First established at Northwestern University in 1974, the Cancer Center was invigorated in 1989 when Ann 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 NCI-designated Comprehensive Cancer Centers in the nation. In addition, the Lurie Cancer Center is a founding member of the National Comprehensive Cancer Network (NCCN), an alliance of 21 of the world’s leading cancer centers dedicated to improving the quality and effectiveness of care provided to patients with cancer.

The Lurie Cancer Center acknowledges and thanks the Lea Charitable Trust for their support and encouragement. A generous donation from the Lea Charitable Trust provides partial support for the publication of The Journal.

“Few will have the greatness to bend history itself, but each of us can work to change a small portion of events, and in the total of all those acts will be written the history of this generation. It is from numberless diverse acts of courage and belief that human history is shaped.”

— Robert F. Kennedy
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Each year, the families of more than 11,000 children in this country receive the devastating news that their child has cancer. Many of these families, alternating between fear, hope, questions, and concern, turn to our affiliate, the new Ann & Robert H. Lurie Children’s Hospital of Chicago, seeking the best care possible for their son or daughter.

We welcomed Lurie Children’s, named in recognition of Ann Lurie’s transformational gift to Northwestern’s medical campus in June, 2012. Already, our pediatric oncology program has been enhanced by the proximity of this state-of-the-art facility to the Lurie Cancer Center and the Feinberg School of Medicine.

The region’s largest provider of pediatric hematology/oncology services, Lurie Children’s Center for Cancer and Blood Disorders offers a powerful blend of clinical expertise and comprehensive services, including one of the nation’s largest pediatric stem cell transplant programs. Children with rare brain tumors have access to advanced therapies at the Midwest’s only Pediatric Brain Tumor Consortium Center.

One of the key areas of collaboration is monitoring the long-term health of pediatric cancer survivors. The STAR (Survivors’ Taking Action & Responsibility) Program provides continuity of care for patients from adolescence through adulthood, with a focus on health maintenance, screening and patient education.

Working together, along with the research arm of Lurie Children’s—Children’s Hospital of Chicago Research Center—we remain committed to training the next generation of pediatric specialists and advancing cancer care for children.

Learn more about the new hospital and the pediatric oncology program at luriechildrens.org.
A self-described Chicago White Sox fan extraordinaire, Stewart Goldman, MD, Associate Professor of Pediatrics at Northwestern University Feinberg School of Medicine, loves team endeavors. Selecting the medical center environment as his home field, he thrives on the multidisciplinary approach needed to deliver the best care for children with brain tumors. “It’s the ultimate team challenge,” he explains. “To this day, I still thoroughly enjoy being part of an effort that requires input from so many specialists to succeed and provide effective care.”

Medical Director and Gus Foundation Chair of Neuro-Oncology at the Ann & Robert H. Lurie Children’s Hospital of Chicago, Goldman focuses his clinical practice and research activities on pediatric brain tumors: specifically, brain stem gliomas. These difficult-to-treat tumors result in progression of 50 percent of patients within nine months leading to death in more than 90 percent in 18 months. Faced with this poor prognosis for his patients, Goldman long ago turned to advancing research in the field. He serves as the Chicago Principal investigator for the Pediatric Brain Tumor Consortium as well as the Children’s Oncology Group’s Developmental Therapeutics Consortium site at Lurie Children’s. As Director of the Clinical Trials Research Center at Children’s Hospital of Chicago Research Center, he is involved in developing and teaching new treatments for brain tumors.
It’s exciting to be able to contribute to the care of these patients through novel therapies—many made possible through our Phase I consortium and collaborations with others around the world,” says Goldman, who is also Interim Division Head of Pediatric Hematology, Oncology and Stem Cell Transplantation at Feinberg, and the Center for Cancer and Blood Disorders at Lurie Children’s. “At Lurie Children’s we offer therapies that can’t be found at other hospitals.”

Goldman and his team recently wrapped up a Phase I study on the drug Xerecept. The trial focused on the drug’s ability to enhance the lives of patients with brain stem gliomas. While not a treatment for attacking the tumors themselves, Xerecept helps control symptoms with fewer of the severe side effects of the currently used steroid-based drug Decadron. Goldman has been partnering with colleagues in Northwestern’s Department of Medical Social Sciences on the outcomes research aspects of the brain tumor survivorship study. The investigators hope to soon move to a Phase III trial to hasten the drug’s commercial availability. He says, “Even while these life-threatening tumors grew, patients and their families still experienced better quality of life with Xerecept than they would have had without it. Finding a cure is always our hope but improving the lives of these kids in the meantime is important, too.”

Another brain stem clinical trial recently launched at Lurie Children’s has Goldman excited about opportunities to better tailor treatment. Investigators hope to use molecular markers identified via brain stem biopsies to individualize therapy in children and young adults with newly diagnosed diffuse intrinsic pontine gliomas. “Lurie Children’s is the second site of some 17 ultimate sites that is currently up and running, and we are leading in enrollments,” says Goldman, who admits he does have a bit of a competitive streak.

Two older sisters kept youngest sibling Goldman in check as kids growing up in the Chicago area. Goldman attended the University of Iowa in Iowa City, where he earned his BS degree in psychology and planned to become a therapist. Several stints as an EMT in Illinois and Iowa, however, eventually pointed him in the direction of becoming a family medicine practitioner. “I was going to be your neighborhood doctor.” While earning his medical degree at Loyola University’s Stritch School of Medicine in Maywood, Illinois, he became enamored with pediatrics during a clinical rotation and completed a pediatrics residency followed by a pediatric oncology fellowship at the University of Chicago. “I fell in love with the subspecialty because I felt it would allow me to be a tertiary care primary care physician,” he says, “There were also wonderful opportunities to see cancer care improvements in the future for patients and their families.” After completing his subspecialty training, Goldman joined the University of Chicago faculty, where among other leadership roles he served as director of the very fellowship program that had shaped him as a pediatric oncologist. Married to Dee, a nurse, and the parent of three children, this Oak Park resident came to Northwestern in 1997.

Nurturing team members is another aspect of Goldman’s passion for the power of teams. He takes great pleasure in helping develop future specialists in pediatric neuro-oncology and neurosurgery through Northwestern’s and Lurie Children’s fellowship program. “We’ve really been blessed to train terrific and compassionate rising stars who are going to be great leaders in the field both nationally and internationally,” says Goldman, who serves as Clinical Practice Director of Pediatric Hematology-Oncology at Lurie Children’s. Several of his former fellows have stayed on, joining the faculty at Northwestern.

In addition to infusing the pediatric neuro-oncology team with new talent, Goldman looks forward to further strengthening ties with the downtown campus now that Lurie Children’s has opened. “The new hospital has greatly enhanced our ability to interact more closely with our adult neuro-oncology colleagues and basic scientists at the Lurie Cancer Center and develop programs together,” he says. “This is definitely a case of one plus one equaling more than two.”
Advocating for children’s cancer care drives everything Morris Kletzel, MD, MBA, does as a pediatrician and specialist in hematology/oncology. “I’m committed to protecting children from being treated as second-class citizens, and ensuring they receive the best of care,” says Kletzel, Professor of Pediatrics, Division Head Emeritus of Pediatric Hematology, Oncology, and Stem Cell Transplantation at Northwestern University Feinberg School of Medicine, and Director Emeritus of the Center for Cancer and Blood Disorders at the Ann & Robert H. Lurie Children’s Hospital of Chicago (formerly Children’s Memorial Hospital). “We have great health care in the United States but we also need to make sure that kids in Central and South America and other parts of the world have access to cancer treatment.”

A pediatric transplant expert, Kletzel founded Lurie Children’s stem cell transplant program 21 years ago. He also developed a program to train visiting Latin American physicians in pediatric transplantation for treating cancer and other diseases like sickle cell anemia. Under his tutelage, program graduates have gone on to lead successful pediatric transplant services in countries including Colombia, Mexico, Chile, and Venezuela. Currently Kletzel is as an advisor to 10 of these programs, and periodically makes on-site visits. He remarks, “Transplantation techniques and outcomes can vary widely and be very different in other countries.”
Born in Mexico City and the oldest of three children, Kletzel decided early on that he was more interested in becoming a physician than joining his father in the business world. “I always wanted to help people,” he says. After earning his medical degree at the National Autonomous University of Mexico and completing an internship at the University of Tel Aviv in Israel, he began an internal medicine residency in Mexico only to discover that pediatrics was his true calling. He sought training in the United States, where he completed his pediatric residency at the University of Arkansas in Little Rock and then served as chief pediatric resident there. With two years left on his five-year student visa, Kletzel went to The University of Texas M.D. Anderson Hospital and Tumor Institute at Houston for a one-year fellowship in pediatric hematology/oncology. He spent an additional year there as chief fellow.

