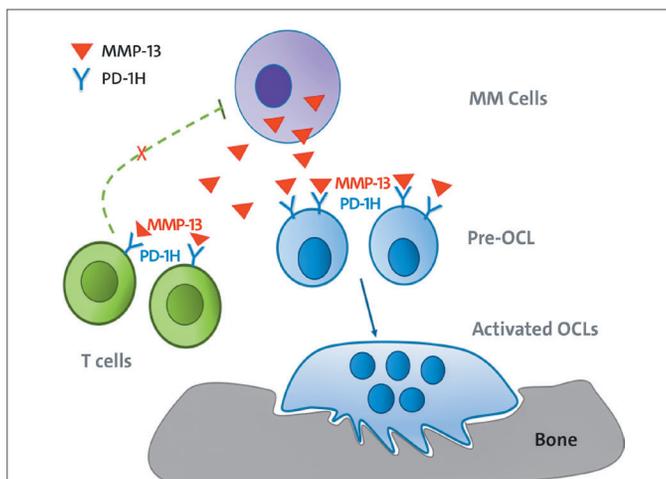
Identifying linkages between MMP13 and both osteoclast activation and immune suppression, the researchers could now target MMP13 for development of a neutralizing antibody to prevent extensive bone disease and the risk of infection that comes with immune suppression. Adds Dr. Lentzsch, “Not only did we identify the mechanism of action of bone disease and suppressed immune system, we also identified a new approach to target both.”

AL Amyloidosis

AL amyloidosis is a rare systemic disorder caused by an abnormality of plasma cells in the bone marrow, which builds up amyloid in and around tissues, nerves, and organs, resulting in progressive and widespread organ damage and high mortality rates. The Columbia Amyloidosis Multi-disciplinary Program (CAMP), under the leadership of Dr. Lentzsch, is an international referral center for this multiorgan disorder, and each year the program cares for more than 100 AL patients. At the same time, innovative research by Dr. Lentzsch and her colleagues has resulted in a series of translational clinical trials, including those studying new treatments for relapsed AL amyloidosis.

“All therapies have focused on the destruction of plasma cells to stop the production of light chains forming the amyloid,” says Dr. Lentzsch. “Because existing amyloid is not affected, impairment of organ function continues. So we turned our attention to monoclonal antibodies, which target the amyloid fibrils directly, destroying the existing amyloid. Several years ago, we tested antibody 11-1F4 against amyloidosis. Not only did we use this antibody to break down amyloid, we could also use it to detect amyloid, which is an extremely unique approach,” says Dr. Lentzsch.

Physicians from Columbia University did the first-in-human clinical trial, which is the only center worldwide that offers treatment with this monoclonal antibody and plan to use this antibody as a theranostic tool, which can image organs with amyloid infiltration and, at the same time, break down amyloid. The antibody will now be tested in a phase 3 clinical trial, with the goal of bringing it to FDA approval.



Findings by Dr. Lentzsch's lab that binding of MMP13 to osteoclasts and T-cells links multiple myeloma bone disease with the suppressed immune environment in multiple myeloma provides new approaches to treat bone disease and restore a suppressed immune environment.

Genitourinary Oncology

Inspiring Research in Immunotherapy



Dr. Charles G. Drake

“Immunotherapy represents a new frontier in genitourinary cancers,” says **Charles G. Drake, MD, PhD**, Director, Genitourinary Oncology and Co-Director of Cancer Immunotherapy, NewYork-Presbyterian/Columbia University Irving Medical Center. “We are looking at how these therapies can be used synergistically with traditional therapies in prostate, kidney, and other urological cancers to improve outcomes.” Under Dr. Drake’s leadership, the GU oncology group at Columbia has nearly 30 ongoing clinical trials.

Prostate Cancer

When Dr. Drake’s research team discovered that standard hormonal therapy, despite initially appearing to activate the immune system to attack prostate cancer, is in fact leaving prostate cancer cells behind, they turned their attention to a chemical called interleukin-8 (IL-8). “The cancer cells that do not respond to hormonal therapy secrete IL-8, which attracts a population of cells that turns off an immune response to the tumor,” explains Dr. Drake. “There are a number of ways to target these cells. Our idea was to stop them from ever getting in there in the first place. IL-8 leaves a ‘trail of bread crumbs’ that these harmful, suppressive immune cells use to find their way into the tumor. By blocking IL-8, we could conceal this trail, preventing the suppressive cells from entering the tumor.”

