"Learn from yesterday. Live for today. Hope for tomorrow.

The important thing is not to stop questioning."

—Albert Einstein

Columbia University
Medical Center

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Columbia University
Medical Center

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Columbia University Medical Center

Letter from the Director

Riccardo Dalla-Favera, MD

Riccardo Dalla-Favera, MD, has been the Director of the Herbert Irving Comprehensive Cancer Center following a national search in March 2005. Dr. Dalla-Favera is an internationally prominent scientist and experienced administrator at CUMC.

Albert Einstein epitomized the essence of the scientific method, where passionate curiosity is a prerequisite for progress. Basic science investigators, clinical researchers, and population scientists at the Herbert Irving Comprehensive Cancer Center (HICCC) of Columbia University share that passionate curiosity. Along with a collegial spirit and the superior resources of a world-class multi-campus university, this combination sets the stage for significant advances in our quest to conquer cancer.

What is it that makes a scientist devote every minute of his workday, and many afterward, thinking about how the Notch protein influences cancer development? Why is a physician so concerned about the side effects of the chemotherapy she prescribes for her patients that she directs clinical research to find ways to ameliorate them? Why does the epidemiologist on West 168th Street work so hard to understand why people in Bangladesh are developing skin cancer from their drinking water? The answer to all of these questions: passionate curiosity.

That passion is what drives HICCC to be an institution dedicated to preventing and curing cancer through innovative research, the education of researchers and clinicians, and the delivery of outstanding patient care. We have more than 200 members from six schools at Columbia University. Our location in one of the most diverse areas of New York City offers us unique opportunities to understand how cancer affects people differently, and also enables us to provide sophisticated care for all people, regardless of their backgrounds.

We've made major innovations in the structure of the HICCC in the past several years to streamline our research programs so they stand to make the most impact on the problem of cancer:

- Our two Basic Science Programs delve into the intricate interplay between genetic factors and signaling pathways that lead to cancer, expanding our knowledge of normal and cancer cell biology and pinpointing targets that may guide the development of novel therapies.
- Our Disease-Specific Programs focus on important and challenging cancers, leading to clinical trials of new therapies and yielding research findings with the most potential to improve the lives of patients with these diseases.
- Our two Population Science Programs harness the renowned epidemiologic expertise of the Mailman School of Public Health to learn how cancer affects different populations in different ways—knowledge which not only may enhance the delivery of care, but also inform new avenues of basic science research. These programs are supported by the expertise and technology of our 12 Shared Resources.
- A vibrant educational program fosters cancer education across the cross section of students from undergraduate to medical school and postdoctoral fellowships.

We are entering a historic moment in oncology. Today more than ever, we are learning how to develop new therapies that zero in on novel molecular targets. What remains a challenge is to effectively educate people about these advances so they can adequately benefit from them. Only when discovery and education go hand-in-hand can we truly move forward in our quest to control cancer.

I'd like to take this moment to thank all of our supporters who helped us reach this point—especially Herbert Irving, whose generosity, foresight, and appreciation of the importance of research strengthened our institution and propelled us into this century. I'd also like to thank all of the faculty and staff of the HICCC, who form the bedrock of our institution and whose passionate curiosity fuels all that we do. It is your dedication, talent, and unflagging commitment that enable us to make headway against this challenging disease.

Riccardo Dalla-Favera, MD
Director, Herbert Irving Comprehensive Cancer Center
Director, Institute for Cancer Genetics
Percy and Joanne Uris Professor of Clinical Medicine
Professor of Genetics & Development
Professor of Pathology & Cell Biology

History of the Herbert Irving Comprehensive Cancer Center

Columbia University was founded in 1754 as King's College by a royal charter of King George II of England. It is the oldest institution of higher learning in New York State, and the fifth oldest in the United States. King's College organized a medical faculty in 1767, and was the first institution in the North American colonies to confer the degree of Doctor of Medicine.

When Columbia-Presbyterian Medical Center officially opened in 1928, it was the first such center to combine teaching, research, and patient care. This multifaceted approach to medicine is now a hallmark of academic medical centers. Cancer research at Columbia dates to 1911, with the creation of the Institute of Cancer Research. The National Cancer Institute formally recognized the Cancer Center at Columbia University in 1972, granting the prestigious "comprehensive" status in 1979 and providing federal funding to bolster our cancer research efforts.

In 1996, New York City philanthropist and food distribution pioneer Herbert Irving, who had begun his relationship with Columbia as a patient, donated $10 million to support cancer research and patient care. His gift made him the largest donor at that time in the history of Columbia-Presbyterian Medical Center, bringing his total contributions to nearly $35 million. The cancer center was named the Herbert Irving Comprehensive Cancer Center in his honor.

Like today's cancer researchers, Mr. Irving was a pioneer. As a returning World War II veteran, he recognized the market potential of the frozen food used to feed troops overseas. On the home front, frozen foods became attractive to consumers because canned foods that made demands on precious metal were rationed, while frozen foods were not.

After the war, Mr. Irving joined Global Frozen Foods, a business started by his brother-in-law a few years earlier. Mr. Irving built Global into the largest frozen food distributorship in New York City. In 1969, Global and eight other distributors from across the country created one of the first and largest successful business partnerships, known today as SYSCO (Systems and Services Company) Corporation.

Speaking on behalf of himself and his wife, Florence, Mr. Irving said, "There is a renaissance in cancer care going on at Columbia-Presbyterian. Florence and I are enormously proud to be a part of it. We hope our contribution will lay the groundwork for advances in research and treatment for this deadly disease."

Riccardo Dalla-Favera, MD, was named Director of the HICCC in March 2005. After an in-depth evaluation of cancer-related research and clinical activities and facilities, the HICCC was subsequently restructured around scientific themes rather than departmental affiliations, and now includes basic science, disease-specific, and population science programs with a greater focus on cancer.

In addition, the Clinical Research Management Office was reorganized to enhance clinical trials enrollment, Shared Resources were expanded, and the HICCC made a significant investment in bioinformatics to support our investigators. The revised structure of the HICCC invigorates and supports the interdisciplinary collaboration and translational research that are so vital for progress to be made against cancer.

These programs bring together HICCC researchers with faculty from other members of the Columbia University family, including the College of Physicians & Surgeons and the world-renowned Mailman School of Public Health. Coupled with its location in one of Manhattan's most diverse neighborhoods, such collaborations place the HICCC at the forefront of research to understand the biology and population dynamics of cancer—yielding knowledge which will ultimately result in better outcomes for patients everywhere.

SENIOR LEADERSHIP:

Riccardo Dalla-Favera, MD
Director, Herbert Irving Comprehensive Cancer Center

Edward P. Gelmann, MD
Deputy Director for Clinical Research

Richard Baer, PhD
Associate Director for Basic Research

Andrea Califano, PhD
Associate Director for Biomedical Informatics

Alfred I. Neugut, MD, PhD
Associate Director for Population-based Science

Benjamin Tycko, MD, PhD
Associate Director for Shared Resources

Cory Abate-Shen, PhD
Associate Director for Education

Sadie Maloof, MBA, MSed
Associate Director for Administration

Carlos Cordon-Cardo, MD, PhD
Chernow Professor of Clinical Urological Sciences (in Urology) and Professor of Clinical Pathology & Cell Biology (in the Herbert Irving Comprehensive Cancer Center)

BASIC SCIENCE PROGRAMS

ASSOCIATE DIRECTOR

Richard Baer, PhD

Richard Baer, PhD, Professor of Pathology, was recruited to CUMC in 1999 and has founded and successfully developed the Institute for Cancer Genetics along with Dr. Dalla-Favera.

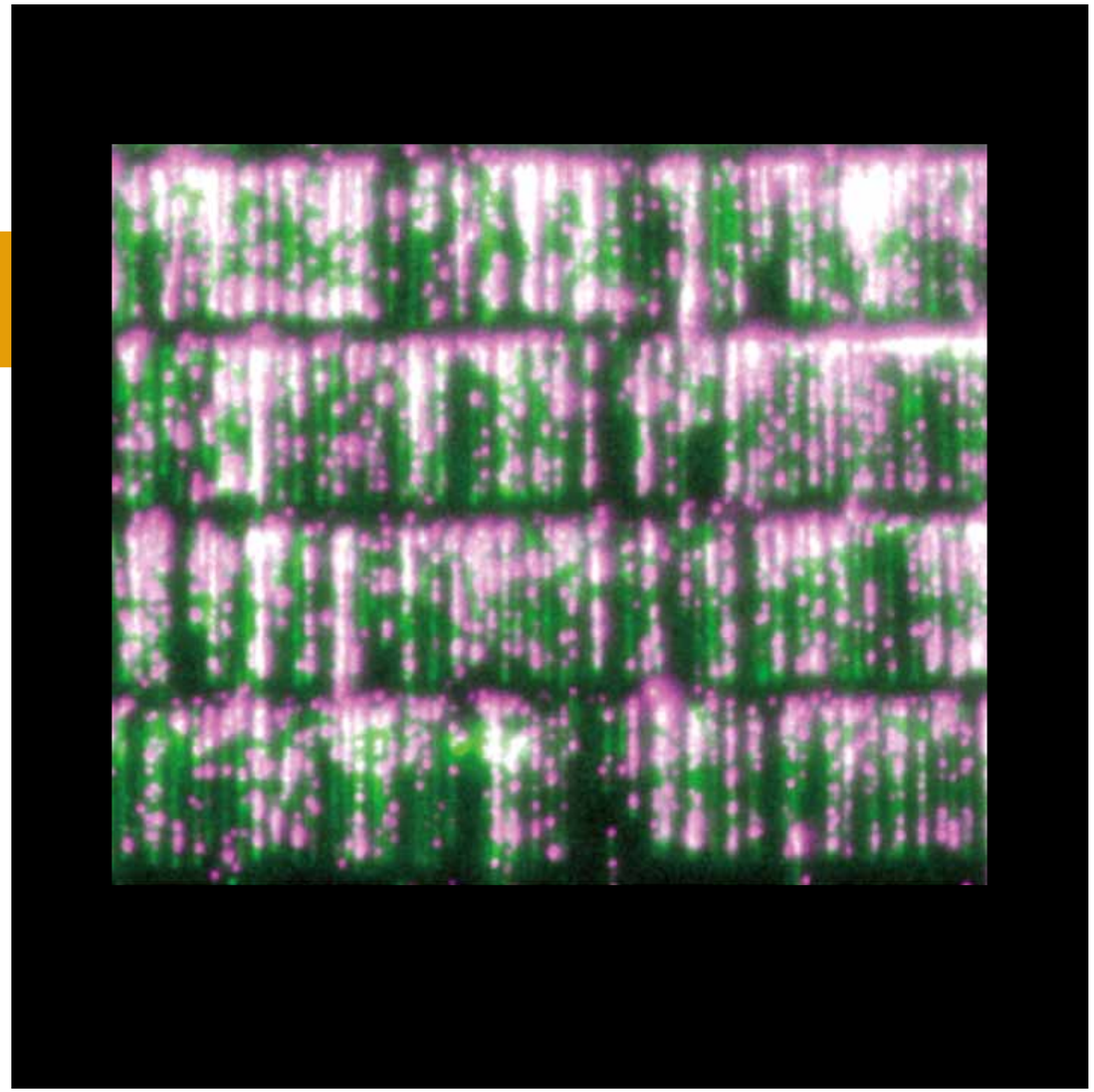
Richard Baer, PhD, Associate Director of Basic Science Programs at the Herbert Irving Comprehensive Cancer Center, was a graduate student in the 1970s when the field of molecular biology first began to bear fruit. As molecular biological techniques were refined in the 1980s and 1990s, many of the human genes responsible for cancer development were identified for the first time. And by the year 2000, the world began to benefit from anticancer drugs that target specific molecules and pathways driving cancer growth and spread.

