

NewYork-Presbyterian

FORUM

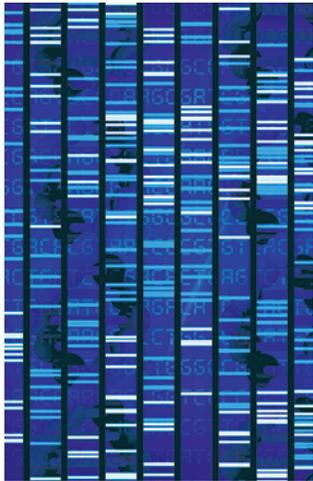
News and Information for the Alumni of NewYork-Presbyterian Hospital Fall 2013

A photograph of two men in dark suits and light blue shirts standing in front of a light-colored stone wall. The man on the left is wearing glasses and a striped tie, while the man on the right has a mustache and a patterned tie. They are both smiling and looking towards the camera. The man on the left has his hands clasped in front of him, and the man on the right has his hands in his pockets.

TARGETED THERAPIES TURNING A CORNER IN CANCER TREATMENT

*Through their leadership of
New York-Presbyterian Hospital's cancer centers,
Stephen G. Emerson, MD, PhD, and Lewis C. Cantley, PhD,
are forging a new era in cancer research and patient care.*

TARGETED THERAPIES: TURNING A CORNER IN CANCER TREATMENT



Since the first sequencing of the human genome was carried out in 2001, scientists and clinicians have been paving the way for a new concept in cancer treatment – precision medicine. With the development of computational tools capable of reading the genome more efficiently and new DNA sequencing that lowers the costs, precision medicine is taking root in the scientific and medical communities. **Lewis C. Cantley, PhD**, Director of the Cancer Center at Weill Cornell Medical College and NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and **Stephen G. Emerson, MD, PhD**, Director of the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/Columbia University Medical Center – pioneering cancer researchers in their own right – are charting an important course in cancer research and treatment as leaders of the Hospital’s cancer programs.

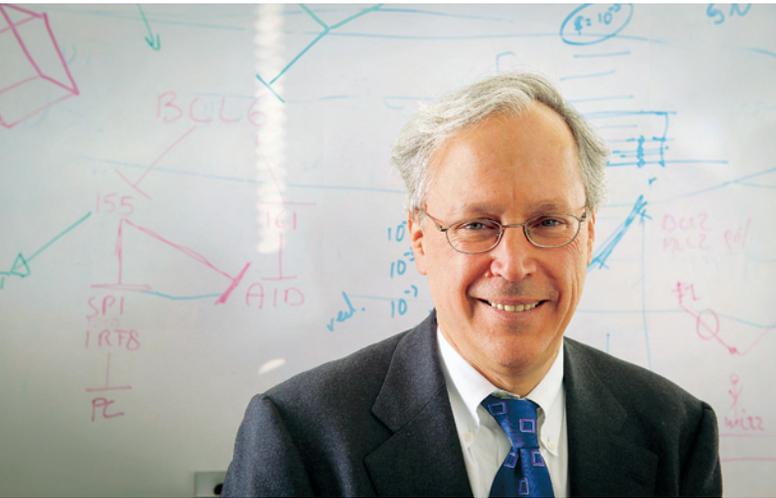
At Weill Cornell, Dr. Cantley – a proponent of team science – is developing an infrastructure for the Cancer Center that will facilitate the transition from identifying drug targets to science-based clinical trials. “In order to figure out how to use these new drugs, you need basic scientists, surgeons and clinicians, and molecular pathologists all working together as a team to identify the targets to go after and, importantly, to then develop biomarker-driven clinical trials,” says Dr. Cantley, the Margaret and Herman Sokol Professor in Oncology Research and Professor of Cancer Biology in Medicine.