Dr. Drake and his colleague **Matthew Dallos, MD**, have turned this hypothesis into an innovative 60-patient trial in which androgen deprivation therapy (ADT) is combined with a novel drug aimed at preventing suppressive myeloid cells from entering the prostate tumor microenvironment at the time of therapy. “To me, this is the most exciting immunotherapy

trial in all of GU cancer,” says Dr. Drake. “These are patients who have high risk prostate cancer that recurred after surgery or radiation. The MAGIC-8 study will test whether nivolumab, an anti-PD-1 antibody, with or without anti-IL-8 therapy, combined with a short course of hormonal therapy, promotes anti-tumor immune responses that prolong time to disease relapse in men with early prostate cancer.”

“In prostate cancer we might be getting a second chance at cure,” says Dr. Drake. “If the surgery or the radiation isn’t successful, attacking the tumor with this combination therapy when the cancer first recurs might lead to long-term remission.” MAGIC-8 is currently accruing patients at Columbia, Weill Cornell Medicine, and Thomas Jefferson University.

“We are looking at how immunotherapies can be used synergistically with traditional therapies in GU cancers to improve outcomes.”

— Dr. Charles G. Drake

Kidney Cancer

A first-of-its-kind pilot study has recently begun at Columbia for patients who present with stage III kidney cancer. “These patients are typically candidates for radical nephrectomy, but surgery will cure only about half of those patients,” says Dr. Drake. “This trial will evaluate the benefit of providing PD-1 targeted therapy in combination with a novel therapy directed against interleukin-1 (IL-1) before surgery to target myeloid-derived suppressor cells with the prospect of increasing the chance for cure.”

The study is, in part, informed by the research of **David Aggen, MD, PhD**, a former hematology/oncology fellow at Columbia, who showed that interleukin 1 is the “bad actor” in kidney cancer, supporting the growth and health of cells that are suppressive and turn off the tumor immune response. “What is particularly interesting about this trial is that not only are we trying to help the patients do better, but we are also trying to see if these two experimental drugs – canakinumab and spartalizumab – can modulate the tumor’s environment that promotes an anti-tumor immune attack,” says Dr. Drake.

Genitourinary Oncology

Expanding the Boundaries of Drug Development



Dr. Cora N. Sternberg

Cora N. Sternberg, MD, a leading international researcher and expert in the field of medical oncology, genitourinary cancers, and drug development, serves as Clinical Director of the Englander Institute for Precision Medicine at Weill Cornell Medicine and is a member of the Genitourinary Oncology Program at NewYork-Presbyterian/Weill Cornell Medical Center. A Professor of Medicine at Weill Cornell Medicine, Dr. Sternberg is well-known for her work in developing novel therapies and targeted agents for the treatment of prostate, renal, and bladder cancers.

A key opinion leader in genitourinary cancers, Dr. Sternberg helped develop the original M-VAC chemotherapy regimen, as well as the double-dose/high-dose/accelerated-dose M-VAC chemotherapy regimens in bladder and urothelial cancers – treatments that became the gold standard. Additionally, she served as Principal Investigator and has been involved in numerous practice-changing studies for prostate cancer leading to FDA approvals of abiraterone acetate and enzalutamide in advanced prostate cancer. Dr. Sternberg also was instrumental in the development of pazopanib, an antiangiogenic targeted therapy, for advanced clear cell renal cell carcinoma and served as lead investigator in the phase 3 international study that culminated in its FDA approval for patients with metastatic kidney cancer. She has also participated in the development of other antiangiogenic agents, such as sunitinib, cabozantinib, tivozanib, and dovitinib to treat renal cell cancer and immunotherapy for bladder cancer.

At Weill Cornell Medicine, Dr. Sternberg is facilitating the continued growth and development of clinical and translational research programs in genitourinary malignancies while continuing her influential research in the field. “Most recently, we published a study on immunotherapy for patients with advanced bladder cancer,” says Dr. Sternberg. “Because immunotherapy works by boosting the patient’s immune system, it is usually not given to patients with any kind of inflammatory disease. In this study, we lowered the entry criteria to include patients with inflammatory and renal disease who are never eligible for these clinical trials. The 1,000-patient trial showed that you could safely administer these drugs even to those patients who theoretically would be more at risk because of their autoimmune diseases or poor renal function.” The results were published in July 2019 in *European Urology*.

Dr. Sternberg’s research also focuses on nonmetastatic castration-resistant prostate cancer. Patients who have a rapidly rising prostate-specific antigen are at high risk for the development of metastasis. “We knew that enzalutamide prolongs overall survival among patients with metastatic castration-resistant prostate cancer, so our thinking was that this drug could also delay metastasis in men with non-metastatic disease,” says Dr. Sternberg.