In 1980 Kletzel returned to his native Mexico and started a pediatric hematology/oncology program at his medical school alma mater and at General Hospital of Mexico, one of the country’s largest public hospitals. For the next four years, he combined private practice with academic medicine. Then his career took a different turn when he ran into some former U.S. colleagues at a medical conference in Mexico City. He recalls, “They knew I was frustrated by not being able to fully do the kind of work I want to do, so they said, ‘You should come back to the States and practice.’” Kletzel did just that. He became a faculty member in the Department of Pediatrics at the University of Arkansas in the mid-80s. An opportunity to launch a pediatric stem cell transplantation program at Children’s Memorial brought him to Northwestern in 1991. “For the first eight years, it was just me, myself, and a nurse practitioner,” says Kletzel, who in 2002 was named the hospital’s Meryl Suzanne Weiss Professor in Pediatric Hematology Oncology. Today the stem cell transplant program boasts five physicians, four nurse practitioners, a social worker, and other support staff.

Groundbreaking Work
Understanding and improving the treatment of neuroblastoma via stem cell transplant has long been a clinical research interest of Kletzel. Two decades ago most pediatric patients with high-risk neuroblastoma tumors did not survive. Then, in 1994, a novel but somewhat controversial experimental treatment was proposed: it involved combining three high doses of chemotherapy with autologous stem cell transplants in short, three-week increments. A highly toxic regimen, this therapy came with significant risks but they proved to be worth taking—it improved the survival rate by 50 percent. Over time, with modifications to the treatment protocol, the rate has increased to 60 percent. Kletzel directed the innovative clinical studies at Children’s Memorial until the trial concluded in 2002. Although he received some criticism at the time for taking such an extreme approach with this therapy, Kletzel is happy with the result: he has patients who are now living 10 to 15 years free of disease.

“My current research focuses on trying to figure out why the other 50 percent didn’t do well,” he says. “We believe for the patients whose transplants failed and/or they relapsed, we couldn’t get rid of the tumor stem cells.”

In addition to cancer treatment, Kletzel has directed transplant studies aimed at sickle cell anemia. “Transplant is the only curative therapy for the condition as long as we can find donors,” he says. Beyond his research and clinical endeavors, Kletzel is a member of numerous national and international professional societies and serves as International Associate Editor of Anales Medicos.

A racquet ball player and an avid cyclist who rides up to 100 miles a week, Kletzel lives in Fort Sheridan, in one of the community’s renovated Army barracks with his wife, Irene. The couple, who met at a New Year’s Eve party in Mexico City, has two children and four grandchildren.

A racquet ball player and an avid cyclist who rides up to 100 miles a week, Kletzel lives in Fort Sheridan, in one of the community’s renovated Army barracks with his wife, Irene. The couple, who met at a New Year’s Eve party in Mexico City, has two children and four grandchildren.
A sepia-toned photograph from a bygone era sits in prominent display in the office of Alexis Thompson, MD, MPH, Professor of Pediatrics at Northwestern University Feinberg School of Medicine. The photo features Thompson’s great-great-aunt, Sophia B. Jones, who graduated from the University of Michigan Medical School in 1885 and became its first black female doctor. “It’s remarkable what Sophia, whose father was born a slave, achieved in just one generation,” shares Thompson.

An interest in genealogy led this Southern California native to the Jones branch of her family tree. She discovered that Jones had a passion for advancing public health and achieving health equity in the post-Civil War era, publishing in 1913 a retrospective article entitled “Fifty Years of Negro Public Health.” “Hopefully we’ve made substantial progress in the last 100 hundred years and will continue to do so.” Fittingly, Thompson has followed in Jones’ footsteps. In her role as the Lurie Cancer Center’s Associate Director for Equity and Minority Health, Thompson helps develop community outreach programs and looks for opportunities to better serve all communities across Chicago and nationwide when it comes to cancer care. “We’re not only interested in the reach of the Lurie Cancer Center’s clinical programs but also ways we can encourage greater participation of underrepresented communities in clinical trials and research,” she explains. “By better understanding the
impact of cancer diagnoses and screening in communities of color, we can begin to reduce health disparities.”

Building Blocks
Growing up in Los Angeles, Thompson knew two things: she loved science and she wanted to make a difference. Medicine fit the bill, and Thompson earned a bachelor’s degree in zoology from Pomona College in Claremont, California, before attending medical school at Tulane University. The dynamics of specializing in pediatrics greatly appealed to her. “Treating the particular diseases that afflict children really allows pediatricians to impact peoples’ lives,” she says. “I enjoy interacting with families and the community.” After a pediatric internship and residency at Children’s Hospital of Los Angeles, Thompson completed a fellowship in pediatric hematology/oncology at Children’s Hospital of Philadelphia. She then returned to Southern California, joining the faculty at UCLA where she earned a MPH degree in health services. Recruited to Northwestern University to build a robust pediatric hematology program, she arrived in Chicago in 2001.

Under Thompson’s leadership as Medical and Scientific Director of Hematology at the Ann & Robert H. Lurie Children’s Hospital of Chicago (formerly Children’s Memorial Hospital), the program has flourished. Although the program was once primarily clinical, it now features a vibrant clinical research component. As many as 700 new patients with non-malignant blood conditions seek care each year through the Center for Cancer and Blood Disorders at Lurie Children’s, and some 500 individuals have been enrolled in clinical trials funded by the National Institutes of Health, Centers for Disease Control and Prevention, U.S. Health Resources and Services Administration, and industry. Says Thompson, “It’s been extremely rewarding to see the program grow and evolve to become one that is incredibly diverse and has attained national stature.”

Clinical and Research Efforts
Seeing patients with sickle cell disease, thalassemia, and other hemoglobinopathies, Thompson’s clinical research focuses on enhancing care and increasing understanding of these disease processes. At Lurie Children’s, she and her colleagues have built one of the most comprehensive pediatric sickle cell programs in the state and the largest thalassemia program in the Midwest. Proud to report that her oldest thalassemia patient turns 61 this year, Thompson has seen vast improvement in her ability to treat this once fatal childhood condition. She credits advances in iron chelation, transfusion practices and new surveillance tools such as magnetic resonance imaging (MRI). “At Children’s Memorial and Northwestern, we were among the first institutions in the United States to use MRI to quantify liver and heart iron in these patients,” says Thompson, who holds the A. Watson and Sarah Armour Endowed Chair for Blood Diseases and Cancer at Lurie Children’s. “Now we can identify iron overload earlier to increase survival.” She sees great potential in expanding collaborations to include adult hematology providers at Lurie Cancer Center and Northwestern Memorial Hospital.

Bone marrow failure syndromes and stem cell transplantation for nonmalignant disorders in pediatric patients also interest Thompson. In the laboratory, she has conducted studies that focus on developmentally regulated genes in early hematopoieses. At a national level, Thompson provides leadership and promotes research in blood disorders as a member of the Executive Committee of the American Society of Hematology (ASH). She also serves on the ASH Committee for Promoting Diversity which seeks to encourage more minority students, trainees and junior faculty to consider academic careers in hematology.

Thompson resides in Chicago’s South Loop neighborhood with her husband, Garry, a fine arts woodworker. She enjoys cycling, gardening, travel and cooking. She has also been exploring different ways to commute to the hospital since its move to Streeterville from Lincoln Park (so far biking has been the fastest and most fun). She reports that the transition to the new building has exceeded her expectations. “We want to provide the same high level of personal care but now in a state-of-the-art facility,” says Thompson, who is thrilled by the new logistics. She has already taken advantage of attending presentations and participating in other activities on the Chicago campus. “It seems we have been able to translate the same warmth of the old hospital that was developed over many years to this new one incredibly well.”
Welcome Ann & Robert H. Lurie Children’s Hospital of Chicago

On June 9, 2012, the Lurie Cancer Center welcomed our academic partner, the Ann & Robert H. Lurie Children’s Hospital of Chicago (formerly Children’s Memorial Hospital), when it opened the doors to its new, world-class hospital at 225 E. Chicago Ave.

Named in recognition of Ann Lurie’s historic $100 million transformational gift, the 23 story facility, widely recognized as the world’s tallest pediatric hospital, offers innovations in medical care and technology, enhanced clinical programs, advanced research and improved family amenities. The new location on the campus of Northwestern University Feinberg School of Medicine enables the hospital to recruit top pediatric specialists, and its close proximity to Prentice Women’s Hospital expedites the care of critically ill newborns.

“One of the unique things about our model of care is that we work very closely with the Lurie Cancer Center,” says Advanced Practice Nurse Karina Danner-Koptik, RN, MSN, APN, CPON. Being part of Northwestern’s medical campus, “gives us even more opportunities to work collaboratively with their researchers as well as the adult clinicians at Northwestern. This means better treatments and targeted research, a smoother transition into adult care, and ultimately, the most expert treatment options and cures for our patients.”

Read more at luriechildrens.org/cancer.

Salem Named Chief of Interventional Radiology

Riad Salem, MD, Professor of Radiology, Medicine, and Surgery, and Director of the Division of Interventional Oncology at Northwestern University Feinberg School of Medicine, was named Vice-Chair of Image Guided Therapy and Chief of Interventional Radiology. “This is a new, vice-chair level role created specifically to take advantage of Dr. Salem’s skills bridging clinical excellence, innovation in programmatic development, research, and administrative expertise,” said Eric Russell, MD, Department of Radiology Chair.