Having witnessed these developments, Dr. Baer understands the clinical potential of basic scientific findings that begin in the laboratory, including research on normal cells that may initially appear to have nothing to do with cancer. Yet the study of normal cells gleans insights into what can go wrong to generate tumors.

"Cancer is a genetic disease, both from an inherited standpoint and, more significantly, because cells become cancerous following genetic changes in their DNA," explained Dr. Baer, whose own research focuses on the pathways through which *BRCA1* gene mutations can lead to hereditary breast cancer.

HICCC investigators benefit from collaborations not only with each other, but also with researchers and faculty in other Columbia University schools—including basic science investigators at the main campus, clinicians at the College of Physicians & Surgeons, and epidemiologists at the Mailman School of Public Health. "As a result, cancer research in the HICCC is greatly enhanced by the broad scope of scientific expertise available at Columbia University," Dr. Baer noted.

Basic science programs at the HICCC include the Cancer Genetics and Epigenetics Program and Cancer Signaling Networks Program.



This image shows an example of a four-tiered DNA curtain (green) bound by fluorescently tagged nucleosomes (magenta). The DNA molecules are aligned at nanofabricated barriers to lipid diffusion. This technology allows the Greene lab to directly visualize DNA and proteins in real-time using total internal reflection fluorescence microscopy. Videos showing examples of these DNA curtains can be found at: thegreenelab.cumc.columbia.edu.

Cancer Genetics and Epigenetics

PROGRAM LEADER

Jean Gautier, PhD

Jean Gautier, PhD, is the Leader of the Cancer Genetics and Epigenetics (CGE) Program. Dr. Gautier has a dual role to encourage interactions among Program members and foster relations with other Programs, and to enhance new developments in cancer research by coordinating resources and opportunities for CGE members.

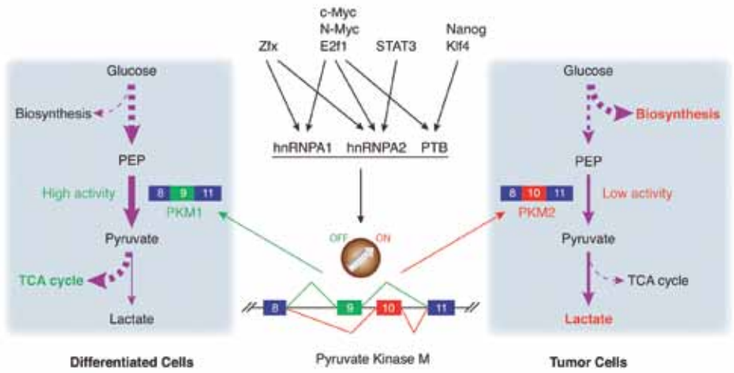
Cancer is a disease of genetic instability—whether due to a mutation in a gene passed down from a parent to a child, or to genetic changes that occur during a person's lifetime. "I don't know of any tumor that doesn't have some type of genetic instability," said Program Leader Jean Gautier, PhD. "Genetic instability can be an early triggering event or a later event. Regardless of when these events occur, the end result can be carcinogenesis."

Investigators in the Cancer Genetics and Epigenetics Program at the Herbert Irving Comprehensive Cancer Center are studying the mechanisms that maintain DNA repair pathways in order to understand normal cells and the genetic instability that arises in cancer and can induce cancer progression. "By clarifying how the normal genome remains stable, we can gain a better understanding of what happens when genetic stability is lost," added Dr. Gautier, whose own lab uses animal models such as frogs and mice to study DNA replication and repair mechanisms.

Since many anticancer drugs work by damaging a cancer cell's DNA, it is important to know how DNA repair occurs in normal cells. Researchers studying "genomic plasticity" at the HICCC are analyzing how DNA repair mechanisms are disrupted in cancer cells to generate genomic instability.

For example, Eric Greene, PhD, and his team are developing new techniques to stretch a single molecule of DNA and visualize how DNA repair proteins can move along the DNA strand, imaging it in real-time using optical microscopy. "We literally watch individual protein molecules or protein complexes as they interact with DNA," explained Dr. Greene. "Our goal is to reveal the molecular mechanisms that cells use to repair, maintain, and decode their genetic information."

Lorraine Symington, PhD, and her lab are making important discoveries regarding genes involved in the repair of DNA double-strand breaks: potentially lethal DNA lesions that can arise spontaneously during normal cell metabolism or upon exposure of cells to certain DNA-damaging agents.[1] Failure of a cell to



hnRNP proteins control the metabolic switch between oxidative phosphorylation (normal cells) and aerobic glycolysis (cancer cells) by regulating alternative splicing of pyruvate kinase (PKM) mRNA.

repair double-strand breaks in DNA can lead to cancer; similarly, inducing double-strand breaks in the DNA of cancer cells can kill them.

In addition to genetic changes in cancer, epigenetics has garnered much attention in recent years, even earning the cover of *TIME* magazine in January 2010. The National Institutes of Health (NIH) has made epigenetics a priority in its research portfolio, announcing in January 2008 that it is allocating some $190 million over five years to support research related to epigenetic gene regulation.

At the HICCC, a vigorous research effort is under way to use "genome-wide association studies" (GWAS) to map the attachment of methyl groups to specific gene components (alleles) on a DNA strand. A GWAS is defined as any study of genetic variation across the entire human genome that is designed to identify genetic features related to observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition (such as cancer).

Benjamin Tycko, MD, PhD, and his colleagues are using GWAS to study DNA methylation in cancer tissue, such as Wilms' tumor (a pediatric kidney cancer) and acute myeloid leukemia.[2] "We're measuring allele-specific methylation as a tool to find differences in cancer susceptibility among individuals," he explained. GWAS offers the potential to increase our understanding of basic biological processes affecting human health, to improve risk assessment and patient care, and ultimately to personalize medicine according to each tumor's genetic profile.

Scientists at the HICCC are also tracking the ways cancer manipulates the cell cycle—the series of steps that normal cells go through to grow, divide, and reproduce—including alterations in checkpoints that normally put the brakes on rampant cell growth. As cancer disrupts this cycle, it creates a wide variety of tumor cells, many of which learn to defy conventional anticancer therapies.

For example, the laboratory of Fred Chang, MD, PhD, is exploring the molecular mechanics of cell division and growth. Many of their studies deal with how cellular scaffolding structures, such as "microtubules" and "actin," are organized in the cell, and how they move key proteins or cellular components (organelles) to specific locations in the cell.[3]

Michael Sheetz, PhD, and his colleagues are designing technologies to monitor mechanical forces in cells that influence their ability to move and adhere to surfaces. They used an approach called laser trapping to identify an enzyme called "focal adhesion kinase" which is involved in the migration and adhesion of metastatic colon cancer cells.[4]

Concluded Dr. Gautier, "The work being done by investigators in this program will have a significant impact on our understanding of carcinogenesis and should enhance the development of novel targeted anti-cancer drugs personalized for each patient."

Publications

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2. Kerkel K et al. Genomic surveys by methylation-sensitive SNP analysis identify sequence-dependent allele-specific DNA methylation. *Nat Genet.* 2008;40:904-908.

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CANCER GENETICS AND EPIGENETICS: PROGRAM MEMBERS

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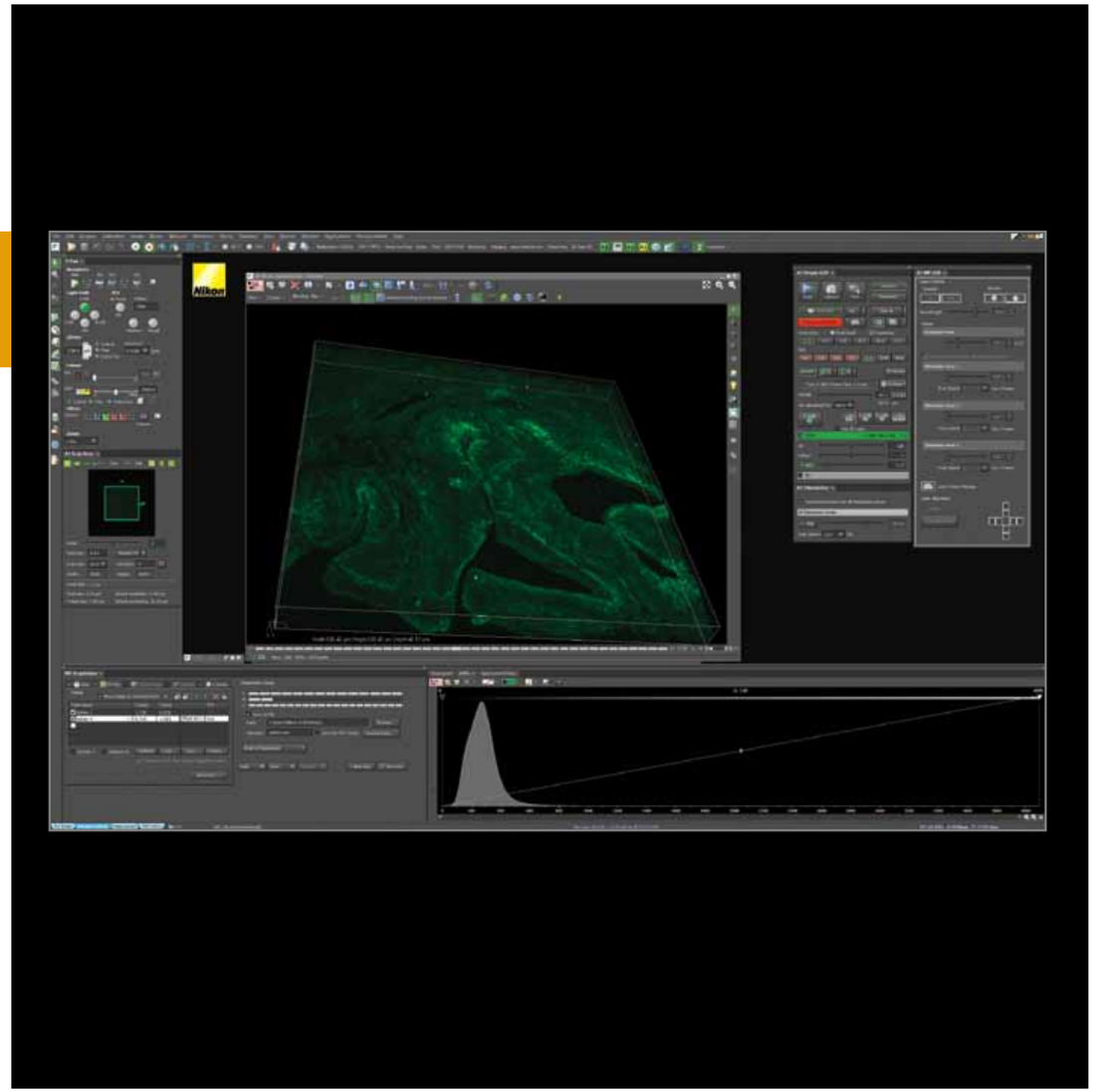


An image used for research from the Confocal Microscopy Shared Resource.

Cancer Signaling Networks

PROGRAM LEADER

Jan Kitajewski, PhD

PROGRAM CO-LEADER

Stephen P. Goff, PhD

Jan Kitajewski, PhD, is the Leader of the Cancer Signaling Networks (CSN) Program. The long-term goals of the program are to elucidate the signaling networks that influence tumor formation, to identify molecular components of these networks with potential clinical utility, and to promote translation of this knowledge into patient care.

