"We are made wise not by the recollection of our past, but by the responsibility for our future."

— George Bernard Shaw
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Erratum


During the production process, an error in figure placement was made such that the image for Figure 2 was used twice, for Figures 2 (correctly) and 3 (in error). Please refer to the online version of Dr. Minella’s article at http://www.cancer.northwestern.edu/public/news/journals/pdfs/journal/2009_SummerFINAL.pdf for the corrected figures.
A unique strength of our Cancer Center is the interaction between biomedical engineering, nanotechnology, chemistry, and biology applied to understanding malignant disease and modern cancer diagnostics and therapeutics. These activities span several schools at Northwestern bridging our Chicago and Evanston campuses.

The talented investigators in these areas have successfully competed for two major National Cancer Institute center grants: the Center for Cancer Nanotechnology Excellence Award (CCNE) (Principal Investigators: Drs. Chad Mirkin & Gayle Woloschak) and the Physical Sciences-Oncology Center Award (PS-OC) (Principal Investigators: Drs. Jonathan Widom & Jonathan Licht).

The currently funded CCNE’s projects include:

1. Development of Barcode Assay for the Detection of Ovarian and Prostate Cancer (Project Leader: Chad Mirkin, PhD)
2. Deconstructing Directional Cell Motility in Metastasis through Nanopatterning (Project Leader: Milan Mrksich, PhD, University of Chicago)
3. BioActivated Nanoprobes for Molecular Imaging of Cancer (Project Leader: Thomas Meade, PhD)
4. Nanoscale Encasement and Targeted Delivery of Multifunctional Therapeutic Agents for Hematological Cancer and Solid Tumors (Project Leader: Thomas O’Halloran, PhD)
5. TiO2 Nanocomposites for Targeted Treatment and Imaging of Prostate Cancer (Project Leader: Gayle Woloschak, PhD)
6. Multifunctional Nanostructures for Therapeutic Targeting of Breast Cancer (Project Leader: Samuel Stupp, PhD)
A new competing application was submitted to the NCI in September 2009. The proposed projects include:

1. **NanoFlares for the Detection of Circulating Cancer Stem Cells** (Project Leader: Chad Mirkin, PhD; Co-Leaders: Vincent Cryns, MD & C. Shad Thaxton, MD, PhD)

2. **Theranostic Magnetic Nanostructures for the Molecular Imaging of Cancer** (Project Leader: Thomas Meade, PhD; Co-Leader: Vinayak Dravid, PhD)

3. **Nanostructured Matrices for Cancer Cell Biology** (Project Leader: Milan Mrksich, PhD, University of Chicago; Co-Leader: Joel Collier, MD, University of Chicago)

4. **Image-Guided Nanoembolization for the Treatment of Pancreatic Cancer** (Project Leader: Reed Omary, MD; Co-Leader: Al Benson, III, MD)

5. **Preclinical Validation of Polyvalent siRNA Gold Nanoparticle Conjugates as Anti-Glioma Therapeutics** (Project Leader: Alexander Stegh, PhD; Co-Leader: Chad Mirkin, PhD)

The PS-OC projects include:

1. Information encoded in the sequence-dependent mechanics of DNA (Robert B. Phillips, PhD and Jonathan Widom, PhD)

2. DNA sequence-encoded nucleosome positioning, and gene regulation (Jonathan Widom, PhD and Jonathan D. Licht, MD)

3. DNA information and organization at supranucleosomal scales: chromatin folding and higher order structure, heterochromatin and domain-wide repression (John F. Marko, PhD)

4. Dynamic nucleosome signatures in epigenetic memory and cancer development (William L. Kath, PhD)

5. Encoding and interpreting information at the protein level (Andreas T. Matouschek, PhD)

The knowledge and creativity of these talented scientists and clinicians has brought significant recognition to our institution. We anticipate that they will make important discoveries to advance the field that lead to improved detection and therapy approaches. These accomplishments reflect the years of training and dedication of each individual striving to advance the care of our patients.
What do Ponderosa Pines have to do with medical research? For Kathleen Green, PhD, Joseph L. Mayberry Professor in the Departments of Pathology and Dermatology at Northwestern University Feinberg School of Medicine, the answer is ‘plenty.’ Dr. Green’s path to medical research began when she was an undergraduate student at Pomona College in California and wrote her undergraduate thesis on the physiological ecology of the Ponderosa Pine. While she studied it, Green says she was drawn to the activities taking place within the tree, at the microscopic level. “I was sitting outside, collecting data on photosynthetic rates, and I kept wondering what was happening inside the cells,” she says. “I wanted to know what was happening to their stomata, the parts of the cell, and how the respiration was occurring at a cellular level.”

Fortunately for Green, there were ample opportunities for students at Pomona to do research. “When I was an undergrad, I loved microscopes,” she says. “And even though it was a small college, we had access to both scanning and transmission electron microscopes.” It was her fascination, first with cell structure, and then with how the structural aspects of the cell function and lead to different behaviors of an entire organism, that drove Green to commit herself to a molecular level of analysis. “To me, the cell seems like the place where it’s all at.”

Dr. Green’s fascination with cell development and behavior coincided with what was then a new direction in science education — integrated studies. While enrolled in the Cell & Developmental Biology (Division of Biology and Biomedical Sciences) doctoral program at Washington University in St. Louis, Green’s
research in a lab that spanned both plant and cellular biology worlds formed the foundation of her work today. Her focus was on the early development of Volvox, an alga that is used as a model system for higher (even mammalian) development. Green was interested in the early portion of Volvox development, especially in the role its cytoskeleton played in cell adhesion. (Unlike humans, whose cells are joined by complex junction molecules, physical bridges connect cells in Volvox embryos.) She studied how these bridges formed, and what role they played in the development process. “I didn’t even realize it at the time, but I think I was always attracted conceptually by how cells interact with each other,” she explains. “And I was interested in how the cytoskeleton collaborated with these adhesions in development and cell behavior.”

After completing her PhD, Green did her postdoctoral work with Dr. Robert Goldman, a well-known expert in the cytoskeleton and the current Stephen Walter Ranson Professor and Chair of the Feinberg School of Medicine’s Department of Cell and Molecular Biology. When Goldman was recruited by Northwestern in the early 1980s, he encouraged Green to join him and continue her work there.

Current Research – Adhesion Biology

Today, a principal focus of Green’s research is adhesion biology, the science of how cells stick to each other and the role this plays in crucial biological processes, such as embryogenesis, adult cell differentiation, and wound healing.

Green’s lab also studies how adhesion molecules regulate signaling pathways. By collaborating with Growth Factor Receptors, adhesion receptors can affect crucial biological processes like cell proliferation, motility, and cell survival.

Cell adhesion plays a role in many diseases, including cancer. When epithelial cells lose their attachment to each other, for example, invasion and metastases can occur. In addition to its cancer research, Green’s lab is also exploring the part cell adhesion plays in many other diseases, including cardiac and dermatologic illnesses. “The heart is a major area that we’re getting into,” says Green. “We believe there may be common threads in adhesion molecule pathways of epithelial and cardiac tissues and we’re interested in how those may be manifested to cause heart disease.”

Bringing Basic Science and Clinical Work Together

Dr. Green says one of her most important goals these days is bringing clinicians and researchers together. “This is a crucial time for translational work,” she says. “There are a lot of important projects going on right now that bring together basic scientists and clinical researchers in an effort to make discoveries manifest in more effective patient treatments.”

Dr. Green was recently elected president of the Society for Investigative Dermatology (SID) and says she looks forward to the many opportunities she will have to facilitate these connections in her new role. “I have the privilege of being one of three PhDs who’ve been elected president of this organization,” she says. As president, her mission will be to increase engagement of young investigators and PhDs in SID. She also holds leadership positions with The American Society for Cell Biology (ASCB) and other professional organizations.

At the Lurie Cancer Center, Green is Co-Director of the Tumor Invasion, Metastasis, and Angiogenesis Program. To facilitate translational research there, basic scientists like herself have been granted greater access to patient materials. In addition, the Green lab has benefited from establishment of a new NIH-funded Skin Disease Research Center. Green says that growing the cells she’s received from them in vitro, trying to understand what is wrong with them, and working to devise effective therapeutic strategies has been very satisfying. “Even though my heart is into reductionist, mechanistic approaches—figuring out how things work—it’s important that researchers like myself apply ourselves to translational research so we can help more patients,” she says. “And we need to reach out to clinicians, as well as to young physicians-in-training, in order to do that.”

Down Time

While she spends much of her time in her lab or travelling for work, when Green has time to relax, she enjoys playing the piano. She prefers classical composers, such as Beethoven, Brahms, and Chopin, and is sometimes accompanied on violin by one of her MD/PhD students. Her husband Rex Chisholm, Dean for Research at Feinberg, also enjoys music and plays the guitar in his off hours.
“I have the best job in the world,” says John Lurain, MD, Marcia Stenn Professor in Gynecologic Oncology at Northwestern University Feinberg School of Medicine. Lurain’s work includes clinical practice, teaching, and research. And he thoroughly enjoys all three.

Dr. Lurain chose the field of gynecologic oncology because it allowed him to be involved with both surgical and medical treatment of cancer patients. “I was really interested in that sort of comprehensive approach to patient care — plus the fact that we can cure a lot of patients with gynecologic malignancies. That made it very attractive to me.”

A Father’s Dream Fulfilled
Dr. Lurain says he has been interested in medicine as far back as he can remember. As a child, “I was always interested in science and medicine,” he says. “And becoming a doctor was my goal.”

But Lurain was also motivated by a wish to fulfill his father’s lost dream. After returning from military service following World War II, Lurain’s father enrolled in medical school only to drop out a year later when he could no longer afford it. “I think my dad always wanted me to become a physician and accomplish what he wasn’t able to,” says Lurain.

Education
After receiving his undergraduate degree from Oberlin College in Ohio, Dr. Lurain enrolled in the University of North Carolina’s School of
Medicine where he received his medical degree in 1972. The school emphasized the importance of teaching, which played a role in Lurain’s choice to become an academician himself. “When I first imagined my life as a physician, I saw myself treating patients,” he says. “But during medical school, I discovered I could also contribute in other areas like teaching and research. That made it the ideal job for me.”

Dr. Lurain did his residency in obstetrics and gynecology at the University of Pittsburgh’s Magee-Women’s Hospital and his fellowship in gynecologic oncology at the Roswell Park Cancer Institute in Buffalo, New York. He joined the Northwestern University Feinberg School of Medicine faculty in 1979.

A Noble Profession
Dr. Lurain’s desire to teach was also influenced by the fact that both of his parents were educators. After leaving medical school prematurely, Lurain’s father became a high school science teacher. “My dad was just a great teacher,” he said. “You could tell he loved his work.” Lurain’s mother was a kindergarten teacher. Both taught in Lurain’s hometown of Hampshire, Illinois, a small town of less than 1,000 residents. “It was a lot like the town in the film, ‘Hoosiers,’” he says. “Everything revolved around the basketball team on which I played and the school gym. I thought it was a great place when I was growing up there because I got to participate in so many different sports and school activities.”

While Lurain enjoys all dimensions of his work, he says he probably enjoys teaching the most. “Teaching is the noblest profession,” he says. “By educating others you make an impact that lasts for generations.” Dr. Lurain has won multiple teaching awards, including the Magnus P. Urnes Award for both resident and medical student teaching from the Department of Obstetrics and Gynecology, and the CREOG National Faculty Award for Excellence in Resident Teaching. He developed and currently directs the only gynecologic oncology fellowship in Illinois. “I like to think that if I teach a student just one thing, it will make a difference in a future patient’s care,” he says.

Research
Dr. Lurain’s principal research focuses on clinical factors associated with the prognosis and treatment of gestational trophoblastic diseases, as well as uterine and ovarian malignancies. He has received support for his research from several prestigious organizations, including the American Cancer Society and the NCI, as well as philanthropic funds. He has authored nearly 200 scientific publications.

Dr. Lurain is the Director of the Feinberg School of Medicine’s John I. Brewer Trophoblastic Disease Center, one of only two such centers in the United States. Gestational trophoblastic diseases involve the proliferation of trophoblastic tissue in pregnant women and include choriocarcinomas, which are rare cancers of the placenta. Since Dr. Lurain began his practice, he says he has witnessed significant advances in the treatment of trophoblastic tumors, including the accurate measurement of the tumor marker HCG (Human Chorionic Gonadotropin), which has helped physicians diagnose and manage these diseases with greater precision, and the identification of prognostic factors, which allow doctors to tailor treatments to the individual patient, reducing side effects and improving outcomes. Because of discoveries such as these, as well as the development of effective new chemotherapies, most patients with gestational trophoblastic diseases can now be cured, even when the disease is detected at an advanced stage.

Putting Patients First
Dr. Lurain is always mindful that caring for patients “is the most important thing we do. It’s such a privilege,” he says. “You may be giving a lecture or engaged in your research, but if there’s a patient who needs your attention she must be your first priority.”

A Family of Scientists
Dr. Lurain lives in Oak Park with his wife of over 40 years, Nell, a virologist at Rush University Medical Center. Their oldest daughter, Alice, earned a PhD in organic chemistry and now teaches high school chemistry in Brooklyn, New York, and their younger daughter, Kate, is a second-year medical student at the University of Virginia. She intends to go into the field of infectious disease.
It's no surprise that many of Dr. Harold Pelzer's patients consider him a friend. Pelzer, DDS, MD, is Chief of Head and Neck Surgical Oncology at the Lurie Cancer Center and Vice Chairman of the Department of Otolaryngology / Head and Neck Surgery at Northwestern University Feinberg School of Medicine. The genuine interest and compassion he has for everyone he treats is apparent. “The best part of being a physician and a surgeon,” he says, “is the relationship one has with their fellow man.”

Despite having practiced for 25 years, Pelzer is still touched and gratified by the doctor-patient relationship. “Total strangers come into your office and five minutes later they’re sharing their lives with you,” he says. For Pelzer, taking care of others is a privilege and a responsibility he embraces.

Most of Dr. Pelzer’s clinical practice is dedicated to head and neck cancers, challenging diseases that affect so much of a patient’s life. While any cancer can be extremely difficult for patients and their families to cope with, Pelzer says those with head and neck malignancies must often endure disfunction and deformity, as well as the more common issues of treatment side effects and fatigue. They may be unable to talk or swallow, and may even be disfigured, making everyday diversions, such as having a meal at a restaurant, especially difficult. “It’s really hard,” Pelzer says sympathetically. “Patients and family members have a lot to adjust to.” But, rather than being put off by these difficulties, Pelzer finds the challenges rewarding—an opportunity to interact with and help others.

From Dentistry to Medical School
A native of Chicago, Dr. Pelzer was always
interested in science and chose to major in biology when he attended Loyola University as an undergraduate. As he neared graduation, Pelzer knew he wanted to pursue a career in science but was undecided about which field to enter. He says he ended up taking the dental school entrance exam and was admitted to Loyola’s dental school the following year.

In dental school Dr. Pelzer’s interest in otolaryngology began to grow. “The more I was exposed to things outside the realm of restorative dentistry, such as cadaver dissections, the more interested I became in head and neck surgery,” he says. After graduating, Pelzer came to Northwestern to pursue a three-year residency in oral surgery. His residency was performed at Northwestern Memorial Hospital where he was able to participate in “some fairly big procedures.” He says, “the more I became involved with head and neck surgery, the more enamored I became with it.”

During his residency, Dr. Pelzer was fortunate to have met and been mentored by Dr. George Sisson, an internationally famous head and neck surgeon who was Chairman and Professor of Otolaryngology-Head and Neck Surgery at Northwestern at the time. This, says Pelzer, was the real turning point in his career. Dr. Sisson encouraged Pelzer to apply to medical school and pursue head and neck surgery. So, following his oral surgery residency, Pelzer entered Northwestern University’s School of Medicine where he graduated in 1979. He performed another residency in otolaryngology followed by a fellowship in head and neck surgical oncology at Northwestern Memorial Hospital, and joined the faculty of Feinberg in 1985.

While the fields intersect, most otolaryngologists do not have both an MD and a DDS degree. Asked how his dental school education has influenced his medical career, Pelzer says it has helped him become a better surgeon. “It may have given me a certain sophistication in that area,” he says.

Teaching the Next Generation
Pelzer says working with Northwestern’s exceptional medical students and residents is one of the most satisfying parts of his career. “It makes my days more enjoyable,” he says. “Year round, I get to work with a junior student on a daily basis for a month at a time. I really get to know my students and can hopefully make a difference in their careers.”

When he reflects on his own life as a student, Dr. Pelzer’s appreciation for Northwestern is apparent. “It was such a vibrant place and there was so much opportunity,” he says. And he believes the school has only gotten better since then. “The bar keeps getting raised higher on the students who are accepted” at the Feinberg School of Medicine, he explains. Pelzer says the students he now teaches no longer routinely come from a pre-med background, which used to be the norm. Instead, he has been delighted to find that many of them have majored in undergraduate disciplines as varied as journalism, anthropology, French, and economics. Some have even worked in other fields between their undergraduate years and medical school, which he says makes them especially multidimensional.

A Loyal “Wildcat”
Dr. Pelzer’s love for Northwestern extends to other members of his family. His son, Jack, graduated from the undergraduate program last year. “It was fun going up there to see him,” Pelzer says. “It’s just such a special place. The culture of the undergraduate school, the graduate schools, the hospital, and the medical school are great. It’s a wonderful, diverse, nurturing academic atmosphere.” (A loyal Wildcat, Dr. Pelzer even uses the team’s fight song as his cell phone ring tone.) “It was a tough call when Northwestern’s football team played Miami of Ohio, where my younger son, Owen, is a student. I love Miami, too, and we all had a great time at the game.”

Family Man
Asked what he is most proud of, Dr. Pelzer says it has been his ability to balance his medical career with his family life. Despite long hours, Pelzer says he has always tried to make family his highest priority and is happy he has managed to play an active role in both his wife’s and children’s lives. “As a physician, I don’t take that much time off, but when I do, I want to spend it with my family,” he says. Dr. Pelzer’s wife, Molly, also has a busy career as an attorney.

The Pelzers love to travel and have enjoyed several trips to some far-flung locals, including Kenya, Tanzania, the Baltics, Western Europe, and Alaska, among others.
Game-Changing Nanodiamond Discovery for MRI

A Northwestern University study shows that coupling a magnetic resonance imaging (MRI) contrast agent to a nanodiamond results in dramatically enhanced signal intensity and thus vivid image contrast. “The results are a leap and not a small one — it is a game-changing event for sensitivity,” said Thomas J. Meade, PhD, the Eileen Foell Professor in Cancer Research in the Northwestern University Weinberg College of Arts and Sciences and the Feinberg School of Medicine. “This is an imaging agent on steroids. The complex is far more sensitive than anything else I’ve seen.”

Meade led the study along with Dean Ho, PhD, Assistant Professor of Biomedical Engineering and Mechanical Engineering in Northwestern’s McCormick School of Engineering and Applied Science. Ho already has demonstrated that the nanodiamonds have excellent biocompatibility and can be used for efficient drug delivery. This new work paves the way for the clinical use of nanodiamonds to both deliver therapeutics and remotely track the activity and location of the drugs. The ability to image nanodiamonds in vivo would be useful in biological studies where long-term cellular fate mapping is critical, such as tracking beta islet cells or tracking stem cells.

A noninvasive medical imaging technique that uses an intravenous contrast agent to produce detailed images of internal structures in the body, MRI is capable of deep tissue penetration, achieves an efficient level of soft tissue contrast with high spatial and time-related resolution, and does not require ionizing radiation. Contrast agents are used in MRI because they alter the relaxivity (contrast efficacy indicator) and improve image resolution. Gadolinium (Gd) is the material most commonly used as an MRI contrast agent, but its contrast efficacy can be improved.

Meade, Ho and their colleagues developed a gadolinium(III)-nanodiamond complex that, in a series of tests, demonstrated a significant increase in relaxivity and, in turn, a significant increase in contrast enhancement. The Gd(III)-nanodiamond complex demonstrated a greater than 10-fold increase in relaxivity — among the highest per Gd(III) values reported to date.

This represents an important advance in the efficiency of MRI contrast agents.

Ho and Meade imaged a variety of nanodiamond samples, including nanodiamonds decorated with various concentrations of Gd(III), undecorated nanodiamonds and water. The intense signal of the Gd(III)-nanodiamond complex was brightest when the Gd(III) level was highest. “Nanodiamonds have been shown to be effective in attracting water molecules to their surface, which can enhance the relaxivity properties of the Gd(III)-nanodiamond complex,” said Ho. “This might explain why these complexes are so bright and such good contrast agents.”

“The nanodiamonds are utterly unique among nanoparticles,” Meade said. “A nanodiamond is like a cargo ship — it gives us a nontoxic platform upon which to put different types of drugs and imaging agents.” Nanodiamonds are carbon-based materials approximately four to six nanometers in diameter. Each nanodiamond’s surface possesses carboxyl groups that allow a wide spectrum of compounds to be attached to it, not just gadolinium(III).