An internationally recognized expert in interventional oncology, Salem helped develop radioembolization, a technique targeting the local treatment of tumors with radiation, sparing the harmful effects of radiation on non-targeted tissues. His research has resulted in more than 145 peer reviewed papers, and he recently assumed the role of global principal investigator of a 400 patient, international, randomized phase III trial comparing radioembolization with the standard of care.
Steven T. Rosen Named Chair of Leukemia & Lymphoma Society Medical and Scientific Advisory Board

Steven T. Rosen, MD, FACP, Genevieve E. Teuton Professor of Medicine at Northwestern University Feinberg School of Medicine and Director of the Lurie Cancer Center, has been named Chair of The Leukemia & Lymphoma Society’s (LLS’s) Medical and Scientific Advisory Board. Rosen is also Director of Cancer Programs at Northwestern Memorial Hospital.

Comprised of leading experts in their fields, members of the Medical and Scientific Advisory Board advise the Board of Directors on a wide range of issues. These include periodically reviewing LLS’s medical affairs and recommending funding for research grant awards. Subcommittees within the Advisory Board work on specific processes that relate to medical and scientific affairs.

Double Assault on Tough Types of Leukemias

Lurie Cancer Center investigators have identified two promising therapies to treat patients with acute megakaryocytic leukemia (AMKL), a rare form of leukemia characterized by an overload of white blood cells that remain forever young because they can’t mature into specialized cells. The study found that the drug with the generic name alisertib (MLN8237), induced division and growth of healthy cells to overtake the proliferation or “blasts” of immature cells.

Alisertib has been tested before in humans with limited success to treat other types of leukemia and lymphoma. However, the drug should be effective against AKML in humans because it specifically targets the enzyme Aurora A kinase, said study senior author John Crispino, PhD, the Robert I. Lurie, MD, and Lora S. Lurie Professor of Hematology/Oncology at Northwestern University Feinberg School of Medicine. “Alisertib was really potent against the proliferation of cancer cells,” said Crispino, who is also Associate Director for Education and Training at the Lurie Cancer Center. “We were incredibly excited when we found that the drug we predict will reverse AMKL is already far along in clinical development. The fact that we don’t have to start from scratch means we could be years closer to finding an effective therapy.”

“This study has given us a scientific rationale to take this drug to an early phase clinical trial in this very challenging form of leukemia,” said Jessica Altman, MD, Assistant Professor of Hematology/Oncology at Feinberg. Together with other leukemia specialists, Altman is designing a multi-center clinical trial planned to open in 2013.

Read more at cancer.northwestern.edu/double-assault.
Lurie Cancer Center Scientists Win Presidential Awards

Two Lurie Cancer Center scientists received the Presidential Early Career Award for Scientists and Engineers (PECASE), the highest honor given by the United States government to outstanding scientists and engineers who are in the early stages of their independent research careers.

**C. Shad Thaxton, MD, PhD**, Assistant Professor of Urology at Northwestern University Feinberg School of Medicine, was recognized for outstanding accomplishments in the field of nanoparticles-based diagnostics and therapeutics and for pioneering research on the synthesis of bio-inspired nanomaterials for toxin sequestration and cellular regulation.

**Steven Kosak, PhD**, Assistant Professor of Cell and Molecular Biology at the Feinberg School, was recognized for his novel research into how the total DNA sequence of an organism (its genome) is non-randomly packaged within the nucleus.

“Discoveries in science and technology not only strengthen our economy, they inspire us as a people,” President Obama said at the awards ceremony in Washington, D.C. “The impressive accomplishments of today’s awardees so early in their careers promise even greater advances in the years ahead.”

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Childhood Cancer Scars Survivors Later in Life

Scars left behind by childhood cancer treatments are more than skin-deep. The increased risk of disfigurement and persistent hair loss caused by childhood cancer and treatment are associated with emotional distress and reduced quality of life in adulthood, according to a new study led by Lurie Cancer Center advanced practice nurse, **Karen Kinahan, RN, APN, P-CNS** and based on data from the Childhood Cancer Survivor Study (CCSS).

The largest study of its kind, published in the *Journal of Clinical Oncology*, compared scarring, disfigurement and persistent hair loss reported by adult survivors of childhood cancer to their siblings, who were not cancer survivors.

“The results show that cancer treatments can affect childhood cancer survivors’ physical appearances and their quality of life long after they turn 18,” said Kinahan. “I have patients who are asymmetrical because of radiation treatments, others with scars on their faces and necks from biopsies and surgeries and some who’ve had the amputation of a limb.”

As a clinical nurse specialist specializing in pediatric oncology, Kinahan helped start the STAR Program (Survivors Taking Action & Responsibility) at the Lurie Cancer Center in 2001. A comprehensive long-term follow-up program for adult survivors of pediatric cancer, STAR follows patients for their chronic medical and psychological conditions into adulthood.

*Read more at cancer.northwestern.edu/childhood cancer scars*
Penedo Joins Northwestern Medical Social Sciences

Frank Penedo, PhD, joined Northwestern University Feinberg School of Medicine as the inaugural Roswell Park Professor of Medical Social Sciences, and is leading the Lurie Cancer Center’s Cancer Control and Survivorship Research Program. A nationally-renowned health psychologist and scholar of health disparities and outcomes in ethnically diverse populations, Penedo will lead research into the most effective ways to promote cancer prevention, early diagnosis, and treatment in local, national, and international communities.

Penedo has served on the faculty at the University of Miami since 2000, most recently as an Associate Professor in Psychology. He also held a secondary appointment as an Associate Professor of Psychiatry and Behavioral Sciences, and has been honored with numerous awards over the past decade, including the Society of Behavioral Medicine Early Career Award in 2005 and its Distinguished Service Award in 2008. The principal investigator of nearly $8 million in National Cancer Institute grants, Penedo has published more than 100 articles and abstracts in his 12-year professional career.

“Dr. Penedo is a very successful researcher in the bio-psychosocial aspects of cancer and he excels at bringing these aspects together into a coherent understanding of the disease,” said David Cella, PhD, Medical Social Sciences Chair.

Swanson Named Professor and Vice Chair of Research for Neurological Surgery

After 12 years at the University of Washington, Kristin Rae Swanson, PhD, has been named Professor and Vice Chair of Research for Neurological Surgery at Northwestern University Feinberg School of Medicine. Swanson comes to Feinberg from the University of Washington.

A pioneer in the field of mathematical neuro-oncology as a novel means to generate personalized medicine approaches for primary brain tumors, Swanson’s talent for developing collaborative networks comprised of strong multidisciplinary researchers, scientists, clinicians, and trainees, will strengthen the Brain Tumor Institute’s research endeavors.

“I am thrilled to be joining the Northwestern Brain Tumor Institute at such an exciting time of growth and opportunity,” said Swanson, who is also a member of the Lurie Cancer Center. “The institutional and community investment in growing the NBTI is astounding and I am delighted to be part of this exceptional group. I know my lab will contribute to this growth through the integration of our science into the clinical and research fabric of the Northwestern community.”

Read more at braintumorinstitute.org/Swanson
Moisturizer Shows Potential for Delivery of Skin Cancer Therapies

A team led by a physician-scientist and a chemist -- from the fields of dermatology and nanotechnology -- is the first to demonstrate the use of commercial moisturizers to deliver gene regulation technology that has great potential for life-saving therapies for skin cancers.

The topical delivery of gene regulation technology to cells deep in the skin is extremely difficult because of the formidable defenses skin provides for the body. The Northwestern University approach takes advantage of drugs consisting of novel spherical arrangements of nucleic acids. These structures, each about 1,000 times smaller than the diameter of a human hair, have the unique ability to recruit and bind to natural proteins that allow them to traverse the skin and enter cells. Applied directly to the skin, the drug penetrates all of the skin’s layers and can selectively target disease-causing genes while sparing normal genes.

“This allows us to treat a skin problem precisely where it is manifesting -- on the skin,” said study co-senior author Amy S. Paller, MD, the Walter J. Hamlin Professor, Chair of Dermatology and Professor of Pediatrics at the Feinberg School of Medicine. “We can target our therapy to the drivers of disease, at a level so minute that it can distinguish mutant genes from normal genes. Risks are minimized, and side effects have not been seen to date in our human skin and mouse models.”

Co-senior author, Chad Mirkin, PhD, first developed the nanostructure platform used in this study in 1996 at Northwestern, and the FDA-cleared technology now is the basis of powerful commercialized medical diagnostic tools. This, however, is the first realization that the nanostructures naturally enter skin and that they can deliver a large payload of therapeutics.

“The skin is a very tough barrier to go through, which is why this effective gene knockdown has not been accomplished before. The power and elegance of this system are in its simplicity,” said Mirkin, the George B. Rathmann Professor of Chemistry in the Weinberg College of Arts and Sciences and Professor of Medicine, Chemical and Biological Engineering, Biomedical Engineering and Materials Science and Engineering. He also is the Director of Northwestern’s International Institute for Nanotechnology.

Read more at cancer.northwestern.edu/moisturizer
Early Cancer Detection Technology Receives NIH Funding

Two Lurie Cancer Center members have received a prestigious 2012 NIH Director’s Transformative Research Award from the National Institutes of Health (NIH) to develop technology to detect cancer metastasis at its earliest stages, allowing for life-preserving interventions.