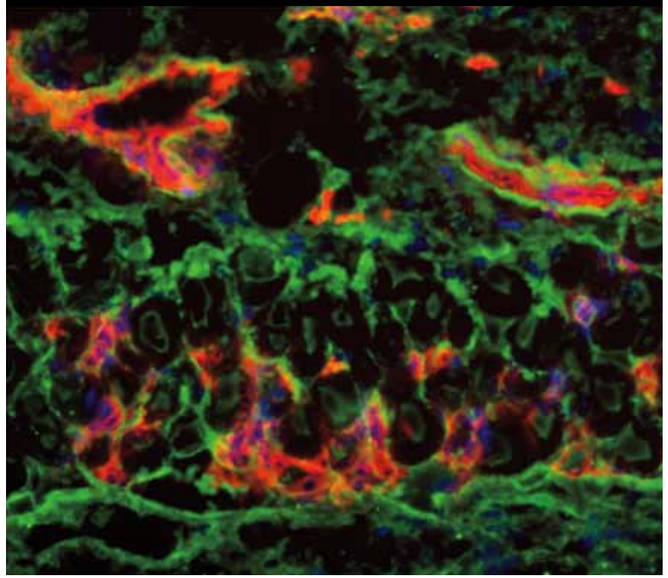
Stephen P. Goff, PhD, is the Co-Leader of the CSN Program. Dr. Goff is the Higgins Professor of Biochemistry at the College of Physicians & Surgeons of Columbia University and an Investigator of the Howard Hughes Medical Institute.

Bevacizumab, sunitinib, and temsirolimus are all novel targeted cancer therapies approved by the FDA. What do these agents have in common? They are anticancer drugs that work by targeting specific molecules in signaling pathways that fuel cancer growth, short-circuiting the lines of communication required for cancer cells to grow and spread. There has been an explosion in the development of such targeted drugs in oncology over the last decade, thanks largely to novel molecular biology techniques and the expanding knowledge of the human genome.

None of these advances would have been possible without the basic science that identified these pathways as critical to carcinogenesis. Researchers in the Cancer Signaling Networks Program of HICCC are elucidating the molecular biology of cell surface receptors, intracellular signaling pathways, proteins that promote or suppress cancer growth, and alterations in the tumor environment (notably, angiogenesis and inflammation).

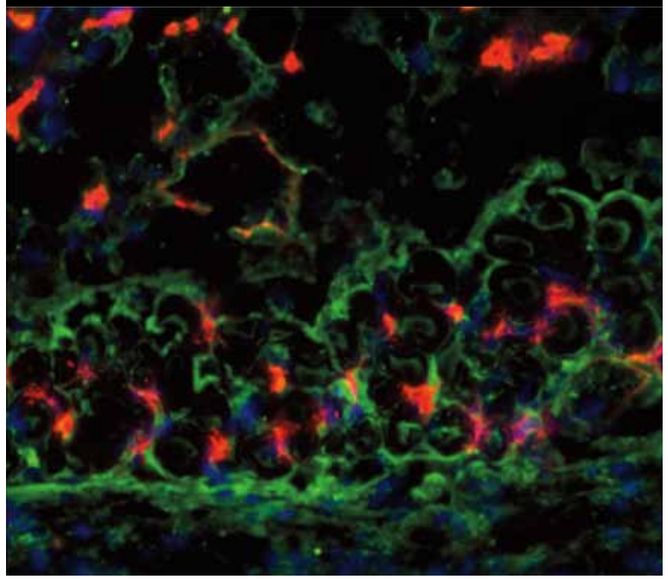
The study of these pathways requires a systems biology approach, a "big picture" look that takes into account the elaborate interplay between genes, proteins, and other molecules inside each and every cell to make an organism function a certain way. "Nothing is achieved by taking a gene-by-gene approach," said Andrea Califano, PhD. "They work together in pathways." Dr. Califano's laboratory uses systems biology to map the molecular interactions in human cells that give rise to malignant diseases such as B-cell lymphoma, breast cancer, and brain cancer.

VEGF



Vascular endothelial growth factor (VEGF) drives the growth of blood vessels (stained red) in an experimental model of pathological angiogenesis. The Notch1 decoy, an experimental therapeutic that targets the Notch pathway, reduces VEGF-driven vessel growth, resulting in smaller caliber vessels. A hallmark of VEGF action is the induction of matrix metalloproteinase 9 (MMP9) expression (stained green), which is reduced as a result of Notch1 decoy.

VEGF/Notch1 Decoy



Just as the various components of a cell interact with each other and their environment, so do the scientific members of the Cancer Signaling Networks Program. Various investigators are collaborating to contribute to our knowledge of angiogenesis—the development of blood vessels that tumors need to grow and spread. Many of the targeted anticancer agents that have been approved by the U.S. Food and Drug Administration in the last several years are angiogenesis inhibitors.

"The study of angiogenesis is here to stay, and is having a major impact on cancer therapy," noted Program Leader Jan Kitajewski, PhD. "The stage is set to make it a part of clinical care, but a lot of challenges remain in learning how to make it more effective." While angiogenesis inhibitors have extended the lives of many patients with advanced cancer, they are rarely curative.

Dr. Kitajewski and his team have learned that a signaling pathway involving the Notch protein regulates angiogenesis, and they have created an agent that restricts tumor growth by inhibiting this pathway. A colleague in the Cancer Signaling Networks Program, Jessica Kandel, MD, is analyzing this agent in models of pediatric tumors. The agent, called the Notch1 decoy, is in preclinical development.[1]

In addition to angiogenesis, chronic inflammation is increasingly being recognized as a biological process that increases the risk of tumor development, but little is known about the signaling pathways underlying this association. NF-kB has been implicated as a pivotal protein related to inflammation and cancer, since it is involved in the inflammatory response and is a hallmark of many tumor types.

At the HICCC, Sankar Ghosh, PhD, and his colleagues are seeking to understand the role of NF-kB in cancer and exploring the inhibition of this protein as a potential cancer treatment. The team had found that NF-kB activity is increased in estrogen-receptor negative breast cancers (which can be difficult to treat), and

that inhibiting the protein sensitizes breast cancer cells to chemotherapy.[2] Today they are continuing to study how NF-kB works and how its dysregulation contributes to cancer.

Oncogenes and tumor-suppressor genes are other critical players in the signaling pathways associated with cancer. HICCC scientists Antonio Iavarone, MD, and Anna Lasorella, MD, study the protein Id2 ("Id" for "inhibitor of differentiation") that is recruited by oncogenes to overcome the Rb (retinoblastoma) tumor-suppressor protein during the development of tumors of the nervous system. Among their current research efforts is the generation of new mouse models of nervous system malignancies that recapitulate the altered expression of Id proteins in human tumors.[3]

The work of investigators in the Cancer Signaling Networks Program is enhanced by the HICCC's cancer systems biology initiative, led by Dr. Califano. Scientists can use computer algorithms to identify master regulators of cancer initiation and progression, as well as their placement within signaling and transcriptional pathways. Said Dr. Kitajewski, "We can use a combination of algorithmic and high-throughput approaches to ask how relevant an activated pathway is in a cancer cell."

Drs. Iavarone and Califano have also shown for the first time how computationally inferred models of cellular regulation can be interrogated to identify genes that are causally related to the implementation of a specific tumor phenotype or characteristic.[4] In particular, they discovered that the simultaneous activation of the signaling molecules C/EBP and Stat3 in high-grade glioma is associated with the most aggressive subtype of the disease.

"The integration of computational models and experimental validation assays is absolutely vital for our work," added Dr. Califano. "Our field is growing so fast that we need the help of complex models running on supercomputers to move it forward."

Publications

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2. Biswas DK et al. NF-kappa B activation in human breast cancer specimens and its role in cell proliferation and apoptosis. *Proc Natl Acad Sci USA.* 2004;101:10137-10142.

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4. Carro MS et al. The transcriptional network for mesenchymal transformation of brain tumours. *Nature* 2010;463:318-25.

CANCER SIGNALING NETWORKS: PROGRAM MEMBERS

Axel, Richard: Professor, Biochemistry & Molecular Biophysics, Pathology

Blaner, William: Professor, Medicine

Breslow, Ronald: Professor, Chemistry

Canoll, Peter: Assistant Professor, Pathology

Cheng, Simon: Assistant Professor, Radiation Oncology

Costantini, Frank: Professor, Genetics & Development

Ghosh, Sankar: Professor and Chairman, Microbiology

Goff, Stephen: Professor, Biochemistry & Molecular Biophysics

Gottesman, Max: Professor, Biochemistry & Molecular Biophysics

Greenwald, Iva: Professor, Biochemistry & Molecular Biophysics

Halmos, Balazs: Assistant Professor, Medicine

Hendrickson, Wayne: Professor, Biochemistry & Molecular Biophysics

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Kandel, Jessica: Professor, Surgery

Lasorella, Anna: Assistant Professor, Institute for Cancer Genetics, Pathology, Pediatrics

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Zheng, Bin: Assistant Professor, Dermatology, Institute for Cancer Genetics, Pathology

DISEASE-SPECIFIC PROGRAMS

DEPUTY DIRECTOR

Edward P. Gelmann, MD

Edward Gelmann, MD, is a physician-scientist with extensive accomplishments in both basic and translational research. Dr. Gelmann brings to the HICCC extensive experience in the organization of clinical research infrastructure.

Investigators in the Herbert Irving Comprehensive Cancer Center's Disease-Specific Programs benefit from close collaboration with basic science investigators delving into the molecular biology of cancers, especially those that inflict the greatest burden on our society. Their ability to interact with population scientists in the Mailman School of Public Health also gives them a distinct advantage over investigators at other cancer centers: the expertise of world-renowned cancer epidemiologists working in one of the most ethnically diverse populations in the country.

As a result, HICCC researchers are in an enviable position, with the resources available to study the variability of different cancers in large populations, armed with the findings of laboratory investigators deciphering the molecular biology of the disease. The HICCC chose to focus its Disease-Specific Programs on the cancers that are among the most common—breast and prostate cancers—as well as the most clinically challenging—brain and hematological cancers. This structure is bolstered by a faculty of basic and clinical scientists, with many who do both, and new faculty are continuing to be recruited.

"Knowledge of the fundamental roots of cancer, coupled with clinicians with experience caring for patients, are what we need to make progress against the disease," said Edward P. Gelmann, MD, Deputy Director of the HICCC. "We've built the ship and we're bringing on the crew. We are well on our way."

Breast Cancer Program

PROGRAM LEADER

Ramon Parsons, MD, PhD

PROGRAM CO-LEADER

Dawn Hershman, MD

Ramon Parsons, MD, PhD, is the Leader of the Breast Cancer Program. Over the course of his career, Dr. Parsons has been the recipient of numerous prizes, grants, and awards. Dr. Parsons has also been a leader in the study of PTEN and PI3K.

Dawn Hershman, MD, MS, is the Co-Leader of the Breast Cancer Program. Since 2001, Dr. Hershamn has been the Director of the Oncology/Hematology Fellowship Training Program and the breast oncology clinic.

Drugs that home in on specific cellular receptors have revolutionized breast cancer care. Women whose cancers contain estrogen or progesterone receptors may benefit from tamoxifen and other drugs that target these proteins. Patients whose cancers overproduce HER2 are candidates for trastuzumab or lapatinib, which target this receptor.

But there is another group of women who do not stand to benefit from any of these drugs: those with "triple-negative" breast cancers, which do not contain estrogen or progesterone receptors or HER2. Triple-negative breast cancers tend to be more aggressive than other types, are more likely to recur, and are more common in African American and Hispanic women. They make up 90 percent of breast cancers that develop in women with a mutated form of the *BRCA1* gene.