Under Dr. Emerson’s direction, the National Cancer Institute-designated Herbert Irving Comprehensive Cancer Center – one of only three centers so designated in New York State – is expanding on its work with a goal of becoming the nexus of cancer prevention, treatment, and lifesaving research. “Our scientists are pursuing basic discoveries in cancer biology that we will directly translate into improved treatments for our local patients, and patients throughout the nation and beyond,” says Dr. Emerson, the Clyde Wu Professor of Immunology and Medicine. “To achieve these goals requires work on many levels, taking advantage of genetics and protein chemistry by using DNA, RNA, and protein sequencing to make personalized medicine a reality.”



Dr. Lewis C. Cantley, Director of the Cancer Center at Weill Cornell Medical College and NewYork-Presbyterian, is developing a research program based in team science.

“I think we are at the tipping point for breakthroughs in targeted therapy in which you develop drugs that hit the very gene, or gene product, that is driving the cancer,” says Dr. Cantley. “This is allowing us to divide cancers into smaller and smaller subgroups.”



As the Director of the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia, Dr. Stephen G. Emerson is growing a major research and clinical program in hematological cancers.

“The challenge is how do we change the testing of patient samples and how do we change the laboratories so that they test for the right things as new information comes along,” adds Dr. Emerson. “And then how do we integrate this into prevention, screening, diagnosis, and treatment. It’s a very exciting time.”

NewYork-Presbyterian Hospital and its affiliated medical schools, Columbia University College of Physicians and Surgeons and Weill Cornell Medical College, have significant efforts underway devoted to doing just this. Here clinicians and scientists are moving research forward in the development of targeted therapies for hematological malignancies and solid tumor cancers.

Transforming Treatment for Hematological Cancers

John P. Leonard, MD, Richard T. Silver Distinguished Professor of Hematology and Medical Oncology and Professor of Medicine at Weill Cornell Medical College, has been with Weill Cornell since his training in the early ‘90s as a resident, chief resident, and hematology/oncology fellow. Today, Dr. Leonard wears many hats, developing and implementing strategic research agendas in hematology/oncology within the institution and at the national level.

Dr. Leonard comes to his recent appointments as Associate Dean for Clinical Research at Weill Cornell and Director of the Joint Clinical Trials Office at Weill Cornell Medical College and NewYork-Presbyterian/Weill Cornell after serving many years as Chief of the Lymphoma/Myeloma

Service, establishing a leading center internationally in lymphoma management. Most recently, he was named Chair of the Lymphoma Committee for the prestigious National Cancer Institute-sponsored group, the Alliance for Clinical Trials in Oncology, where he is spearheading the national agenda for lymphoma research and shepherding Phase II and Phase III clinical trials funded by the National Cancer Institute at medical centers across the country. In this role, Dr. Leonard is directing a team of clinical and translational lymphoma researchers to create and implement new standards of treatment, as well as foster the development of novel therapeutics.

Dr. Leonard became involved in lymphoma research about 15 years ago. “That was a time when monoclonal antibody-based therapies were coming onto the scene,” he says. “In fact, the biggest impact in lymphoma over the last decade or so has been through the incorporation of monoclonal antibodies. We were involved in many of the pivotal trials leading to the approval of new drugs, and we continue to be a center for the development of new monoclonal antibody therapies.”

We have to integrate our clinical information and our historical data in ways to treat patients with newer data based on molecular targets. That’s the challenge for us.

– Dr. John P. Leonard

Dr. Leonard’s research endeavors have taken a number of different turns since then, some of which are based on laboratory collaborations with colleagues in other fields. With **Ari M. Melnick, MD**, Director of the Epigenomics Core Facility at Weill Cornell, and his team, Dr. Leonard and his group are looking at therapies to alter the epigenome in order to make cells more sensitive to chemotherapy and other treatments. With **Selina Chen-Kiang, PhD**, in Pathology and Laboratory Medicine, they are pursuing both



Dr. John P. Leonard is guiding the future of lymphoma research at the national level as Chair of the Lymphoma Committee for the National Cancer Institute-sponsored group, the Alliance for Clinical Trials in Oncology.

new strategies to target the cell's cycle in lymphoma and novel combinations of cell cycle-targeted drugs.