She served as a Principal Investigator and the results, published in the October 4, 2018 issue of *The New England Journal of Medicine*, demonstrated dramatic improvements in metastasis-free survival, leading to the approval of enzalutamide for treatment of this patient population. “This is a population for whom there were previously no approved therapeutics. When given early, the drug reduces the risk of metastasis or death by more than 70 percent.”

More recently, Dr. Sternberg served as a lead investigator in an international study of cabazitaxel versus an androgen-signaling-targeted inhibitor (abiraterone or enzalutamide) in patients with metastatic castration-resistant prostate cancer that recurred after being treated with docetaxel and an androgen-signaling targeted inhibitor. The results, published in the September 30, 2019 issue of *The New England Journal of Medicine*, demonstrated that cabazitaxel significantly improved clinical outcomes, including progression free survival and overall survival.

Glioblastoma

Will Immunotherapy Play a Role?

“Glioblastoma, unlike lung cancer and some other solid tumors like melanoma, does not typically respond to immunotherapy,” says **Rohan Ramakrishna, MD**, a surgical neuro-oncologist with NewYork-Presbyterian/Weill Cornell Medical Center. “For example, in lung cancer, you have proteins expressed, such as PDL1, that correlate with a response to immunotherapy. Unfortunately, glioblastoma

does not respond to immunotherapy in a way that correlates with PDL1 expression. Moreover, GBM does not appear to be intrinsically immunogenic given its relatively low mutational load and associated low neoantigen expression. It is thought that tumors with high mutational burdens have significantly elevated numbers of neoantigens that make it possible for the immune system to recognize the

tumor and eliminate it. Therefore, GBM doesn’t appear to be intrinsically responsive to immunotherapy via checkpoint inhibition, at least in trials conducted so far.”

Despite these challenges, neuro-oncologists and neurosurgeons are not deterred in their pursuit of immunotherapy approaches that can surmount the unique treatment obstacles presented by malignant tumors within the brain. “Although we don’t have the data yet to be confident,

the effect of neoadjuvant immunotherapy on GBM is an exciting area to look into and the immunosuppressive microenvironment remains a potential target for treatment,” notes Dr. Ramakrishna, who serves as Co-Director of the William Rhodes and Louise Tilzer-Rhodes Center for Glioblastoma at NewYork-Presbyterian and the Director of the Brain Metastases Clinic at Weill Cornell. “Some recent studies have shown that immunotherapy via checkpoint inhibition alters the tumor microenvironment and causes genetic changes in the tumor itself, despite mixed clinical results. This is definitely an area to potentially exploit.”

At Weill Cornell Medicine, Dr. Ramakrishna is the Principal Investigator of the CAPTIVE trial. This innovative phase 2 clinical trial for recurrent glioblastoma evaluates a combination of DNX-2401, a genetically modified common cold virus, followed by pembrolizumab, an immunotherapy given every three weeks for up to two years or until disease progression. “When you inject the virus into the tumor, it triggers an immune response against the tumor,” he says. “The dying tumor cell releases signals and generates neoantigens that stimulate the immune system to kill additional tumor cells. By selectively replicating within cancer cells, but not normal cells, the virus sets off a chain reaction of tumor cell killing and further spreads the oncolytic virus to adjacent tumor cells. A week after the virus injection the patient starts treatment with pembrolizumab that activates an immune response against tumor cells.”

Preliminary results demonstrated that the combination of the two agents is well tolerated and associated with promising survival. The trial recently closed enrollment and results are now being processed.



Dr. Rohan Ramakrishna

“Pink Drink” Paves the Way in Glioma Surgery

Gleolan (aminolevulinic acid hydrochloride) is one of the newest tools for use in glioma surgery. The optical imaging agent when given orally has a remarkable ability to pass through the blood-brain barrier and penetrate a tumor. Viewed under blue light during surgery, Gleolan, which was FDA approved in 2017, fluoresces as a hot pink indicator distinguishing tumor cells from healthy brain tissue. **Theodore H. Schwartz, MD**, Co-Director of Surgical Neuro-Oncology at Weill Cornell, has used

the agent on several patients undergoing surgery for glioblastoma. “The ability to identify the full extent of a tumor is invaluable for resecting an aggressive tumor, particularly glioblastoma,” says Dr. Schwartz. “Often in these tumors, we cannot tell if there are small amounts of residual tumor. Using Gleolan, we can now see tumor cells that were previously invisible. In all my cases, post-operative MRI scans showed that the entire tumor had been removed.”