With the ethnically diverse population of the Columbia University Medical Center neighborhood, a quarter of women with breast cancer treated at the Herbert Irving Comprehensive Cancer Center have the triple-negative type. HICCC investigators in the Breast Cancer Program are world leaders in the study of the molecular biology of this disease, working to delineate the pathways underlying its development and to pinpoint new therapeutic targets.

The study of signaling pathways involved in breast cancer is a major focus of HICCC investigators, who are also assessing novel treatments as well as the side effects of therapy. The program brings together basic science and clinical investigators as well as public health specialists. Much of the research in the program is funded by the U.S. Department of Defense and the Avon Foundation.

By its very nature, breast cancer is a tenacious disease. Breast cancer cells can leave the breast and travel throughout the rest of the body, seeding metastases along the way, and eventually make their way back to their original site. Unlike many cancers, which are often considered "cured" if the patient survives five years beyond diagnosis, breast cancers may lay dormant and then resurface ten years later, or even more.

"We need to identify a way to control breast cancer in a logical and rational way so that when a woman develops it, we can offer her effective, targeted treatment," said Program Leader Ramon Parsons, MD, PhD. "We have a healthy and vibrant program with investigators working toward that goal."

In 1997, Dr. Parsons and his colleagues identified a tumor-suppressor gene called *PTEN,* which when altered has been implicated in cancers of the breast, prostate, and brain. Normally, *PTEN* puts the brakes on the kind of rampant cell growth that leads to cancer. But when the *BRCA1* gene is mutated, *PTEN* loses its tumor-suppressing power.

Dr. Parsons and other HICCC scientists are evaluating an enzyme in the same signaling pathway as *PTEN*, called PI3 kinase, and its role in "basal-like" breast cancers (which make up the majority of triple-negative tumors).[1] "PI3 kinase is commonly mutated and *PTEN* is commonly inactivated in many breast cancers," he explained. "We want to see if we can target this pathway and intervene with effective new therapies." Richard Baer, PhD, and Thomas Ludwig, PhD, are also key investigators in this effort, working with a mouse model that mimics the development of breast cancer when *BCRA1* is mutated.

Dr. Parsons and other basic science researchers at the HICCC work closely with clinicians to obtain breast cancer tissue for their studies. The knowledge gleaned from such research can inform the direction of clinical trials. "Our goal is to have a clinical trial to offer every patient who walks in the door," said Dawn Hershman, MD, Program Co-Leader. Investigators are assessing new drugs and new combinations of existing drugs, and rotating the order of medications given to see what is most effective for shrinking and eliminating breast tumors.

One fruitful approach they use includes "window-of-opportunity" studies. During these clinical trials, women who have had a breast biopsy receive a particular drug before they have breast cancer surgery. Researchers analyze the breast tissue removed during the subsequent surgery. "This is a very good way for us to understand how the drug affects breast cancer tissue itself," noted Dr. Hershman. One such avenue of study involves the diabetes drug metformin, which lowers insulin levels by targeting the insulin growth factor receptor pathway—a chain of signals implicated in basal-like breast cancers.

While breast cancer therapies have improved patient outcomes, they are not without their side effects. A strong component of the HICCC's Breast Cancer Program is the study of the short-term and long-term side effects of treatment, how they influence a patient's compliance with therapy, and how to ameliorate them. For example, aromatase inhibitors (such as letrozole) can cause joint pain, paclitaxel can cause nerve damage, and doxorubicin and trastuzumab can affect heart function.

"If we can understand what puts people at risk of these toxicities and how to assess them, we can implement strategies to reduce those side effects," Dr. Hershman contended. Strategies under assessment include acupuncture for joint pain, coenzyme Q for cardiovascular side effects, and exercise for weight gain. Dr. Hershman has led studies showing that zoledronic acid can reduce the bone loss associated with some breast cancer therapies.[2,3]

Every step taken by HICCC Breast Cancer Program researchers propels the entire field forward. Concluded Dr. Hershman, "Each thing we do adds on to something else, reduces the rate of recurrence, and ultimately saves lives."

Publications

1. Maurer M et al. 3-Phosphoinositide-dependent kinase 1 potentiates upstream lesions on the phosphatidylinositol 3-kinase pathway in breast carcinoma. Cancer Res. 2009;69:6299-6306.

2. Hershman DL et al. Zoledronic acid prevents bone loss in premenopausal women undergoing adjuvant chemotherapy for early-stage breast cancer. *J Clin Oncol.* 2008;26:4739-4745.

3. Hershman DL et al. Prevention of bone loss by zoledronic acid in premenopausal women undergoing adjuvant chemotherapy persist up to one year following discontinuing treatment. *J Clin Endocrinol Metab.* 2010;95(2):559-566.

BREAST CANCER: PROGRAM MEMBERS

Baer, Richard: Professor, Institute for Cancer Genetics, Pathology

Chung, Wendy: Assistant Professor, Pediatrics

Clynes, Raphael: Associate Professor, Medicine, Microbiology

Crew, Katherine: Assistant Professor, Medicine

Desperito, Elise: Assistant Professor, Radiology

Fawwaz, Rashid: Professor, Radiology

Feldman, Sheldon: Associate Professor, Surgery

Gu, Wei: Professor, Institute for Cancer Genetics, Pathology

Hershman, Dawn: Assistant Professor, Epidemiology, Medicine

Hibshoosh, Hanina: Professor, Pathology

Hielscher, Andreas: Associate Professor, Radiology

Hsu Rohde, Christine: Assistant Professor, Surgery

Kalinsky, Kevin: Assistant Professor, Oncology, Division of Hematology and Medical Oncology

Konofagou, Elisa: Associate Professor, Biomedical Sciences

Lee, Francis: Associate Professor, Orthopedic Surgery

Ludwig, Thomas: Associate Professor, Institute for Cancer Genetics, Pathology

Maurer, Matthew: Assistant Professor, Medicine

McKinley, Paula: Assistant Professor, Psychiatry

Oster, Martin: Associate Professor,

Parsons, Ramon: Professor, Institute for Cancer Genetics, Pathology

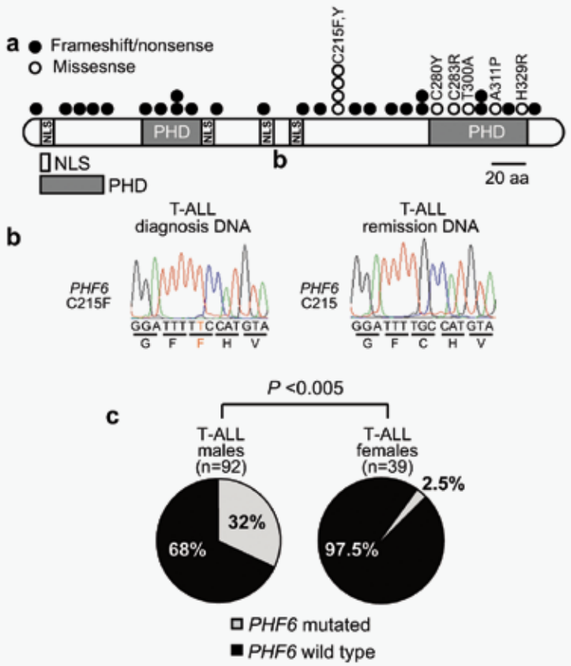
Russo, Donna: Genetic Counselor, Genetics & Development

Silva, Jose: Assistant Professor, Institute for Cancer Genetics

Taback, Bret: Assistant Professor, Surgery

Tager, Felice: Assistant Professor, Psychiatry

Van Heertum, Ronald: Professor, Radiology



T-cell acute lymphoblastic leukemia T-ALL is three times more frequent in males than in females. Based on this intriguing observation, the Ferrando lab aimed to identify a possible new T-ALL tumor-suppressor gene in chromosome X. Using exon capture and nextgen sequencing, they analyzed all coding exons in chromosome X in DNA samples from male T-ALL patients and demonstrated the presence of inactivating mutations and deletions in the X-linked plant homeodomain finger 6 (PHF6) *gene in about 20 percent of primary T-ALLs. Notably,* PHF6 *mutations are almost exclusively found in T-ALL samples from male patients. These results identify* PHF6 *as a new X-linked tumor suppressor in T-ALL. The importance of these results is highlighted by the proposed role of PHF6 as an epigenetic regulator of gene expression.*

PHF6, a new X-linked tumor suppressor gene mutated in human leukemia. a. *Schematic representation of the domain structure of the PHF6 protein, indicating the location of* PHF6 *mutations found in human leukemias.* ***b.*** *DNA sequence analysis of* PHF6 *in diagnostic and remission leukemia samples.* ***c.*** *Mutations in* PHF6, *located in chromosome X, are almost exclusively found in male leukemia patients.* Van Vlierberghe et al. Nature Genetics 2010;42:338 and Leukemia 2011;25:130.

Lymphoid Development and Malignancy Program

PROGRAM LEADER

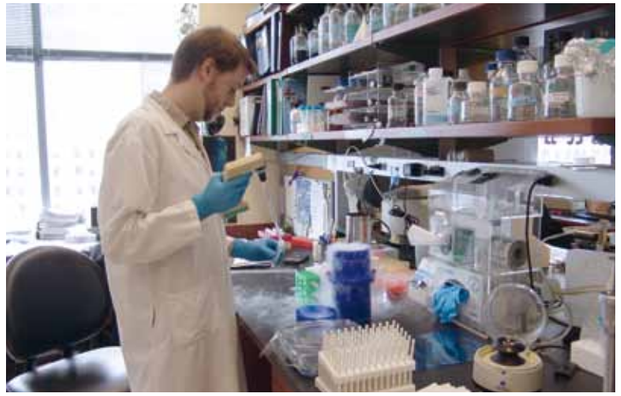
Riccardo Dalla-Favera, MD

Riccardo Dalla-Favera, MD, is the Leader of the Lymphoid Development and Malignancy (LDM) Program. The goal of the LDM Program is to improve outcomes and seek cures for patients with lymphoid malignancies, including acute lymphoblastic leukemia (ALL) and B-cell non-Hodgkin lymphoma (B-NHL).

Hematologic cancers, such as lymphoma and leukemia, consistently rank among the top ten most commonly diagnosed cancers in the United States. Nearly 75,000 people were diagnosed with lymphoma and over 43,000 with leukemia in 2010.

Members of the Lymphoid Development and Malignancy Program at the Herbert Irving Comprehensive Cancer Center are scrutinizing the unique biology of the major immune lymphoid cell types, B cells and T cells, to learn more about their specialized functions. B cells and T cells play vital roles in the body's immune response against foreign substances, but when their function goes awry, it can trigger the development of cancers such as acute lymphoblastic leukemia (ALL) and B-cell non-Hodgkin lymphoma (B-NHL).

A major strategy of the program has been to incorporate advanced bioinformatics and systems biology as critical tools for both basic and translational research. "By applying the tools of advanced genomics and bioinformatics with *in vivo* studies using genetically engineered mouse models, we are deciphering the signaling pathways underlying both normal lymphocyte development as well as the pathogenesis of B-cell lymphoma and T-cell leukemia," explained Program Leader and HICCC Director Riccardo Dalla-Favera, MD.