Meade has pioneered the design and synthesis of chemical compounds for applications in cancer detection, cellular signaling and gene regulation. Dr. Ho has pioneered the development of nanodiamonds and has demonstrated their efficiency as drug delivery vehicles. For more information on their research, visit www.northwestern.edu/newscenter/stories/2010/01/mri.html
NCI Awards 13.6 Million Grant for Physical Sciences-Oncology Center

Northwestern University has been awarded a $13.6 million five-year grant from the National Cancer Institute (NCI) to establish an interdisciplinary research center for the study of genes and their role in cancer. A better understanding of the mechanisms could lead to better diagnostics and therapeutics and open up new directions for research. Northwestern’s Physical Sciences-Oncology Center (PS-OC), one of 12 funded nationwide by the NCI, brings together physical scientists and cancer biologists to use non-traditional, physical-sciences based approaches to understand and control cancer.

"Our center will be studying the regulation and expression of genes in both normal health and development and in cancer," said principal investigator Jonathan Widom, PhD, the William Deering Professor in Biological Sciences in the Weinberg College of Arts and Sciences, and Lurie Cancer Center member. "We need to understand healthy cells to understand and control cancer." The PS-OC initiative is expected to generate new knowledge in order to identify and define critical aspects of physics, chemistry and engineering that shape and govern the emergence and behavior of cancer at all scales.

New Chemo Cocktail Blocks Breast Cancer Like a Fence

Think of a protective fence that blocks the neighbor’s dog from charging into your backyard. The body, too, has fences — physical and biochemical barriers that keep cells in their place. When breast cancer spreads or metastasizes, it crashes through the body’s protective fences. The disease becomes fatal when it travels outside the mammary ducts, enters the bloodstream and spreads to the bones, liver or brain. Currently, there are only drugs that try to stem the uncontrolled division of cancer cells within the ducts. Until now, no drugs specifically targeted the invasion and spread of breast cancer to the organs.

Northwestern University researcher Seth Corey, MD, has discovered that when a drug normally used to treat leukemia is added to a commonly used breast cancer drug, the potent new chemotherapy cocktail strengthens the “fence,” that helps prevent breast cancer cells from invading.

"This is an entirely new way of targeting a cancer cell," said Corey, the Sharon B. Murphy-Steven T. Rosen Research Professor of Cancer Biology and Chemotherapy at the Feinberg School of Medicine and Leader of the Pediatric Oncology Program at the Lurie Cancer Center. Working in the lab with women’s breast cancer cells, Corey found that when the leukemia drug dasatinib is combined with the breast cancer drug doxorubicin, the potent mix inhibits breast cancer cell invasion by half. Dasatinib targets an enzyme called the Src kinase, which is believed to play a key role in breast cancer invasion and metastases. "Perhaps this drug could be given to prevent invasion from happening in the first place," said Corey, who is also a pediatric oncologist at Children’s Memorial Hospital. "This might keep the disease in check and prevent it from progressing."
MAGGIE DALEY CENTER FOR WOMEN’S CANCER CARE DEBUTS AT NORTHWESTERN

The Maggie Daley Center for Women’s Cancer Care was unveiled at a ceremony that marked the debut of the novel center for treating breast and gynecologic cancers. The Center for Women’s Cancer Care is part of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and is located within Northwestern Memorial Prentice Women’s Hospital. Mrs. Daley, who receives treatment for breast cancer at the Lurie Cancer Center, attended the ceremony accompanied by Mayor Richard M. Daley.

The new two-floor center offers a unique holistic approach that addresses and centralizes all of a woman’s needs – emotional, aesthetic and physical – during treatment. Patients can easily access services to improve their quality of life in the same place they are seeing internationally renowned medical oncologists, gynecologic oncologists and receiving cutting-edge therapy for breast and gynecological cancers.

Steve Rosen, MD, Director of the Lurie Cancer Center and of Cancer Programs at Northwestern Memorial, noted Mrs. Daley’s “heroic strength” in fostering vital programs that benefit the public while contending with the challenge of breast cancer. “The Maggie Daley Center for Women’s Cancer Care will be a unique resource for our community and the nation. We are indebted to you for your commitment to this important cause,” he said.

The Center for Women’s Cancer Care offers patients access to novel therapies and drugs, and the access to more than 100 clinical trials for women with gynecologic and breast cancers. A cancer genetics program within the center screens patients at higher than average risk for cancer and provides education and guidelines for early detection and possible prevention of the disease. The center includes 11 private chemotherapy rooms, most with lake views, and a group chemotherapy area, providing patients with a choice of environments.

A new program offers rehabilitation services for women to maximize their strength and endurance. Women can also get acupuncture or Reiki, visit a nutritionist or see a health psychologist, and a new “healing boutique” offers wig and prosthesis fittings, hats and makeup consultations for patients undergoing chemotherapy and radiation treatments.

"This represents an opportunity to care for the whole patient in one place," said Julian Schink, MD, Medical Director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University at Northwestern Medical Faculty Foundation and Associate Director for Clinical Affairs at the Lurie Cancer Center. "We identified what someone really needs to be well in addition to their cancer therapy. “
Lurie Cancer Center Pioneers Use of caBIG® to Improve Patient Experience

According to Lyle Berkowitz, MD, an internist with Northwestern Memorial Physicians Group (NMPG), a diagnosis of cancer marks “an inflection point in healthcare,” that triggers a series of complex and potentially confusing actions. Berkowitz recognized the need to provide guidance to patients and their physicians at these points, and turned to a combination of process and technology built upon the Cancer Biomedical Informatics Grid (caBIG) Patient Study Calendar (PSC), an open-source, standards-based software application intended for use by organizations to centrally and consistently manage study participant schedules in clinical trials. “We recognized that PSC could be easily modified to do exactly what we needed,” says Warren Kibbe, PhD, Director of Bioinformatics at the Lurie Cancer Center, who led the development effort.

“Most primary care physicians do not deliver a diagnosis of cancer very frequently,” explains Berkowitz. “They may not be current on the protocol for workup or exactly what the patient should do next.” Berkowitz led a research effort under the auspices of the Szollosi Healthcare Innovation Program (SHIP), a nonprofit organization he founded and directs.

Dr. Berkowitz and his colleagues at the Lurie Cancer Center created a five-step checklist to provide the formal guidance, but he also recognized that if the list could be translated into a technology tool, it would be simpler for physicians to use and acceptance would be higher. When Kibbe learned more about the functional requirements for this tool, he realized that a foundation was already available in the caBIG® Patient Study Calendar (PSC), a tool to help patients and their care providers follow the protocols while on a clinical trial.

Kibbe also recognized that if the checklist could be translated into a technology tool, it could provide a much simpler workflow for physicians to use, resulting in a higher rate of acceptance. As he learned more about the functional requirements sought from this tool, Kibbe realized that a solid technology foundation was already available in the caBIG® Patient Study Calendar (PSC).

The modified PSC (called iNav), now in place at Northwestern University, leverages existing resources to help physicians communicate important information to their patients, consistently and easily. This powerful combination of process, technology, and personnel is the pilot for a Northwestern comprehensive Patient Navigator Program which is currently being used with patients initially seen at NMPG.

iNav is now freely accessible to the global bioinformatics community under an MIT Open Source license. The full code base may be found online at http://github.com/mgurley/inv. Questions may be directed to Mike Gurley at m-gurley@northwestern.edu, Sean Whitaker at s-whitaker@northwestern.edu, or Warren Kibbe at wakibbe@northwestern.edu.
Lurie Cancer Center Named Commission on Cancer Outstanding Achievement Award Winner

The Lurie Cancer Center has been named a 2009 Commission on Cancer (CoC) Outstanding Achievement Award winner by the American College of Surgeons. The prestigious honor recognizes cancer programs that strive for excellence in providing quality care to cancer patients and represents an elite group of hospitals across the country.

The award is granted to facilities that demonstrate a Commendation level of compliance with six standards that represent five areas of cancer program activity – cancer committee leadership, cancer data management, research, community outreach and quality improvement. In addition, facilities must receive a compliance rating for the remaining 30 cancer program standards. Of 432 programs surveyed by the CoC in 2009, only 82 programs, or 18 percent, received an Outstanding Achievement Award.

Established in 1922 by the American College of Surgeons, the Commission on Cancer is a consortium of professional organizations dedicated to improving survival and quality of life for cancer patients through standard-setting, prevention, research, education, and the monitoring of comprehensive quality care. Its membership includes Fellows of the American College of Surgeons and representatives of 47 national organizations that reflect the full spectrum of cancer care.

The Lurie Cancer Center is one of only six Illinois cancer programs to receive a 2009 Outstanding Achievement Award.

Malcolm DeCamp Joins Northwestern as Chief of Thoracic Surgery

Malcolm M. DeCamp, MD, has joined Northwestern as Chief of the Division of Thoracic Surgery at Northwestern Memorial Hospital, Professor of Surgery at Northwestern University’s Feinberg School of Medicine, and as a member of the Lurie Cancer Center.

Most recently, Dr. DeCamp served as Visiting Associate Professor of Surgery at Harvard Medical School and Chief of the Division of Cardiothoracic Surgery at Beth Israel Deaconess Medical Center in Boston. Previously, he directed the lung transplant program at the Cleveland Clinic. Dr. DeCamp’s research focus is on genetic, phenotypic and physiologic mechanisms to explain the response to interventions for severe emphysema.

Clinically, Dr. DeCamp’s research is centered on outcome analysis following the multidisciplinary management of lung, esophageal and thymic malignancy as well as on innovation and refinement of minimally invasive techniques for thoracic surgery.

Board-certified in general surgery and thoracic surgery, Dr. DeCamp specializes in surgery for benign and malignant lung, tracheo-bronchial, esophageal, mediastinal and chest wall disorders. In addition to thoracic oncology, he maintains an interest in advanced lung diseases, lung transplantation, lung volume reduction surgery and minimally-invasive surgery for a variety of chest diseases.

His academic achievements include the President's Award for original research from the Southern Thoracic Surgical Association. On the national level, Dr. DeCamp chairs the Workforce on General Thoracic Surgery for the Society of Thoracic Surgeons. While at Beth Israel, he directed the Thoracic Oncology Program and the Chest Diseases Center and served as Program Director for their Cardiothoracic Residency Program. He has lectured on four continents, authored more than 100 articles in numerous professional publications and contributed 30 chapters to a variety of medical, surgical and oncologic texts.

Malcolm DeCamp
Al B. Benson III, Named President of the Association of Community Cancer Centers

Al B. Benson III, MD, Professor of Medicine at the Feinberg School of Medicine and Associate Director for Clinical Investigations at the Lurie Cancer Center, was named President of the Association of Community Cancer Centers (ACCC). ACCC is dedicated to promoting professional learning opportunities and to providing a forum for members to network and enhance their skills in the business, clinical and management aspects of care for the cancer community.

"I am honored to serve as President of the Association of Community Cancer Centers," said Dr. Benson. "During my year as ACCC President, I hope to give voice to the importance of putting comparative effectiveness research and evidence-based medicine into practice. ACCC needs to be at the table with other oncology organizations. Oncology must have a definitive voice in the comparative effectiveness debate and how it evolves."

Dr. Benson has served on ACCC’s board of directors since 2003 and has been active on ACCC’s Strategic Planning Committee, Editorial Committee, New Technology Committee, Corporate Development Committee, Awards Committee, Bylaws Committee, Program Committee, and Membership Committee.

Dr. Benson’s research is primarily in the areas of gastrointestinal cancer clinical trials, biologic therapies, Phase I cancer clinical trials, and cancer guideline development. He has authored or co-authored numerous reports, reviews, and book chapters focusing on these topics. His research in biologics, cancer therapy, and cancer prevention has been awarded funding from a variety of sources including the NIH.

Dr. Benson has served on a number of committees for the American Society of Clinical Oncology (ASCO) and is currently a member of the Task Force on Quality of Cancer Care, and the co-chair of ASCO’s Colorectal Cancer Surveillance Guidelines Panel, the Stage II Colon Cancer Guidelines Panel and the RFA for colorectal cancer liver metastases panel. He is also the chair of the Eastern Cooperative Oncology Group Gastrointestinal and Data Monitoring Committees. In addition, he is a member of several medical societies, and serves as past-president of the Illinois Medical Oncology Society, past-president of the International Society of GI Oncology, and is a member and immediate past-chair of the board of directors of the National Comprehensive Cancer Network (NCCN). He was recently appointed as a Scientific Advisory Board member of both the Patient Advocacy Foundation and the National Patient Advocacy Foundation.
Lifestyle behaviors influence the risk of developing cancer; they can also modulate cancers’ effects on symptoms and quality of life. Up to 35-50% of all cancer deaths are estimated to result from risk behaviors that are potentially modifiable (Danae, Vander Hoorn, Lopez et al, 2005). Smoking, low fruit and vegetable intake, obesity, and physical inactivity head the list of behaviors that influence cancer onset and progression. Behavior change that results in a healthier lifestyle holds the potential to lower cancer risk, reduce recurrence, and lessen the pain, depression, and fatigue that often accompany cancer. To advance the knowledge base in this domain, in 2005 the Lurie Cancer Center established a program in Cancer Behavioral Science. Program faculty are housed...
in the Behavioral Medicine Section of the Department of Preventive Medicine. All faculty are funded by National Institutes of Health grants to develop, test and disseminate behavior change interventions that reduce cancer risk, promote early detection, and decrease adverse effects of existing cancers on quality of life.

Bonnie Spring, PhD, Professor of Preventive Medicine, heads the Behavioral Science program and is Co-Program Leader in Cancer Prevention. A clinical health psychologist, Dr. Spring trained at Harvard University and is the Immediate Past President of the Society of Behavioral Medicine. Her research addresses the problem of how to achieve change in multiple, interrelated risk behaviors. For example, most people gain weight after quitting smoking primarily because when they discontinue self-administration of cigarettes, they substitute self-administration of preferred foods. To address that problem, Dr. Spring studies the optimal design, timing and behavioral targets for interventions to prevent post-cessation weight gain (Spring, Pagoto, Pingitore et al, 2004; Spring, Howe, Berendson et al, 2009). Her ongoing NIH and VA-funded clinical trials test whether supportive technologies can help people to change bundled maladaptive diet and activity behaviors that comprise an unhealthy, obesogenic lifestyle. Dr. Spring’s research addresses the question of whether it is more effective to frame behavior change goals in terms of increasing healthy low rate behaviors or decreasing unhealthy high rate behaviors. Also under study is whether positive change in specific risk behaviors reliably produces desirable synergistic change in other risk behaviors. At a practical level, Dr. Spring tests whether supportive technologies that deliver tailored coaching via distance channels (mail, telephone, internet, mobile device) can preserve the effectiveness of in-person professionally delivered behavioral interventions, while reducing treatment costs and increasing population reach.

Brian Hitsman, PhD, Assistant Professor of Preventive Medicine, is a clinical health psychologist and was a faculty member at Brown University before joining the Lurie Cancer Center. An expert on the determinants and treatment of smoking, Dr. Hitsman is a contributing author to the 2010 Surgeon General’s Report on Tobacco. All Cancer Behavioral Science faculty share an interest in depression because the comorbidity heightens the risk and persistence of unhealthy lifestyle behaviors and complicates recovery from cancer. In research supported by a K08 award, Dr. Hitsman is contrasting the neuropsychological and emotional features of smokers with versus without comorbid depressive vulnerability (Ziedonis, Hitsman, Beckham, et al, 2008; Hitsman, Moss, Montoya & George, 2009). His aim is to understand the psychobiological substrate of smoking persistence. For many smokers, especially those who experience depression, tobacco use begins in early adolescence and persists across adulthood with multiple periods of remission and relapse back to smoking. That observation raises the question of whether tobacco use should be conceptualized as a chronic condition and treated accordingly. Dr. Hitsman is addressing that question in a randomized clinical effectiveness trial that contrasts usual duration nicotine replacement treatment (12 weeks) versus extended treatment (24 weeks) versus maintenance treatment (52 weeks). The trial of 660 smokers is supported by an NIH R01 and conducted in collaboration with Dr. Spring at Northwestern and Drs. Robert Schnoll and Caryn Lerman at the University of Pennsylvania.

David Mohr, PhD, Professor of Preventive Medicine, is a clinical psychologist who joined Lurie Cancer Center after serving as a faculty member at University of California San Francisco. Dr. Mohr’s research examines how to overcome barriers to behavioral care. In depression, where evidence-based behavioral and pharmacologic treatments are both available, 2/3 of patients prefer behavioral intervention (Dwight-Johnson, Sherbourne, Liao, Wells, 2000). However, because behavioral care usually requires patients to attend multiple in-person treatment sessions, numerous barriers impede access. Relevant barriers include cost, time constraints, transportation problems, or mobility impairments. Dr. Mohr studies ways to bring care into the patient’s own environment via home visits (Mohr, Moran, Kohn et al, 2003), telephone delivery (Mohr, Hart, Julian et al, 2005), and most recently internet. A current NIH R01 grant compares the effectiveness of telephone-delivered versus in-person depression treatment. In addition to being highly effective, telephone-administered treatments appear to result in levels of attrition below those seen in face-to-face treatments. Internet interventions
offer another way to take behavioral care out of
the clinic and extend it into the patient’s
environment. However, internet interventions
are plagued by high dropout, and low
utilization among those who stay enrolled. To
combine the low cost of internet intervention
with the high retention of telephone treatment,
Dr. Mohr has begun testing a web-based
depression intervention supported by a brief
weekly call to enhance adherence. He plans
next to tailor the intervention for patients with
cancer.

Lynette Craft, PhD, Assistant Professor of
Preventive Medicine, is a kinesiologist who
studies physical activity interventions to
improve mental and physical health. She
recently completed data collection in the FEMS
study, which examines associations among
physical activity, sedentary time, physical fitness
and mammographic breast density (a risk factor
for breast cancer) among 100 women, 40-75
years of age, who underwent screening
mammography at the Lynn Sage
Comprehensive Breast Center. Among women
with early stage breast cancer, Dr. Craft finds
that negative emotion and psychosocial barriers
both correlate with diminished physical activity
(Perna, Craft, Carver & Antoni, 2008).
However, she also finds that early stage breast
cancer patients can feasibly engage in structured
exercise during adjuvant treatment with
beneficial effects on depression (Perna, Craft,
Freund, et al., 2010). Currently, with support
from an NCI K07 award, Dr. Craft is
comparing the effects of a standard versus an
intermittent exercise intervention, on the
symptom cluster of pain, depression, and
fatigue in breast cancer survivors. Finally, Dr.
Craft and the Lurie Cancer Center have
partnered with the Pin-A-Sister Mother’s Day
breast cancer screening program offered in
African American and Latino churches around
Chicago to offer a Wellness Walking program.
To date, 8 churches and nearly 180 women
have committed to group walking and received
pedometers to reinforce their efforts.

Juned Siddique, PhD is an Assistant Professor
in the Department of Preventive Medicine and
biostatistician for the cancer behavioral science
program. After receiving his doctorate from
UCLA, Dr. Siddique worked as faculty for
several years at the University of Chicago before
coming to Northwestern. His methodological
research has been in the fields of missing and
latent data. Missing data are a problem in most
datasets and are ubiquitous in the social and
health sciences. Failure to adequately account
for missing values can lead to biased estimates,
loss of information, and overestimates of
precision. One approach for handling missing
values is imputation: replacing missing values
with plausible values. Dr. Siddique’s research
has involved multiple imputation, where two or
more values are imputed for each missing value
(Siddique & Belin, 2008; Siddique & Harel,
2009). By using multiple imputations,
uncertainty due to missing values is propagated
into parameter estimates. Dr. Siddique is
applying his methodologic interest in latent
variables to measure unobservable but
important, well-conceived constructs in
behavioral science. Such constructs can be
measured indirectly by using multiple items as
indicators of the nonobservable (latent)
characteristics. For example, he is currently
developing methods to measure factors related
to a healthy lifestyle such as dietary quality,
physical activity, and sedentary activity. With
support from an NIH R03 grant, he is also
developing growth mixture models for
behavioral data. Many behavioral interventions
are characterized by heterogeneity in patient
outcomes over time. One approach for
modeling these data is to assume that
participants fall into different latent classes that
explain their trajectories over the course of the
study. In a weight loss study, for example, three
possible classes might be: no change over time,
weight loss then weight regain, and steady
weight loss. An added benefit of growth
mixture models is that they permit
identification of the predictors of these latent
classes, making it feasible to design targeted
interventions.

The Cancer Behavioral Science faculty is excited
to participate in the Lurie Cancer Center. We
intend for our research to contribute to the full
spectrum of cancer prevention research and
intervention. By developing and disseminating
behavioral treatments to reduce smoking,
unhealthy diet, physical inactivity, and obesity,
we aim towards primary prevention – to reduce
the risk that cancer will develop. By fostering
screening to detect cancers early (Costa-
Woerpel et al, 2009), we aim towards secondary
prevention – to prevent cancer progression. By
developing interventions to alleviate the
psychological sequelae of cancer and
transporting these treatments into the patient’s
environment, we aim at tertiary prevention – to
improve disease-related quality of life. The past year has seen exciting developments in cancer behavioral science at Northwestern University with the founding of the new Department of Medical Social Sciences, led by David Cella, PhD. We look forward enthusiastically to collaborating with behavioral scientists in the new department.

References


The terms euchromatin and heterochromatin were first coined back in the late 1920s by Emil Heitz to describe cytological observations of eukaryotic chromosomes. Euchromatin describes the portion of chromatin that decondenses at telophase while heterochromatin describes the portion that remains visibly condensed after the completion of mitosis. Classical studies of inversion mutations resulting in juxtaposition of eye color genes with heterochromatin in Drosophila revealed heterochromatin could spread into and silence neighboring euchromatic genes resulting in mosaic inactivation of gene expression. This phenomenon, position-effect variegation (PEV), further defined heterochromatin as inhibitory to transcriptional activity. Heterochromatin has been implicated in the regulation of various forms of epigenetic phenomena (heritable changes in gene expression that are not the result of altered DNA sequence) in a broad range of eukaryotic species including animals, fungi and plants. These phenomena include genomic imprinting, dosage compensation and paramutation. The linking of defects in heterochromatin assembly to various forms of human disease including cancer has fueled interest in a clearer understanding of the mechanisms involved in heterochromatin regulation.