Glioblastoma

Enhancing Convection-Enhanced Delivery



Dr. Peter D. Canoll and Dr. Jeffrey N. Bruce

“There are many drugs that are very effective at killing glioma cells, at least in the laboratory, but in order to get enough of the drug into the brain, you have to give a high enough dose, which causes too much toxicity in the rest of the body,” says **Jeffrey N. Bruce, MD**, Director, Bartoli Brain Tumor Research Laboratory, and Co-Director, Brain Tumor Center, at NewYork-Presbyterian/Columbia University Irving Medical Center. “Overcoming the blood-brain barrier poses an additional challenge by limiting the systemic delivery of therapeutics to the tumor.”

While studies have shown that prolonged infusion in small amounts improves survival, intracerebral convection-enhanced delivery (CED) has been limited to short durations due to a reliance on externalized catheters. “One of the problems in our earlier studies was that the catheters needed to be hooked up to a pump at the side of the bed, and we could only give the drug for about four days for fear of infection,” notes Dr. Bruce.

To address this, Dr. Bruce and his colleagues developed a novel drug delivery strategy that utilizes a microinfusion pump to establish a positive pressure gradient in the brain via an implanted catheter. The pump could be implanted in the abdomen to facilitate chronic infusion and is controlled by Bluetooth. This CED strategy has been pioneered in the Bruce and Canoll laboratories with basic studies to select appropriate anti-tumor agents, preclinical testing in animal models, and a phase 1 clinical trial in patients with recurrent malignant gliomas.

The researchers tested the delivery system in a porcine model. The infusion was tolerated without serious adverse events and a large volume of distribution was achieved. Following extensive preclinical studies, a phase 1 dose escalation trial of topotecan by CED was performed in patients with recurrent malignant gliomas with clinical, radiographic, and neuropsychological testing for toxicity and anti-tumor response. “We turned the pump on for two days and then off for five days for four rounds of treatment over a month,” says Dr. Bruce. “Median survival and median time to progression and at six months compared favorably with the best standard treatment available for this tumor group. The pilot study, the first of its kind, was recently completed and was successful in all patients.”

“There is another element of this research that is unprecedented in its efforts,” says **Peter D. Canoll, MD, PhD**, Director of Neuropathology at Columbia. “At the time of catheter placement and following treatment, many MRI-localized biopsies of the patient’s brain tissue are taken from the tumor and the surrounding infiltrated areas. Each of those biopsies is then analyzed for tumor content using immunohistochemical and molecular analyses. With two sets of biopsies pre- and post-treatment for each patient, we can directly assess the effects of the treatment in different areas of the tumor.” Furthermore, in collaborations with **Peter A. Sims, PhD**, Director, Columbia Single Cell Analysis Core, they are testing the effects of topotecan on surgical samples using single cell sequencing analysis.

“If we find a population of cells pre-treatment that have disappeared post-treatment, it’s very good evidence that they are being targeted by the drug,” says Dr. Canoll. “Because the analysis of the tissue is so comprehensive, it addresses another major obstacle. These are spatially and genetically heterogeneous tumors, so sampling these tumors is an unmet challenge. Most everything we know comes from a single piece of tissue. By taking biopsies from multiple areas and documenting their locations, we have been able to create a very large data set that not only captures the heterogeneity of each person’s tumor, but also allows us to make predictions about the unsampled areas of the tumor.”

“When we look at the tissue, it shows that the approach is working,” says Dr. Bruce. “It’s killing the tumor cells and it’s safe for the normal cells.”

Research Update

Glioblastoma: Evaluating Multiple Drug Candidates at One Time



Dr. Andrew B. Lassman

Columbia University Irving Medical Center is among the first to enroll patients with glioblastoma in a new type of clinical trial that plans to speed the identification and development of the most promising therapies for the disease. Instead of evaluating each therapy in its own separate clinical trial, GBM AGILE (Adaptive Global Innovative Learning Environment) is designed to evaluate several drug candidates at once by studying multiple treatment groups

concurrently without the need for separate protocols. “There’s really no limit to the number of therapies that can be tested with this design for first-line and recurrent disease,”

says **Andrew B. Lassman, MD**, Chief of Neuro-Oncology at NewYork-Presbyterian/Columbia, and a GBM AGILE global study chair and member of the arm selection committee.

Because all treatments are compared to one common control group, patients are more likely to get an experimental therapy. Tumor tissue from participants will undergo analyses to identify biomarkers that may be associated with a patient’s response. As the trial accumulates data, its algorithm refines the randomization process, so that patients have a better chance of getting a treatment that appears to show benefit. This also allows investigators to quickly identify treatments that are more encouraging than the standard of care, while less promising therapies can be dropped. “This trial design offers a way to lower the cost, time, and number of patients needed to test new therapies for newly diagnosed or recurrent glioblastoma,” says Dr. Lassman.