Research in the Lymphoid Development and Malignancy Program focuses on three primary areas:

Exploration of the cellular and molecular mechanisms regulating the normal development of B cells and T cells. In an effort to determine the role of microRNAs in B-cell development and the development of lymphoma, HICCC investigators led by Katia Basso, PhD, are constructing libraries of microRNAs that are expressed by mature B cells. RNA governs the production of proteins; microRNAs are short RNA segments that can interfere with protein synthesis, and alterations in microRNAs have been implicated in cancer development. The researchers have identified more than 75 new microRNAs that are specifically regulated during B-cell development and deregulated when lymphoma is developing. This library is a resource for studying the role of microRNAs in B-cell development, immune function, and lymphomagenesis.[1]

Identification of genes that are altered in T-cell acute lymphoblastic leukemia (T-ALL) and B-NHL, as well as their functions. A major effort supported by the HICCC has been initiated to sequence all of the genes involved in T-ALL and diffuse large B-cell lymphoma (DLBCL). Adolfo Ferrando, MD, PhD, and his colleagues are elucidating the role of the activation of the Notch1 protein in T-ALL and defining the significance of mutations in this protein for predicting patient outcome. They have found that inhibition of Notch signaling can reverse the resistance to glucocorticoid treatment that some patients with T-ALL develop, and that glucocorticoid treatment reduces the digestive side effects associated with Notch inhibitors. Their findings have expanded our knowledge of the molecular basis of Notch1-induced T-ALL and have opened new avenues for evaluating Notch-inhibiting drugs in combination with glucocorticoids in patients with T-ALL.[2,3]

Using genome-wide genomic analysis, scientists led by Dr. Dalla-Favera and Laura Pasqualucci, MD, are identifying the genetic lesions that lead to the development of DLBCL. Recently, they identified a new set of genetic alterations in the NF-κB pathway associated with the development of this cancer. Activation of NF-κB fuels DLBCL growth, while inactivation of this pathway leads to DLBCL death, indicating that NF-κB is a critical target for DLBCL therapy.[4]

Development of new drugs and drug combinations for T-ALL and B-NHL. Much of the work performed to assess new drugs for T-cell lymphomas was conducted by investigators while at HICCC. Clinical trials are currently under way to assess novel therapeutic approaches for lymphoid cancers. Patients receive individualized care from a multidisciplinary team.

Concluded Dr. Dalla-Favera, "The knowledge we gain from these studies can be used to identify targets for novel therapies which can be evaluated in clinical trials, and ultimately improve the lives of patients."

Publications

1. Basso K et al. Identification of the human mature B cell miRNome. *Immunity.* 2009;30:744-752.

2. Sulis ML et al. NOTCH1 extracellular juxtamembrane expansion mutations in T-ALL. *Blood.* 2008;112:733-740.

3. Real PJ et al. Gamma-secretase inhibitors reverse glucocorticoid resistance in T cell acute lymphoblastic leukemia. *Nat Med.* 2009;15:50-58.

4. Compagno M et al. Mutations of multiple genes cause deregulation of NF-kappaB in diffuse large B-cell lymphoma. *Nature.* 2009;459:717-721.

LYMPHOID DEVELOPMENT AND MALIGNANCY: PROGRAM MEMBERS

Bhagat, Govind: Associate Professor, Pathology

Brown, Truman: Professor, Radiology

Cairo, Mitchell: Professor, Pediatrics

Califano, Andrea: Professor, Biomedical Informatics

Dalla-Favera, Riccardo: Professor, Institute for Cancer Genetics, Pathology

Diacovo, Thomas: Associate Professor, Pathology, Pediatrics

Ferrando, Adolfo: Assistant Professor, Institute for Cancer Genetics, Pediatrics

Flamm, Michael: Associate Professor, Medicine

Gu, Hua: Associate Professor, Microbiology

Jiang, Hong: Associate Professor, Medicine

Klein, Ulf: Assistant Professor, Pathology

Liu, Kang: Assistant Professor, Microbiology

Mears, Gregory: Professor, Medicine

Mukherjee, Siddhartha: Assistant Professor, Medicine

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Pasqualucci, Laura: Assistant Professor, Institute for Cancer Genetics, Pathology

Phillips, Adrienne: Assistant Professor, Medicine

Reizis, Boris: Assistant Professor, Microbiology

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Sulis, Maria-Luisa: Assistant Professor, Pediatrics

Weiner, Michael: Professor, Pediatrics

Zha, Shan: Assistant Professor, Institute for Cancer Genetics

Columbia University Medical Center

Prostate Cancer Program

PROGRAM LEADER

Carlos Cordon-Cardo, MD, PhD

PROGRAM CO-LEADER

Daniel Petrylak, MD

Carlos Cordon-Cardo, MD, PhD, is the Leader of the Prostate Cancer Program. The goal of the program is to elucidate the pathogenesis of prostate cancer and implement novel approaches to its prevention, early diagnosis, and individualized treatment.

Daniel Petrylak, MD, is the Co-Leader of the Prostate Cancer Program. Dr. Petrylak is recognized internationally as a leader in the field of prostate cancer. He provides continued guidance in clinical trial design and implementation for the Program.

Enormous strides have been made in the management of prostate cancer. According to the American Cancer Society, the five-year cause-specific survival rate for men with stage I prostate cancer is 100 percent. Many prostate cancers are now diagnosed at that early stage, thanks to screening approaches such as PSA testing and therapies that effectively eliminate tumors.

For men with metastatic prostate cancer, however, the picture is not as rosy: just 31.7 percent of them survive five years after diagnosis. Advanced disease, which is initially fueled by androgenic hormones such as testosterone, eventually continues progressing despite androgen-deprivation therapy—transforming the disease into "castration-resistant" prostate cancer.

Herbert Irving Comprehensive Cancer Center investigators, led by Program Co-Leader Daniel Petrylak, MD, developed and demonstrated the value of docetaxel as a treatment for men with metastatic prostate cancer—the first time any agent was shown to extend survival for men with castration-resistant disease. This 2004 advance changed clinical practice and remains the standard of care for men with this stage of the disease.[1]

Despite this advance, however, the disease eventually marches on in its advanced stages, and at that point genitourinary oncologists have few other effective options. Clearly a new approach is needed to reduce the number of prostate cancer deaths, which currently exceeds 27,000 per year in the United States.

Investigators in the Prostate Cancer Program at the HICCC are focusing their studies on the earliest stages of prostate carcinogenesis in an effort to glean insights into the molecular underpinnings of this disease. There is great excitement in the program now with the discovery of something truly revolutionary: prostate cancer stem cells. "In the book of cancer, the first pages are blank," said Program Leader Carlos Cordon-Cardo, MD, PhD. "This is the place where we can start writing about it. We are on the verge of a quantum change in learning how cancer is initiated."

Like many research initiatives at the HICCC, the Prostate Cancer Program brings together experts from a variety of areas—molecular and cell biology, urology, medical oncology, radiology, pathology, genetics, bioinformatics, and population science—who together take a systems biology approach to understanding how the disease develops. They also understand that progress against cancer does not happen overnight.

"It's one thing to generate data, but another to generate knowledge," noted Dr. Cordon-Cardo. "We live in a world where urgency is confused with importance. With our multidisciplinary team, we are taking the time it takes to generate knowledge."

That approach is paying off. In September 2009, investigators led by Michael Shen, PhD, used a mouse model of prostate cancer developed by Cory Abate-Shen, PhD, to identify a type of prostate cancer stem cell. Cancer stem cells behave differently than mature cancer cells. They don't divide as quickly and are resistant to the toxic effects of anticancer drugs. They may lurk in the tissues where they reside, waiting to re-emerge after a course of therapy is completed to generate new tumor cells.

Dr. Shen and his colleagues pinpointed a gene called *Nkx3.1* which is required for the maintenance of a family of stem cells involved in prostate regeneration. The investigators found a group of cells that express *Nkx3.1* and can continue to grow in the absence of androgens, naming them "castration-resistant *Nkx3.1*-expressing cells," or CARNs. They also learned that deletion of the *PTEN* tumor-suppressor gene—which was identified by other HICCC investigators—leads to prostate cancer.[2] These findings have tremendous implications for delineating the earliest stages of the development of castration-resistant prostate cancer.

Knowledge of cancer initiation at such a seminal point may lead to novel therapies that target these pathways, and then to new clinical trials to evaluate them. If scientists could learn how to short-circuit the creation of prostate cancer stem cells, they could potentially prevent the progression to castration-resistant disease, which is ultimately what claims the lives of men who die from prostate cancer.

HICCC investigators benefit from the resources offered by other Columbia University family members, including the Mailman School of Public Health, as well as the large and diverse communities in and around New York City. The presentation of prostate cancer varies among populations; for example, African American men and Jamaican men of African descent have the highest prostate cancer incidence rates in the world, and researchers are seeking to explain these disparities.

"We are in a very privileged situation, with access to many individuals at risk," concluded Dr. Cordon-Cardo. "We care for a region of some 19 million people in the tri-state area—an ethnically diverse population larger than most European countries. It is a world by itself that offers a holistic approach for the study of disease. Studies of cancer need this kind of variation in order for us to make progress."

Publications

1. Petrylak DP et al. Docetaxel and Estramustine Compared with Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer. *New Engl J Med.* 2004;351:1513-1520.

2. Wang X et al. A luminal epithelial stem cell that is a cell of origin for prostate cancer. *Nature.* 2009;461:495-500.

PROSTATE CANCER: PROGRAM MEMBERS

Abate-Shen, Corinne: Professor, Urology

Badani, Ketan: Assistant Professor, Urology

Benson, Mitchell: Professor and Chairman, Urology

Cordon-Cardo, Carlos: Professor, Pathology, Urology

Feinmark, Steven: Pharmacology

Fine, Robert: Associate Professor, Medicine, Oncology, Division of Hematology and Medical Oncology