Lonnie D. Shea, PhD, and Vadim Backman, PhD, Professors at Northwestern’s McCormick School of Engineering and Applied Science will receive $4.2 million over five years for their innovative project. The grant is one of only 20 Transformative Research Awards given nationwide by the NIH.

With the NIH support, Shea and Backman will work to develop an implant material that creates a localized biological environment that will attract metastatic cancer cells and a sensor that indicates when cells have colonized the implant. The sensor also will monitor cell growth.

Shea’s role is to adapt techniques from his tissue engineering research to develop the biomaterial implant, and Backman’s contribution centers on applying his non-invasive imaging technologies to act as the sensor.

Read more at cancer.northwestern.edu/metastasis

NU NEIGHBORS Established to Reduce Cancer Health Disparities

A $1.2 million grant from the National Cancer Institute’s Center to Reduce Cancer Health Disparities will support NU NEIGHBORS, a partnership between the Lurie Cancer Center and Northeastern Illinois University (NEIU) to help reduce inequalities related to cancer care.

This collaboration is one of 12 in the nation, and the first in Illinois, funded by the Comprehensive Partnerships to Reduce Cancer Health Disparities program. The program will foster community-engaged cancer disparities research, build a platform for improved public health-related curriculum, and further the development of well-trained and experienced cancer researchers and students who choose health and science-related careers.

Read more at cancer.northwestern.edu/NU NEIGHBORS
Overweight and obesity for children and adolescents is of growing concern. National estimates show that 17 percent of children and adolescents ages 2-19 are obese, defined as body mass index (BMI) at or above the 95th percentile. These children are at increased risk for the development of health problems such as hypertension, high cholesterol, cardiovascular disease and diabetes, all of which can affect them in their youth and persist or can present in adulthood.

Weight gain both during and after treatment has been documented for patients with a variety of cancers. Data from the Childhood Cancer Survivor Study (CCSS) showed survivors of childhood acute lymphoblastic leukemia (ALL) who received cranial radiation to be at increased risk of obesity and to have a greater increase in BMI over time when compared with a sibling population. Survivors of ALL and other childhood cancers have also been shown to be at an increased risk for developing chronic health conditions later in life, including cardiovascular disease and diabetes mellitus.

These issues are not limited to oncology patients, as evidence also suggests that exercise and the physical activity of patients suffering from hemophilia and other blood disorders are limited due to parental concerns. Recent studies show that obesity and overweight are more prevalent amongst hemophilia patients than in previous generations. The prevalence of obesity has also tripled amongst hemophiliac
boys and doubled in adults from 1992 to 2001, illustrating the need for educational intervention. In previous studies from our hematology group and others, some patients with sickle cell have been shown to have reduced exercise tolerance and eating habits that cannot sustain their increased resting energy expenditures.

National agencies including the National Institutes of Health and Centers for Disease Control have made concerted efforts to disseminate health related information to youths. However, the impact of these efforts on oncology and hematology patients is unclear. Evidence suggests that childhood cancer survivors and hematology patients are no more likely to engage in health-promoting activities than the general population. A review of the literature in childhood cancer survivors showed that the majority of studies found low levels of physical activity among survivors, particularly among adult survivors, and unhealthful diets were reported across all age groups. Because children with chronic conditions such as cancer and certain blood disorders are at risk for developing complications that can potentially be modified by a healthy lifestyle, the Division of Hematology / Oncology-Transplant at Ann & Robert H. Lurie Children’s Hospital of Chicago has started a Healthy Living Initiative (HOTHLI) to promote wellness for our patients and families. Approximately 2500 to 3000 children with cancers and blood disorders currently receive care at Lurie Children’s, and HOTHLI activities are available to all families.

Clinical Activities
The HOTHLI is a grassroots effort first suggested by Dr. Alexis Thompson, Hematology Section Head at Lurie Children’s and Associate Director for Associate Director for Equity and Minority Health at the Lurie Cancer Center. A multi-disciplinary team including physicians, nurses, genetic counselors, social workers, research coordinators, child life specialists, exercise physiologists, and nutritionists, in cooperation with a number of health-oriented community-based organizations, design and implement ongoing fun and creative projects for HOTHLI including monthly in-clinic demonstrations of simple nutritious child-centered food preparation and physical fitness. Bulletin boards provide information on wellness themes such as healthy eating, stress management, physical fitness, and sleep hygiene. A wellness prescription was created to facilitate dialogue between providers and families during clinic visits. HOTHLI recently hosted a Healthy Family Fair at Lurie Children’s which included 32 of these community partners offering information and demonstrations to more than 200 attendees (see photo). Notably, a satisfaction survey is used to gather participant feedback for all activities.

In addition to the services mentioned above, the HOTHLI has a strong interest in research to better inform the interventions we deliver. A number of projects have been undertaken to provide an evidence base for the best approaches to health behavior change for pediatric hematology and oncology patients and their families.

ReCharge!™ Project
ReCharge!™ is an after-school program from Action for Healthy Kids and The National Football League. As a part of the HOT Healthy Living Initiative, a group of team members created a clinical research study that proposed to increase self-esteem and attitudes towards healthy lifestyles in children with blood disorders using the ReCharge!™ Program. The
The ReCharge!™ Program met for two hours on four consecutive Saturdays in April and May 2011. Each session had a physical activity, a healthy snack and an educational session on nutrition and activity. Each subject received a Player Binder that includes weekly Energy-In (food eaten) and Energy-Out (exercise) trackers that each subject utilized at home. The Rosenberg Self-Esteem Scale, the Peds QL Multi-dimensional Fatigue Scale (Peds QL) & the ReCharge!™ Student Surveys were completed at the beginning & end of the program. 19 subjects between the ages of 8-12 years and in grades 2-6 were consented for the ReCharge!™ Program; 14 subjects with sickle cell disease, 1 with hemophilia, and 4 with ALL. Response to the ReCharge!™ study was positive with 14 of the 19 subjects consented attending the first week of the program, 13 the second week, 12 the third week, and 13 attending the final week.

The Rosenberg Self-Esteem Scale revealed that although all subjects had chronic blood disorders they entered the program already having positive self-esteem. The ReCharge!™ Student Pre & Post Surveys showed an increase in knowledge regarding food consumption and physical activity for all domains (Figure 1). The ReCharge!™ Parent Pre & Post Surveys showed that family interactions were affected by program activities and participating families reported making positive changes in their eating and physical activity habits (Figure 2). 91.7% of parents responded positively that because of their child’s participation in the ReCharge!™ Program, their families were trying to eat a healthier, balanced diet. 100% of parents positively responded that as a result of their child’s participation, their family was trying to be more physically active.

Perceptions of Health and Healthy Behaviors
While health-related quality of life has been studied fairly extensively in pediatric oncology and hematology, perceptions of health and patient and family beliefs about the importance of healthy habits have not been previously described in detail. Under the auspices of HOTHILI, a survey study was conducted in 2011 and presented in spring of 2012 at the American Society of Pediatric Hematology-Oncology national meeting in which we examined knowledge, habits and attitudes around healthy eating and physical activity in patients and families attending oncology and hematology clinics. Patients 10 to 18 years and parents of children any age were offered an anonymous survey while attending a hematology or oncology clinic. The survey was only available in English. 72 patient surveys were collected, 42 oncology and 30 hematology. 134 parent surveys were collected, 80 oncology and 54 hematology. 76.3% of patients were Caucasian, 20.3% African-American/Black and 3.4% Asian. 30.6% identified as Latino. Parent distributions were similar. With regards to current health
behaviors, 73.6% of patients (67.7% parents) reported the child eats ≤1 serving of fruit per day and 79.2% (79.7% parents) reported eating ≤1 vegetable per day. Patients reported widely varied exercise frequency from none to daily. Parent responses were also widely distributed but more reported higher frequency of child exercise. Comparison of the habits reported for high school aged patients to nationally representative data from the Center for Disease Control’s Youth Risk Behavior Surveillance 2011 data\textsuperscript{15} shows similarly poor intake of fruits and even worse intake of vegetables for the patients, with patients also less likely to be physically active at least 5 days per week.

Figure 3 shows that most patients and their parents consider themselves to be “healthy”, a term which was purposely not defined on the survey. Importantly, both patients and their parents reported an interest in learning more about the recommendations for the child’s health (71.4% of parents and 59.2% of patients surveyed agreed or strongly agreed). Combined with the reported belief that current health choices affect future health (95.3% of parents and 91.5% of patients), these results suggest that this population is inclined to be positively influenced by targeted educational interventions. However, only about half of patients and parents overall felt that their current disease affects their future health, and the hematology patients were less likely than the other groups to agree with this statement (Figure 4).

A notable limitation of this study was the inability to survey Latino parents who do not speak English, since this is a sizeable population for all pediatric practices in Chicago including the referral and specialty clinics at Lurie Children’s. The semi-quantitative survey study provides preliminary evidence to support that further qualitative research on health perceptions and possible health behavior change interventions for the pediatric hematology and oncology population is warranted, and next steps will include focus groups in both English and Spanish. This follow-up study is currently recruiting both adolescent and young adult (AYA) patients as well as parents of children greater than 2 years, with the first focus groups to be conducted in fall 2012.