The basic building blocks of chromatin are nucleosomes. These structures consist of approximately two turns of DNA wrapped around a core histone octamer containing two molecules each of histone H2A, H2B, H3, and H4.
H4. A number of histone modifications have been identified that occur on the amino terminal tails of core histone proteins. These include methylation, acetylation, phosphorylation, ADP ribosylation, ubiquitination, and sumolation. Interestingly, many histone modifications, such as methylation of histone H3 lysine 9 (H3mK9) and methylation of histone H3 lysine 4 (H3mK4) are associated with heterochromatin or euchromatin regions respectively leading to the idea that these modifications mark chromatin via a "histone code." These marks can be interpreted by adaptor proteins that dictate the chromatin state of the modified chromosomal region. For example, the HP1-like protein Swi6 is required for transcriptional silencing and binds centromeric heterochromatin via its amino-terminal chromodomain that specifically binds histone H3 tails methylated at lysine 9. It is believed that Swi6 can also interact with Chr4, the sole S. pombe histone H3 lysine 9 methyltransferase, leading to a model whereby Swi6 binding, and subsequent recruitment of Chr4, results in spreading of heterochromatin to nearby sequences.

Many of the enzymes responsible for catalyzing histone modifications have been identified. How these factors initially become targeted to specific regions of the genome, however, is not clear. Recent work in fission yeast has implicated RNA interference (RNAi) in targeting histone modifications to centromeric repeats providing insight into the sequence specificity of heterochromatin assembly.

RNAi is a process whereby processing of double-stranded RNA (dsRNA) results in post-transcriptional silencing of cognate genes via sequence specific degradation of endogenous transcripts. Studies in various eukaryotes have identified several genes involved in RNAi including an RNase III helicase, or Dicer, several members of the ARGONAUTE gene family, and an RNA dependent RNA polymerase (RdRP). Dicer specifically cleaves dsRNA into small interfering RNAs (siRNA) 21-24nt in length. These siRNAs can then guide effector complexes such as the RNA-induced silencing complex (RISC) to endogenous transcripts in a sequence specific manner resulting in their cleavage and subsequent degradation. Argonaute, provides the “slicer” activity of RISC which functions to cleave endogenous messages via its RNase domain. RdRP is thought to be involved in amplification of small interfering RNAs (siRNAs), possibly by using endogenous messages as templates to generate additional dsRNA substrates.

Contrary to the classical belief that heterochromatic regions are transcriptionally inert, analysis of nascent transcripts in wild type cells reveals heterochromatin centromeric repeats are expressed. In addition, in RNAi mutants, Swi6/HP1 protein is greatly reduced at centromeres, centromeric H3mK9 is replaced by H3mK4, and euchromatic reporter genes integrated within centromeric repeats are derepressed. Taken together, these results suggest processing of centromere transcripts by RNAi leads to the sequence specific targeting of heterochromatin to centromeres.

Interestingly, portions of centromeric repeat sequences are also found at other heterochromatic regions in S. pombe including the silent mating type loci (MAT-K) and telomeres suggesting these regions are regulated by common mechanisms. Indeed, at MAT-K, initiation of heterochromatin formation requires the RNAi machinery as well as a region of centromere homology contained within the silent mating type locus (cen-h). Interestingly, several labs have demonstrated the ability of centromere sequences integrated at normally euchromatic chromosomal regions to recruit heterochromatin that can then spread into and silence adjacent reporter genes. It is unclear whether the various regions of centromere homology within the genome can interact to strengthen silencing, however, the high sequence identity shared between these regions suggests that “cross talk” between these sequences is likely.

Heterochromatin was once thought to highly stable but has recently been shown to be quite dynamic. One example of this is the heterochromatin protein Swi6/HP1 that, contrary to early models, binds heterochromatin only transiently and is replaced in milliseconds. Similar results were also found in human cells. Other studies on chromatin dynamics observed HP1 being more mobile in stem cells than in differentiated cells. These results led to a “breathing chromatin” model whereby chromatin is maintained in a mobile state until cell fate is determined via cell differentiation. The interesting questions we
face now are 1) what role, if any, does dynamic heterochromatin play in the cell? and 2) what factors are involved in heterochromatin dynamics? We have recently addressed these questions in fission yeast and have not only identified a factor involved in heterochromatin mobility but have also uncovered an extremely interesting mechanism involved in heterochromatin regulation.

Our studies began with analysis of msc1Δ mutants on centromere silencing in S. pombe. Msc1 is a homolog of mammalian RB binding protein 2 (RBP2) and was recently isolated as a suppressor of DNA damage checkpoint mutations. Msc1 contains a PHD/JmjC domain. PHD/JmjC domain proteins are of particular interest to us since this domain has recently been implicated in erasure of histone methyl marks via histone demethylation. While no obvious histone demethylase activity was observed for Msc1 the mutant phenotype includes increased repression of euchromatic reporter genes integrated within heterochromatin centromere repeats. High resolution mapping of Swi6/HP1 in the absence of Msc1 reveals an overall increase in Swi6/HP1 occupancy throughout heterochromatin centromere repeats compared to wild-type suggesting Msc1 acts to antagonize the stability of centromere heterochromatin.

Interestingly, the opposite was observed when the ability of ectopic centromere sequences to silence adjacent reporter genes was assayed. In this case ectopic silencing was greatly reduced in the absence of Msc1 (Lawrence and Volpe, unpublished data). These results demonstrate that Msc1 acts to both antagonize heterochromatin stability at centromeres but also acts to promote efficient heterochromatin assembly elsewhere in the genome.

Based on our observations that Msc1 antagonizes heterochromatin stability and Swi6 binding to centromeres, we hypothesized that Msc1 could function to facilitate the dynamic binding of Swi6/HP1 to heterochromatin. Fluorescence recovery after photo-bleaching (FRAP) of GFP-Swi6 reveals a decrease in Swi6/HP1 mobility in the absence of Msc1 (320ms to 840ms). The decrease in Swi6/HP1 mobility observed in msc1 mutants suggests Msc1 promotes the dynamic nature of Swi6/HP1 association with heterochromatin. This could potentially explain the observed increase in heterochromatin stability in the absence of Msc1. We reasoned that increased stability of centromere heterochromatin could result in sequestering of heterochromatin proteins, such as Swi6/HP1, at the centromeres. Thus, a titration of available Swi6/HP1 could account for the inefficient assembly of heterochromatin observed at ectopic centromere sequences in the absence of Msc1. Increased efficiency of ectopic silencing when Swi6/HP1 is over-expressed supports this idea.

Msc1 appears to be involved in promoting efficient heterochromatin assembly at ectopic centromere sequences through increasing mobility of centromere bound Swi6/HP1 and antagonizing heterochromatin stability. These observations do not, however, reveal much about the endogenous function of Msc1 (and dynamic chromatin) in wild type cells. One critical function of heterochromatin in S. pombe is cell fate determination via mating type switching. The ability to switch mating type insures cells have a nearby mating partner when nutrients are low and survival depends on sporulation. Interestingly, we observe a defect in mating-type switching in the absence of Msc1. Although we see a striking effect on mating-type switching in the absence of Msc1 we do not detect any enrichment of Msc1 at the silent mating-type locus. This suggests that Msc1 acts to regulate mating type heterochromatin indirectly via destabilization of Swi6/HP1 binding at centromeres that then promotes recruitment of Swi6/HP1 to MAT-K.

These results fit well with previous models suggesting chromatin is maintained in a highly mobile state until differentiation occurs. Thus, the function of “breathing chromatin” may be to maintain chromatin in an uncommitted state until cell fate has been determined. Although alternation of cell fate through mating type switching, at first glance, does not appear to resemble the complexity of cell fate decisions in higher eukaryotes a strong argument can be made for S. pombe mating type switching as a model for cellular differentiation in multi-cellular organisms. This is due to the “consecutive switching” rule observed in mating type switching. This rule describes the phenomenon whereby a “switchable” P type (PS) cell gives rise to another “switchable” P type as well as an “unswitchable” M type cell (MS). Therefore, the lineage of “switchable” P type cells always maintains a cell that is “like” itself not unlike a stem cell in multi-cellular organisms (Figure 1).
There are many questions left to be answered regarding the role of Msc1 in heterochromatin regulation. One key question that remains is how Msc1 acts to destabilize heterochromatin specifically at centromere repeats. One idea is that Msc1 could act to promote transcription within heterochromatin regions. Therefore, it may simply be the act of transcription that leads to dynamic Swi6/HP1 binding (Figure 2). We are currently testing this idea. Another major question is whether Msc1 homologs in higher eukaryotes have roles in heterochromatin dynamics and stem cell maintenance. Ultimately, we may only be scratching the surface with regard to our understanding of the mechanisms involved in the regulation and function of heterochromatin dynamics. Further investigations will determine whether this is the case.

References


Cell-cell adhesion and communication maintains epithelial tissue homeostasis.

Epithelial cells construct strong physical and chemical ties with their neighbors to maintain tissue integrity and homeostasis. In cancer, these cell-cell adhesion structures often lose their mechanical strength and communication between carcinoma cells becomes miswired. Our laboratory aims to understand the molecular basis underlying normal epithelial cell-cell adhesion and communication and to further determine how cross-talk between these cellular processes becomes distorted during neoplastic transformation.

Cadherins are a family of transmembrane adhesion molecules that not only stabilize cell-cell contacts but also regulate intracellular signaling pathways that influence cell migration and proliferation. For example, E-cadherin interacts with a like molecule on an adjacent cell to initiate cell-cell adhesion and also dampens epidermal growth factor receptor (EGFR/ErbB1)-related mitogenic signaling to keep epithelial growth in check when cells become tightly packed in culture. Importantly, the expression and/or function of this adhesion molecule is often compromised during oncogenesis. Less is known about the related...


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Photos: Samantha Lin (top), Kristin Gordon (lower left), and Spiro Getsios (lower right).
desmosomal cadherins in cancer, although we have recently shown that these too serve dual roles as adhesion and signaling molecules in epithelial tissues that undergo extensive mechanical stress such as the skin. In particular, desmoglein 1 maintains tissue integrity in the epidermis and also functions to suppress EGFR activity, providing a contextual cue for these epithelial cells (termed keratinocytes) to differentiate. Building on this foundation of knowledge, our group strives to identify novel adhesion-signaling networks that contribute to the maintenance of the normal epithelial phenotype with the hope that we will be able to therapeutically harness these networks and restore tissue architecture during pathological conditions such as skin hyperplasia and cancer.

The Eph family of receptor tyrosine kinases are common targets in cancer

Eph receptor tyrosine kinases are ideal candidates for regulating epithelial adhesion-signaling networks since these transmembrane proteins become activated by ephrin-ligands residing on adjacent cell surfaces in a manner that is facilitated by cadherin-based cell-cell adhesion complexes. Similar to other receptor tyrosine kinases, once an Eph receptor engages with its ligand in the extracellular domain, several tyrosine residues on the intracellular tail become phosphorylated and act as docking sites to recruit downstream signaling effectors that control cell adhesion, migration and proliferation (Fig. 1). The Eph family of receptors and ephrin ligands are involved in directing cell patterning events during neural, vascular and bone development by maintaining proper tissue boundaries. However, their roles in regulating epithelial tissues formation and homeostasis remain less clear.

Although EphA2 is a major epithelial receptor tyrosine kinase that is abundantly expressed in adult tissues such as the skin, most of what we know about EphA2 comes from cancer studies. That is likely because EphA2 is frequently overexpressed in a variety of cancers, where its levels are directly correlated with tumor malignancy. Forcing increased EphA2 expression in a non-transformed breast epithelial cell causes malignant transformation and also destabilizes cadherin-based cell-cell junctions, supporting a tumor promoting role for this kinase. Interestingly, breast cancer tumors that overexpress the human epidermal growth factor receptor-2 (HER-2/neu/ErbB2) can be treated with trastuzumab to block this kinase and limit tumor growth. However, a subpopulation of breast cancer cell lines that becomes resistant to trastuzumab therapy switch to using EphA2 in order to escape these effects of the drug and continue to grow.

EphA2 has tumor promoting characteristics in the breast; yet this receptor is surprisingly also capable of suppressing tumor growth in the skin. For example, mice deficient for EphA2 that are induced to develop skin cancer display an increased susceptibility to tumor growth. Moreover, targeting EphA2 with pharmacological peptides that mimic the ephrin-A1 ligand leads to the suppression of
mitogen-activated protein kinase (MAPK) signaling and proliferation. However, the ability of EphA2 to regulate ERK1/2 signaling in response to artificial ephrin ligands appears to be complex and cell-type specific since these recombinant ephrin-A1-Fc peptides can either stimulate or inhibit ERK1/2 activity in normal and transformed cells. For example, peptidomimetic activation of EphA2 can recruit the Grb2:Sos1 complex in breast epithelial cells, which activates Ras, an upstream regulator of ERK1/2-MAPK signaling. On the other hand, in prostate epithelial cell lines, EphA2 is capable of interacting with p120RasGAP, a negative regulator of Ras and ERK1/2-MAPK. These observations provide a possible explanation for the seemingly paradoxical effects on ERK1/2 activity in response to peptide-ligand activation of EphA2.

The epidermis is a stratified squamous epithelium that serves as the outermost compartment of the skin and its first layer of defense against the outside world. To maintain an intact skin barrier, the epidermis is constantly renewed throughout our lives. The ERK1/2-MAPK pathway is essential to this regenerative process, as it drives keratinocyte proliferation in the basal layer of the epidermis and must be dampened for cell cycle exit and differentiation in the suprabasal layers. EphA2 is expressed in an increasing basal to suprabasal gradient that is inversely correlated with ERK1/2 activity. In addition, EphA2’s high affinity ephrin-A1 ligand is also localized to the basal layer of the epidermis. Collectively, these observations led us to hypothesize that native EphA2/ephrin signaling complexes may function to regulate mitogenic ERK1/2 signaling and growth in human keratinocytes.

EphA2 mediates cell-cell communication to restrain growth of normal skin epithelial cells

Pharmacological ephrin-A1 peptidomimetics target EphA2 to suppress ERK1/2-MAPK signaling and growth of primary human epidermal keratinocytes. To study normal epithelial cell-cell communication pathways, our laboratory employs primary epidermal keratinocytes that are isolated from human skin. By manipulating levels of extracellular calcium, we can modulate the extent of cell-cell adhesion and communication in these primary cultures. Our initial studies showed that EphA2 and its high affinity ephrin-A1 ligand were abundantly expressed in normal human epidermal keratinocytes just as in intact skin. As a first step towards understanding the effects of EphA2 on ERK1/2-MAPK signaling in the human epidermis, keratinocytes were maintained in low calcium in order to limit the formation of endogenous EphA2/ephrin signaling complexes and alternative cell-cell communication pathways that may also regulate ERK1/2 activity. Stimulating these cultures with recombinant ephrin-A1-Fc peptides induced the robust activation of EphA2 and led to a profound suppression in the ERK1/2-MAPK signaling cascade (Fig. 2). These findings strongly support the notion that EphA2 is a potent inhibitor of ERK1/2 signaling in response to ectopic ephrin ligand treatment in normal epithelial cells.

Long-term peptide-ligand treatment not only activated EphA2 but eventually led to its internalization and degradation. EphA2-mediated downregulation of ERK1/2 was further limited to a relatively short time period (< 1 h) after ligand stimulation. Given the transient suppression in ERK1/2 activity, we
next asked whether these ephrin peptides would be capable of regulating the long-term growth of keratinocytes. Surprisingly, keratinocyte growth was relatively normal under low calcium conditions but became severely restricted in high calcium, where cadherin-mediated adhesion is most efficient (Fig. 3). In addition, we found that long-term peptide-ligand treatment accelerated terminal differentiation in keratinocytes maintained in high calcium. Thus, keratinocytes grown under contact naïve conditions in low calcium manage to escape the growth inhibitory effects of ephrin-A1 peptides but likely work in concert with cadherins to restrict epithelial growth and promote terminal differentiation in elevated calcium.

EphA2 and E-cadherin collaborate to suppress ERK1/2-MAPK signaling and keratinocyte growth.

To better understand the relationship between EphA2 and E-cadherin in ERK1/2-MAPK signaling and epithelial growth, we took advantage of a classical calcium switch assay. Since raising extracellular calcium concentrations leads to the stabilization of cell-cell contacts, we reasoned this would facilitate the engagement of EphA2 with ephrin-ligands residing on adjacent cell surfaces. In support of this possibility, we found that EphA2 was rapidly recruited to putative cell-cell communication sites and co-localized with E-cadherin following a calcium switch (Fig. 4). Moreover, E-cadherin-mediated adhesion was required for normal EphA2 localization, highlighting the collaborative nature of these two proteins during epithelial cell-cell communication. Importantly, EphA2 was robustly activated during a calcium switch in a manner that could be blocked by drugs that interfere with the ability of ephrin ligands to engage with EphA2. These observations

Figure 3. Ephrin-A1 peptide-ligand treatment restricts keratinocyte growth in high calcium. Sparse keratinocyte cultures were treated with recombinant EphrinA1-Fc or control Fc peptides in low and high Ca²⁺ for 10 days. Keratinocyte cultures were fixed and stained to assess clonal growth capacity, which was limited by ephrin-A1-Fc treatment only in high Ca²⁺.

Figure 4. EphA2 is phosphorylated in response to calcium induced cell-cell contact formation. (A) Schematic representation of putative EphA2/ephrin-A1 juxtamembrane signaling complexes in keratinocytes grown in low and high Ca²⁺. Stabilization of cell-cell contacts via E-cadherin-mediated adhesion is predicted to enhance ephrin-A1 induced activation of EphA2. (B) Dual-label indirect immunofluorescence of EphA2 in green and E-cadherin in red in keratinocytes switched from low to high Ca²⁺ for 24 hours.
demonstrated that calcium-mediated stabilization of cell-cell contacts induces the formation of native EphA2/ephrin signaling complexes.

Concomitant with EphA2 phosphorylation during a calcium switch, we found reduced ERK1/2-MAPK activity (Fig. 5). However, the contact-dependent suppression of ERK1/2 only occurred when EphA2 was present in keratinocytes and not if it had been experimentally removed by gene silencing. Furthermore, keratinocytes lacking EphA2 failed to undergo normal terminal differentiation. These observations indicated that E-cadherin uses EphA2 as a tool to signal for contact-mediated growth suppression in epithelial tissues. We speculate that when E-cadherin is lost during cancer, EphA2 may no longer be capable of binding to its ephrin ligand resulting in unrestrained mitogenic signaling through the ERK1/2 pathway.

**Summary**

In conclusion, we have identified a novel and important adhesion-signaling network in the epidermis that is mediated by E-cadherin and EphA2/ephrin-A1 signaling complexes. We found that ectopic-ligand stimulation of EphA2 was capable of suppressing mitogenic ERK1/2 signaling. This effect was recapitulated in keratinocytes undergoing a calcium switch where EphA2 could be endogenously activated by native ephrin ligands. Moreover, we determined that chronic-peptide treatment of keratinocytes maintained in high calcium led to growth suppression and accelerated differentiation. These findings support a model of epidermal homeostasis, where the formation of native EphA2/ephrin-A1 signaling complexes function to downregulate mitogenic-ERK1/2 signaling in keratinocytes leading to the progression into a more terminally differentiated state (Fig. 6). On the other hand, the loss of cell-cell contacts during carcinogenesis may prohibit EphA2 activation by ephrin ligands residing on adjacent cell surfaces. As a consequence, this would contribute to increased ERK1/2 signaling activity and excessive cell proliferation. We propose that treating these cancer cells with exogenous ephrin-A1 ligands could dampen ERK1/2 and growth to ultimately restore normal epithelial architecture.

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**References**


Asbestos exposure results in pulmonary fibrosis (asbestosis) and malignancies (bronchogenic carcinoma and mesothelioma) by mechanisms that are not fully established. Despite a dramatic reduction in asbestos use worldwide, asbestos-related lung diseases continue to pose significant health concerns largely because of the vast amounts of fibers that have been mined, processed and used as well as the long latency period of 20 to 40 years between exposure and disease. The extent of alveolar epithelial cell (AEC) injury and repair are critical determinants of the fibrogenic potential of toxic agents such as asbestos. Previous studies, including ones from our group, have identified some of the important factors contributing to the adverse effects of asbestos as well as strategies that are protective. We have shown that iron-derived reactive oxygen species (ROS) from the mitochondria electron transport chain mediate asbestos-induced AEC DNA damage and apoptosis by a p53- and mitochondria-regulated (intrinsic) death pathway. Our more recent data implicate an important role for p53-dependent transcription of NOXA (a BH3-only protein) as well as a novel mechanism by which mitochondrial human 8-oxoguanine-DNA glycosylase 1 (mt-hOgg1) prevents oxidant-induced AEC apoptosis by preserving mitochondrial aconitase. Herein, we review the key findings of our group that have been published over the last several years, some of which is only in abstract form.
Asbestos causes apoptosis in alveolar epithelial cells
Alveolar epithelial cell injury is an important early event in the pathogenesis of chronic interstitial lung fibrosis including asbestosis. The alveolar epithelium is comprised of type I (AT1) cells, that cover ~90% of the alveolar surface area and are susceptible to an oxidant stress, and type II (AT2) cells, which produce surfactant and can proliferate and differentiate into type I cells. The early stage of asbestosis is characterized by discrete foci of fibrosis within the respiratory bronchiole walls and alveolar duct bifurcations associated with the accumulation of asbestos bodies. Similar to the well-established increased risk of lung cancer in patients with IPF, there is a direct relationship between excess asbestosis cases and lung cancer mortality. Our general hypothesis is that asbestos pulmonary toxicity results from an imbalance between too much AEC apoptosis (promotes fibrosis) caused by iron-derived ROS from the mitochondria that activate p53 and insufficient apoptosis (malignant predisposition) in part due to inadequate DNA repair. A hypothetical model of AEC apoptosis depicting some of the key events described herein is shown in Figure 1.