Gelmann, Edward: Professor and Division Chief, Medicine, Pathology, Urology

Kahn, Scott: Assistant Professor, Urology

Karsenty, Gerard: Professor, Genetics & Development

Katz, Aaron: Professor, Urology

Mckiernan, James: Assistant Professor, Urology

O'Toole, Kathleen: Professor, Pathology

Petrylak, Daniel: Professor, Medicine

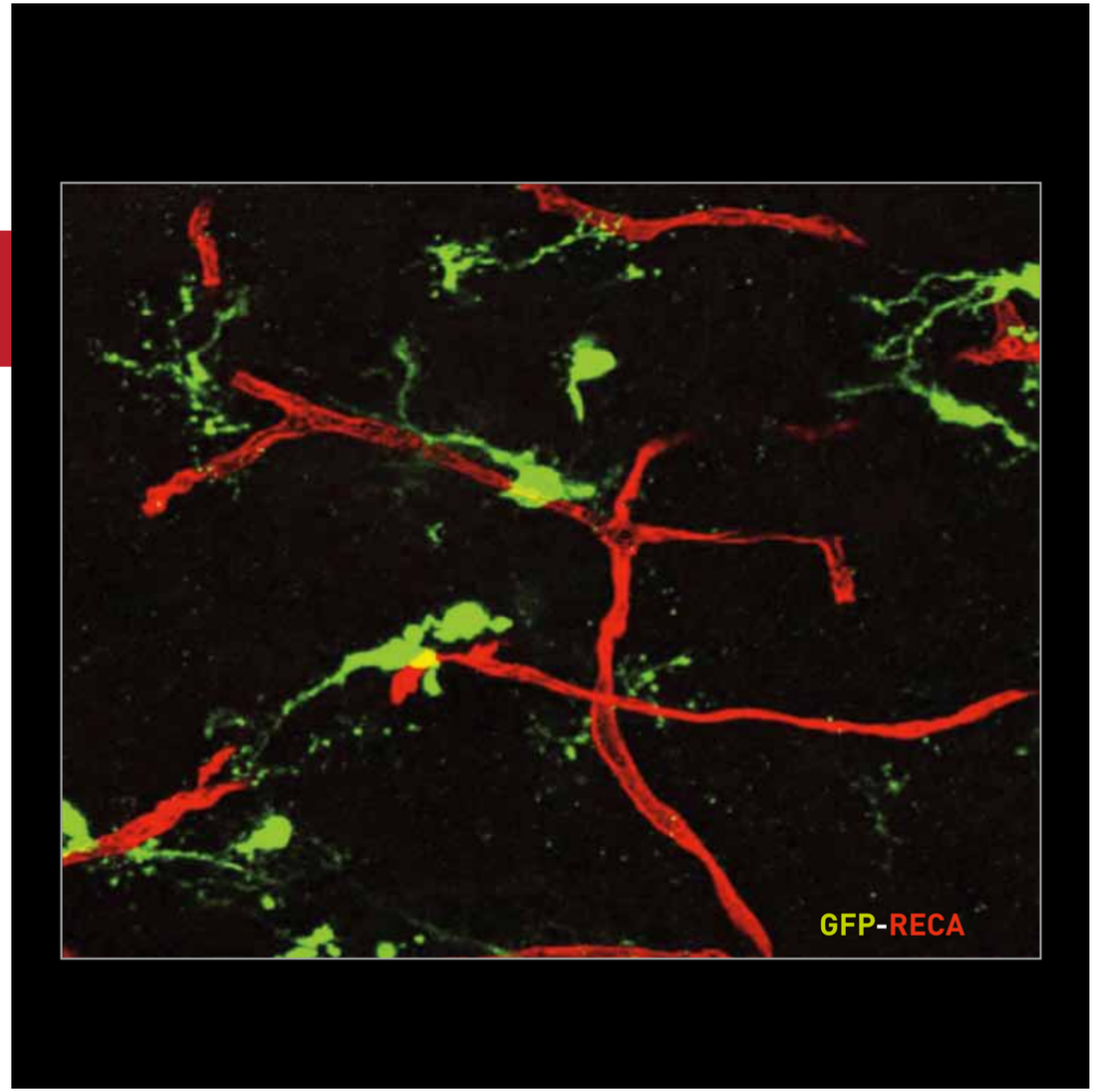
Rai, Alex: Assistant Professor, Pathology

Rosner, William: Professor, Medicine

Schwartz, Lawrence: Professor and Chairman, Radiology

Shen, Michael: Professor, Genetics & Development, Medicine

Spencer, Benjamin: Assistant Professor, Urology



Confocal microscopy shows GFP-tagged glioma cells (green) invading the brain by crawling along cerebral blood vessels (red). This image is taken from a retrovirus-driven rodent model of glioblastoma. (Assanah et al., 2009)

Neuro-Oncology Program

PROGRAM LEADER

Steve Rosenfeld, MD, PhD

PROGRAM LEADER

Jeffrey Bruce, MD

Steve Rosenfeld, MD, PhD, and Jeffrey Bruce, MD, are the Leaders of the Neuro-Oncology Program. This Program encompasses three scientific themes: glioma pathogenesis, epidemiology, and early-phase clinical trials.

Brain tumors such as glioblastomas and astrocytomas frequently become resistant to treatment and remain a significant challenge. They are also extremely complex at the molecular level. Advances against tumors such as glioblastoma multiforme (GBM) can only come about through intensive research to understand how they develop and progress—research that begins in the laboratory, extends to the clinic, and circles back again to inform new scientific avenues.

At the Herbert Irving Comprehensive Cancer Center, clinicians and laboratory investigators collaborate to decipher the molecular underpinnings of brain tumors and identify potential new targets for therapy. This work is facilitated by the HICCC's large bank of brain tumor tissue specimens. Animal models also form a vital component of such research.

"We've done great work with models that recapitulate the histology and genetic changes that correlate with human brain tumor development," explained Program Director Steven Rosenfeld, MD, PhD. "These models enable us to study the signaling pathways driving tumor development. Because we can induce tumors in these models, we can tell where and when they start."

HICCC investigators are deciphering the mechanisms behind brain tumor migration and invasion. They are learning more about the roles of *PTEN* and *p53,* two genes that normally put the brakes on rampant

cell growth, which are mutated in some patients with GBM. They're also scrutinizing the activity of glial progenitor cells that give rise to a specific subset of gliomas.

Tumor invasion is an impediment to effective treatment. To get a better handle on this phenomenon, Peter Canoll, MD, PhD, created a mouse model and devised a way to tag tumor cells with a fluorescent protein to watch them move through brain tissue. Using this model, he and his colleagues have identified intracellular forces exerted against cancer cells during tumor invasion, leading to the identification of new therapeutic targets.

In addition, Antonio Iavarone, MD, and Andrea Califano, PhD, are exploring the molecular roots and master regulators of mesenchymal GBM—an end-stage form of the disease which is associated with poor outcome—with a goal of finding new targets for novel therapies.

Angiogenesis inhibitors—drugs, such as bevacizumab, that block the development of the blood vessels tumors need to grow and spread—can actually increase tumor invasiveness. Thirty to 60 percent of patients who respond to bevacizumab rebound with uncontrollable tumor invasion within six months. Dr. Canoll has developed another animal model which replicates the tumor invasion that occurs in response to sunitinib, another angiogenesis inhibitor, to study this process.

The blood-brain barrier is an obstacle to anticancer drugs, limiting the passage of only the smallest molecules from the bloodstream into brain tissue. Investigators led by neurosurgeon and Program Co-Director Jeffrey Bruce, MD, demonstrated the safety and preliminary effectiveness of a novel approach called "convection-enhanced delivery" in patients with recurrent malignant gliomas. In this approach, the chemotherapy drug topotecan is infused via a catheter directly into the tumor and surrounding brain. They also completed a pilot study of this therapy for brainstem gliomas in children.

The catheter is connected to a micro-infusion pump that administers just a few drops of a chemotherapy agent each hour. The infusion pressure pushes the drug through the space between the tumor cells, thereby avoiding toxicity, bypassing the blood-brain barrier, and delivering high drug concentrations directly to the tumor. A multicenter phase II study is now being planned.

Rose Lai, MD, is leading epidemiological studies to identify risk factors for brain tumors and identify potential measures to reduce risk (such as the possible use of statins). The HICCC is participating in GLIOGENE, an international study of hereditary factors associated with glioblastoma risk.

Dr. Bruce led the HICCC's participation in a phase II clinical trial of the Oncophage® vaccine in patients with recurrent GBM, which showed that the vaccine stimulated an immune response and was associated with survival rates better than historical controls. This unique treatment is made from a patient's own tumor tissue, and is used to stimulate the immune system to zero in on cancer cells while sparing healthy cells. A phase III study is now being planned, as well as a clinical trial in patients with newly diagnosed tumors.

Other projects under way to study brain tumor progression include studies of:

- The influence of immune cells in the tumor microenvironment (Jeffrey Bruce, MD, and Richard Anderson, MD)
- RNA-building proteins in glioma development (James Manley, PhD)
- Optical imaging of brain tumors (Elizabeth Hillman, PhD)
- The development of pediatric gliomas (Anna Lasorella, MD)
- Mutations in *IDH1* and their role in glioma development (Darrell Yamashiro, MD, PhD, and Peter Canoll, MD, PhD)
- Outcomes of patients with pituitary tumors following surgery versus conservative treatment (Pamela Freda, MD)

"Malignant brain tumors are diseases where translational research is absolutely critical," concluded Dr. Canoll. "In the Neuro-Oncology Program, scientists and clinicians are collaborating to understand how molecular alternations lead to the formation of brain tumors and to apply this understanding to the development of more effective therapy."

Publications

Bohman LE et al. Magnetic Resonance Imaging Characteristics of Glioblastoma Multiforme: Implications for Understanding Glioma Ontogeny. *Neurosurgery.* 2010;67:1319-1328.

David CJ et al. HnRNP proteins controlled by c-Myc deregulate pyruvate kinase mRNA splicing in cancer. *Nature.* 2010;463:364-368.

Lai R et al. The timing of cranial radiation in elderly patients with newly diagnosed glioblastoma multiforme. *Neuro Oncol.* 2010;12:190-198.

Freda PU and Bruce JN. Surgery: Risks of pituitary surgery in the elderly. *Nat Rev Endocrinol.* 2010;6:606-608.

NEURO-ONCOLOGY: PROGRAM MEMBERS

Balmaceda, Casilda: Associate Professor, Neurology

Bruce, Jeffrey: Professor, Neurological Surgery, Pathology

Canoll, Peter: Assistant Professor, Pathology

Delapaz, Robert: Professor, Radiology

Freda, Pamela: Associate Professor, Endocrinology, Medicine

Garvin, James: Professor, Pediatrics

Goldman, James: Professor, Pathology

Greene, Lloyd: Professor, Pathology

Hamberger, Marla: Associate Professor, Neurology

Isaacson, Steven: Professor, Otolaryngology/Head and Neck Surgery, Radiation Oncology

Jessell, Thomas: Professor, Biochemistry & Molecular Biophysics

Lai, Rose: Assistant Professor, Neurology

McKhann, Guy: Associate Professor, Neurological Surgery

Rosenfeld, Steven: Professor, Neurology

Sisti, Michael: Associate Professor, Neurological Surgery

Tikofsky, Ronald: Radiology

POPULATION SCIENCE PROGRAMS

ASSOCIATE DIRECTOR

Alfred I. Neugut, MD, PhD

Alfred Neugut, MD, PhD, is an internationally known figure in the field of cancer prevention. He was chosen to lead the Population Science Programs of the HICCC based on his expertise in both the clinical and population science components of cancer research.

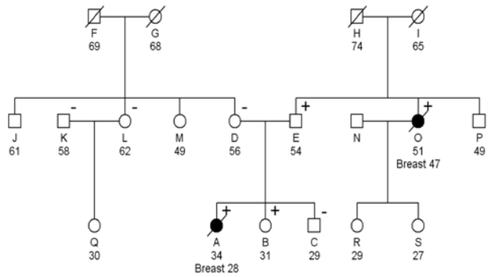
Since 1923, Columbia University's Mailman School has been at the forefront of public health research, education, and community collaboration. The members of the HICCC's two population science programs—the Cancer Epidemiology Program and the Prevention, Control and Disparities Program—benefit from this association as they explore cancer at the level of populations, looking for patterns that yield insights into its causes and its effects and how it might be prevented.

"Population scientists apply their statistical expertise to assess the role of environmental and genetic risk factors in cancer in people, rather than at the cellular or organ level, and help other researchers with the appropriate conduct of studies in humans from a study design and statistical point of view," said Associate Director Alfred I. Neugut, MD, PhD. "They also explore ways to lower the incidence of cancer, make treatment more effective, reduce side effects, and improve the quality of life for patients with cancer and their families."

Between the diverse neighborhoods surrounding the HICCC and dotting the tri-state area and the collaborations with investigators within and outside of Columbia University—including those across the globe—researchers in the Population Sciences Programs are making significant contributions to our understanding of how cancer affects different groups of people.

Above: This green-labeled well in Bangladesh signals water with low levels of arsenic, indicating it is safe to drink.

Right: Pedigree of a family in the breast cancer family registry.



Cancer Epidemiology Program

PROGRAM LEADER

Regina Santella, PhD

PROGRAM CO-LEADER

Mary Beth Terry, PhD

Regina M. Santella, PhD, is the Leader of the Cancer Epidemiology (CE) Program. Her area of area of expertise encompasses laboratory-based biomarker studies and epidemiology. The goals are to investigate environmental, lifestyle, and genetic factors that lead to increased incidence, morbidity, and mortality from cancer and to integrate biomarkers into these studies.