"We're also using imaging, including PET scans and other technologies, to predict who is going to do better or do worse, and tailor treatments on that basis," adds Dr. Leonard. "We're working with pharmaceutical and biotech companies to identify the most promising drugs that target new pathways in lymphoma, helping to identify the appropriate combinations and in what patient populations. And on the national level, we are participating in large international and national Phase III trials that can lead to new standards of care."

A United Front in Leukemia Research

Earlier this year, the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia welcomed five clinician-scientists specializing in leukemia and related diseases from Memorial Sloan-Kettering Cancer Center. Among them is **Nicole Lamanna, MD**, who joined the Hematologic Malignancies Section of the Hematology/Oncology Division. An experienced clinical investigator, Dr. Lamanna is developing a clinical trial portfolio in chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL) for patients who are

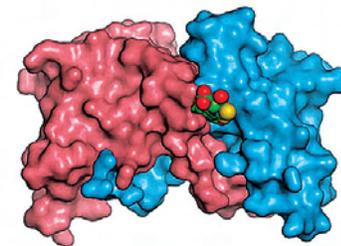
newly diagnosed and untreated; for those who require multiple or salvage chemotherapy as their disease progresses over the years; and for patients over the age of 65 who are more vulnerable to the toxic effects of current therapies. She

is particularly involved in the clinical trial development of combination therapies that include chemoimmunotherapy, immunomodulatory drugs, novel kinase inhibitors, and monoclonal antibodies for both CLL and ALL.

"My focus is not only on novel chemotherapies, but also on traditional chemoimmunotherapy drugs combined in different ways," says Dr. Lamanna. "We're looking to improve the efficacy of these drugs and to increase their safety profiles as well. There are several novel therapies for CLL ready for clinical trials that patients can't access outside an academic medical center until they are approved. We're trying to expedite taking these drugs into late phase studies and then onto the FDA for approval."

According to Dr. Lamanna, because many of these drugs are more targeted, she and her colleagues are hopeful that they are getting closer to identifying therapies that are potentially curative for CLL. "The world of CLL is rapidly changing and it's exciting to be part of the national and international teams that are looking at these novel therapies," adds Dr. Lamanna. "We want to change the paradigm of treatment of CLL by moving away from the more toxic therapies and allow for more targeted therapies."

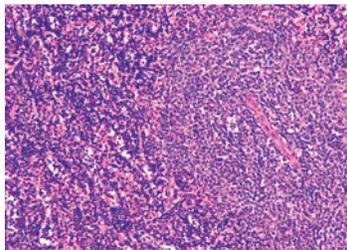
Specifically, Dr. Lamanna is looking at small molecule inhibitors, such as Bruton's tyrosine kinase inhibitor (BTK), PI3-kinase (PI3K), and Bcl-2 inhibitor, which target the B-cell pathway development. "There are now targeted therapies for these specific kinases," says Dr. Lamanna. "The focus on some of these new, novel kinase inhibitors – particularly the BTK inhibitor – is what's causing all the excitement in CLL. Of course, monoclonal antibodies in CLL are very, very important as well. A lot of these new inhibitors are being combined with some of these monoclonal antibodies because they're also less toxic than traditional chemoimmunotherapy regimens."



Transcription factors have been shown to play critical roles in tumorigenesis, especially in the hematological malignancies.

Unlike CLL or acute myeloid leukemia, there are only a few thousand cases a year of ALL. A much smaller number of these are of a particular subtype of ALL called Philadelphia Chromosome-positive ALL. In this particular subset one of the tyrosine kinase inhibitors that has been developed for a different chronic leukemia, called chronic myelogenous leukemia (CML), also works for Philadelphia Chromosome-positive ALL. “It’s amazing in the world of leukemia that these diseases are uncommon compared to breast cancer and lung cancer, yet, some of these targeted therapies are being found to work in rare diseases,” says Dr. Lamanna.