The Mitochondria-Regulated Death Pathway Mediates Asbestos-Induced Alveolar Epithelial Cell Apoptosis
Mitochondrial DNA damage may be important in the pathogenesis of asbestos pulmonary toxicity but this area has received little investigative effort. Others and our group have shown that asbestos fibers are taken up by AEC shortly after exposure. Mammalian cells typically contain thousands of mitochondria, each with 2-10 copies of double stranded closed circular genomic DNA (16.5 kb) located in the inner mitochondrial membrane (IMM) space that encode 13 of the ~80 polypeptides involved in the ETC and ATP synthase, 22 tRNAs and 22 rRNAs. The mitochondria is not only the ATP-generating power-house of cells but also an organelle that is critically important in regulating complex survival signals that determine whether cells live or die.

Accumulating evidence convincingly show that mtDNA damage and mutations contribute to tumorigenesis and aging. mtDNA is more susceptible to oxidative damage than nuclear DNA; with a mutation rate that is 10-fold greater than genomic DNA.

Given the role of the prominent role of the mitochondria in regulating the cellular DNA damage response and apoptosis, we reasoned that the mitochondria are crucial for mediating asbestos-induced AEC cell apoptosis. Others as well as our group have shown that asbestos causes mitochondria-derived ROS production, AEC DNA damage and mitochondria-regulated (intrinsic) apoptosis. We showed that asbestos causes a dose- and time- dependent reduction in mitochondrial membrane potential change (Δψm) in primary isolated rat alveolar epithelial type II (AT2) cells as well as human A549 cells (malignant line of cells with AT2-like features). These changes were accompanied by the release of cytochrome c, caspase-9 (but not caspase-8) activation and apoptosis (Figure 2). A role for iron-derived ROS was suggested by the finding that an iron chelator (phytic acid or deferoxamine) or a free radical scavenger (sodium benzoate) each blocked asbestos-induced reductions in Δψm, caspase-9 activation and apoptosis. Notably, overexpression of Bcl-XL, an anti-apoptotic
Bcl-2 family member, in A549 cells blocked asbestos-induced reductions in \( \Delta \psi_m \), caspase-9 activation and apoptosis\(^\text{12}\). The protective effects of Bcl-X\(_L\) overexpression suggest that the permeability of the outer mitochondrial membrane is a crucial regulating target for asbestos-exposed AECs. In a separate study we showed that A549 cells incapable of mitochondrial ROS production (\( \rho^0\text{-A549} \)) are completely protected against asbestos-induced mitochondrial dysfunction and apoptosis\(^\text{14}\). Thus, the mitochondria have a prominent role in regulating asbestos-induced AEC apoptosis.

**P53 Regulates Asbestos-Induced AEC Intrinsic Apoptosis**

The tumor suppressor protein p53, a transcriptional factor that is a critical DNA damage response molecule, causes mitochondrial dysfunction and apoptosis. p53 affects numerous genes that inhibit cell growth to allow time for DNA repair and, if DNA damage is extensive, augment apoptosis in part by the mitochondria-regulated death pathway\(^\text{10, 15, 17}\). A normal functioning p53 response after exposure to DNA damaging agents prevents mutations from accumulating. Not surprisingly, the most common mutations in human tumors involve the p53 gene family members\(^\text{16, 17}\). There is some evidence implicating altered p53 expression in the pathophysiology of pulmonary fibrosis, including that due to asbestos, as well as asbestos-associated malignancies. For example, increased p53 protein expression occurs in the bronchiolar and alveolar epithelium of humans with IPF as well as rodents exposed to asbestos\(^\text{18-21}\). It is established that asbestos induces p53 and p21 expression in lung epithelial and mesothelial cells and that this results in cell cycle arrest\(^\text{22-26}\). Further, p53 levels accumulate in lung cancers of patients with asbestos and p53 point mutations are widely evident in the respiratory epithelium of smokers\(^\text{27, 28}\). Collectively, these data suggest that p53 has an important pathophysiologic role in regulating the lung epithelial cell DNA damage response after exposure to oxidative stress as occurs with asbestos and tobacco smoke.

The mechanisms by which p53 modulate apoptosis are complex and incompletely understood but one established pathway involves activating the mitochondria-regulated death pathway by increasing gene expression of pro-apoptotic stimuli (e.g. BAX and BH3-only proteins [PUMA, Noxa, and others]) while inhibiting the expression of anti-apoptotic Bcl-2 family members\(^\text{16, 17, 29-31}\). We showed that inhibitors of p53-dependent transcriptional activation (pifithrin and type 16-E6 protein) block asbestos-induced AEC \( \Delta \psi_m \), caspase 9 activation, and apoptosis\(^\text{32}\). We found that asbestos activates p53 promoter activity within hours of asbestos exposure, which in turn increases p53 protein expression as well as mitochondrial translocation of Bax and p53. Asbestos-induced p53 activation was completely blocked by either pifithrin, a phytic acid ans was not accident in \( \rho^0\text{-A549} \) cells (cells incapable of mitochondrial ROS production). Finally, we demonstrated that asbestos augments p53 expression in cells at the broncho-alveolar duct junctions of rat lungs and that phytic acid prevents this\(^\text{32}\). Our more recent findings show that asbestos preferentially triggers NOXA...
mRNA and protein expression and that AT2 cells from noxa-/- mice are resistant to asbestos-induced apoptosis. These findings with asbestos parallel those with airborne particulate matter, which also mediates AEC apoptosis by a p53- and mitochondria-regulated death pathway. Two recent microarray gene expression profile studies demonstrated that asbestos-exposed AEC and mesothelial cell lines had increased expression of p53 as well as PKCδ, thioredoxin, and many other intriguing genes. Thus, these studies firmly implicate a prominent role for p53 in regulating asbestos-induced mitochondrial dysfunction and apoptosis that may have broader implications for our understanding of pulmonary fibrosis and lung cancer.

Mitochondrial 8-oxoG DNA glycosylase and aconitase

Over 95% of ROS produced during normal metabolism occur by the electron transport chain in the inner mitochondrial membrane in close proximity to mtDNA. The mechanisms by which cells repair mtDNA and maintain mitochondrial function are incompletely understood. Base excision repair (BER) is the major repair mechanism for oxidized DNA bases in mammalian mitochondria. All mtDNA repair proteins, including those involved with BER such as Ogg1, are nuclear encoded and imported into mitochondria. 8-oxoGuanine (8-oxoG), the most common of ~50 DNA changes that occur with oxidative stress, is highly mutagenic by causing G:C -> A:T transversions in replicating cells. Glycosylases are the critical first step in BER by recognizing the 8-oxoG and then excising it. Several lines of evidence support a key role for Ogg1: (1) OGG1-/- mice, as compared to wild-type mice, have a 20-fold increased level of mitochondrial 8-oxoG. (2) Mutations in the hOGG1 gene occur in patients with lung cancer as well as other malignancies. (3) Mitochondria-targeted hOgg1 overexpression prevents mitochondria-regulated apoptosis caused by asbestos-exposed HeLa cells.

Although Ogg1 is thought to prevent activation of the intrinsic apoptotic pathway in response to oxidative stress by augmenting DNA repair, the predominance of the β-Ogg1 isoform, which lacks 8-oxoG DNA glycosylase activity, suggests that mitochondrial Ogg1 functions in a role independent of DNA repair. Others have shown that aconitase is crucial for maintaining mtDNA in yeast by mechanisms that are unclear. Mitochondrial aconitase co-precipitates with frataxin, an iron chaperone protein that blocks aconitase oxidative inactivation. We reported that overexpression of mitochondria-targeted human α-hOgg1 (mt-hOgg1) in A549 cells prevents oxidant-induced mitochondrial dysfunction and apoptosis by preserving mitochondrial aconitase. Notably, mitochondrial α-hOgg1 mutants lacking 8-oxoG DNA repair activity were as effective as wild-type mt-hOgg1 in preventing oxidant-induced caspase-9 activation, reductions in mitochondrial aconitase and apoptosis suggesting that the protective effects of mt-hOgg1 occur independent of DNA repair. We also observe that mt-hOgg1 co-precipitates with mitochondrial aconitase and that overexpression of mitochondrial aconitase abolishes oxidant-induced apoptosis. These data suggest a novel mechanism where by mt-hOgg1 acts as a mitochondrial aconitase chaperone protein to block oxidant-mediated mitochondrial dysfunction and apoptosis.

Conclusions

Asbestos-related lung diseases remain a significant challenge to health care providers as well as to investigators studying the basic mechanisms that underlie asbestos-induced pulmonary toxicity. Our data demonstrate that asbestos induces AEC intrinsic apoptosis by mechanisms regulated by mitochondrial ROS, p53, NOXA, and hOgg1. We believe that the asbestos paradigm has broad translational significance for our understanding of other pulmonary diseases where comparable mechanistic pathways are implicated and for which innovative management approaches are urgently required (e.g. interstitial pulmonary fibrosis and lung cancer).

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Thrombocytopenia (low platelet count) can be caused by hematologic malignancies including myelodysplastic syndromes (MDS), and often occurs as a side effect of chemotherapy. Several million units of platelets are transfused each year in the US and Europe. Each dose typically contains $3-6 \times 10^{11}$ platelets, and larger doses are more effective. Although widely used, there are problems associated with platelet collection and transfusions. Collecting enough platelets for a single transfusion requires either expensive apheresis equipment or the pooling of platelets isolated from 4 to 8 different donors. Platelets must be stored at 20–24°C, which increases the risk of bacterial contamination. Blood-borne pathogens also pose a risk. Finally, even with leukocyte depletion, alloimmunization of recipients remains an important problem. Production of autologous or antigen-matched platelets in culture using Good Manufacturing Practices (GMP) would greatly decrease adverse immune responses, as well as bacterial and viral contamination. Several groups have produced small quantities of culture-derived platelets with functional activity similar to that of freshly harvested platelets. However, producing one transfusion dose of 500 billion platelets using current technology would require 5-10 umbilical cord blood harvests or a full hematopoietic stem and progenitor cell (HSPC) harvest from the peripheral blood of donors mobilized with cytokines (mPB), so the ex vivo platelet yield must be increased by several orders of magnitude to be clinically viable.
Mk differentiation – clues from the bone marrow niche

Megakaryopoiesis comprises HSPC commitment to the megakaryocytic cell (Mk) lineage, the production of Mk progenitors and mature Mks, polyploidization, and platelet release. Due to metabolic activity within the intravascular space, substantial gradients in pH and oxygen partial pressure (pO₂) are established between the bone surface and the bone marrow (BM) sinuses. The arrangement of diverse hematopoietic cell lineages within the BM suggests that their development is differentially orchestrated by the microenvironment. Hematopoietic stem cells are widely accepted to reside in niches at the bone surface, far from the sinuses. In contrast, production of mature erythroid cells and Mks occurs adjacent to the sinus wall. Thus, megakaryopoiesis and erythropoiesis are associated with increasing pH and pO₂ as cells move from the endosteal surface to the sinuses (Figure 1). Consistent with this observation, the production of mature erythroid cells and Mks is increased at 20% vs. 5% O₂ and the differentiation of Mks and erythroid cells is more rapid at higher pH. We have previously shown that culture at 5% (vs. 20%) O₂ inhibits Mk apoptosis and increases the number of Mk progenitors (Mk colony-forming units or CFU-Mks), and that cells cultured under 5% O₂ yield a much greater fraction of more primitive large-colony CFU-Mks. We also showed that culture at pH 7.2-7.4 (vs. 7.6) slows the decline of large-colony CFU-Mks. In contrast, culture at 20% O₂ yielded 3 times as many Mks, and the fractions of high-ploidy (≥ 8N) and proplatelet-forming Mks were twice as great. Also, the fraction of high-ploidy Mks increased with pH over the range from 7.2 to 7.6 in mPB CD34⁺ cell cultures.

Nicotinamide greatly increases Mk ploidy

Our transcriptional analysis of Mk differentiation revealed the up-regulation of several members of the silent information regulator 2 (Sir2) family of histone/protein deacetylases (SIRTs), which play a role in lifespan extension and apoptosis in various cell types. Therefore, we examined the effects of the SIRT inhibitor nicotinamide (NIC; one form of vitamin B3), on megakaryopoiesis in vitro. Mks in cultures with NIC were much larger and had more highly lobated nuclei than those cultured with thrombopoietin (Tpo) alone. Mks treated with NIC reached ploidy levels of 64N compared to 16N with Tpo only and exhibited twice the fraction of high-ploidy Mks. NIC also increased the frequency of proplatelet-forming Mks, and the cytoplasmic extensions were larger and more elaborate with NIC. However, NIC did not affect Mk commitment, as evidenced by similar fractions of CD41⁺ cells. NIC-treated Mks exhibited normal structure via electron microscopy – with alpha-granules, dense granules, and a demarcation membrane system. Further, the overall transcriptional patterns with NIC were very similar to those in cultures with Tpo only. Previously identified Mk-associated genes were strongly up-regulated with Mk differentiation in the presence or absence of NIC. Greater Mk maturation with NIC is due at least in part to SIRT inhibition because the SIRT1/SIRT2 inhibitor cambinol yielded a similar Mk ploidy.
distribution and increased the fraction of high-ploidy Mks to a similar extent as NIC20.

**Multi-phase Mk production**

Because the process by which HSPCs differentiate into high-ploidy Mks consists of multiple, sequentially-dependent steps, we hypothesized that production of high-ploidy Mks from mPB CD34+ cells could be greatly enhanced by dividing the process into three separate phases – with environmental conditions and growth factors separately optimized for Mk commitment and progenitor expansion, mature Mk production, and Mk polyploidization (Figure 3). Consistent with the pH and pO2 gradients in the BM niche, we are using subvascular pH and pO2 for the first phase of Mk progenitor expansion. Many cytokines have been shown to enhance different aspects of megakaryopoiesis, but there have been conflicting reports regarding the effects of individual cytokines and combinations. Therefore, we used a factorial design approach to identify cytokine combinations that yield the greatest number of CD34+CD41+ Mk progenitors. CD34+ HSPCs were cultured at pH 7.2 and 5% O2 with stem cell factor (SCF), Tpo, and all combinations of Interleukin (IL)-3, IL-6, IL-11, and Flt-3 ligand to promote Mk progenitor expansion23. Cytokine cocktails with IL-3 yielded more progenitors and mature Mks, although the purities were lower. Using Tpo+SCF+IL-3+IL-11, we expanded Mk progenitors from 0.01 to 3.5 CD34+CD41+ cells per input CD34+ cell at day 11, while increasing CD34+CD41+ cell purity from 1% to 17%23. Although CD34+CD41+ cell production continued to increase until day 11, Mk clonogenic capacity decreased after day 5. Cells cultured with selected cytokines were shifted to pH 7.4 and 20% O2 at various times to increase production of mature Mks. Although fewer progenitors were present, shifting to 20% O2/pH 7.4 at day 5 (vs. days 7 or 9) yielded the greatest mature Mk production – 14 per input HSPC23. Simultaneous NIC addition decreased Mk production, but more than doubled the fraction of high-ploidy Mks to 40%. Initial phase II factorial design experiments to optimize cytokines for Mk production at 20% O2 and pH 7.4, after 5 days at 5% O2 and pH 7.2, indicate that we should be able increase mature Mk production by at least another two-fold. We anticipate that delayed NIC addition and optimization of polyploidization conditions in phase III at pH 7.6 will greatly increase high-ploidy Mk production. Finally, it will be necessary to show that the high-ploidy Mks produced have the potential to generate proplatelets and functional platelets.

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**Figure 2.** Nicotinamide increases primary human Mk size and DNA content. (A) Morphology of Mks examined by staining Day 11 cells with Wright-Giemsa. mPB CD34+ cells were cultured with 100 ng/ml thrombopoietin (Tpo). 6.25 mM nicotinamide (NIC) was added to selected cultures at day 5. A dramatic dose-dependent increase in cell size, along with more highly-lobated nuclei, was observed with NIC treatment. (B) DNA content was evaluated via propidium iodide (PI) staining of permeabilized Mks. Gate shows high-ploidy (≥ 8N) CD41+ Mks. (Image taken from: Giammona, L.M., P.G. Fuhrken, E.T. Papoutsakis, and W.M. Miller, Nicotinamide (vitamin B3) increases the polyploidisation and proplatelet formation of cultured primary human megakaryocytes. Br J Haematol, 2006. 135(4): p. 554-566).

**Figure 3.** Schematic of experimental plan to promote large-scale platelet production in vitro. The diagram shows sequentially dependent steps from which proplatelet-forming Mks, and ultimately platelets, are formed from CD34+ hematopoietic stem and progenitor cells obtained from cord blood (CB) or mobilized peripheral blood (mPB) donors. Increasing pH and pO2 values with the stage of Mk maturation are employed to mimic environmental conditions found in vivo. The cytokine combinations are changed based on how they affect specific stages of Mk maturation, and nicotinamide (NIC) is added to promote polyploidization.
Future directions
Recent studies suggest a role for SIRT1 and/or SIRT2 in the differentiation of vascular and neural tissues, as well as granulocytic cells. In particular, SIRT2 regulation of tubulin acetylation plays an important role in modulating the extension of neurite and oligodendrocyte cell processes. Our results are the first to suggest that SIRT1 and SIRT2 also modulate Mk differentiation and proplatelet production. Deacetylation by SIRT1 regulates the activity of a number of proteins associated with DNA repair, apoptosis, and cell cycle regulation that are likely to be important in Mk differentiation and endomitosis including p53, FOXO3a, RelA/p65 (NF-κB), and Ku70. We have shown that treatment with NIC increases acetylation of p53 and nuclearosome levels in Mks.

We are currently validating the hypothesis that NIC increases Mk ploidy predominantly via SIRT inhibition by knocking down SIRT1 and SIRT2 mRNA levels in mBP CD34+ cells using lentiviral vectors to deliver complementary shRNA. We will then examine the acetylation and activity of SIRT target proteins that have the potential to alter Mk ploidy and proplatelet formation. Finally, we will modulate the activity of the most promising SIRT target proteins and/or their downstream targets, e.g., via overexpression or RNAi-mediated knockdown, to directly assess their roles in megakaryopoiesis. Elucidating the downstream signaling pathways of NIC may reveal particular transcriptional targets that are primarily responsible for NIC-mediated increases in Mk ploidy. Direct manipulation of these targets, via acetylation, activation, inhibition, or other methods may allow us to further increase Mk ploidy, and thus proplatelet-producing potential.

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Wilm's Tumor is the most common malignant renal tumor of childhood, with approximately 500 new cases annually in the United States. For several decades Wilm's tumors have been treated by the National Wilms Tumor Study Group (NWTSG), which joined the Children's Oncology Group (COG) in 2002. These efforts have resulted in an increase in survival from 20% to over 90% in just a few decades. This success has been achieved while using shorter duration and total amount of chemotherapy and lower doses of radiation therapy, resulting in decreased morbidity. NWTS/COG Renal Tumor Committee has a long-standing emphasis on the establishment of a robust infrastructure for banking of tumor samples, normal kidney samples, patient blood, and parental blood. Over 95% of the >2000 patients registered on NWTS-5 have banked biologic samples. Faculty members at Northwestern have played an important role within the Renal Tumor Committee: Dr. Perlman, Dr. Perlman, Head, Pathology and Laboratory Medicine at Children’s Memorial Hospital, is the central pathology reviewer, and Dr. John Kalapurakal is the radiation oncology representative.

Two genetic loci have been shown to be associated with the pathogenesis of Wilm's tumor, namely the WT1 gene at 11p13, and the WT2 locus at 11p15. WT1 encodes a transcription factor that plays an important role in several phases of normal renal development.  

Germline mutations or
deletions of WT1 result in several syndromes that are associated with an increased frequency of Wilms tumor (Denys-Drash, WAGR, Frasier syndromes). Somatic mutations of WT1 occur in approximately 10-20% of sporadic Wilms tumors. In recent years evidence has mounted that activation of the canonical Wnt pathway frequently accompanies WT1 mutations in Wilms tumors. Thus far, Wnt activation has been shown to be due to activating mutations of beta-catenin and to inactivating mutations of WTX, a protein that contributes to beta-catenin degradation.