Mary Beth Terry, PhD, is the Co-Leader of the Cancer Epidemiology Program. Dr. Terry has been involved in case-control studies of breast and colorectal cancer for over ten years. She currently leads several large epidemiologic studies focusing on the role of prenatal and postnatal factors in breast cancer risk.

What do studies of arsenic-induced skin cancer in Bangladesh and liver cancer in Taiwan have to do with cancer in New York City? If you're an epidemiologist—everything. Exploring how environmental factors trigger the carefully orchestrated series of events that culminate in tumor development sheds light on this complex process, and generates knowledge that can be used to help people with cancer everywhere.

That's just the type of research being conducted by investigators in the Cancer Epidemiology Program at the Herbert Irving Comprehensive Cancer Center, who are collaborating with other epidemiologists in the New York area and around the world to glean insights into environmental risk factors for the kinds of cancers that pose the largest impact on society, especially breast cancer, and how an individual's genes can modify that risk. As leaders in Columbia University's prestigious Mailman School of Public Health, the HICCC's cancer epidemiologists are advancing the field.

In the area of molecular epidemiology, investigators led by Program Leaders Regina Santella, PhD, and Mary Beth Terry, PhD, are comparing sisters in the Breast Cancer Family Registry where one sister developed breast cancer while another did not. "This study offers an opportunity for assessing the effects of environmental factors later in life on cancer within families, because sisters have similar exposures when they are growing up together," said Dr. Santella.

The researchers found that women whose DNA repair was impaired were more likely to develop breast cancer.[1] "Studies like these allow us to quantify the effects of environmental exposures within families," added Dr. Terry, a coauthor of the study.

Similarly, through participation in the Long Island Breast Cancer Study Project—an ongoing project comparing 1,500 breast cancer patients with 1,500 healthy controls—the researchers showed that women were more likely to develop breast cancer if they were exposed to polycyclic aromatic hydrocarbons (such as those found in diesel exhaust) and had a certain DNA repair profile.[2] This type of research can help investigators identify biomarkers that may signal that a person has an increased risk of developing a certain cancer when exposed to specific carcinogens.

HICCC cancer epidemiologists are also participating in large-scale international studies to assess the effects of DNA methylation on cancer risk. The attachment of methyl groups (a carbon atom attached to three hydrogen atoms) to a DNA strand can turn certain genes on (such as genes that fuel cancer growth) and off (including those that prevent cancer growth)—in some cases, making an individual more susceptible to cancer.

Such "epigenetic" changes are under study through the Dutch Famine Birth Cohort Study, in which HICCC investigators are collaborating with researchers in the Netherlands to analyze individuals whose mothers were pregnant with them during the Dutch Hunger Winter of 1944-1945, just before the end of World War II. During this time, rations were as low as 400 to 800 calories a day—less than a quarter of the recommended adult caloric intake.

Lambert Lumey, MD, PhD, and his colleagues found that women prenatally exposed to this famine were more likely to have less DNA methylation of the insulin growth factor-2 gene—a pathway involved in breast cancer development—providing the first empirical evidence that early-life environmental conditions can cause epigenetic changes in humans that persist throughout life.[3]

Closer to home and enriched by the cultural diversity of New York City, Drs. Terry and Santella and their colleagues are conducting a "life course" study of a multiethnic cohort of women in New York City born between 1959 and 1963, to study the effects of prenatal exposure and environmental exposures occurring after birth and throughout life. They found that DNA methylation of white blood cells differed by ethnicity and was significantly associated with maternal smoking during pregnancy, longer birth length, later age for the onset of menstruation, never giving birth, and later age at first birth.[4]

"Many cancers—especially those that are hormonally driven, like breast cancer—are influenced by exposures early in life," said Dr. Terry. "These factors suggest that risk factors across the life course may be associated with DNA methylation in adulthood."

The identification of biomarkers such as DNA methylation may also lead to improved cancer screening and chemoprevention. Dr. Santella and her colleagues were the first to identify an epigenetic biomarker for liver cancer risk in a study of patients in Taiwan. Asian populations have the highest incidence of liver cancer in the world, and the increase in Asian immigrants in the United States—many with hepatitis B virus infection (a major risk factor for liver cancer)—as well as the rising rate of hepatitis C virus-induced liver cancer are making the disease a significant public health concern in this country.

The investigators pinpointed a substance called 15-F2t-isoprostane, a marker of lipid oxidation, that was increased in the urine of liver cancer patients with a history of aflatoxin exposure (a grain fungus) and which was further magnified in those infected with hepatitis B.[5] "These results suggest that elevated levels of urinary 15-F2t-isoprostane may be related to increasing aflatoxin exposure and are associated with an increased risk of liver cancer," concluded Dr. Santella.

In Bangladesh, arsenic in well water has been linked to an increase in skin cancers among people who drink from contaminated wells. Although contaminated wells are marked, for a number of reasons (such as distance to a clean well), some people continue to obtain their daily ration of drinking water from the tainted wells.

HICCC investigators led by Mary Gamble, PhD, found that people who were deficient in folic acid were less likely to have DNA methylation of their white blood cells and were more likely to develop arsenic-induced skin lesions—information that yields insights into arsenic-related skin cancer and may lead to the development of chemoprevention efforts such as folic acid supplementation.[6]

Publications

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CANCER EPIDEMIOLOGY: PROGRAM MEMBERS

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Tsai, Wei-Yann: Professor, Biostatistics

Prevention, Control and Disparities Program

PROGRAM LEADER

Alfred I. Neugut, MD, PhD

Alfred Neugut, MD, PhD, is the Leader of the Prevention, Control and Disparities Program. The goal of the Program is to study how the findings of basic, epidemiologic, and clinical research have been or should be disseminated and applied in real life.

The Herbert Irving Comprehensive Cancer Center is located in one of the most ethnically and racially diverse communities of New York City: the Washington Heights neighborhood, which is home to a largely African American and Hispanic population. Taking advantage of this special location and a collegial partnership with Columbia University's Mailman School of Public Health, the HICCC has created a range of clinical research and patient care programs offering state-of-the-art cancer care.

HICCC community-focused programs enhance recruitment of minorities into clinical trials, facilitate screenings, and provide education and services for women at increased risk of breast cancer, to name just a few. Such efforts help reduce disparities in cancer incidence and service utilization.

Tertiary prevention—the reduction in the risk of disease progression and recurrence—has become a major focus of the program, especially as it relates to breast cancer outcome. One way to do this is to study the reasons why patients don't complete cancer treatment. "We've made great strides in developing better anticancer drugs, but that doesn't help if the patients don't take them as prescribed," said Program Leader Alfred Neugut, MD, PhD. "It's a problem that is not fully appreciated in oncology."

For example, up to five years of hormonal therapy may be used to reduce a woman's risk of breast cancer recurrence. But in a study of more than 8,700 women led by Dr. Neugut and his colleague, Dawn

Hershman, MD, Co-Leader of the Breast Cancer Program, less than half of all women who were prescribed this medication—especially women under age 40—finished the full course of therapy.[1]

They have also identified disparities in the receipt of care. For example, elderly women (those over age 65) with breast cancer were more likely to receive chemotherapy for their disease if they were treated by a doctor primarily employed in a private practice.[2] In another study of more than 56,000 elderly women with early-stage breast cancer, Drs. Neugut and Hershman found that women were 40 percent more likely to have breast-conserving surgery (lumpectomy) than mastectomy if their surgeons were female.[3]

HICCC investigators are also collaborating with Long Island University researchers to study cancer incidence among and the use of screening by Afro-Caribbean residents of Brooklyn, who tend to be diagnosed with cancers seen more often in developing nations (such as cervical cancer). Pathologist Thomas Wright, MD, is devising a means of screening for human papilloma virus (HPV, the leading cause of cervical cancer) in resource-limited settings using a device that a woman can insert herself, potentially increasing the number of women with this disease whose cancers are detected in their earlier, more curable stages.

Charles Basch, PhD, received the largest individual research grant in the history of the American Cancer Society to determine the best approach to encouraging colon cancer screening among members of the 1199 Healthcare Workers Union in New York City. This $2.2 million study randomizes some participants to receive customized telephone messages encouraging them to seek colon cancer screening, to determine if this is an effective means of increasing screening rates in this group. For people with a family history of colon cancer, Fay Kastrinos, MD, is establishing a registry for patients with cancer family syndromes and restructuring the HICCC cancer genetics clinic.

Identifying risk factors and how to control them is another important avenue of investigation. Denise Kandel, PhD, is following a cohort of teens to determine why they start to smoke and why some of them choose not to continue. David Brenner, PhD, has published seminal papers regarding the cancer risk associated with radiation exposure from imaging tests such as CT scans—research which has influenced medical practice.[4]

Several studies are evaluating potential chemopreventive approaches. Andrew Joe, MD, and Charles Lightdale, MD, are leading a study to see if an antioxidant green tea derivative called polyphenon E can prevent Barrett's esophagus from progressing to esophageal cancer, and Dr. Hershman is evaluating the effectiveness of this substance in women with early-stage hormone receptor-negative breast cancer.

HICCC community outreach programs truly set the institution apart from other major cancer centers, including others in New York City, and yield information that can be used to improve the understanding of cancer and the care of patients everywhere.

Publications

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3. Hershman DL et al. Surgeon characteristics and use of breast conservation surgery in women with early stage breast cancer. *Ann Surg.* 2009;249:828-833.

4. Brenner DJ. Computed Tomography—An Increasing Source of Radiation Exposure. *N Engl J Med.* 2007;357:2277-2284

PREVENTION, CONTROL AND DISPARITIES: PROGRAM MEMBERS

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SHARED RESOURCES

ASSOCIATE DIRECTOR

Benjamin Tycko, MD, PhD

Benjamin Tycko, MD, PhD, is both a basic scientist studying the genetics and epigenetics of human cancer and a clinician in diagnostic pathology. Dr. Tycko therefore has a unique knowledge of the research infrastructure needed for basic, clinical, and population science research.

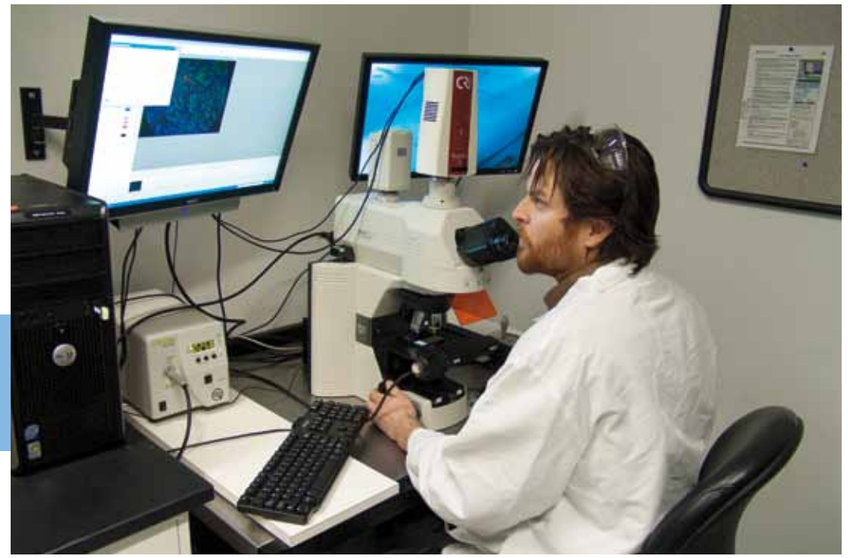
"The most recent progress in cancer research and treatment has been technology-driven," explained Benjamin Tycko, MD, PhD, Associate Director of the HICCC's Shared Resources. To fuel that progress, cancer centers create Shared Resources—specialized laboratories and data centers that investigators can use to support their research. Herbert Irving Comprehensive Cancer Center scientists rely on Shared Resources for guidance, to use state-of-the-art equipment, and for instruction in the tools of their trade.