Dr. Lamanna also focuses on developing safe therapies for older patients with leukemia. “We used to open clinical trials for everyone with CLL, but the median age for these patients is 72. Many of the therapies that we’ve been using for years are much more toxic to older individuals,” she says. “Patients shouldn’t be excluded because of their age, so we have started to develop trials that are specific for patients 65 years and older.” In fact, Dr. Lamanna was one of the first to initiate clinical trial development exclusive to older individuals. “I have hundreds of CLL patients in my practice because it’s the majority of what I do – probably



Chronic lymphocytic leukemia cells

more than most clinicians in the country. Also, by being at Columbia, I am able to take my patients’ care to the next level. There are a lot of side effects with treatment for leukemia – infections and dermatological issues, among others – that require interdepartmental services. The university setting allows us to do new research programs involving these other issues.”

Dr. Lamanna is joined in her efforts by **Joseph G. Jurcic, MD**, whose research focuses on using antibodies to harness the body’s immune system to kill leukemia cells and to deliver radiation treatment directly to leukemia cells; **Mark G. Frattini, MD**, whose laboratory research seeks to define more precise targets for the development of novel anti-cancer therapies; **Mark L. Heaney, MD, PhD**, who studies myeloproliferative diseases; and **Todd L. Rosenblat, MD**, whose clinical research is in acute myelogenous leukemia.

“Because we work so well together, even though each of us has individual expertise with different leukemias, we are able to pool our findings to influence treatment for all hematological cancers,” says Dr. Lamanna.

“There are a few cancers that are the result of only one mutation, including one type of leukemia, called CML, and a type of lymphoma, called Burkitt’s lymphoma,” says

Dr. Emerson. “Every other cancer is most likely caused by at least two mutations – probably more. If we’re going to effect a cure, we will have to identify each of those mutations and then target them.”

The additional layer of complexity, notes Dr. Emerson, is that there are mutations in our cells all of the time. “Most of these mutations don’t matter because they are silent – they don’t cause a change in the protein,” explains Dr. Emerson. “So when you look at a tumor you have to distinguish those that matter from those that don’t. Researchers are also



Drs. Joseph G. Jurcic, Nicole Lamanna, and Mark G. Frattini are among the faculty of the Hematology/Oncology Division at NewYork-Presbyterian/Columbia who are making major inroads in the development of targeted therapies for leukemia and related diseases.

identifying the right targets to try to kill the cancer while avoiding normal cells. What precision medicine should do is guide a patient's rational place in a clinical trial."

The research in bone marrow stem cell biology of Dr. Emerson has led to new medical therapies in use worldwide. He continues to pursue research on what makes bone marrow blood stem cells grow into mature, functional blood cells. "We're investigating how they respond to signals that make them stop growing when cancer develops and how to fix that," says Dr. Emerson. "We don't have to understand the biology of every cell; we have to understand the biology of the one cell in a thousand that gives rise to new cells. Imagine not treating patients with toxic blasts of chemotherapy, but just picking out the stem cells that matter most with a magic bullet. It's a Copernican Revolution."

A drug may work for one individual, but based on molecular genetic profiling, may not be good for another individual. We're trying to hone down and find targeted therapies for each person's disease.

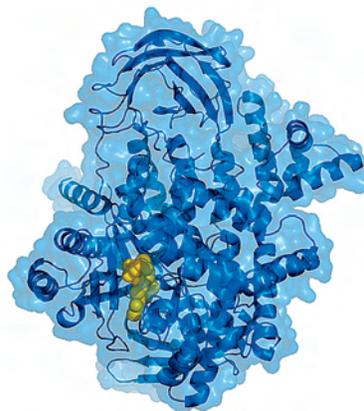
– Dr. Nicole Lamanna

Targeting Cancer Subtypes: A New Way of Thinking

Dr. Cantley's breakthrough discovery of PI3-kinase (PI3K), the most frequently mutated gene in cancer, continues to inform his research. There are now 20 different PI3K inhibitor drugs in Phase I, II, and III clinical trials, including for lymphomas and breast and prostate cancers. PI3K is also linked to diabetes, and Dr. Cantley and his colleagues are exploring how insulin is driving cancer since insulin is the "champion activator of PI3K."