The WT2 chromosomal region was brought to scientific attention by the discovery of imprinting abnormalities in patients with Beckwith-Wiedemann syndrome, an overgrowth syndrome that carries an increased risk of Wilms tumor. Indeed, loss of imprinting (LOI) or loss of heterozygosity (LOH) at 11p15 occurs in up to 70% of sporadic Wilms tumors. While imprinting in this region is complex, it appears to largely be associated with aberrant methylation of the maternal allele of H19, which encodes an untranslated RNA, and biallelic expression of IGF2, normally expressed only from the paternally inherited allele. In addition to 11p13 and 11p15, multiple other loci have been implicated in the development or progression of Wilms tumor in small numbers of patients. In particular, an association between relapse and LOH for 1p and 16q has been demonstrated. While the potential role for stratifying patients using LOH for 1p and 16q is currently being investigated within the COG therapeutic protocols, the precise gene/genes within these regions that can explain this association are not known.

In summary, Wilms tumor is genetically heterogeneous and the pathogenesis for the majority of patients is not entirely clear. For the last ten years a goal of our laboratory has been to investigate the global gene expression patterns of Wilms tumors. These efforts were funded through the NCI’s Director’s Challenge Grant followed by the Strategic Partners for the Evaluation of Cancer signatures. Our first studies described gene expression signatures that allow the distinction of Wilms tumors from other pediatric renal tumors. This was followed more recently by the analysis of FHWT for signatures of relapse. Most currently, our studies are focused on the identification of subgroups of Wilms tumors based on their gene expression and to characterize such groups by their clinical and pathologic features. The long term goal is to define subtypes of Wilms tumors that may merit therapeutic stratification or may respond to specific therapeutic targets. We will take this opportunity to review this data.

Methods
Clinical samples: 1451 patients with favorable histology Wilms tumor for whom pre-treatment tumor tissues and clinical follow-up were available were registered on NWTS-5 from 8/1995-6/2002. From these a case:cohort of 600 tumors was created by taking all those patients known to have relapsed, and a random sampling of approximately 30% of the remainder. Frozen tumor specimens were obtained from the initial nephrectomy, prior to the initiation of therapy.

Gene Expression Analysis: RNA was extracted and hybridized to Affymetrix U133A arrays as previously described. Data was normalized using robust multi-array average (RMA) method. Unsupervised analysis was performed to detect subsets using average-linkage clustering using CLUSTER and the results were displayed using TREEVIEW (http://rana.lbl.gov/EisenSoftware.htm). Gene Set Enrichment Analysis (GSEA) compared the genes most highly defining each subset with available gene sets within GO and in the literature (http://www.broadinstitute.org/gsea).

Methylation analysis at 11p15: The paternally methylated H19 DMR (which is aberrantly methylated in many Wilms tumors), and the maternally methylated KvD MR1 (whose methylation is independent of H19), both contain specific restriction sites recognized by methylation-sensitive enzyme HpaII, and by MspI, which cuts irrespective of methylation. A PCR reaction compared the levels of uncut (and hence amplified) product following HpaII restriction versus the levels following MspI digestion. The normal pattern consists of 50% methylation of both H19DMR and KvDMR (Figure 1).

Results and Discussion
Overall unsupervised analysis reveals two distinctive subsets of FHWT based on gene expression: Hierarchical clustering of 224 of the 300 tumors meeting all quality control parameters (half of the case:cohort, randomly selected) was performed using the 4000 most variable genes.
in order to distinguish two discrete subclasses of FHWT based on gene expression, referred to as Subsets 1 and 2 (Figure 2). All 22,000 probesets were then entered into GSEA and the gene lists from the Gene Ontology (GO) C5 Biologic Functions categories, the C2 curated gene sets were evaluated. The gene expression of S1 and S2 tumors was compared with those tumors falling outside of S1 and S2.

The majority of Wilms tumors show early developmental arrest and either loss of imprinting or loss of heterozygosity at 11p15:

The majority of Wilms tumors (those outside of Subsets 1 and 2) demonstrated up-regulation of genes normally expressed very early in renal development, consistent with arrest during early pre-induction renal development. This is illustrated by the high expression of HMG2, SIX2, WAPF3, HOXA11, CCND2, and DBC1 within the group of 180 tumors falling outside of subsets 1 and 2. As an example, the expression of WASF3 is illustrated in Figure 3. In addition, this group of tumors showed a high rate of 11p15 methylation abnormalities: 10% retained the normal imprinting pattern (ROI, Figure 1), 56% showed loss of imprinting (LOI), and 34% loss of heterozygosity (LOH). Therefore, 90% of the tumors outside of S1 and S2 demonstrate full methylation of H19, which correlates with biallelic expression of IGF2. Further, no overt evidence for activation of canonical Wnt signaling can be found for this majority of Wilms tumors outside of S1 and S2 based on gene expression.

Subset 1 includes epithelial differentiated tumors with low stage and low relapse rate, and developmental arrest following mesenchymal-to-epithelial transition: Subset 1 contains eleven tumors (ten stage I, one stage II) with a distinctive epithelial differentiated histologic pattern and no conclusive precursor lesions known as nephrogenic rests. The median age at
presentation is 14 months, compared with a median age at presentation of 42 months in the entire group. No patients with Subset 1 tumors relapsed, compared with an overall relapse rate within the entire case-cohort of 32%. Nine of ten analyzed Subset 1 tumors retained the normal methylation pattern for 11p15 (ROI).

In contrast to the majority of Wilms tumors, S1 is characterized by decreased levels of genes expressed in the pre-induction mesenchyme, and increased levels of genes expressed following mesenchymeto-epithelial transition and in terminally differentiated epithelium. Genes previously reported to show increased expression in Wilms tumors (PRAME, CRABP2, NNT, UCHL1, DBC1, GPR64, HAS, COL2A1, WASF3, CCND2) were all down-regulated in S1 tumors. Genes of potential interest with regard to the pathogenesis of S1 tumors include increased expression of CUGBP2. The expression patterns of representative genes are illustrated in Figure 3.

**Subset 2** tumours are characterized by skeletal muscle differentiation, intralobar nephrogenic rests, a low relapse rate, decreased WT1 expression and activation of Wnt signaling:

Subset 2 contained 23 tumors (6 Stage I, 10 Stage II, 6 Stage III, and 1 Stage IV). The median age at diagnosis was 13 months, compared with a median age of 42 months in the tumor set overall. The majority of Subset 2 tumors had a mixed histology; skeletal muscle differentiation was present in 20/23 tumors. Nephrogenic rests were identified in 18/23 tumors, and all were of the intralobar type. Subset 2 tumors had a relapse rate of 13%, compared with 32% within the total tumor group. Analysis for methylation of 11p15 revealed 7/22 (32%) with ROI, 14/22 (64%) with LOH, and 1/22 (4.5%) with LOI. The overall gene expression pattern of S2 tumors is that of marked increase in expression of genes normally expressed in the very earliest mesenchepbic mesenchyme prior to induction and marked increase in expression of genes expressed in the renal interstitium when compared with most Wilms tumors. This is consistent with arrest of S2 tumors prior to that of most Wilms tumors. Most noteworthy was down-regulation of WT1 and genes reported to be regulated by WT1 (including PAX2, PAX8, FGFR2). This was confirmed by mutation analysis which demonstrated mutation of WT1, WTX, CTNNB1 in 58%, 21%, and 89%, respectively, of subset 2 tumors. (Mutation analysis was performed by Dr. Vicki Huff, MD Anderson Cancer Center). In addition, there was increased expression of members of the canonical Wnt signaling pathway, and downregulation of Wnt inhibitors FZD6, WISP3, TFAP2A. Lastly, Subset 2 tumors showed increased expression of genes involved in muscle differentiation, a finding described previously in Wilms tumors with CTNNB1 and WT1 mutation. An example is ACTC1, illustrated in Figure 3. Genes previously demonstrated to be up-regulated in Wilms tumors were largely down-regulated in S2 tumors (including CRABP2, DBC1, GPR64, HAS2, COL2A1, WASF3).

**Summary**

Our gene expression data support the presence of two pathogenetically distinct subsets within the larger group of Wilms tumors that show IGF2 over-expression. Subset 1 is seen as low stage tumors in infants, with a very low risk of relapse. They are histologically unique and do not arise within precursor lesions. Subset 2 tumors are those with WT1 inactivation and Wnt activation, with a high percentage of WT1 and CTNNB1 mutation. These tumors have an
early age of onset, but an overall better survival than the entire group. The key differences between the different subsets are illustrated in Table 1. These groups were validated in an independent set of 105 Wilms tumors. Furthermore, we have demonstrated these two subsets to be important in the prediction of relapse for a group of stage 1 Wilms tumors weighing less than 550g involving patients less than 24 months of age which are currently treated without chemotherapy.20

Future Studies
The availability of our large dataset will allow for a large number of future studies which are in progress:

1. Transcriptomic analysis, which analyzes gene expression as a function of chromosomal position, will enable us to infer genetic changes.

2. Little is known about WTX and its pathogenetic role in the development of Wilms tumor is controversial. We will analyze WTX wild-type vs WTX mutant tumors.

3. Comparison between the gene expression of nephrogenic rests and tumors that derive from these precursor lesions will allow us to detect genetic changes associated with precursor lesions as well as clonal changes resulting in Wilms tumors.

4. Several studies, including our gene expression analysis, demonstrate an association between gain of chromosome 1q and relapse in FHW T. With the expertise of Dr. Lawrence Jennings, Director of CMH Molecular Diagnostics Laboratory, we are developing a clinical test for 1q gain using Multiplex Ligation-Dependent Probe Amplification.

Lastly, we look forward to working with the Northwestern Bioinformatics Core through our participation in the ARRA funded expansion of the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) initiative. This study will target high-risk Wilms tumors (those that relapse and those that show anaplasia) and will entail comprehensive “omic” analysis, including gene expression, SNP, methylation, and miRNA analysis as well as whole genomic sequencing.

References
10 Huang CC, Cutcliffe C, Coffin C, Sorensen PH, Beckwith JB, and Perlman EJ. Classification of

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<td>PLNR: 28/180</td>
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Table 1: Molecular Categories of Favorable Histology Wilms Tumor
malignant pediatric renal tumors by gene expression. 


Patient Navigation Research in the Chicagoland Area: Reducing barriers to cancer care follow-up among the medically underserved

Melissa A. Simon, MD MPH1, Narissa Nonzee2, Thanh Ha Luu2, Belinda Reyes MSW3, Shaneah Taylor MPH3, Nadia Hajjar MPH3, Dora Monroe3, Carmi Frankovich3, Charito Bulzarik3, Kara Murphy3, Richard Endress, PhD3, XinQi Dong, MD4

Understanding the high diagnosis and treatment attrition rates for lower income, medically underserved patients requires a multidisciplinary and multi-system collaborative approach to public health surveillance, combined with the ability to mobilize community resources beyond the traditional boundaries of medical care. Patient navigation interventions, based on community health workers (CHW) allied with safety net institutions and community organizations, provide a potentially powerful, culturally competent intervention for activating and empowering lower income, medically underserved patients struggling with the care of their health.

Disparities in cancer outcomes are prevalent and well documented. Poor cancer outcomes have often been linked with late-stage diagnosis and treatment primarily among lower-income populations. Barriers such as access to transportation, fear/anxiety, and low health literacy prevent patients from seeking care in a timely manner. Patient navigation and CHW models are gaining recognition around the country as effective strategies to facilitate health education and promotion among low income, medically underserved populations. Leveraging intimate knowledge of culture and social
networks, community-based CHWs can be highly effective disseminators of health information to members of their own communities- in this they are el cambio y la voz del pueblo (change agents and the voice of the community). This is particularly true for minority patient’s health issues, where minority patients often are most comfortable voicing concerns and seeking assistance in a culturally welcoming health care environment.

Nationwide Patient Navigator Programs
In 2003, the National Cancer Institute (NCI) conducted a survey and found more than 200 patient navigator programs currently in existence in the United States [Hede 2006]. Today, this number has more than tripled. Most of these programs are funded by small grants from foundations. These programs vary in their applications of patient navigation. Thus, even though the adoption rate of navigator programs is increasing, evidence of efficacy remains in its infancy [Wells 2008; Freund 2008].

In this brief overview of patient navigation, we will focus on the the Robert H. Lurie Comprehensive Cancer Center of Northwestern University supported, NIH funded, patient navigation activities: The Chicago Cancer Navigation Project (CCNP) (NIH NCI U01 CA116875 PI: Rosen), and the DuPage Patient Navigator Project (DPNP) (NCMHD R-24 5R24MD001650-02 PI: Simon).

History of Patient Navigation
Patient navigation holds roots in CHW models. CHW programs have been implemented at many medical centers and are slightly different than patient navigation programs. CHW programs are much larger in scale and will often provide patients with navigators, but are not confined to strictly navigation. CHW strive to better the community in which they came from and in which they work. The fundamental theory of CHWs includes empowerment of community members to identify their own needs and implement their own solutions [Witmer 1995].

The actual phrase “Patient Navigation” dates back to the Harlem Cancer Education and Demonstration Project spearheaded by Dr. Harold Freeman in 1990 [Freeman 1995, 2004]. The project showed that 85.7% of patients receiving navigation after suspicious findings from a breast exam or mammogram received recommended biopsies compared to 56.6% of non-navigated patients [Freeman 1995]. This program also showed improved five-year survival rates for intervention patients as compared with historical controls [Freeman 2004]. This first Patient Navigator Program was well received and was the nidus to fund many other similar programs nationwide.

Despite this lineage of patient navigation, there is still a lack of a clear definition of navigators and navigator services. Such lack of uniform definitions makes it difficult to aggregate data across programs and establish evidence-based efficacy of practices [Dohan 2005]. The National Cancer Institute (NCI) Patient Navigation Research Program (PNRP) of which (Northwestern’s Lurie Cancer Center is one of the funded sites) seeks to more rigorously study patient navigation with nine sites across the nation [Freund 2008].

Definition of Patient Navigation
There are many terms for community members or matched peers who connect with individuals to focus on improving one aspect of health: access, education, or behavior. Terms range from CHWs, lay navigators, case managers, peer counselors, to patient navigators. Tasks among these various named positions runs the gamut from connecting community members to available resources; serving as a translator of information given from a member of the health care team to a patient, facilitating timely follow-up into care. A CHW, for instance, has been defined broadly as a community member who works almost exclusively in community settings and who serves as connectors between health care consumers and providers to promote health among groups that have traditionally lacked access to adequate care [Reinschmidt 2006].

Patient Navigation is a process by which an individual, the patient navigator, guides patients into screening for cancer or guides them with suspicious findings (e.g. abnormal cancer screening test or abnormal laboratory blood value) through and around barriers in a complex cancer care system to help ensure timely diagnosis and treatment. Patient navigation aims to ensure patients receive culturally competent care that is confidential, respectful, compassionate and mindful of patient safety.

Definition of patient navigator
A patient navigator is someone who helps
patients move from one part of the health care system to another. He or she may be full or part-time, employee or volunteer. Although many types of navigators exist, there is not one standard definition of a patient navigator, and the profile of a patient navigator varies widely by program [Freund 2008]. The variation of occupational titles within navigation range from community health worker, patient navigator and case manager; with a few other variations. Although the terms are similar in definition, each one is slightly different. A patient navigator is one who is a hybrid of sorts of a CHW and a case manager. Patient navigators are often from the community the program is in, and are often matched on age range, gender, and race/ethnicity. Case managers perform the majority of work in an office, making sure that all of the appropriate paperwork and forms are ready upon each patient’s appointment.

Some patient navigators focus on one or several of these tasks along the cancer prevention and care continuum. Patient navigators assist patients and their families to navigate the fragmented maze of doctors’ offices, clinics, hospitals, outpatient centers, payment systems, support organizations, complex paperwork, and other components of the healthcare system. Barriers to quality care fall into a number of categories: financial and economic; language and cultural; communication; health care system; transportation; bias based on culture, race, age; and fear. Navigators ensure appropriate medical records are available at medical appointments; as well as cater to provide emotional support and encouragement; and improve access to clinical trials. Patient navigators are able to engage communities through outreach and partnership building with local agencies and groups. They are able to leverage their intimate knowledge of community resources and link community members to such resources. Navigators also proactively anticipate problems and activate patients through teaching, coaching and visit preparation. Patient navigators can help improve the quality of care patients receive. Improving the quality of care may help extend or even save patients’ lives.

Training of Patient Navigators
All officially employed patient navigators must complete some level of training before entering the field [Calhoun 2008]. Navigator training varies though due to the fact that there has not been a national training with a defined curriculum for patient navigators implemented as of yet. However, the curriculum for training patient navigators was created by experts from the NCI, PNRP, American Cancer Society (ACS), and Center for Medicare and Medicaid Services (CMS).

The training of patient navigators differs depending on prior training and credentials but often includes how to anticipate, address, and overcome barriers to care and to guide patients through the health care system during a very difficult time. The NCI-PNRP, ACS and CMS employ patient navigators who are trained, culturally competent health care workers who assist patients to overcome barriers to care, negotiate health care systems, and access quality care [Dohan 2005]. PNRP requires minimal basic computer skills, and fluency in English, whereas the ACS Patient Navigator Program employs, primarily but not strictly, professional (Bachelors degree or higher) level staff including nurses, social workers, and cancer survivors. To ensure all three programs (PNRP, ACS, and CMS) had adequate preparation across core competencies; a standardized national training program was implemented [Calhoun 2008].

The type and length of patient navigator training depends on the range of services provided. Training periods vary from weeks to six or more months, and usually will combine lectures with supervised field experiences. Training of the PNRP navigators is conducted in conjunction with the centralized ACS patient navigation program. This program lasts three days. Topics in the training include: knowledge development on patient navigation and cancer; practicum on patient assessment, barriers, resources, skills development in research, communication, culture and diversity. Patient actors were employed in role-plays that occurred in a simulated clinical laboratory setting – the Observed Standardized Clinical Experience (OSCE). Used in medical schools throughout the country, the OSCE lab resembles a hospital exam room and is equipped with video cameras connected to a command center that allows instructors and supervisors to view the interactions and assess performance [Calhoun 2008].

Underlying Theory of Patient Navigation
For both of the Lurie Cancer Center Patient
Navigator studies, the Chronic Care Management Model was used to derive the model of patient navigation. Our conceptual framework is based on the original insights of the chronic care model (CCM) popularized by E. Wagner and others in the early 2000s [Wagner 1996, 2001]. The precepts of the CCM were based on clinical delivery system redesign, which was then (as now) being pioneered by large integrated delivery systems, with staff model clinical facilities and capitated payment incentives. The CCM was grounded on improving patient self management of chronic conditions and emphasized the use of chronic disease registries and clinical decision support capabilities. Unlike disease management programs in place under insurer managed care initiatives, CCM was based on a healthcare organization’s commitment to redesigning care, with primary care physicians as key to the success of behavioral health interventions. Proposals and recent pilot studies of certified ‘medical home’ practices are one outgrowth of new thinking inspired by CCM.

Within the CCM, and among the least well developed of its domains, there was an additional component that often was described as “community resources”. Primary care physician offices could gain a great deal from connecting their patients to existing community-based programs that encouraged patients to seek assistance in the community for increasing physical activity, maintaining or losing weight, quitting smoking, as well as for mental health problems, stress reduction, substance abuse or intimate partner violence. Yet specifying such community resources inherently varies based on patients’ socioeconomic status, insurance coverage, and access to health promotion and counseling programs. Making successful linkages requires very specialized knowledge of local communities on the part of physician practices. Indeed the level of need among low income populations for such assistance is growing rapidly in Chicago, and referring patients to obtain community resources presents busy clinicians with very complex logistic headaches.

**Chicago Cancer Navigation Project**

The CCNP is one of nine national sites of the NCI/ACS funded Patient Navigator Research Program and was designed to guide further development of Patient Navigation models. Northwestern University implemented a program focused on prostate cancer at the Jesse Brown VA Medical Center, and in collaboration with the University of Illinois and ACS, a program focused on breast and cervical cancer at Access Community Health Network and the University of Illinois Medical Center. Specific aims of the CCNP are (1) to increase the proportion of patients with diagnostic evaluations (2) for patients who do get follow-up diagnostic evaluations, to improve mean time to a diagnostic resolution between abnormal screening and definitive follow-up (3) to shorten the time to initiation of treatment (4) to evaluate the cost-effectiveness of the navigation intervention (5) to identify psychosocial and demographic factors associated with navigation non-compliance and (6) to assess patient satisfaction with the navigation experience.

Thus far our CCNP has enrolled 347 females with 405 controls with positive screening tests for cancer of the cervix or breast and 216 males with 188 controls with positive screening tests for cancer of the prostate. Major assessed barriers to follow-up include clinic-patient miscommunication, noncompliance with biopsy preparatory instructions, and uncertainty and/or fear among patients. Key Navigator actions included phone calls and in-person meetings to improve communication between the clinic and patient, health education regarding cancer, and patient support and counseling.

**DuPage Cancer Navigation Project**

The DPNP, extends Patient Navigation to medically underserved women in the suburbs of DuPage County. It is a five year intervention study, started in July 2008. It extends NU investigators’ work on the NCI/ACS CCNP. The DuPage R24 grant uses community-based participatory research (CBPR) framework throughout every phase of the research from inception to dissemination. The DPNP uses a diverse local team of community health workers to assist low income uninsured women in follow-up of abnormal breast and cervical cancer findings and cancer. Thus far, it has enrolled 110 participants in its first year in the field.