At the HICCC, 12 Shared Resources provide centralized expertise and eliminate the duplication of costly equipment. Ten of the Resources are technology-based, while two others (the Clinical Research Management Office and Research Recruitment and Minority Outreach) support clinical research efforts.

Many of the HICCC's Shared Resources contribute to the institution's broad systems biology approach to the study of cancer, which brings together investigators tackling the problem of cancer from different angles in an effort to paint a bigger picture of the disease and its development. The HICCC's Shared Resources include:

Biomarkers: This resource provides a centralized, efficient, and cost-effective resource for receiving, handling, and storing human samples that are collected as part of research studies in molecular epidemiology and other types of cancer-related research. HICCC laboratory investigators benefit from the close collaboration with clinical research programs that facilitate the acquisition of tissue samples.

Molecular Pathology: This resource provides access to well-characterized human normal and tumor tissues, macromolecule (DNA/RNA) extraction/quantification services, and expert histopathology



evaluation. As targeted therapies expand and personalized medicine grows as a field, the molecular pathological analysis of tumor tissues is becoming a vital component of cancer care.

Genomics Technologies: Consisting of the Microarray and Molecular Cytogenetics facilities, this resource provides access to specialized instrumentation and technical expertise in high-throughput genomic technologies and molecular cytogenetics to support basic and translational genomics research related to cancer. HICCC investigators now have access to one of the most sophisticated "next-generation" sequencing systems in the city, enabling gene sequencing to be completed rapidly and accurately.

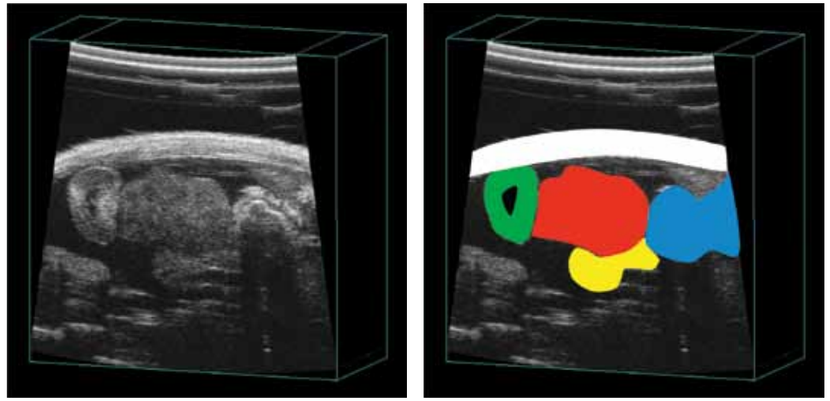
Flow Cytometry: The ability to separate a diverse mixture of cells into distinct populations for characterization or analysis has become increasingly important for biomedical research. Flow cytometry is especially valuable for this purpose.

Confocal and Specialized Microscopy: This resource provides advanced microscope systems for multidimensional optical imaging of living and fixed cells and tissues. Four different modes of 3D fluorescence microscopy are offered, in addition to conventional transmitted-light and fluorescence microscopy.

Proteomics: Just as genomics has revolutionized our understanding of the genetic basis of disease, the identification of proteins and their functions—proteomics—is also expanding our knowledge of cancer development. Proteomics resource staff offer a deep level of expertise, using mass spectrometry to analyze proteins and protein complexes.

Radiation Research: This resource provides a comprehensive irradiation service, with the capability to expose small animals, mammalian cells in culture, microorganisms, and macromolecules to gamma rays, x-rays, and ultraviolet light.

Transgenic Mouse: The generation and analysis of genetically modified mice, including transgenic and knockout animals that recapitulate human diseases, is an essential technology for cancer research. The Transgenic Mouse Shared Resource makes these powerful technologies available to all HICCC members.



From the Mouse Imaging facility: High-resolution ultrasound image of a 4 x 7mm pancreatic ductal adenocarcinoma arising in a genetically engineered mouse. Axial section of a supine mouse imaged with a 35MGz transducer. Structures from the left image are mapped at right. (White: skin and abdominal wall. Green: proximal duodenum. Blue: pylorus. Red: pancreatic tumor. Yellow: adjacent normal head of pancreas tissue.)

Biomedical Informatics: As one of the strongest computational biology centers in the country, this resource provides investigators with access to key expertise in the use of advanced data analysis tools and methodologies for research publications and grant proposals, and access to a high-performance computing infrastructure for data analysis and sharing.

Biostatistics: An essential component of cancer research, the Biostatistics Shared Resource provides the necessary infrastructure to facilitate collaboration between an investigator and a biostatistician from the planning stage of a project to its execution, analysis, interpretation, and dissemination.

Clinical Research Management Office: Clinical trials are absolutely necessary for progress to be made in the prevention, diagnosis, and treatment of cancer. This office supports research staff and clinical investigators with a comprehensive range of services to assist with the initiation and conduct of clinical trials in cancer.

Research Recruitment and Minority Outreach: This resource works to enhance the recruitment of minority and medically underserved patients to clinical trials by partnering with community-based and faith-based organizations. Featuring multilingual staff and culturally appropriate educational materials, its mission is to reduce barriers to participation in clinical research.

The HICCC is also expanding a new facility which offers imaging using luminescence and ultrasound in mice.

The HICCC's Shared Resources enhance collaboration among investigators while enabling them to pursue their individual research goals. Concluded Dr. Tycko, "There's a culture of innovation here, where collaboration is encouraged while individualism is respected."

EDUCATION

ASSOCIATE DIRECTOR

Cory Abate-Shen, PhD

Cory Abate-Shen, PhD, became the Associate Director for Education in 2010. Her roles in that position include the organization of several campus-wide events related to the mission of the Cancer Center. In addition, the HICCC hosts eight Distinguished visitors for its campus-wide Distinguished Lecture series annually.

A visitor sitting in the office of Cory Abate-Shen, PhD, cannot help but spy the multiple rows of empty champagne bottles aligned like soldiers along the top of a bookshelf in her office. Turn around and look up, and you'll see yet another collection behind you.

"Each bottle celebrates an advance in my lab," explained Dr. Abate-Shen, whose research focuses on the biology of prostate cancer. "For every advance there are ten setbacks. So each time we make progress, it is an event worth commemorating."

Fledgling investigators setting out to build a career in scientific research need to know that science makes progress in fits and starts. Not every experiment is going to produce a breakthrough, and perseverance is a must. It's a good lesson, and one of many taught through the Herbert Irving Comprehensive Cancer Center's educational programs.

"We have the benefit of exceptionally strong basic research and clinical programs, coupled with one of the oldest population science programs in the nation," said Dr. Abate-Shen, Associate Director for Education at the HICCC. "It is the breadth of our research programs and our affiliation with the other components of the Columbia University family that make us so strong."

For aspiring cancer researchers, the HICCC offers Columbia University-affiliated training programs in the areas of basic laboratory research, epidemiology and public health, and clinical science. These programs include:

Cancer Biology Training Program: Initiated in 1984, this program prepares talented scientists for highly productive careers in basic cancer research. This goal is

achieved through a rigorous didactic curriculum and opportunities to study in the laboratories of Columbia University faculty. Students take courses in the cellular and molecular biology of cancer, proteomics, and genomics, among others. The program is funded by the National Cancer Institute (NCI).

Cancer Epidemiology/Biostatistics/Environmental Health: Funded by the NCI, this program trains predoctoral and postdoctoral trainees for careers in areas related to cancer and public health. Students benefit greatly from the association with Columbia's renowned Mailman School of Public Health.

Hematology and Medical Oncology Fellowship Program: This program provides intensive training in all clinical aspects of hematology and medical oncology, followed by the opportunity to develop an in-depth research project in a defined area of basic science, clinical, or public health research.

Pediatric Hematology/Oncology/Bone Marrow Transplantation Program (BMT): This program is coordinated through two divisions in the Department of Pediatrics—the Division of Pediatric Hematology/BMT and the Division of Pediatric Oncology. The design of the program encourages trainees to develop an interest in clinical and basic research.

"Our educational programs are thoughtfully designed so trainees have exposure to all aspects of cancer research, including basic science and population science," Dr. Abate-Shen noted.

The HICCC offers students as well as all staff opportunities for continued growth and development. Monthly seminars featuring invited speakers from across the country provide timely exposure to the most relevant advances in cancer research.

The HICCC sponsors an annual one-day retreat during which various members of the Cancer Center formally present their research progress. The retreat stimulates interactions between the many cancer researchers at Columbia University and fuels collaborations between basic, translational, and clinical scientists. It is also a valuable educational experience for trainees in the Cancer Biology Training Program, who gain exposure to new findings and a wide spectrum of cancer research activities.

An annual symposium features HICCC investigators commenting on a specific topic. Last year's symposium on Cancer Systems Biology, held in May 2010, featured speakers from within HICCC and from other institutions. Regular social hours bringing together investigators from different laboratories also help to foster and nurture collaboration.

HICCC scientists take their expertise and enthusiasm out into the community to share with budding investigators. They organized a Columbia-sponsored Science Festival, an outreach program for elementary school students at The School at Columbia University. The theme of the 2009 event was "inquiry." HICCC scientists told students about genetics, bringing 54 first-graders to an HICCC laboratory to learn how to make DNA.

Educational events at the HICCC have grown so much in popularity that they are now usually standing-room-only. "The word is getting out," said Dr. Abate-Shen. "Through these educational activities, we've created a real community here."

ADMINISTRATION

ASSOCIATE DIRECTOR FOR ADMINISTRATION

Sadie Maloof, MBA, MSed

As Associate Director for Administration, Sadie Maloof serves as chief administrative officer for the HICCC. She provides leadership and oversight of Center operations, finances, budget, and Shared Resource facilities. Ms. Maloof also serves as administrative liaison between the Center Director, members, advisory committees, Columbia University Medical Center administration, NewYork-Presbyterian Hospital administration, and external groups.

The Administrative Office of the Herbert Irving Comprehensive Cancer Center (HICCC) supports and promotes HICCC research programs and initiatives by providing assistance to leadership and members. The office supports researchers and clinicians spanning basic science, clinical research, and epidemiology and other population sciences with the potential to improve the understanding and treatment of cancer.

Administrative support includes:

- Operations Management
- Financial Management
- Grants & Contracts Administration
- Human Resource Management
- Administrative Oversight for Shared Resources

HICCC Administration recently rolled out a Shared Resources management system, offering investigators an online calendar that facilitates efficient and convenient scheduling of services provided by these facilities.

The Administrative Office also developed an online tracking system that enables users to monitor JCAHO adherence, staff immigration matters on a departmental level, and publications. These efforts are examples of approaches the office has implemented that are environmentally friendly while adhering to the National Cancer Institute's requirements to streamline processes.

HOW YOU CAN HELP

Your gift to the Herbert Irving Comprehensive Cancer Center will make a difference in the lives of people with cancer, both now and in the future, by supporting innovative patient care programs, basic science and clinical research, educational efforts, and prevention initiatives at one of the world's most outstanding comprehensive cancer centers.

To make a contribution online, visit www.hiccc.columbia.edu/administration/giving and follow the link to the donation page. You may also call Sadie Maloof at 212.851.4739 or e-mail her at sm3011@columbia.edu. The Herbert Irving Comprehensive Cancer Center appreciates your support.