"In fact, in the subset of cancers where there is a strong correlation between obesity and diabetes you see very high frequencies of mutations in PI3K," says Dr. Cantley. "Endometrial and breast cancers, for example, have very high rates. There's a lot of excitement in my lab and in **Andy Dannenberg's** lab about the connection between obesity in type 2 diabetes and breast cancer. If one can prevent diabetes and prevent obesity, then we can lower the risk of the cancer. We're trying to understand why those correlations occur because it may suggest the potential for targeted approaches."

One concept that Dr. Cantley's lab has been exploring is the idea that very high levels of serum insulin cause



When Dr. Lewis Cantley and his colleagues discovered phosphoinositide 3-kinase, they opened the door to countless new drug targets in cancer.

accelerated breast cancer. "I think we will we learn in the future that patients with high levels of insulin receptor in their tumor should probably avoid insulin," says Dr. Cantley.

In collaboration with researchers at MD Anderson Cancer Center, Dr. Cantley and his team are investigating endometrial cancers in obese versus non-obese patients, specifically looking at gene mutations. "Most patients with endometrial cancer are cured by surgery if you find it early enough, but about 20 percent are not," says Dr. Cantley. "The disease is either too advanced or they've relapsed. There has not been a new drug approved in 30 years, so the prognosis is the same as it was 30 years ago. We need better therapies in that setting.

"Interestingly, endometrial cancer correlates strongly with obesity and diabetes more than any other disease," continues Dr. Cantley. "We're asking if the same frequency of mutations exists in patients who are obese versus those who are not. Ultimately, you want to know if that insulin receptor is present in that cancer and then the outcome. This is a type of precision medicine that may even help us prevent cancer if we do it in a logical way. It can certainly help prevent the re-emergence of cancer, or enable patients to respond better to existing therapies."

In applying precision medicine to his current research, Dr. Cantley follows two precepts: "Know your enemy," and, "Divide and conquer." "Once you understand the mechanisms in the various subsets of cancer, you can divide them into clinical trials based on what's happening in a particular patient," notes Dr. Cantley. "That's what we mean by precision and what we mean by targeted. It's a lot of work up front, but once we've solved it, we've solved it forever, making cancer only a nuisance disease for our grandchildren. That's my goal."

NEW INSTITUTE FOCUSES ON PRECISION MEDICINE



Mark A. Rubin, MD, the Homer T. Hirst III Professor of Oncology, Professor of Pathology and Laboratory Medicine, and Professor of Pathology in Urology, is among the country's foremost board-certified, academic anatomic pathologists and has received wide recognition for advancing the field of biomarkers in prostate cancer. Now, as Director of the new Institute for Precision Medicine at Weill Cornell Medical College and NewYork-Presbyterian Hospital, Dr. Rubin is leading efforts to replace the traditional one-size-fits-all medicine model with one that focuses on targeted, individualized patient care using a patient's own genetic profile and medical history.

"We're looking for very specific alterations or mutations that are seen in an individual's tumor and target therapy so that it really caters to that one specific case," says Dr. Rubin. "Genomic analyses of tumor tissue will enable researchers to help patients with advanced disease and no current treatment options, as well as isolate the causes of drug resistance in patients who stop responding to treatments, redirecting them to more successful therapies. This will revolutionize the way we treat disease, linking cutting-edge research and next-generation sequencing

Renowned prostate cancer and genomics expert, Dr. Mark A. Rubin is leading a cutting-edge center at NewYork-Presbyterian/Weill Cornell for targeted, individualized patient care based on genetic profiles.

in the laboratory to the patient's bedside. It's a game-changing time in medicine."

In his own laboratory, Dr. Rubin uses whole genome sequencing to investigate DNA mutations that lead to prostate cancer. His groundbreaking research investigating molecular biomarkers distinguishing indolent from aggressive disease has led to landmark discoveries that revolutionized the understanding of prostate cancer's molecular underpinnings. This includes co-discovering two of the most common mutations in prostate cancer, the TMPRSS2-ETS rearrangements and SPOP mutations. Dr. Rubin is one of the principal investigators of a multi-institutional \$10 million grant from Stand Up 2 Cancer and the Prostate Cancer Foundation, addressing patients with advanced prostate cancer through a multi-phase approach employing next generation sequencing to help guide the direction of future clinical trials.