**Growth of Suburban Poverty and Health Disparities in DuPage**

There have been significant increases in poverty rates in Midwestern suburban areas and this
poses marked challenges for reduction of health disparities [Berube 2006]. Yet there is a paucity of intervention research focused on suburban health disparities [Menck 2001]. “Growing suburban poverty is often invisible. Even many households that are impoverished may not see themselves as poor, but rather as working households who increasingly find that they cannot make ends meet. This raises new and important challenges for our community.” - DuPage Resident. More than 121,000 (13%) in DuPage County had an income below the federal poverty level in 2005, a 75% increase from 1990 [US Census 2005]. There are now an estimated 44,000 uninsured adults and 90,000 adult Medicaid enrollees in DuPage. Nearly all of the net population growth has been among immigrant, low income and minority populations. Although the population of DuPage only grew by 1% since 1990 (9,225 people), the number of persons >100% below the federal poverty level grew by 27% (25,740 people) [US Census 2005]. The percentage of the minority populations increased 139% (242,000) during this same 15 year timeframe [US Census 2005]. In one township, West Chicago, 50% of the population is Hispanic of largely Mexican origin [Tables 1 & 2].

**DPNP Community Based Participatory Research Approach**

The CBPR approach of the DPNP is an essential approach to implementing community-level interventions targeting minority participants in order to end health disparities. It is comprised of an integrated partnership with the DuPage Health Coalition (DHC), Access DuPage and the DuPage County Health Department. Since its inception in 2002, DHC and its Access DuPage Program is a major not-for-profit organization comprised of many community members and stakeholders. DHC has worked diligently trying to forge a strong healthcare safety net for the influx of poor into DuPage County in order to decrease current health disparities and prevent the existing disparities from widening.

Increased awareness of health disparities makes the case for research in academic medical centers to bridge the gap between scientific knowledge and medical advancement and between medical advancement and health of communities [Michener 2007]. The DPNP is based on the study team’s long-standing engagement with the DuPage community and as such, it is designed to meet the needs of medically underserved women within the community. Thus, services are brought to the participants within the realm of their own lives and their own community. Most importantly, this project is being driven by community desire to build a unit of free standing community health workers that can eventually address a broad range of health issues. The DPNP’s patient navigators have intimate knowledge of the community’s resources, social networks, and are culturally and linguistically matched to the participants. All of these advantages increase the overall buy-in from the community, incentive for participation, retention of participants, and chance for sustainability.

The DPNP’s team of patient navigators is comprised of 6 women all who are from the community of DuPage County and include: 3 native Spanish speakers, 1 white woman who speaks fluent Spanish, 1 Muslim woman who is bilingual in Arabic and English, and 1 African American woman. This diversity has proven essential to the recruitment for this study as our patient navigators are able to connect with multiple sectors of the low income community on whom this project is focused. Additionally, as over half of the participants are Spanish-
Speaking, the team has developed and tested tools and health messages in both English and Spanish alongside community member input. By utilizing both the active Community Advisory Board and a series of focus groups, the DPNP has achieved extensive community input on these developments and in the design and operationalization of the intervention.

Conclusion
The clinical paradigm in cancer care and its follow-up has been based on surgeon and oncologist follow-up care, and sometimes palliative care, all of which are less directly associated with primary care practice. While primary care physicians may recommend cancer screening, they may not be sufficient to provide comprehensive medical follow-up of abnormal screening results, particularly for low income, often uninsured patients- and even those few low income patients with stable, long-term ‘medical home’ primary care physician office relationships.

To date, cancer navigation has often reflected the chaotic, extreme dis-functionality of our health care delivery system for cancer screening and treatment. The navigator log books from our current two studies reflect a panoply of both individual patient and health care system obstacles to receiving appropriate services. Traditional cancer navigation was designed to help patients (especially poor patients) who otherwise would have an exhausting and overwhelming task of seeking and completing appropriate care at multiple sites for a condition which inspires fear and frequent rejection of evident cancer signs and symptoms.

Our team is studying the relationship between physician offices or clinics and free-standing patient navigators and CHWs. While CHWs who are directly employed by clinics are an increasingly accepted component of patient self-management for traditional chronic diseases managed by primary care physicians, the role of ‘freestanding’ cancer care patient navigators has often differed from this model.

The DPNP extends our knowledge of the value of ‘freestanding’ CHWs in linking patients to community resources. This model reflects the potential superiority of independent CHWs who can command the widest possible base of community resources for their patient and truly bridge communities and physician practice. This work has most recently been presented as part

of the ‘citizen-centered’ approach advocated by family medicine researchers affiliated with the Robert Wood Johnson-funded Prescription for Health Study [Woolf 2005; Etz 2008]. This research program found positive effects associated with 17 web-based, telephone, home and educational interventions designed to enhance patient behavior change through use of public, community based behavior change counseling and allied resources.

In summary, our patient navigation projects at the Lurie Cancer Center are currently studying efficacy of patient navigation. We are examining the differences among patient navigators that are hospital or clinic based or freestanding, community-based. Patient navigators strive to alleviate barriers for patients at each point of contact in the healthcare system. They aim to increase patients’ determination to obtain screening tests and improved follow-up after abnormal screening tests. These interventions are 1) provider-targeted, focused on reminding physicians on the best methods to discuss and describe cancer prevention and needed reforms in clinic design; 2) patient targeted, utilizing a variety of strategies including education, direct assistance (with childcare, transportation, and many other logistical problems) as well as psychological counseling; and 3) system targeted that test methods to improve epidemiologic tracking systems and allow community residents to evaluate medical care variations that affect their residents. The future directions of patient navigation hold promise in assisting low income, medically underserved patients in navigating a excessively complex system of health care. Importantly, the future of patient navigation will be dependent on the impact and extent of health care reform.

References
1 ACS. At a most critical juncture, ‘patient navigators’ are there to help. 2007. http://www.cancer.org/docroot/SPC/content/SPC_1\_ACS_Patient_Navigator_Program.asp


The Robert H. Lurie Comprehensive Cancer Center of Northwestern University funds shared facilities and resources that provide services, equipment and expertise that assist researchers in understanding the basic biology and clinical manifestations of cancer. These facilities and resources are accessible to all of the members of the Lurie Cancer Center and support the Lurie Cancer Center’s mission to foster basic and translational research in the mechanisms and treatment of cancer.

Bioinformatics Core Facility
Director: Warren Kibbe, PhD
312.695.1334 or wakibbe@northwestern.edu
The Bioinformatics Core Facility provides analysis, support and design for microarrays, proteomics, clinical trial informatics as well as custom web-based database development for basic science and clinical projects.

Biostatistics Core Facility
Director: Alfred Rademaker, PhD
312.908.1970 or rademaker@northwestern.edu
The Biostatistics Core Facility provides biostatistical and data management support including such services as: data analysis, clinical trial design, database design and management, design and analysis of clustered data, diagnostic screening tests, protocol preparation, and sample size determination.

Cancer Therapeutics and Diagnostic Screening Core Facility
Director: Eric Weiss, PhD
Managing Director: Chi-Hao Luan, PhD
847-491-5643 or luanch@northwestern.edu
The Cancer Therapeutics and Diagnostic Screening Core Facility helps investigators design, validate, and conduct diverse high throughput assays. These can be virtually any assay with a photometric readout, such as absorbance, luminescence, and fluorescence polarization. The facility has recently added capability for high throughput microscopy, including sophisticated software for analysis of large image databases. Additionally, the facility provides access to advanced platforms for large scale liquid handling, plasmid preparation, generations and manipulation of arrayed microbial strains, and protein affinity purification.

Cell Imaging Core Facility
Director: Teng-Leong Chew, PhD
312.503.4445 or t-chew@northwestern.edu
The Cell Imaging Facility offers state-of-the art instrumentation and services for the study of biological processes at the tissue, cellular and subcellular levels. The facility’s services include light, fluorescence, confocal, and electron microscopy, microinjection, digitally controlled temperature stage for live cell observation, computerized image analysis, and digital image manipulation.
Clinical Research Office  
**Director:** Timothy Kuzel, MD  
**Administrative Director:** Renee Webb  
312.908.4026 or t-kuzel@northwestern.edu  
r-ripenburg@northwestern.edu  

The Clinical Research Office (CRO) provides a centralized resource to facilitate the development, conduct, quality assurance monitoring, compliance with regulatory agency requirements, and evaluation of clinical research/trials at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. As such, the office coordinates the majority of clinical research conducted in medical oncology, malignant hematology, gynecologic-oncology, neuro-oncology, radiation oncology, surgical oncology, and chemoprevention.

Mary Beth Donnelley Clinical Pharmacology Core Facility  
**Director:** Michael Avram, PhD  
312.908.0638 or mja190@northwestern.edu  

The Donnelley Clinical Pharmacology Core Facility was established to provide investigators with pharmacokinetic support for clinical studies, including Phase I and Phase II clinical trials, of cancer chemotherapeutic agents and analgesics. Support includes optimizing the design, conduct, analysis, and interpretation of the pharmacokinetic portion of the proposed clinical study. Chemotherapeutic and analgesic concentrations in body fluids are measured using a state-of-the-art Agilent high performance liquid chromatography system linked to an Applied Biosystems API 3000 triple quadrupole mass spectrometer. Drug concentration histories are fitted to various compartmental pharmacokinetic models using commercially available and specialized software. Standard statistical criteria are used for model selection.

Flow Cytometry Facility  
**Director:** Charles Goolsby, PhD  
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The Flow Cytometry Core Facility provides cell sorting services and access to routine flow cytometry assays such as immunophenotyping and DNA analysis as well as guidance, technical assistance and equipment for the investigators to utilize more complex multi-parametric, multi-laser measurement and cell sorting in their research. The recent acquisition of the MoFlo high-speed sorter has increased the facilities technical capabilities. The facility serves as a focus for studies of cellular heterogeneity in disease. Services range from consultation on experimental design, sample preparation and data analysis to instrument operation and set-up for cell sorting and multi-laser operation.

Genomics Core Facility  
**Director:** Naderah Jafari, PhD  
312.503.3702 or n-jafari@northwestern.edu  

The genomics core at the Center for Genetic Medicine is a shared resource facility that provides a wide range of services to Cancer Center members and the Northwestern University research community. Our goal is to provide services using the state-of-the-art technologies at an affordable price. Currently, we provide expression analysis and SNP analysis using both Affymetrix and Illumina platforms, RT-PCR and low density SNP analysis using 7900HT from ABI, RNA quality control using the Agilent 2100, DNA sequencing using 3730 from ABI, custom array fabrication using MicroGridII and high through put DNA extraction by Autopure LS from Gentra.

Keck Biophysics Facility  
**Director:** Jonathan Widom, PhD  
847.491.7610 or j-widom@northwestern.edu  

The Keck Biophysics Facility is a unique resource that provides researchers with 24-hour access to state of the art instruments. The facility is designed to facilitate biophysical and biochemical characterization of macromolecules. Services include use of fluorometers, spectrometers, calorimeters, imagers, fermentors, a light scattering instrument, an HPLC and a real-time PCR machine.

Monoclonal Antibody Facility  
**Director:** Jonathon Jones, PhD  
**Operations Manager:** Izolda Popova  
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i-popova@northwestern.edu  

The Monoclonal Antibody Facility provides investigators access to the technology for the efficient creation of hybridoma cell lines and the production of monoclonal antibodies from these cell lines. These services include immunization of animals, somatic cell fusions, cloning and screening of hybridomas, subcloning and establishment of antibody producing cell lines, and production of active antibodies from hybridoma lines. In addition to providing these services, the facility provides consultation and training for investigators.
interested in establishing any of these activities in their own research laboratory or using monoclonal antibodies in their research.

Mouse Histology and Phenotyping Laboratory
Director: Warren G. Tourtellotte, MD
Facility Manager: Donna Emge
312.503.2679 or d-emge@northwestern.edu

The purpose of the facility is to assist investigators with gross and histological characterization of genetically modified murine models. Studies can be performed on individual organs or involve a systemic overview of all major organ systems to identify new target organs for genes. Pathologist consultation will allow the development of strategies to elucidate the phenotype and gain mechanistic insight regarding the biologic actions of the targeted molecule. Investigators can be trained in dissection techniques, as well.

Outcomes Measurement and Survey Core
Director: Elizabeth Hahn, PhD
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The mission of this core facility is to provide consultation and support for research that involves collecting, analyzing or interpreting self-report data, and to promote the understanding of measurement fundamentals and the improvement of research practice. The facility provides consultative and analytic expertise on the best ways to measure outcomes derived by self-report, serve as a central resource for state-of-the-art instruments and measurement methods, and provides in-house research support services for the collection of outcomes data.

Pathology Core Facility
Director: Ximing Yang, MD, PhD
Administrative Director: Eric Odulio
Facility Manager: Adekunle Raji
312.908.9595 or xyang@northwestern.edu
a-rajii@northwestern.edu

The Pathology Core Facility has three main components: research histology, specimen procurement and protocol review. The research histology component provides all of the tissue processing and histology services typically performed in a clinical laboratory but it is specifically dedicated to the needs of the Northwestern University research community in general and the Cancer Center research community in particular. The Pathology Core Facility is unique in that it has the capability and flexibility to address specific research

protocol needs. The tissue procurement component of the Pathology Core Facility has two main functions: (1) human tissue and fluid procurement, storage and distribution and (2) quality assurance and protection of research subjects. The tissue procurement component addresses the growing need for human tissue and serves as an “honest broker” with HIPAA-covered entities in an effort to expedite research activities, particularly in the use of human biological materials and associated data.

Structural Biology Facility
Director: Alfonso Mondragon, PhD
Facility Manager: Pamela Focia, PhD
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focia@northwestern.edu

The facility is essential for the research programs of investigators who are studying the relationship between macromolecular structure and function or who are using protein structure as the starting point for structure-based drug design. The Structural Biology Facility is a unique resource at Northwestern University that capitalizes on the extensive expertise of a large group of users and regular access to the synchrotron radiation X-ray source at the DND-CAT beamline at the Advanced Photon Source at Argonne National Laboratories. This resource also serves to nucleate the development of a local community with expertise in structural and computational biology.

Transgenic and Targeted Mutagenesis Laboratory
Director of Core Operations: Lynn T. Doglio, PhD
312.503.0088 or l-doglio@northwestern.edu

The Transgenic and Targeted Mutagenesis Core Facility is a university-wide shared resource dedicated to generating genetically-modified animals for investigators within the research community at Northwestern University and its affiliate institutions. Transgenic and gene targeting technologies are used to generate animal models in which the complexities of gene function and regulation can be studied. The ability to either express or functionally inactivate, in genetically modified animals, defined genes in a developmentally- and tissue-specific manner has lead to significant insights into and the understanding of the role genes play under both normal and abnormal conditions in many different and diverse fields of scientific study.
Chromatin binding of SRp20 and ASF/SF2 and dissociation from mitotic chromosomes is modulated by histone H3 serine 10 phosphorylation.


Abstract
Histone H3 serine 10 phosphorylation is a hallmark of mitotic chromosomes, but its full function remains to be elucidated. We report here that two SR protein splicing factors, SRp20 and ASF/SF2, associate with interphase chromatin, are released from hyperphosphorylated mitotic chromosomes, but reassociate with chromatin late in M-phase. Inhibition of Aurora B kinase diminished histone H3 serine 10 phosphorylation and increased SRp20 and ASF/SF2 retention on mitotic chromosomes. Unexpectedly, we also found that HP1 proteins interact with ASF/SF2 in mitotic cells. Strikingly, siRNA-mediated knockdown of ASF/SF2 caused retention of HP1 proteins on mitotic chromatin. Finally, ASF/SF2-depleted cells released from a mitotic block displayed delayed G0/G1 entry, suggesting a functional consequence of these interactions. These findings underscore the evolving role of histone H3 phosphorylation and demonstrate a direct, functional, and histone-modification-regulated association of SRp20 and ASF/SF2 with chromatin.

The perinucleolar compartment is directly associated with DNA.


Abstract
The perinucleolar compartment (PNC) is a nuclear subdomain that is unique to tumor cells, and the percentage of cells in a population containing PNCs (PNC prevalence) indicates the level of malignancy of that population. Here, we utilize anti-cancer drugs and other exogenous stimuli to investigate the structure and function of the PNC. Screening of clinically used anti-cancer drugs revealed two types of drugs disassemble PNCs and do so through their specific molecular actions. Transcription inhibitors reduce PNC prevalence in parallel with RNA polymerase III transcription reduction, and a subset of DNA-damaging drugs and stimuli (UV radiation) disassemble the PNC. Inhibition of cellular DNA damage response demonstrated that the DNA damage itself, not the response or polymerase III inhibition, is responsible for PNC disassembly, suggesting that the maintenance of the PNC is dependent upon DNA integrity. Analyses of the types of DNA damage that cause PNC disassembly show that interstrand DNA base pairing, not strand continuity, is important for PNC integrity, indicating that the PNC components are directly interacting with the DNA. Complementary cell biology experiments demonstrated that the number of PNCs per cell increases with the rounds of endoreplication.
and that PNCs split into doublets during mid S phase, both of which are phenotypes that are typical of a replicating DNA loci. Together, these studies validate PNC disassembly as a screening marker to identify chemical probes and revealed that the PNC is directly nucleated on a DNA locus, suggesting a potential role for the PNC in gene expression regulation.

Adrian K, Strouch MJ, Zeng, Q; Barron, MR; Cheon, EC; Honasoge, A, Xu, Y; Phukan, S; Sadim, M; Bentrem, DJ; Pasche, B; Grippio, PJ

Tgfbr1 haploinsufficiency inhibits the development of murine mutant Kras-induced pancreatic precancer.


Abstract
To dissect the role of constitutively altered Tgfbr1 signaling in pancreatic cancer development, we crossed Elastase-Kras(G12D) (EL-Kras) mice with Tgfbr1 haploinsufficient mice to generate EL-Kras/Tgfbr1(+/-) mice. Mice were euthanized at 6 to 9 months to compare the incidence, frequency, and size of precancerous lesions in the pancreas. Only 50% of all EL-Kras/Tgfbr1(+/-) mice developed preinvasive lesions compared with 100% of EL-Kras mice. Yet, the frequency of precancerous lesions was 4-fold lower in haploinsufficient than in control mice. Paradoxically, the precancerous lesions of EL-Kras/Tgfbr1(+/-) mice were considerably larger than those in EL-Kras mice. Yet, the mitotic index of precancerous cells and the observable levels of fibrosis, lipoatrophy, and lymphocytic infiltration were reduced in EL-Kras/Tgfbr1(+/-) mice. We conclude that Tgfbr1 signaling promotes the development of precancerous lesions in mice. These findings suggest that individuals with constitutively decreased TGFBR1 expression may have a decreased risk of pancreatic cancer.

Mehta, J; Frankfurt, O; Altman, JK; Evens, A; Tallman, MS; Gordon, LI; Williams, Stephanie; Winter, JN; Krishnamurthy, Jairam; Duffey, Sara; Singh, Veerpal; Meagher, Richard; Grinblatt, David; Kaminer, Lynne, Singhal, S

Optimizing the CD34 + cell dose for reduced-intensity allogeneic hematopoietic stem cell transplantation.


Abstract
Low CD34 + cell doses increase allograft-related mortality and very high doses increase the risk of graft-versus-host disease. The optimum CD34 + cell dose remains undefined. The effect of the CD34 + cell dose based on ideal weight was analyzed in 130 patients with hematologic malignancies undergoing reduced-intensity allogeneic blood cell transplantation in the context of factors known to affect the outcome: chemosensitivity, donor age, lactate dehydrogenase (LDH), human leukocyte antigen (HLA) match, performance status, and platelet count. The survival of patients receiving >8 x 10(6)/kg CD34 + cells was not significantly different from those receiving <6. The outcome of those receiving 6-8 x 10(6)/kg CD34 + cells was significantly better than the rest. This superiority was confirmed in multivariable analysis. Among patients receiving 8) needs further confirmation.

Malinge, Sebastien; Izraeli, Shai, Crispino, J

Insights into the manifestations, outcomes, and mechanisms of leukemogenesis in Down syndrome.


Abstract
Children with Down syndrome (DS) show a spectrum of clinical anomalies, including cognitive impairment, cardiac malformations, and craniofacial dysmorph. Moreover, hematologists have also noted that these children commonly show macrocytosis, abnormal platelet counts, and an increased incidence of transient myeloproliferative disease (TMD), acute megakaryocytic leukemia (AMKL), and acute lymphoid leukemia (ALL). In this review, we summarize the clinical manifestations and characteristics of these leukemias, provide an update on therapeutic strategies and patient outcomes, and discuss the most recent advances in DS-leukemia research. With the increased knowledge of the way in which trisomy 21 affects hematopoiesis and the specific genetic mutations that are found in DS-associated leukemias, we are well on our way toward designing improved strategies for treating both myeloid and lymphoid malignancies in this high-risk population.
Lankees, Heather A; Fought, Angela J; Evens, A; Weisenburger, Dennis D; Chiu, Brian C-H

Vaccination history and risk of non-Hodgkin lymphoma: a population-based, case-control study.