Complementary Division Activities
HOTHLI is an innovative program encompassing a large number of different clinicians and community partners designed to reach out to families and improve overall wellness, with particular emphasis on healthy behaviors. A number of other activities in the
Pediatric HOT Division involve members of HOTHLI and are also aligned to improve wellness and health outcomes for our patients, including an AYA oncology collaboration with partners at Northwestern Memorial and a research study on vocational outcomes conducted within the Survivors Taking Action and Responsibility cancer survivor clinic. All of these initiatives share the common methodology of assessing the unmet health and wellness needs of our patient population with use of feedback from programming and original qualitative and quantitative research to design future intervention studies. The ultimate aim for HOTHLI is to facilitate health behavior change in order to improve outcomes for pediatric hematology and oncology patients including prevention of long-term complications such as preventable metabolic disease.

References


5 Hudson, K., et al. Health Status of Adult Long-term Survivors of Childhood Cancer: A Report From the...


Colon cancer is one of the most common cancer types in both men and women and associated with high mortality, particularly at advanced stages. Markers that can help to define individual risk signatures in colon cancer patients are of great clinical value, as they might allow for a more precise targeting of therapies. Alternative splicing has been described in many cancers, but is not fully understood. Traditionally, oncogenic function has been attributed to aberrant variants. It remains unclear whether and how splice variants may influence cancer development. Possibilities include direct involvement through novel proteins with independent functions, or indirect involvement via regulation of full-length proteins. We have shown the presence of 19 distinct splice variants of the BRCA1-binding partner BARD1 in colon cancers that are abundantly expressed. Contrary to previous assumptions, the splice variants not only occurred in cancer, but also occurred in adjacent colon and other normal tissues, pointing towards a complex function in health and disease. The mechanism of regulation of splice variant expression remains to be elucidated. It is thus far unclear if BARD1 splice variants directly influence full-length protein expression or function, as previously postulated.

Novel BARD1 splice variants occur in primary colon cancer samples and matched normal colon tissue. We used 2 approaches to investigating the role of BARD1 splice variants (Figure 1A,B) in
colon cancer and characterized 19 distinct splice variants (Figure 1C), 11 of which are novel. Eighteen of the 19 splice variants lack one or more complete exons and one variant lacks part of an exon, thus creating new and specific exon boundaries.

As the designation of the BARD1 splice variants has thus far been inconsistent, we created a systematic approach using the structure of the splice variant highlighting the newly created exon boundaries, which can exploited for specific qPCR (Table 1) and later antibody generation.

BARD1 splice variants account for a considerable amount of the total BARD1 transcript in colon cancer. In order to quantify the above-described BARD1 splice variants in normal colon and colon cancer, we performed qPCR assays targeting the new variant specific exon junction, which allowed the design of 13 primer pairs targeting a total of 16 splice variants. We found that BARD1 splice variants account for a considerable percentage of the total BARD1 transcript (Figure 2A) both in colon cancer and matched normal colon samples. Further, we found a significant downregulation of BARD1_1-4a/5-11 and the variants detected by primer pair 3/5 (BARD1_1-3/5-11 and BARD1_1-3/5-7/10-11) (Figure 2A).

To further analyze the tissue specific expression pattern of the BARD1 variants, we performed quantitative assays on pooled cDNA from 16 human tissues and calculated the percentage expression for each variant in each tissue from various sites (Figure 2B). The splice variants could be detected at varying levels in different tissues creating tissue specific profile. This finding underscores that BARD1 splice variants are also a common feature in normal cells and suggests a complex function in health and disease.

Distinct BARD1 splice variants show a cancer specific regulation pattern

To focus on the differences between cancer and normal colon samples, we calculated the ratio of the normalized relative quantity for each matched pair. We found two different regulation patterns: One group, consisting of 4a/5, 3/5 and 1/5, showed a tendency of downregulation, while the second group, consisting of 2/4, 1/4 and 2/5 showed overall an upregulation in cancer versus normal tissue.
Expression of the full-length BARD1 protein correlates with outcome in colon cancer samples
To quantify full-length BARD1 expression, we performed immunohistochemical stainings on 81 colorectal cancer samples using a BARD1 antibody detecting full-length BARD1\(\alpha\) (Figure 3A), given that qPCR does not allow for quantification of full-length BARD1 expression, as there is no exon boundary which is specific for full-length BARD1 (Figure 1C). We found that the expression levels of full-length BARD1 correlated significantly with survival in this and a second independent cohort\(^6\). High expression of full-length BARD1 predicted a favorable outcome, while loss of expression was associated with a worse prognosis (Figure 3B). To control for possible effects of age, sex and staging, a multivariate model for BARD1 was estimated by Cox regression. Pairwise comparisons show a significant difference in survival probability for patients with low expression of BARD1 (Expr.1) versus patients with intermediate or high expression of BARD1 (Expr.2, Expr.3) supporting the potential usefulness of BARD1 as a predictive biomarker.

In patients with stage II and III disease, expression of full-length BARD1 protein showed a significant difference in survival with weak expression predicting a worse prognosis. Interestingly, there was a significant difference in survival comparing stage II and III within the group of intermediate/strong BARD1 expression (Figure 3C).

In summary, we have shown that expression of BARD1 can predict outcome in colon cancer patients. This suggests an important role of the BARD1/BRCA1 pathway in colon cancer and identifies BARD1 as a novel tool for risk stratification. Moreover, we analyzed the occurrence of BARD1 splice variants, characterized novel splice variants and quantified the mRNA expression of BARD1 isoforms in colon cancer samples and matched normal colon tissue. We found 19 distinct BARD1 splice variants, of which 11 have not been described before. These splice variants

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Table 1: Structural characterization of BARD1 splice variants. All variants and full-length are detected by the primer pair spanning exon 10/11. For loss of domains expected with each variant, see \(^6\).
Figure 2A: Quantitative real-time PCR analysis of BARD1 splice variants. Expression of splice variants were quantified by qPCR, transformed to relative quantities and normalized to the total BARD1 transcript of the same sample. % expression of cancer vs. matched normal samples for the six most abundant splice variants was plotted, indicating the standard deviation within the 15 samples and significant (p<0.05) expression differences (**) as determined by t-test (right panel).

Figure 2B: Direct quantification of BARD1 splice variants using pooled cDNA from 16 different human tissues shows a tissue specific expression pattern of BARD1 splice variants. The percentage expression for the six most abundant splice variants (>1% of total BARD1 transcript) was plotted.

Figure 2C: BARD1 splice variants show distinct expression patterns in colon cancer compared to normal tissue. The six most abundant splice variants were addressed in further detail (4a/5, 2/4, 3/5, 2/5, 1/4, 1/5).
account for a significant amount of the total BARD1 mRNA either in colon cancer and normal colon samples and distinct splice variants show a cancer specific regulation pattern in the 6 most abundant variants. Further, splice variant mRNA is associated with polysomes, indicating ongoing translation.

Investigations under way aim at deciphering functions of individual splice variants as well as their respective contribution to both full length BARD1 expression and function in colon cancer.

References
Expression of RORγt Marks a Pathogenic T-Regulatory Cell Subset in Human Colon Cancer

Nichole R. Blatner, PhD1, Mary F. Mulcahy, MD2, Kristen L. Dennis1, Denise Scholtens, PhD3, David J. Bentrem, MD4, Joseph D. Phillips, MD4, Soo Ham1, Barry P Sandall1, Mohammad W Khan BVSc, PhD1, David M Mahvi, MD4, Amy L Halverson, MD4, Steven J Stryker, MD4, Anne-Marie Boller, MD4, Ashima Singal1, Rebekka K Sneed1, Bara Sarraj, PhD5, M. Javeed Ansari, MBBS5, Martin Oft, MD7, Yoichiro Iwakura, DSc8, Liang Zhou, PhD9, Andreas Bonertz10, Philipp Beckhove, MD1,10, Fotini Gounari, PhD, DSc11, Khashayarsha Khazaie, PHD, DSc1,5*

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Tregs that expand in human colon cancer have pro-inflammatory properties and contribute to tumor progression.

T-regulatory cells are attractive targets for immune therapy of cancer. Foxp3+ T-regulatory cells (Tregs) have potent immune suppressive properties, expand in pre-neoplasia and cancer, have preferential access to tumors, and can hinder anti-tumor CD8 T-cell responses in a TGF-β dependent manner (Chen et al., 2005; Khazaie and von Boehmer, 2006; Klein et al., 2005; Klein et al., 2003). Interestingly, they have significant differences with effector T-cells in their T-cell receptor (TCR) repertoire and therefore tend to recognize different antigens than effector T-cells (Bonertz et al., 2009; Cabarrocas et al., 2006; Khazaie et al., 2009). These observations render Tregs attractive as targets for immune therapy of cancer.