Colon Cancer: High-Fructose Corn Syrup Fuels Tumor Growth

In a study published in the March 22, 2019 issue of *Science*, researchers at Weill Cornell Medicine showed how high-fructose corn syrup fuels the growth of colon tumors in mice and demonstrated a potential strategy to block this excess tumor growth. “The study shows that colorectal polyps feed on high-fructose corn syrup and explains the molecular mechanism by which this drives the growth of the tumor,” says **Lewis C. Cantley, PhD**, Meyer Director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine, and co-senior author.

“When you give the mice this additional sugar the tumors grow much bigger,” says lead author **Marcus D. Goncalves, MD, PhD**, an endocrinologist at NewYork-Presbyterian/Weill Cornell Medical Center. “If you are predisposed to getting polyps, you should not be drinking any sugar-sweetened beverages.”

When mice are fed high-fructose corn syrup, the sweetener delivers an excess of both glucose and fructose to the colon. The researchers showed colon tumors readily take in both sugars. The enzyme ketohexokinase (KHK) changes the fructose into fructose-1-phosphate, which



Dr. Lewis C. Cantley



Dr. Marcus D. Goncalves

was found to promote the tumor’s ability to use glucose for energy and generate the fats necessary for tumors to grow. “We expect that consuming beverages or processed foods with added sucrose is likely to have the same effect as consuming drinks with high-fructose corn syrup, since sucrose has a similar composition,” says Dr. Cantley. “Our study showed two genetic ways to reverse the high-fructose corn syrup’s effects by targeting KHK and an enzyme necessary for fat production.”

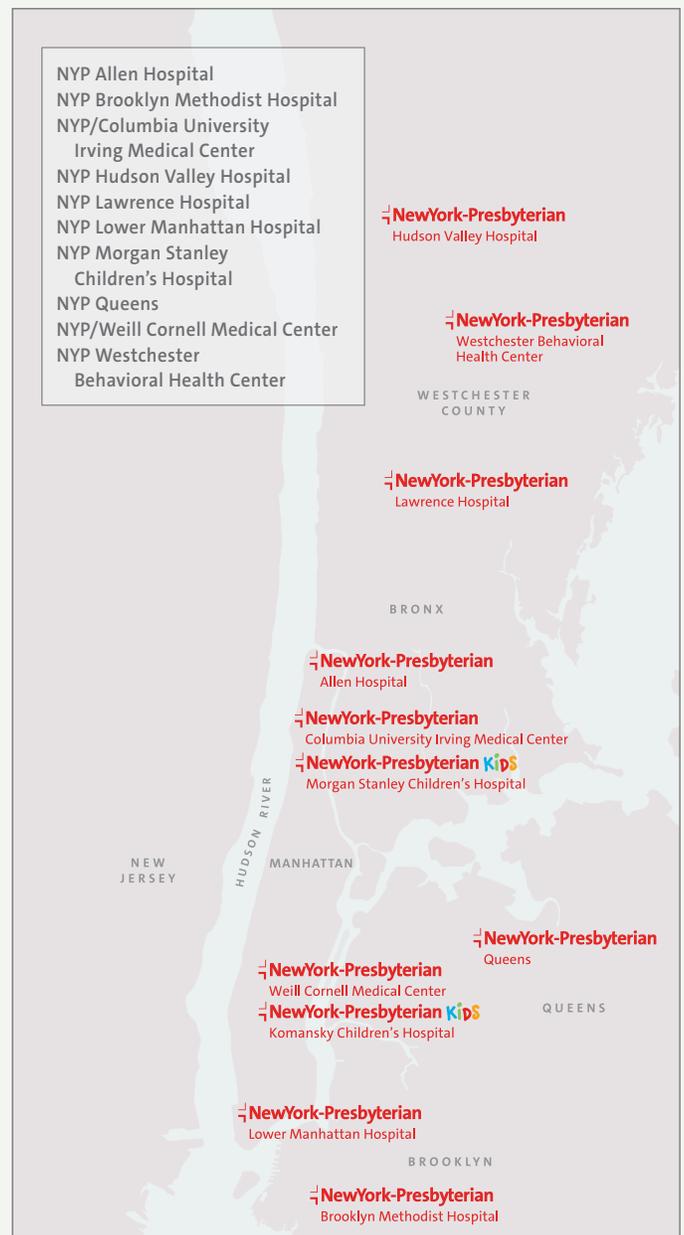
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