"We are going to be doing this in real time for men with advanced cancers," notes Dr. Rubin. "So we'll learn about why they are responding and, importantly, about why they are not responding. The team science element is absolutely critical. It allows the handoff from discovery all the way to clinical implementation to occur much more rapidly. Everyone is talking and learning — we understand what may be a limitation to one lab is something that another lab can readily do. These are the types of communications through team science that are key to making advances."

ALUMNI NEWS

NewYork-Presbyterian/Columbia Society of the Alumni

On Tuesday, October 29, 2013, the Society honored two distinguished alumni: Donald S. Kornfeld, MD, Attending Psychiatrist and Professor Emeritus of Psychiatry at NewYork-Presbyterian Hospital/Columbia University Medical Center, and Paul B. Rothman, MD, Dean of the Medical Faculty and Chief Executive Officer of Johns Hopkins Medicine at the Annual

Alumni Dinner. Barbara Barlow, MD, FACS, FAAP, Founder and Executive Director of Injury Free Coalition for Kids and Professor of Surgery in Epidemiology at Columbia University Mailman School of Public Health, was the keynote speaker.

For information about the NewYork-Presbyterian/Columbia Society of the Alumni, please contact the Alumni Office at alumnisociety@nyp.org or (212) 342-0954.

Office of Medical Affairs

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Continuing Medical Education (CME) activities are provided through **Columbia University College of Physicians and Surgeons**: (212) 305-3334 and **Weill Cornell Medical College**: (212) 746-2631. Both institutions are accredited by the Accreditation Council for Continuing Medical Education (ACCME) to authorize and issue CME credit. For all upcoming education events through NewYork-Presbyterian Hospital, visit www.nyp.org/pro.

Brain and Spine 2013

Date: November 15, 2013
Location: Weill Cornell Medical College
1300 York Avenue, New York, NY 10065
For more information and registration, contact Jessica Grajales, CME Coordinator, at (212) 585-6800 or nypcme@nyp.org.

Update in Gastroenterology, Hepatology and Nutrition

Dates: December 6-7, 2013
Location: Columbia University Medical Center
Hammer Health Sciences Building
Room 401
701 West 168th Street, New York, NY 10032
For more information and registration: (212) 305-3334 or cme@columbia.edu.

7th Minimally Invasive Spine Surgery and Navigation Hands-on Symposium

Dates: December 12-14, 2013
Location: Weill Cornell Medical College
1300 York Avenue, New York, NY 10065
For more information and registration, contact Jessica Grajales, CME Coordinator, at (212) 585-6800 or nypcme@nyp.org.



The Herbert Irving Comprehensive Cancer Center (HICCC) of Columbia University is dedicated to understanding the biology of cancer and to applying that knowledge to the design of cancer therapies and prevention strategies that reduce its incidence and progression and improve the quality of the lives of those affected by cancer. The HICCC is one of only 41 NCI-designated comprehensive cancer centers in the United States.

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PROFESSIONAL RESOURCES

NewYork-Presbyterian Alumni Website – nyp.org/alumni

The Alumni Association website is a valuable resource for the more than 10,000 physicians who have trained at NewYork-Presbyterian.

Educational Programs – nyp.org/pro

- CME Activities
- Newsletters

For more information about campus-specific Alumni Associations, contact:

Tamiko B. Collier NewYork-Presbyterian Hospital/ Columbia University Medical Center 654 West 170th Street New York, NY 10032 (212) 342-0954 tac9036@nyp.org	NewYork Weill Cornell Medical Center Alumni Council (CAC) 525 East 68th Street, Box 123 New York, NY 10065 (646) 317-7418 center_alumni_council@nyp.org weill.cornell.edu/about-us/cac
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