There is however much controversy about the role of Tregs in cancer. A particular case to consider is colon cancer. Colon cancer patients elicit pre-existing CD8+ T-cell responses that recognize and can eliminate tumor cells in an antigen specific manner (Bonertz et al., 2009; Khazaie et al., 2009). Infiltration of colon cancer tumors with lymphocytes is an independent predictor of longer patient survival (Galon et al., 2006). These observations have raised hope that immune surveillance can keep tumor cells at bay and vaccination can eradicate colon cancer (Khazaie et al., 2009). One might
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think that eliminating Tregs in colon cancer would be beneficial, and indeed there are reports that high densities of tumor infiltrating Tregs correlate with poor clinical outcome in colon cancer (Sinicrope et al., 2009). But, more recent findings challenge this view and suggest that higher densities of Tregs in tumors correlate with better clinical outcomes in human colon cancer (Correale et al., 2010; Salama et al., 2009) and in several other cancers (Badoual et al., 2006; Haas et al., 2007). These new observations are in line with the role of Tregs in controlling inflammation, particularly at mucosal surfaces, which are boundaries to the outside and separate us from the microbial world. The anti-inflammatory property of Tregs is strictly IL-10 dependent (Asseman et al., 1999). Expression of IL-10 by Tregs is required for suppression of the so-called T-helper-17 (TH17) response (Chaudhry et al., 2011; Huber et al., 2011), the major pro-inflammatory T-helper response that is characterized by elevated levels of the cytokine IL-17, and for suppression of polyposis (Erdman et al., 2003b; Serebrennikova et al., 2012). Interestingly, TH17 response while being critical for control of microbes is also a hallmark of inflammatory bowel diseases, polyposis, and colon cancer; several studies including work from our lab suggest that TH17 cytokines are causatively linked with predisposition to and progression of colon cancer (Wilke et al., 2011) (see below).

Chronically elevated inflammation predisposes to colon cancer (Khazaie et al., 2011), and non-steroidal anti-inflammatory agents help prevent colon cancer (Jacoby et al., 2000; Steinbach et al., 2000). Furthermore, inflammation is an inherent response to cancer and contributes not only to tumor initiation but also to progression (Coussens and Werb, 2002; Luster et al., 2005). Our previous work has detailed the contribution of mast cells and TH17 inflammation to pre-neoplasia and cancer of the small intestine and colon (Gounaris et al., 2009b; Gounaris et al., 2007; Gounaris et al., 2008). TH17 cytokines are elevated in mouse polyposis and human colon cancer (Blatner et al., 2010; Gounaris et al., 2009a). TH17 cells are a subclass of CD4+ helper T cells that express the transcription factor retinoic orphan nuclear receptor-γT (RORγT) and produce IL-17A (Korn et al., 2009; Littman and Rudensky, 2010; Weaver et al., 2006). Expression of IL.17 is contingent upon activity of the transcriptional factors RORγT (Ivanov et al., 2006), RORα (Yang et al., 2008b), and KLF4 (Lebson et al., 2010). Differentiation of TH17 cells occurs in the presence of key pro-inflammatory cytokines, TGFβ, IL6, IL1β, IL23 and TNFα (Bettelli et al., 2006; Manel et al., 2008; Mangan et al., 2006; Yang et al., 2008a). TH17 cells are generated in the duodenum (Esplugues et al., 2011) and migrate in response to chemokines to the colon, where they stimulate inflammation and control microbiota at mucosal surfaces.
IL-17 produced by TH17 cells stimulates production of other pro-inflammatory cytokines IL-6, TNFα, and IL-1β, chemokines, prostaglandin E₂, nitric oxide and metalloproteinases from various tissues and cells and mobilize inflammatory cells. It is this ability to induce a robust inflammatory response that allows the TH17 cells to compensate for the inability of other major types of T-helper responses, TH1 (that is characterized by the cytokine INF-γ and stimulation of cytotoxic T-cells) and TH2 (that is known for helping antibody responses) to clear certain pathogens (Korn et al., 2009). Persistent TH17 inflammation predisposes to inflammatory bowel diseases (Dubinsky et al., 2007; Duerr et al., 2006; Maloy, 2008; Rioux et al., 2007), and infiltration of tumors with IL-17 expressing lymphocytes negatively correlate with patient survival in colon cancer (Tosolini et al., 2011). Ablation of IL-17A or IL-17F protect mice against polyposis (Chae and Bothwell, 2011; Chae et al., 2010).

The two distinct properties of Tregs, their ability to suppress other T-cells and also suppress inflammation, make their role in colon cancer uncertain. An additional complexity is the ability of Tregs to change properties and emerge as the very inflammation promoting cells that they normally suppress, the TH17 cells (Bailey-Bucktrout and Bluestone, 2011; Hovhannisyan et al., 2011; Parisinos, 2011). This plasticity of Tregs allows for rapid and robust changes in the level of inflammation when needed, but is highly deleterious when it happens in the context of tissue damage and cancer. Molecular mechanisms responsible for Treg plasticity remain to be elucidated.

Different sub-sets of T-regulatory cells can protect or promote colon cancer. The protective role of Tregs in colon cancer is supported by observations in mouse models. Adoptive transfer of Tregs from healthy mice protect against experimental colitis (Asseman et al., 2003), and against microbial induced colitis and cancer (Erdman et al., 2003a). Furthermore, Treg transfer also protects against polyposis in mice genetically predisposed to this disease; this protection is attributed to the ability of Tregs to suppress inflammation, including mast cells, macrophages, granulocytes, and to lower levels of TH17 cytokines, leading to active regression of polyps (Gounaris et al., 2009a) (Figure 1). However, a confounding fact is that endogenous Tregs expand and home to polyps in mice without any apparent detrimental effect on the polyps. Obviously, there must be functional differences between Tregs isolated from healthy versus polyp-ridden mice. Indeed, Tregs isolated from poly-p-ridden mice not only do not suppress inflammation and polyposis, but even have a tendency to do the opposite (Gounaris et al., 2009a) (Figure 2). These cells are clearly Tregs, by virtue of their expression of the transcriptional factor Foxp3 and suppression of proliferation of ex vivo stimulated CD4⁺ T-cells; however, they differ from Tregs that abound in healthy mice by their expression of the transcription factor RORγt, their inability to produce IL-10, and their tendency to express IL-17 (Gounaris et al., 2009a). Interestingly, we can recapitulate this Treg phenotype by co-culture of Tregs with mast cells (Colombo and Piconese, 2009; Khazaie et al., 2011). This may not be coincidental, as mast cell progenitors are sentinel cells that are activated in response to pathogens as well as the cancer-initiating event (loss of APC) in gut epithelial cells. These are in effect the very first pro-inflammatory cells that appear in aberrant crypts as early as 2.5 weeks after stabilization of β-catenin in

![Figure 3: Impact of TH17 cytokines on polyposis. (A) APC⁶⁻⁶ mice were reconstituted with bone marrow (BM) from control IL6, IL23, IL17A, TNFα, or RORγt defective mice, then aged to 4-months.](image)
intestinal epithelial cells, and persist as lesions progress to invasive cancer (Gounaris et al., 2007). TH17 cytokines are causatively related to polyp-formation as genetic ablation of these cytokines protect in a hierarchal manner against polyposis (Figure 3A). Expression of RORγt by T-lymphocytes is essential for cancer associated inflammation, in part because of the role of this transcription factor in TH17 commitment of T-cells but also and perhaps more importantly because RORγt is responsible for gain of pro-inflammatory properties by Tregs. Indeed, the best protection in mouse models of polyposis was provided by bone marrow or even Treg specific ablation of RORγt (Figure 3A) (Blatner et al, Science Translational Medicine, 2012, in press). It is the compromise of Treg functions that opens the gates to uncontrolled inflammation in the tumor microenvironment.

Interestingly, the IL-17 deficient chimeras tell us that there is more to be learned about the quality of inflammation and cancer since these mice had fewer benign polyps but more invasive cancers, which was not the case for RORγt defective mice that were truly protected (Figure 3B). A novel first generation RORγt inhibitor reduced polyp counts in APCΔ468 mice, treated for two weeks, opening the path to clinical trials targeted at Treg plasticity in cancer. We conclude that expression of RORγt by Tregs is causatively related to cancer.

Expansion of RORγt expressing Tregs and deregulation of inflammation in colon cancer. Colon cancer patients have elevated levels of circulating and tissue infiltrating Tregs. However, these cells are unable to control inflammation, while remaining potently T-cell suppressive (Blatner et al., 2010). The dual properties are attributed to the co-expression of the transcription factors Foxp3 and RORγt. In effect, Tregs that expand in colon cancer have TH17 characteristics. This is a turning point that selectively compromises the ability of Tregs to control inflammation, thus promoting cancer.