**Abstract**

**Objective:** As factors that alter the immune system have been implicated in non-Hodgkin lymphoma (NHL) etiology, it is of interest to explore the association between vaccination and risk of NHL. Results of few epidemiologic studies conducted thus far are inconsistent, and only one has examined the association by histologic subtype. **Subjects:** A population-based, case-control study of 387 patients with NHL and 535 controls conducted in Nebraska between 1999 and 2002. **Methods:** Information on vaccination for tetanus, polio, influenza, smallpox, and tuberculosis, as well as important environmental factors, was collected by telephone interview. Risk was estimated by odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for confounders. **Results:** We found that NHL risk was inversely associated with ever receiving a polio (OR = 0.59, CI = 0.40-0.87) or smallpox (OR = 0.71, CI = 0.51-0.98) vaccination, and positively associated with influenza vaccination (OR = 1.53, CI = 1.14-2.06). No significant association was found for tetanus or tuberculosis vaccination. The patterns of association were similar between men and women. Analysis by histologic subtypes showed that polio vaccination was associated with a lower risk of follicular (OR = 0.54, CI = 0.31-0.92) and chronic lymphocytic leukemia/small lymphocytic lymphomas (OR = 0.29, CI = 0.12-0.69) and smallpox vaccination was associated with a lower risk of marginal zone lymphoma (OR = 0.41, CI = 0.19-0.88). In contrast, ever receiving an influenza vaccination was associated with a higher risk of follicular (OR = 1.98, CI = 1.23-3.18) and diffuse large B cell lymphomas (OR = 1.88, CI = 1.13-3.12). **Conclusion:** Risk of NHL is inversely associated with polio and smallpox vaccination and positively associated with influenza vaccination. These associations appear to differ by histologic subtype.

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Zhang, Q; Helfand, Brian T; Jang, Thomas L; Zhu, Lihua J; Chen, Lin; Yang, X; Kozlowski, James; Smith, Norm; Kundu, Shilajit D; Yang, Guangyu; Raji, Adekunle A; Javonovic, Borko; Pins, Michael; Lindholm, Paul; Guo, Yinglu; Catalonia, W; Lee, C

Nuclear factor-kappaB-mediated transforming growth factor-beta-induced expression of vimentin is an independent predictor of biochemical recurrence after radical prostatectomy.


**Abstract**

**Purpose:** Transforming growth factor-beta (TGF-beta)-mediated epithelial-to-mesenchymal transition (EMT) has been shown to occur in some cancers; however, the pathway remains controversial and varies with different cancers. In addition, the mechanisms by which TGF-beta and the EMT contribute to prostate cancer recurrence are largely unknown. In this study, we elucidated TGF-beta-mediated EMT as a predictor of disease recurrence after therapy for prostate cancer, which has not been reported before. **Experimental Design:** We analyzed TGF-beta-induced EMT using nuclear factor-kappaB (NF-kappaB) as an intermediate mediator in prostate cancer cell lines. A total of 287 radical prostatectomy specimens were evaluated using immunohistochemistry in a high-throughput tissue microarray analysis. Levels of TGF-beta signaling components and EMT-related factors were analyzed using specific antibodies. Results were expressed as the percentage of cancer cells that stained positive for a given antibody and were correlated with disease recurrence rates at a mean of 7 years following radical prostatectomy. **Results:** In prostate cancer cell lines, TGF-beta-induced EMT was mediated by NF-kappaB signaling. Blockade of NF-kappaB or TGF-beta signaling resulted in abrogation of vimentin expression and inhibition of the invasive capability of these cells. There was high risk of biochemical recurrence associated with tumors that displayed high levels of expression of TGF-beta1, vimentin, and NF-kappaB and low level of cytokeratin 18. This was particularly true for vimentin, which is independent of patients' Gleason score. **Conclusions:** The detection of NF-kappaB-mediated TGF-beta-
induced EMT in primary tumors predicts disease recurrence in prostate cancer patients following radical prostatectomy. The changes in TGF-beta signaling and EMT-related factors provide novel molecular markers that may predict prostate cancer outcomes following treatment.

Park, Irwin I; Zhang, Q; Liu, Victoria; Kozlowski, James M; Zhang, Ju; Lee, C

17Beta-estradiol at low concentrations acts through distinct pathways in normal versus benign prostatic hyperplasia-derived prostate stromal cells.


Abstract
The aim of this study was to identify differential responses to low concentrations of 17beta-estradiol (E2) in primary stromal cell cultures derived from either normal organ donors or benign prostatic hyperplasia or hypertrophy (BPH) specimens. Furthermore, we sought to identify the potential mechanism of E2 action in these cell types, through either a genomic or non-genomic mechanism. We initially treated stromal cells derived from five normal prostates or five BPH specimens with low concentrations of E2 (0.001-1.0 nM) and analyzed their growth response. To determine whether genomic or non-genomic pathways were involved, we performed studies using specific estrogen receptor antagonists to confirm transcriptional activity or MAPK inhibitors to confirm the involvement of rapid signaling. Results of these studies revealed a fundamental difference in the mechanism of the response to E2. In normal cells, we found that a non-genomic, rapid E2 signaling pathway is predominantly involved, mediated by G protein-coupled receptor-30 and the subsequent activation of ERK1/2. In BPH-derived prostate stromal cells, a genomic pathway is predominantly involved because the addition of ICI 182780 was sufficient to abrogate any estrogenic effects. In conclusion, prostate stromal cells respond to far lower concentrations of E2 than previously recognized or examined, and this response is mediated through two distinct mechanisms, depending on its origin. This may provide the basis for new insights into the causes of, and possible treatments for, BPH.

Gradishar, WJ; Krasnojon, Dimitry; Cheporov, Sergey; Makhson, Anatoly N; Manikhas, Georgiy M; Clawson, Alicia; Bhar, Paul

Significantly longer progression-free survival with nab-paclitaxel compared with docetaxel as first-line therapy for metastatic breast cancer.


Abstract
PURPOSE: In patients with metastatic breast cancer (MBC), nab-paclitaxel produced significantly higher antitumor activity compared with patients who received solvent-based paclitaxel. This phase II study examined the antitumor activity and safety of weekly and every 3 week (q3w) nab-paclitaxel compared with docetaxel as first-line treatment in patients with MBC. PATIENTS AND METHODS: In this randomized, multicenter study, patients (N = 302) with previously untreated MBC received nab-paclitaxel 300 mg/m² q3w, 100 mg/m² weekly, or 150 mg/m² weekly or docetaxel 100 mg/m² q3w. RESULTS: nab-Paclitaxel 150 mg/m² weekly demonstrated significantly longer progression-free survival (PFS) than docetaxel by both independent radiologist assessment (12.9 v 7.5 months, respectively; P = .0065) and investigator assessment (14.6 v 7.8 months, respectively; P = .012). On the basis of independent radiologist review, both 150 mg/m² (49%) and 100 mg/m² (45%) weekly of nab-paclitaxel demonstrated a higher overall response rate (ORR) than docetaxel (35%), but this did not reach statistical significance. This trend was supported by statistically significant investigator ORR for both weekly nab-paclitaxel doses versus docetaxel. nab-Paclitaxel q3w versus docetaxel was not different for PFS or ORR. On the basis of both the independent radiologist and investigator review, disease control rate was significantly higher for patients receiving either dose of weekly nab-paclitaxel compared with docetaxel. Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in all nab-paclitaxel arms. The frequency and grade of peripheral neuropathy were similar in all arms. CONCLUSION: This randomized study in first-line MBC demonstrated superior efficacy and safety of weekly nab-paclitaxel compared with docetaxel, with a statistically and clinically significant prolongation of PFS (> 5 months) in patients
receiving nab-paclitaxel 150 mg/m(2) weekly compared with docetaxel 100 mg/m(2) q3w.

Maher, Meghan T; Flozak, Annette S; Stocker, Adam M; Chenn, A; Gottardi, C

Activity of the beta-catenin phosphodestruction complex at cell-cell contacts is enhanced by cadherin-based adhesion.


**Abstract**

It is well established that cadherin protein levels impact canonical Wnt signaling through binding and sequestering beta-catenin (beta-cat) from T-cell factor family transcription factors. Whether changes in intercellular adhesion can affect beta-cat signaling and the mechanism through which this occurs has remained unresolved. We show that axin, APC2, GSK-3beta and N-terminally phosphorylated forms of beta-cat can localize to cell-cell contacts in a complex that is molecularly distinct from the cadherin-catenin adhesive complex. Nonetheless, cadherins can promote the N-terminal phosphorylation of beta-cat, and cell-cell adhesion increases the turnover of cytosolic beta-cat. Together, these data suggest that cadherin-based cell-cell adhesion limits Wnt signals by promoting the activity of a junction-localized beta-cat phosphodestruction complex, which may be relevant to tissue morphogenesis and cell fate decisions during development.

Stocker, Adam M; Chenn, A

Focal reduction of alphaE-catenin causes premature differentiation and reduction of beta-catenin signaling during cortical development.


**Abstract**

Cerebral cortical precursor cells reside in a neuroepithelial cell layer that regulates their proliferation and differentiation. Global disruptions in epithelial architecture induced by loss of the adherens junction component alphaE-catenin lead to hyperproliferation. Here we show that cell autonomous reduction of alphaE-catenin in the background of normal precursors in vivo causes cells to prematurely exit the cell cycle, differentiate into neurons, and migrate to the cortical plate, while normal neighboring precursors are unaffected. Mechanistically, alphaE-catenin likely regulates cortical precursor differentiation by maintaining beta-catenin signaling, as reduction of alphaE-catenin leads to reduction of beta-catenin signaling in vivo. These results demonstrate that, at the cellular level, alphaE-catenin serves to maintain precursors in the proliferative ventricular zone, and suggest an unexpected function for alphaE-catenin in preserving beta-catenin signaling during cortical development.

** getsios, S; Simpson, Cory L; Kojima, Shin-ichiro; Harmon, Robert; Sheu, Linda J; Dusek, Rachel L; Cornwell, Mona; Green, KJ

Desmoglein 1-dependent suppression of EGFR signaling promotes epidermal differentiation and morphogenesis.


**Abstract**

Dsg1 (desmoglein 1) is a member of the cadherin family of Ca(2+)-dependent cell adhesion molecules that is first expressed in the epidermis as keratinocytes transit out of the basal layer and becomes concentrated in the uppermost cell layers of this stratified epithelium. In this study, we show that Dsg1 is not only required for maintaining epidermal tissue integrity in the superficial layers but also supports keratinocyte differentiation and suprabasal morphogenesis. Dsg1 lacking N-terminal ectodomain residues required for adhesion remained capable of promoting keratinocyte differentiation. Moreover, this capability did not depend on cytodomain interactions with the armadillo protein plakoglobin or coexpression of its companion suprabasal cadherin, Dsc1 (desmocollin 1). Instead, Dsg1 was required for suppression of epidermal growth factor receptor-Erk1/2 (extracellular signal-regulated kinase 1/2) signaling, thereby facilitating keratinocyte progression through a terminal differentiation program. In addition to serving as a rigid anchor between adjacent cells, this study implicates desmosomal cadherins as key components of a signaling axis governing epithelial morphogenesis.
Nanoscale cellular changes in field carcinogenesis detected by partial wave spectroscopy.


**Abstract**

Understanding alteration of cell morphology in disease has been hampered by the diffraction-limited resolution of optical microscopy (>200 nm). We recently developed an optical microscopy technique, partial wave spectroscopy (PWS), which is capable of quantifying statistical properties of cell structure at the nanoscale. Here we use PWS to show for the first time the increase in the disorder strength of the nanoscale architecture not only in tumor cells but also in the microscopically normal-appearing cells outside of the tumor. Although genetic and epigenetic alterations have been previously observed in the field of carcinogenesis, these cells were considered morphologically normal. Our data show organ-wide alteration in cell nanoarchitecture. This seems to be a general event in carcinogenesis, which is supported by our data in three types of cancer: colon, pancreatic, and lung. These results have important implications in that PWS can be used as a new method to identify patients harboring malignant or premalignant tumors by interrogating easily accessible tissue sites distant from the location of the lesion.

Fackler, Mary Jo; Rivers, Aeisha; Teo, Wei Wen; Mangat, Amrit; Taylor, Evangeline; Zhang, Zhe; Goodman, Steve; Argani, Pedram; Nayar, Ritu; Susnik, Barbara; Sukumar, Saraswati; _Khan, SA_

Hypermethylated genes as biomarkers of cancer in women with pathologic nipple discharge.


**Abstract**

PURPOSE: In a pilot study of women with pathologic nipple discharge (PND) undergoing ductoscopy, we tested quantitative assessment of gene promoter hypermethylation using quantitative multiplex methylation-specific PCR (QM-MSP) to enhance detection of duct carcinoma in situ (DCIS). EXPERIMENTAL DESIGN: Women with PND underwent ductoscopy; ducts with significant lesions were surgically resected (36 ducts in 33 women) and those with minimal findings were not (28 ducts in 16 women). QM-MSP was done on ductoscopy cell samples. Results were compared with cytology and tissue histology. RESULTS: Cells from ducts with significant lesions on ductoscopy had significantly higher levels of methylation than those with minimal findings. Furthermore, cells from ducts with DCIS displayed higher levels of methylation than those with benign lesions such as papilloma (P = 0.006); or ducts with minimal findings on ductoscopy (P = 0.0001). Cumulative RASSF1A, TWIST1, and HIN1 gene methylation accurately distinguished ducts with cancerous versus benign lesions (100% sensitivity, 72% specificity, and area under the curve of 0.91 according to receiving operating characteristic analyses). QM-MSP analysis was more informative than cytology (100% versus 29% sensitivity, respectively), for detecting DCIS. In a validation set of paraffin-embedded DCIS and papilloma samples from women presenting with PND, QM-MSP was significantly higher in DNA from DCIS than papilloma sections (P = 0.002). CONCLUSION: The positive predictive value of ductoscopy was more than doubled (19% versus 47%) with the addition of QM-MSP, demonstrating the benefit of targeting ducts having both high methylation and significant abnormalities on ductoscopy for surgical excision. Future large-scale studies to validate this approach are needed.

Gounaris, Elias; Blatner, Nichole R; Dennis, Kristen; Magnusson, Fay; Gurish, Michael F; Strom, Terry B; Beckhove, Philipp; Gounari, Fotini; _Khazaie, K_

T-regulatory cells shift from a protective anti-inflammatory to a cancer-promoting proinflammatory phenotype in polyposis.


**Abstract**

T-regulatory (Treg) cells play a major role in...
cancer by suppressing protective antitumor immune responses. A series of observations (from a single laboratory) suggest that Treg cells are protective in cancer by virtue of their ability to control cancer-associated inflammation in an interleukin (IL)-10-dependent manner. Here, we report that the ability of Treg cells to produce IL-10 and control inflammation is lost in the course of progressive disease in a mouse model of hereditary colon cancer. Treg cells that expand in adenomatous polyps no longer produce IL-10 and instead switch to production of IL-17. Aberrant Treg cells from polypridden mice promote rather than suppress focal mastocytosis, a critical tumor-promoting inflammatory response. The cells, however, maintain other Treg characteristics, including their inability to produce IL-2 and ability to suppress proliferation of stimulated CD4 T cells. By promoting inflammation and suppressing T-helper functions, these cells act as a double-edged knife propagating tumor growth.

Lai, J; Butt, Zeeshan; Wagner, LI; Sweet, Jerry J; Beaumont, Jennifer L; Vardy, Janette; Jacobsen, Paul B; Shapiro, Pamela J; Jacobs, Sheri R; Cella, D

Evaluating the dimensionality of perceived cognitive function.


Abstract

Decrement in cognitive function are common in cancer patients and other clinical populations. As direct neuropsychological testing is often not feasible or affordable, there is potential utility in screening for deficits that may warrant a more comprehensive neuropsychological assessment. Furthermore, some evidence suggests that perceived cognitive function (PCF) is independently associated with structural and functional changes on neuroimagery, and may precede more overt deficits. To appropriately measure PCF, one must understand its components and the underlying dimensional structure. The purpose of this study was to examine the dimensionality of PCF in people with cancer. The sample included 393 cancer patients from four clinical trials who completed a questionnaire consisting of the prioritized areas of concerns identified by patients and clinicians: self-reported mental acuity, concentration, memory, verbal fluency, and functional interference. Each area contained both negatively worded (i.e., deficit) and positively worded (i.e., capability) items. Data were analyzed by using Cronbach's alpha, item-total correlations, one-factor confirmatory factor analysis, and a bi-factor analysis model. Results indicated that perceived cognitive problem items are distinct from cognitive capability items, supporting a two-factor structure of PCF. Scoring of PCF based on these two factors should lead to improved assessment of PCF for people with cancer.

Small, W; Du Bois, Andreas; Bhatnagar, Saurabh; Reed, Nick; Pignata, Sandro; Potter, Richard; Randall, Marcus; Mirza, Monsoor; Trimble, Edward; Gaffney, David

Practice patterns of radiotherapy in endometrial cancer among member groups of the gynecologic cancer intergroup.


Abstract

PURPOSE: To describe radiotherapeutic practice of the treatment of endometrial cancer in members of the Gynecologic Cancer Intergroup (GCIG). METHODS: A survey was developed and distributed to the members of the GCIG. The GCIG is a global association of cooperative groups involved in the research and treatment of gynecologic neoplasms. RESULTS: Thirty-four surveys were returned from 13 different cooperative groups. For the treatment of endometrial cancer after hysterectomy, mean (SD) pelvic dose was 47.37 (2.32) Gy. The upper border of the pelvic field was L4/5 in 14 respondents, L5/S1 in 13 respondents, and not specified in 6 surveys. When vaginal brachytherapy (VBT) was used in conjunction with external beam radiotherapy, most groups used high dose rate versus low dose rate on 24 versus 5 respondents, respectively. Twenty-eight of the 34 respondents performed computed tomographic simulation. Intensity-modulated radiotherapy was used routinely in 3 of the 34 respondents. For a para-aortic field, the upper border was,
most commonly, at the T12-L1 interspace (17 of the 28 respondents), and the mean (SD) dose was 46.15 (2.18) Gy. For VBT alone after hysterectomy, 23 groups performed high-dose-rate brachytherapy (27.57 [10.13] Gy in a mean of 4.3 insertions), and 5 groups used low-dose-rate brachytherapy (41.45 [17.5] Gy). Nineteen of the 28 respondents measured the doses to the bladder and the rectum when performing VBT. For brachytherapy, there was no uniformity in the fraction of the vagina treated or the doses and schedules used. CONCLUSIONS: Radiotherapy practices among member groups of the GCIG are similar in doses and dose per fraction with external beam. There is a moderate discrepancy in the brachytherapy practice after hysterectomy. There are no serious impediments to intergroup participation in radiation oncology practices among GCIG members with the use of external beam.

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Mulcahy, MF; Lewandowski, R; Ibrahim, Saad M; Sato, Kent T; Ryu, Robert K; Atassi, Bassel; Newman, Steven; Talamonti, Mark; Omary, R; Benson, AB; Salem, R

Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres.


Abstract

BACKGROUND:: The objective of the current study was to determine the safety and efficacy of Yttrium-90 (Y90) microsphere treatment in patients with liver-dominant colorectal metastases. METHODS:: Seventy-two patients with unresectable hepatic colorectal metastases were treated at a targeted absorbed dose of 120 Gray (Gy). Safety and toxicity were assessed using version 3 of the National Cancer Institute Common Terminology Criteria. Response was assessed by anatomic imaging and positron emission tomography (PET). Survival from the first hepatic metastases and Y90 treatment, respectively. CONCLUSIONS:: Y90 liver therapy appears to provide sustained disease stabilization with acceptable toxicity. Asymptomatic patients with preserved liver function at the time of Y90 appeared to benefit most from treatment.
deliver cohort-defined RAD (1 to 17 Gy) to critical organs with three to six patients per cohort. The therapeutic dose of (90)Y ibritumomab tiuxetan was followed by high-dose BEAM and autologous transplantation. RESULTS: Forty-four patients were treated. Thirty percent of patients had achieved less than a partial remission to their most recent therapy and would not have been eligible for autologous transplantation at most centers. The toxicity profile was similar to that associated with high-dose BEAM chemotherapy. Two dose-limiting toxicities occurred at the 17 Gy dose level, which made 15 Gy the recommended maximum-tolerated RAD. Although eight patients received at least twice the conventional dose of 0.4 mCi/kg, a weight-based strategy at 0.8 mCi/kg would have resulted in a wide range of RAD; nearly 25% of patient cases would have received 17 Gy or more, and many would have received less than 10 Gy. With a median follow-up of 33 months for all patients, the estimated 3-year progression-free and overall survivals were 43% and 60%, respectively. CONCLUSION: Dose-escalated (90)Y ibritumomab tiuxetan may be safely combined with high-dose BEAM with autologous transplantation and has the potential to be more effective than standard-dose radioimmunotherapy. Careful dosimetry is required to avoid toxicity and undertreatment.

Jacobsohn, D; Tse, William T; Chaleff, Stanley; Rademaker, AW; Duerst, Reggie; Olszewski, Marie; Huang, Wei; Chou, Pauline M; Kletzel, M

High WT1 gene expression before haematopoietic stem cell transplant in children with acute myeloid leukaemia predicts poor event-free survival.