Unlike mice where expression of Foxp3 strictly identifies suppressive cells, in humans Tregs express Foxp3 transiently upon activation. To distinguish Tregs, a novel scheme subdivides human Foxp3⁺ cells into resting Tregs (rTreg/Fr.I=CD4⁺CD45RA⁻Foxp3int⁺), activated Tregs (aTreg/Fr.II=CD4⁺CD45RA⁺Foxp3high⁺), and activated T-cells (Fr.III =CD4⁺ CD45RA⁻Foxp3int⁺) (Miyara et al., 2009). Using this scheme a minor Fr.II subpopulation that expresses IL17 in healthy donors (HD) was shown to expand in patients with sarcoidosis (Miyara et al., 2009), a TH17 driven disease (Parisinos, 2011). “IL17 expressing Tregs” have been also reported by others (Beriou et al., 2009) and expand in the inflamed mucosa of human tonsils (Voo et al., 2009) and in Crohn’s disease (Hovhannisyan et al., 2011). Using this scheme we could show that expansion of Treg cells in colon cancer patients is accounted for by proliferation of aTreg/Fr.II and that frequencies of RORγt⁺IL17⁺ Tregs in this fraction are significantly elevated in a large number of colon cancer patients (Blatner et al., 2010) (Blatner et al Science Translational Medicine, in press). These patients have compromised Treg functions, with preferential loss of anti-inflammatory properties.

To test Treg properties in cancer, we obtained peripheral blood (PB), from 94 individuals with stages I-IV non-mismatch repair sporadic colon cancer who were undergoing surgical resection. Blood samples were obtained at seven different time points before and after surgery (T1-T7), and from 23 healthy individuals. When we subdivided Foxp3⁺ lymphocytes into fractions (Fig. 4A) it became clear that aTreg/
Fr.II Tregs preferentially expanded in colon cancer and that in the majority of patients tested, this Treg subset expressed the signature TH17 transcription factor RORγt, and IL17 (Fig. 4B and C). By contrast IL10 expression by Tregs was diminished in colon cancer (Fig. 4D). Observing such significant changes in the peripheral blood of cancer patients was encouraging for the use of this Treg subset as a biomarker for cancer. This notion was strengthened by follow up studies of patients post surgery. After surgery, Treg frequencies generally returned to physiological levels and Tregs recovered both their IL10 expression and their anti-inflammatory properties, suggesting that expansion of Tregs and in particular of RORγt+ Tregs is tumor dependent. Thus far, one patient who showed high post surgery Treg counts, has had a recurrence; over 80% of this patient’s Tregs were RORγt+.

Prospects.
Our observations suggest a vicious cycle in cancer whereby inflammatory cues induce expression of RORγt by Tregs, whose altered properties then in turn support inflammation and promote tumor growth. Understanding these events will provide new opportunities for cancer prevention and therapy. We are pursuing these studies with gene expression analysis of the altered Tregs to find additional markers and key fate determining molecules. Our pilot studies show that inhibitors of RORγt can prevent polyposis in mice genetically predisposed to develop polyps. Furthermore, these inhibitors allow recovery of anti-inflammatory properties of Tregs isolated from cancer patients. These findings open the path to clinical trials with these inhibitors for treatment of solid tumor cancers.

Acknowledgments.
Dr. Nichole Blatner (Res Assistant Professor) and Ms Kristen Dennis (PhD student) are to be credited for the presented work. Translational studies were made possible because of intense interest and cooperation of clinical colleagues, most notably daily interactions with Dr. Mary Mulcahy (GI Oncology) and Dr. David Bentrem (Surgical Oncology). Dr. Steve Rosen is kindly acknowledged for relentless support and encouragement of our research. The presented work was funded by the Cancer Center and by NIH1R01CA160436-01.

References


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Gold Nanostars as Delivery Vehicles for Nuclear-Targeted Therapeutics

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Conventional cancer treatments, including surgery, radiation, and chemotherapy, often cause severe side effects and require long recovery times.¹, ² Targeted cancer therapy has been shown to reduce some adverse effects by delivering anticancer agents directly to the cancer cells based on surface-receptor recognition.¹, ³⁻⁵ Currently, monoclonal antibodies (mAbs) are the most utilized targeting chemotherapeutic agents;⁶ they take advantage of surface-receptor recognition of epidermal growth factors and insulin-like growth factors to deliver drugs across the plasma membranes of cancer cells.⁴, ⁵ Despite their recognition abilities, mAbs have several drawbacks, including poor tumor uptake, increased immunogenicity, and uncontrolled drug release.⁷ Although targeted therapy holds potential to improve traditional cancer therapeutics, two major barriers must be overcome: (1) pre-mature degradation and fast clearance of anti-cancer agents in vivo; and (2) the low overall concentration of drugs reaching the intended targets.

Recently, nanoparticles (NPs) have been explored as one approach to overcome challenges in molecular targeting.¹, ⁸, ⁹ Due to their high surface-to-volume ratios, a large density of targeting ligands and drug molecules
can be attached to the particle surface or contained within the inner core.\textsuperscript{8, 10} The tight packing of ligands on the NP surface (1) stabilizes the anti-cancer agents, (2) reduces the susceptibility of the ligands to degradation in physiological environments, and (3) allows for high local drug concentrations to be delivered directly to cancer cells.\textsuperscript{8, 9, 11} The most popular NP drug carriers are made from polymers, which are in phase I and II clinical trials.\textsuperscript{1} Other work on NP targeted therapeutics has focused on drug carriers such as DNA assemblies and gold NPs. For example, self-assembled DNA tetrahedra have been used to deliver small interfering RNA (siRNA) to cancer cells through folate receptors.\textsuperscript{12} A major advantage of these structures is that their sizes (>20 nm) are large enough to prevent renal filtration yet small enough to penetrate leaky tumor vasculatures.\textsuperscript{1} Gold NPs have also been considered as delivery vehicles because of their low biological activity and toxicity.\textsuperscript{13} Similar to DNA-based carriers, the gold particle sizes can be tailored to prevent filtration and optimize tumoral uptake.\textsuperscript{13}

The two most important organelles are the mitochondrion and the nucleus because they control major biological activities of the cell.\textsuperscript{14, 15} Because the inner mitochondrial membrane is impermeable, however, the nucleus is a more attractive target.\textsuperscript{16-18} Small drug molecules can penetrate the nuclear envelope (NE) via transport through nuclear pore complexes (NPCs) and cause DNA damage and cell cycle arrest.\textsuperscript{15} Nuclear targeting introduces additional requirements for NP-based therapeutics, such as (1) the drug-loaded NPs must be smaller than the size of the NPCs (~50 nm) and (2) the drugs should be released near or inside the cancer cell nucleus. To date, there have only been a few examples of particle platforms used for intracellular targeting. Polymer NPs have been used to release drugs into the nucleus using a pH triggered swelling mechanism.\textsuperscript{19-22} Noble metal NPs functionalized with nuclear and cytoplasmic targeting peptides have been shown to disturb the cell cycle and to result in apoptosis and cell death.\textsuperscript{23, 24} Porous silica NPs have also been used for intracellular release of chemotherapeutic agents.\textsuperscript{25} Although these nanocarriers have shown progress toward nuclear-targeted drug delivery, there is still

Figure 1: Nucleolin-mediated transport of Apt-AuNS to the cancer cell nucleus. (A) Scheme of nanoconstruct consisting of nucleolin-specific aptamers AS1411 (Apt) and gold nanostars (AuNS). (B) TEM images of different AuNS. (C) Scheme highlighting three key steps of intracellular delivery from (1) binding of Apt-AuNS to surface nucleolin receptors; (2) transport of Apt-AuNS by nucleolin to locations near the cell nucleus; and (3) interactions with the nuclear envelope. Adapted with permission from ref. 26, (2012) American Chemical Society.
little control over drug release and a lack of understanding in how these drug-loaded NPs interact with the nucleus.

Drug-loaded gold nanostars: nanoconstructs designed to target the cancer cell nucleus

We have developed a drug-stabilized, nuclear delivery system that combines the properties of aptamers (Apt) and gold nanostars (AuNS) for on-demand release of drug molecules. This nano-construct (Apt-AuNS) enables a general strategy for drug delivery in different cancer cell lines. For our first studies, we selected Apt as the single-stranded DNA aptamer AS1411 (26 mer, 7.8 kDa) because of its cancer targeting and therapeutic abilities; the drug is currently in trials for acute myeloid leukemia and renal cancers.26-28 AS1411 targets cancer cells by binding with high affinity (Kd is in the pM to low nM range) to nucleolin, a nucleolar protein overexpressed on the surface of rapidly dividing cells.29-31 After binding, the aptamer blocks functions of nucleolin and results in arrest of DNA repair as well as destabilization of bcl-2 mRNA.29, 32 To synthesize the Apt-AuNS nanoconstruct, we loaded approximately 1000 AS1411 strands on the AuNS surface via thiol linkages.26 Once bound to nucleolin, the construct can exploit the shuttling properties of the protein and be transported from the cell membrane to locations near the nucleus (Fig. 1).31, 33

The unique chemical and physical properties associated with the AuNS make these particles ideal not only as drug carriers but also as imaging markers in transmission electron microscopy (TEM).26 Therefore, we could directly visualize how drugs loaded on NPs affected sub-cellular structures. TEM analysis indicated that Apt-AuNS often clustered within vesicles located a few microns from the nuclear membrane. When this distance was less than ca. 1 μm, the constructs caused folds in the NE that intruded into the nucleoplasm (Fig. 2A). Extremely deformed nuclei were found in over 60% of HeLa cells incubated with the Apt-AuNS construct, and over 80% of the folds correlated with the location of the Apt-AuNS near the cancer cell nucleus.26 NE folding was only observed in cancer cell samples treated with Apt-AuNS, which confirms that Apt were primarily responsible for the NE deformations. In control experiments, we tested AuNS loaded with aptamers not specific for nucleolin (cApt) and found no deformations in the nucleus.