Abstract

WT1 gene expression has been proposed as a useful marker of minimal residual disease in leukaemia. Its utility in paediatric haematopoietic stem cell transplantation (HSCT) has not been studied. We studied the prognostic value of WT1 expression in peripheral blood prior to HSCT in 36 children with acute myeloid leukaemia (AML). Samples were obtained 2 weeks pre-transplant to determine the level of WT1 expression. WT1 expression was normalized using K562 cells as a control and a relative value of 0.5 was chosen as the cut-off point between high and low WT1 expression. The median level of pre-transplant WT1 expression in the 36 patients was 0.09 (range 0.0001-11.0), with 11 patients having WT1 \( \geq 0.5 \) and 25, WT1 < 0.5. After HSCT, 76% of patients with high pre-transplant WT1 expression relapsed, in contrast to 0% of the patients with low WT1 expression. Those with high WT1 expression had significantly lower 5-year event-free survival (EFS) (18%, 95% CI 0-40%) as compared to those with low WT1 expression (68%, 95% CI 50-86%, \( P = 0.007 \)). Multivariate analysis showed that pre-transplant WT1 level is the only significant prognostic factor for the difference in EFS. Our finding suggests that elevated WT1 gene expression before HSCT in paediatric AML predicts relapse and poor long-term EFS. A larger prospective study is warranted to compare the value of high WT1 expression and other markers of minimal residue disease in predicting clinical outcomes after HSCT.

Chamberlain, Marc C; Raizer, J

Extended exposure to alkylator chemotherapy: delayed appearance of myelodysplasia.


Abstract

OBJECTIVE: A case series of gliomas treated with alkylator-based chemotherapy who subsequently developed myelodysplastic syndrome (tMDS) or acute myelocytic leukemia (AML). BACKGROUND: Alkylator-based chemotherapy is recognized to be leukemogenic; however, it is infrequently described as a delayed consequence of anti-glioma treatment. Methods: Seven patients (4 men; 3 women) ages 34-69 years (median 44), with gliomas (3 Grade 2; 4 Grade 3) were treated with surgery, all but one with involved-field radiotherapy and all with alkylator-based chemotherapy (temozolomide; 6 patients, nitrosoureas; 5 patients, both agents; 5 patients). RESULTS: Exposure to alkylator-based chemotherapy ranged from 8 to 30 months (median 24). The diagnosis of tMDS was determined by bone marrow biopsy in 7 patients. Seven patients showed chromosomal abnormalities consistent with chemotherapy.
induced MDS. Three patients were diagnosed with AML as well (in two determined by bone marrow and one at autopsy). Interval from last chemotherapy exposure to diagnosis of tMDS/AML ranged from 3 to 31 months (median 24 months). Two patients were treated with bone marrow transplantation and 5 received supportive care only. Five patients have died, 2 as a consequence of recurrent brain tumor, 1 as a complication of transplantation, and 2 due to AML. CONCLUSIONS: Although rare, induction of tMDS/AML following extended use of alkylator-based chemotherapy may become more relevant with the evolving practice to treat gliomas for protracted periods. Future work to determine at risk patients would be important.

Yadav, Ajay K; Renfrow, Jaclyn J; Scholtens, Denise M; Xie, Hehuang; Duran, George E; Bredel, Claudia; Vogel, Hannes; Chandler, James P; Chakravarti, Arnab; Robe, Pierre A; Das, Sunil; Scheck, Adrienne C; Kessler, JA; Soares, M; Sikic, Branimir I; Harsh, Griffith R; Bredel, M

Monosomy of chromosome 10 associated with dysregulation of epidermal growth factor signaling in glioblastomas.


Abstract

CONTEXT: Glioblastomas--uniformly fatal brain tumors--often have both monosomy of chromosome 10 and gains of the epidermal growth factor receptor (EGFR) gene locus on chromosome 7, an association for which the mechanism is poorly understood.

OBJECTIVES: To assess whether coselection of EGFR gains on 7p12 and monosomy 10 in glioblastomas promotes tumorigenic epidermal growth factor (EGF) signaling through loss of the annexin A7 (ANXA7) gene on 10q21.1-q21.2 and whether ANXA7 acts as a tumor suppressor gene by regulating EGFR in glioblastomas.

DESIGN, SETTING, AND PATIENTS: Multidimensional analysis of gene, coding sequence, promoter methylation, messenger RNA (mRNA) transcript, protein data for ANXA7 (and EGFR), and clinical patient data profiles of 543 high-grade gliomas from US medical centers and The Cancer Genome Atlas pilot project (made public 2006-2008; and unpublished, tumors collected 2001-2008). Functional analyses using LN229 and U87 glioblastoma cells. MAIN OUTCOME MEASURES: Associations among ANXA7 gene dosage, coding sequence, promoter methylation, mRNA transcript, and protein expression. Effect of ANXA7 haploinsufficiency on EGFR signaling and patient survival. Joint effects of loss of ANXA7 and gain of EGFR expression on tumorigenesis. RESULTS: Heterozygous ANXA7 gene deletion is associated with significant loss of ANXA7 mRNA transcript expression (P = 1 x 10(-15); linear regression) and a reduction (mean [SEM]) of 91.5% (2.3%) of ANXA7 protein expression compared with ANXA7 wild-type glioblastomas (P = .004; unpaired t test). ANXA7 loss of function stabilizes the EGFR protein (72%-744% increase in EGFR protein abundance) and augments EGFR transforming signaling in glioblastoma cells. ANXA7 haploinsufficiency doubles tumorigenic potential of glioblastoma cells, and combined ANXA7 knockdown and EGFR overexpression promotes tumorigenicity synergistically. The heterozygous loss of ANXA7 in approximately 75% of glioblastomas in the The Cancer Genome Atlas plus infrequency of ANXA7 mutation (approximately 6% of tumors) indicates its role as a haploinsufficiency gene. ANXA7 mRNA transcript expression, dichotomized at the median, associates with patient survival in 191 glioblastomas (log-rank P = .008; hazard ratio [HR], 0.667; 95% confidence interval [CI], 0.493-0.902; 46.9 vs 74.8 deaths/100 person-years for high vs low ANXA7 mRNA expression) and with a separate group of 180 high-grade gliomas (log-rank P = .00003; HR, 0.476; 95% CI, 0.333-0.680; 21.8 vs 50.0 deaths/100 person-years for high vs low ANXA7 mRNA expression). Deletion of the ANXA7 gene associates with poor patient survival in 189 glioblastomas (log-rank P = .042; HR, 0.686; 95% CI, 0.476-0.989; 54.0 vs 80.1 deaths/100 person-years for wild-type ANXA7 vs ANXA7 deletion). CONCLUSION: Haploinsufficiency of the tumor suppressor ANXA7 due to monosomy of chromosome 10 provides a clinically relevant mechanism to augment EGFR signaling in glioblastomas beyond that resulting from amplification of the EGFR gene.
The DNA-encoded nucleosome organization of a eukaryotic genome.


**Abstract**

Nucleosome organization is critical for gene regulation. In living cells this organization is determined by multiple factors, including the action of chromatin remodelers, competition with site-specific DNA-binding proteins, and the DNA sequence preferences of the nucleosomes themselves. However, it has been difficult to estimate the relative importance of each of these mechanisms in vivo, because in vivo nucleosome maps reflect the combined action of all influencing factors. Here we determine the importance of nucleosome DNA sequence preferences experimentally by measuring the genome-wide occupancy of nucleosomes assembled on purified yeast genomic DNA. The resulting map, in which nucleosome occupancy is governed only by the intrinsic sequence preferences of nucleosomes, is similar to in vivo nucleosome maps generated in three different growth conditions. In vitro, nucleosome depletion is evident at many transcription factor binding sites and around gene start and end sites, indicating that nucleosome depletion at these sites in vivo is partly encoded in the genome. We confirm these results with a micrococcal nuclease-independent experiment that measures the relative affinity of nucleosomes for approximately 40,000 double-stranded 150-base-pair oligonucleotides. Using our in vitro data, we devise a computational model of nucleosome sequence preferences that is significantly correlated with in vivo nucleosome occupancy in Caenorhabditis elegans. Our results indicate that the intrinsic DNA sequence preferences of nucleosomes have a central role in determining the organization of nucleosomes in vivo.

**Kaplan, Noam; Moore, Irene K; Fondufe-Mittendorf, Yvonne; Gossett, Andrea J; Tillo, Desiree; Field, Yair; LeProust, Emily M; Hughes, Timothy R; Lieb, Jason D; Widom, J; Segal, Eran**

Bogojevic, Andrej; Mohammed, Jameel; Chang, Jeen-Soo; Backman, V

Nanoscale cellular changes in field carcinogenesis detected by partial wave spectroscopy.


**Abstract**

Understanding alteration of cell morphology in disease has been hampered by the diffraction-limited resolution of optical microscopy (>200 nm). We recently developed an optical microscopy technique, partial wave spectroscopy (PWS), which is capable of quantifying statistical properties of cell structure at the nanoscale. Here we use PWS to show for the first time the increase in the disorder strength of the nanoscale architecture not only in tumor cells but also in the microscopically normal-appearing cells outside of the tumor. Although genetic and epigenetic alterations have been previously observed in the field of carcinogenesis, these cells were considered morphologically normal. Our data show organ-wide alteration in cell nanoarchitecture. This seems to be a general event in carcinogenesis, which is supported by our data in three types of cancer: colon, pancreatic, and lung. These results have important implications in that PWS can be used as a new method to identify patients harboring malignant or premalignant tumors by interrogating easily accessible tissue sites distant from the location of the lesion.

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**Subramanian, Harihara; Roy, Hemant K; Pradhan, Prabhakar; Goldberg, Michael J; Muldoon, Joseph; Brand, Randall E; Sturgis, Charles; Hensing, Thomas; Ray, Daniel; Malkani, Roneil G; Tallman, MS; Gottardi-Littell, Numa; Karpus, W; Marszalek, Laura; Variakojis, Daina; Kaden, Bruce; Walker, Matthew; Levy, Robert M; Raizer, J**

Bing-Neel syndrome: an illustrative case and a comprehensive review of the published literature.


**Abstract**

Waldenstrom’s macroglobulinemia (WM) is a chronic lymphoproliferative disorder within the spectrum of lymphoplasmacytic lymphoma characterized by proliferation of plasma cells, small lymphocytes, and plasmacytoid lymphocytes. Central nervous system involvement is very rare (Bing-Neel [BN] syndrome). We present the case of a 62-year-
old woman previously diagnosed with WM who presented with Bing-Neel syndrome and review the published literature which consists of only case reports. We performed a Medline search using the terms "Waldenstrom’s macroglobulinemia and central nervous system" and "Bing-Neel" collecting data on presentation, evaluation, treatment, and outcome and summarizing these findings in the largest pooled series to date. Central nervous system manifestations are localization related. Serum laboratory testing reflects systemic disease. Cerebrospinal fluid analysis may show lymphocytic pleocytosis, elevated protein, and IgM kappa or lambda light chain restriction; cytology results are variable. Imaging is frequently abnormal. Biopsy confirms the diagnosis. Treatment data are limited, but responses are seen with radiation and/or chemotherapy. BN syndrome is a very rare complication of WM that should be considered in patients with neurologic symptoms and a history of WM. Treatment should be initiated as responses do occur that may improve quality of life and extend it when limited or no active systemic disease is present.

Khazaie K, Bonertz A, Beckhove P.

Current developments with peptide-based human tumor vaccines.


Abstract

Cancer immunology became scientifically credible only some 20 years ago with the demonstration of the existence of human tumor antigens. In this short time span, outcomes of cancer vaccine trials have raised hopes and also surfaced disappointments. This review focuses on the prospects of peptide-based vaccines in cancer immunotherapy. RECENT FINDINGS: Accurate descriptions of the natural immune responses to cancer allow for a more precise targeting of such tumors by boosting preexisting antitumor immune responses in patients. The development of synthetic long-peptide vaccines avoids many of the pitfalls of previous vaccination trials through the presence of multiple epitopes that may elicit memory antitumor immune responses. Furthermore, the combination of standard therapy with newly developed immunomodulating agents, such as antibodies blocking cytotoxic T lymphocyte-associated antigen-4 or programmed death receptor-1, and more efficient immune adjuvants has shown promising results.

SUMMARY: Immunotherapy is becoming an effective means of targeting human cancers, and the application of such approaches in combination with current standard schemes of treatment can lead to a significant benefit in survival and quality of life for cancer patients.

Deng J, Larson AC.

Multishot targeted PROPELLER magnetic resonance imaging: description of the technique and initial applications.


Abstract

OBJECTIVES: To test the feasibility of combining inner-volume imaging (IVI) techniques with conventional multishot periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) techniques for targeted-PROPELLER magnetic resonance imaging. MATERIALS AND METHODS: Perpendicular section-selective gradients for spatially selective excitation and refocusing RF pulses were applied to limit the refocused field-of-view (FOV) along the phase-encoding direction for each rectangular blade image. We performed comparison studies in phantoms and normal volunteers by using targeted-PROPELLER methods for a wide range of imaging applications that commonly use turbo-spin-echo (TSE) approaches (brain, abdominal, vessel wall, cardiac). RESULTS: In these initial studies, we demonstrated the feasibility of using targeted-PROPELLER approaches to limit the imaging FOV thereby reducing the number of blades or permitting increased spatial resolution without commensurate increases in scan time. Both phantom and in vivo motion studies demonstrated the potential for more robust regional self-navigated motion correction compared with conventional full FOV PROPELLER methods. CONCLUSION: We demonstrated that the reduced FOV targeted-PROPELLER technique offers the potential for reducing imaging time, increasing spatial resolution, and targeting specific areas for robust regional motion correction.

Concordance with NCCN Colorectal Cancer Guidelines and ASCO/NCCN Quality Measures: an NCCN institutional analysis.


Abstract

The National Comprehensive Cancer Network (NCCN) Outcomes Database was created to assess concordance to evidence- and consensus-based guidelines and to measure adherence to quality measures on an ongoing basis. The Colorectal Cancer Database began in 2005 as a collaboration among 8 NCCN centers.

**METHODS:** Newly diagnosed colon and rectal cancer patients presenting to 1 of 8 NCCN centers between September 1, 2005, and May 21, 2008, were eligible for analysis of concordance with NCCN treatment guidelines for colorectal cancer and with a set of quality metrics jointly developed by ASCO and NCCN in 2007. Adherence rates were determined for each metric. Center-specific rates were benchmarked against mean concordance rates for all participating centers.

**RESULTS:** A total of 3443 patients were evaluable. Mean concordance rates with NCCN colorectal cancer guidelines and ASCO/NCCN quality measures were generally high (>or= 90%). However, relatively low mean concordance rates were noted for adjuvant chemotherapy treatment recommendations within 9 months of diagnosis of stage II to III rectal cancer (81%), and neoadjuvant chemoradiation in clinical T4 rectal primaries (83%). These low rates of concordance seemed to be consistent across centers.

**CONCLUSIONS:** Adherence to guidelines and quality measures is generally high at institutions participating in the NCCN colorectal cancer database. Lack of documentation, patient refusal, delayed treatment initiation, and lack of consensus about whether treatment was essential were the primary reasons for nonconcordance. Measurement of concordance and the reasons for nonconcordance enable participating centers to understand and improve their care delivery systems.


Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization.


Abstract

**PURPOSE:** To describe volumetric changes of "radiation lobectomy," a manifestation of hepatic parenchymal response to lobar (90)Y microsphere radioembolization. **METHODS:** Twenty patients exhibiting this phenomenon were identified. Pre- and posttreatment absolute right and left hepatic lobe volume (HLV), relative HLV (rHLV = HLV/total liver volume), and degree of lobar atrophy (DA) or hypertrophy (DH) (DA or DH = [posttreatment rHLV - pretreatment rHLV]) were determined. Laboratory toxicities, tumor response, and patient survival were also assessed. **RESULTS:** Twenty patients with primary (HCC, n = 17; peripheral cholangiocarcinoma, n = 3) liver malignancies demonstrated findings of radiation lobectomy. Initial absolute right and left HLV was 955 cm(3) (range 644-1,842 cm(3), rHLV = 57%) and 719 cm(3) (range 328-1,387 cm(3), rHLV = 43%), respectively. Following (90)Y, absolute right HLV decreased to 460 cm(3) (range 185-948 cm(3), 52% reduction, rHLV = 31%, DA = 26%, P < 0.0001), while absolute left HLV increased to 1,004 cm(3) (range 560-1,558 cm(3), 40% increase, rHLV = 69%, DH = 26%, P < 0.0001). No grade 3 or 4 bilirubin toxicities were encountered. Tumor response ranged from 55% to 70% by size criteria. Forty-six percent 5-year survival was achieved in HCC patients. **CONCLUSIONS:** Radiation lobectomy following (90)Y radioembolization of right lobe tumors manifests extensive contralateral lobar hypertrophy, high response rates, and prolonged survival. This phenomenon was noted in 6.4% (20/315) of the entire cohort and 19.8% (20/101) of patients with unilobar right lobe tumors. Further investigation is necessary to determine contributing factors that may predict this effect.
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Cancer Center Events

PROFESSIONAL EDUCATION PROGRAMS
Throughout the year, the Lurie Cancer Center offers professional education programs on various cancer specialties. Below is a list of programs for 2010. For registration and additional information visit cancer.northwestern.edu/education or 312.695.1204.

4th Annual Argonne Conference: Biomedical Applications of X-ray Microprobes III
August 13-14, 2010
Robert H. Medical Research Center, Hughes Auditorium
Chair: Gayle Woloschak, PhD

Inaugural Prostate Cancer Forum
September 11, 2010
Robert H. Lurie Medical Research Center, Hughes Auditorium
Chairs:  Chung Lee, MD and William Catalona, MD

First World Congress of Cutaneous Lymphomas
September 22-25, 2010
Prentice Women’s Hospital, 3rd Floor (9/22)
Feinberg Pavilion, 3rd Floor (9/23-9/25)
Chairs: Joan Guitart, MD and Steven Rosen, MD

8th Joint Conference of the International Society for Interferon and Cytokine Research (ISICR) and the International Cytokine Society (ICS)
October 3-7, 2010
Hyatt Regency Chicago
Chair: Leon Platanias, MD, PhD

Nathaniel Berlin Lectureship
October 12, 2010
Robert H. Lurie Medical Research Center
Speaker: Kevin Shannon, MD

12th Annual Lynn Sage Breast Cancer Symposium
October 28-31, 2010
Fairmont Chicago
Chair: William Gradishar, MD
lynnsagebreastcancer.org

Cancer Survivorship 101: Educating Primary Care Providers in Their Treatment of Cancer Survivors
November 12, 2010
Prentice Women’s Hospital, 3rd Floor
Chairs: Aarati Didwania, MD and Karen Kinahan, MS, RN

Pamela Katten Memorial Foundation Lectureship: Chronic Lymphocytic Leukemia
November 18, 2010
Robert H. Lurie Medical Research Center
Speaker: Thomas Kipps, MD, PhD

(continued, next page)
13th Annual Oncology Nursing Conference  
December 3, 2010  
Prentice Women’s Hospital, 3rd Floor  
Chairs: Marge Pierce, RN, BSN, OCN and Maria Kordas, RN, BSN, CMS  

8th Annual Complimentary, Integrative, and Preventive Therapies 2010:  
How Great Are These Data?  
"Focus on the Cancer Patient, and on Controversies in Prevention"  
December 10-12, 2010  
Feinberg Pavilion, 3rd Floor  
Chairs: Melinda Ring, MD and Michael Roizen, MD  

COMMUNITY EVENTS / PATIENT PROGRAMS  
The Lurie Cancer Center is committed to educating the public about cancer prevention and treatment, and offers a wide range of community events and patient programs throughout the year. For more information about these programs, visit cancer.northwestern.edu/events or call 312.695.1304.  

Inaugural Prostate Cancer Forum  
Dual Track Program for Patients & Professionals  
September 11, 2010  
Robert H. Lurie Medical Research Center, Hughes Auditorium  
Chairs: Chung Lee, MD and William Catalona, MD  

Conversations about Colorectal Cancer  
October 2, 2010  
Feinberg Pavilion, 3rd floor  
Chair: Mary Mulcahy, MD  

Brain Tumor Patient and Caregiver Forum  
October 12, 2010  
Robert H. Lurie Medical Research Center, Baldwin Auditorium  
Chair: Laurie Rice, RN, MS, NP  

Lynn Sage Breast Cancer Town Hall Meeting  
October 24, 2010  
Arthur Rubloff Building, Thorne Auditorium  
Chair: William Gradishar, MD  

Integrative Medicine and Oncology Patient Education Symposium  
December 11, 2010  
Prentice Women’s Hospital, 3rd Floor  
Chair: Melinda Ring, MD
The Robert H. Lurie Comprehensive Cancer Center of Northwestern University is the focus of cancer research, treatment and education at Northwestern University. The Lurie Cancer Center coordinates and integrates the University’s cancer and cancer-related activities and unites scientists, clinicians and educators in the fight against cancer. The Lurie Cancer Center’s administrative offices and many of its basic science research activities are at Northwestern University’s Feinberg School of Medicine on the Chicago campus. Additional offices and basic science research labs are located on the Evanston campus. Clinical research is conducted at the Feinberg School of Medicine’s various affiliated teaching hospitals: Northwestern Memorial Hospital, Children’s Memorial Hospital, the Rehabilitation Institute of Chicago and Jesse Brown VA Medical Center.
First established at Northwestern University in 1974, the Cancer Center was invigorated in 1989 when Ann Lurie and Robert H. Lurie made a commitment to endow an institution dedicated to research and advancement in the battle against cancer. In 1991, the Cancer Center was dedicated as the Robert H. Lurie Cancer Center of Northwestern University. This title was modified in 1998, when the National Cancer Institute (NCI) awarded the Cancer Center the highly competitive “comprehensive” designation. Today, the Robert H. Lurie Comprehensive Cancer Center of Northwestern University stands among the country’s leaders as one of only 41 cancer centers in the nation to hold this NCI distinction.

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