Drug delivery and light-triggered release of AS1411 from AuNS nano-carriers

Besides the physical effects observed in TEM images, anti-cancer effects from the targeting of Apt-AuNS near the nucleus can be measured using biochemical assays that test for apoptosis, double-stranded DNA damage, and cell viability. Although the drug-stabilized nanoconstruct resulted in only minimal DNA damage within the cell nucleus (Fig. 3A), an increase in apoptosis (Fig. 4) and a 25% decrease in cancer cell viability (Fig. 5) was observed. There was no increase in apoptosis or cell death when HeLa cells were subjected to a control aptamer nanoconstruct (cApt-AuNS) that did not target nucleolin. In another control experiment, non-cancerous MCF-10A cells treated with the same concentration of Apt-AuNS ((M)Apt-AuNS) did not exhibit any adverse effects. To determine whether the anti-cancer effects could be enhanced, we used ultra-fast (femtosecond, fs) laser pulses at the localized surface plasmon (LSP) resonance34 of the AuNS to release the
AS1411 from the nano-carrier. For *in vitro* and *in vivo* release, the LSP wavelength needs to occur within the biologically transparent optical window (650-850 nm). We designed the size and shape of the AuNS to produce an optical resonance (780 nm) within this range; the sharp tips readily concentrate the light and facilitate Apt release from the AuNS.

Femtosecond laser pulses centered at 800 nm were used to irradiate Apt-AuNS/cancer cell samples for 2 s. This irradiation time is much shorter than previous reports (6 min) that relied on heat-induced release of molecules using continuous-wave irradiation.\(^{34-36}\) After exposure, release of Apt from the AuNS produced a partial deterioration of the vesicle membrane surrounding the Apt-AuNS and an increase in number of cells displaying NE folding. TEM images revealed that more than 95% of the cells containing Apt-AuNS showed NE folding immediately after irradiation (Fig. 2B).

Possible disruption of nuclear function was tested by an immunoassay that uses fluorescently tagged antibodies to indicate double-stranded DNA breaks. The assay showed multiple foci of DNA breaks in the cell nucleus (Fig. 3B), indicating that the released Apt was delivered into the nucleus, most likely via the nucleolin shuttle. Also, elevations in the markers for both apoptosis and cell death were higher compared to the Apt-AuNS without Apt release. There was a 1.5-time increase in caspase 3 and 7 activities (Fig. 4) and an increase in cell death immediately after irradiation (Fig. 5). Further analysis showed that >70% of the population died between 48-72 h after the initial release of AS1411.\(^{26}\)

To verify that the Apt-AuNS formulation increased the efficacy of AS1411, we carried out a side-by-side comparison of the therapeutic efficacy of the drug-loaded NS (0.3 nM) and equal concentrations of free Apt (450 nM). The latter was determined based on the number of aptamers attached to each AuNS and the concentration of AuNS. We found that aptamer released from the surface of the AuNS produced similar apoptosis and viability results as clinical dosages of free AS1411 (10 μM). Therefore, the Apt-AuNS platform is desirable for delivering high local concentrations of anti-cancer drugs that can maximize therapeutic efficacy.
Conclusions and next steps
In summary, we have developed a nanoconstruct that opens up new opportunities in nuclear-targeted therapy. The Apt-AuNS drug delivery platform followed by light-triggered drug release provides the basis for a flexible carrier design in which internalization of NPs inside the nucleus may not be required to disrupt nuclear function. Thus, size constraints relative to the NPC opening can be lifted. Moreover, light-triggered release of drug without damaging surrounding subcellular components has resulted in on-demand delivery at specific intracellular locations. Our future work will investigate the generality of the nucleolin shuttling mechanism which, if positive, would have important implications for how nuclear-targeted therapy can be tested in multiple cancer cell types.

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The discipline of integrative medicine has evolved over the past several decades in response to patient interest, expanding scientific evidence and socioeconomic forces. In 1993 the landmark publication by Harvard researcher David Eisenberg informed the medical community for the first time that approximately one third of their patients were engaging in some form of complementary and alternative medicine (CAM). The even greater percentages documented in the follow up survey as well as the expansive 2007 National Health Interview Survey study reinforced that consumer interest in these approaches is robust and growing. The field of integrative medicine aims to provide CAM services in a way that ensures safe and appropriate access for patients.

The Consortium of Academic Health Centers for Integrative Medicine defines Integrative Medicine as “the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals, and disciplines to achieve optimal health and healing.” Integrative medicine treatment plans often incorporate complementary health practices, which can be defined as a group of diverse medical and health care systems, therapies, and products whose origins come from outside of mainstream medicine. Examples of complementary therapies include natural...
products, such as dietary supplements, herbs, and probiotics, mind/body practices, such as meditation, acupuncture, and massage.

A growing number of complementary practices are being recognized for their beneficial role in cancer treatment – not as a substitute for conventional cancer treatment, but rather as an enhancement of conventional treatment, supporting the patient throughout the healing process. Research now supports some approaches for ailments such as cancer-related pain, psychological distress and cancer and treatment related symptoms. Indeed surveys of cancer populations have recorded incidences ranging from 10 to >80% engagement in CAM.5-10 Patient motivations for using CAM with their cancer care include a desire to reduce symptoms, support the immune system, relieve pain and, significantly, gain a sense of control over their own care. However, many patients rely on unsubstantiated claims or questionable recommendations, raising concerns about adverse reactions or interference with conventional medical therapy. The Society for Integrative Oncology published practice guidelines to help healthcare professionals make evidence-based treatment decisions in integrative oncology with recommendations based on the strength of the evidence and the risks/benefits ratio.11 To help address the need for reputable information and expert guidance in our community; Northwestern Integrative Medicine and the Robert H. Lurie Comprehensive Cancer Center have partnered to create a multi-faceted integrative oncology program.

About Northwestern Integrative Medicine
Since 1998, Northwestern Integrative Medicine (formerly the Center for Integrative Medicine and Wellness) has offered Northwestern Medicine and the community a holistic approach to patient care. NIM, is a division of the Northwestern Memorial Physician’s Group, is conveniently located in the Avenue Office Building at 150 E. Huron in a 10,000 sq. foot center designed to provide an optimal healing environment. The center provides care for patients with acute and chronic medical conditions using traditional and a broad array of complementary approaches including:

- Traditional Chinese Medicine (e.g. acupuncture, herbal therapy, tui na),
- Manual therapies (e.g. neuromuscular massage, craniosacral therapy, manual lymphatic drainage and chiropractic)
- Energy medicine including Reiki and Healing Touch
- Naturopathic medicine, functional medicine and registered dieticians
- A comprehensive movement therapy program including yoga, Nia and Zumba
- Counseling on dietary supplements

The center is staffed by eight physicians and advance practice nurses, including 3 integrative medicine fellowship-trained physicians; three clinical psychologists; three Traditional Chinese Medicine practitioners; four massage therapists; a chiropractor; a naturopathic physician; two registered dieticians; a smoking cessation counselor and a movement instructors. Integration of care occurs on many levels, including practitioner discussions with referring physicians, informal discussions in the center, and patient care conferences.

In addition to high-quality clinical care, Northwestern Integrative Medicine is committed to education and research. NIM faculty provides medical student, resident, nurse practitioner and continuing medical education. NIM additionally spearheaded the Northwestern Campus Collaborative for Integrative medicine, which hosts quarterly integrative medicine grand rounds for the whole medical campus. NIM is currently collaborating with several departments to perform research studies on quality of life issues related to use of complementary therapies.

The 360 Program in Integrative Oncology
The 360 Program, supported by a generous donation from Abra Prentice Wilkin, enhances the support of cancer patients through a “360-degree” approach to addressing the entirety of the patient: mind, body, and spirit. As part of this initiative, in early 2009, NIM began offering a broad range of integrative medicine services to cancer patients. The program has grown steadily, with hundreds of patients annually availing themselves of integrative services in the outpatient, inpatient and infusion suite setting. Through the 360
program, patients who are already receiving cancer services at Northwestern may receive two free treatments from the following: acupuncture, massage therapy, energy medicine (Reiki, Healing touch), or naturopathic medicine, as well as complimentary inpatient massage, and acupuncture and massage in the chemotherapy units.

Northwestern Integrative Medicine and the 360 Integrative Oncology program were recently highlighted in the 2012 report *Medicine in America – How integrative medicine is being practiced in clinical centers across the United States.*

For details about the 360 Integrative Oncology program see http://www.cancer.northwestern.edu/pdfs/Oncology_Cancer_Patient’s_Guide.pdf.

Close-Up on Services

**Acupuncture**
The traditional Chinese medical practice of acupuncture involves the stimulation or insertion of sterile ultra-fine needles into specific points on the surface of the body. This practice is an energy-based approach that attempts to restore balance in deficiencies throughout the body. Acupuncture affects the organs and their function to treat a variety of exogenous and endogenous pathologies. Acupuncture can be used specifically in cancer patients to relieve several symptoms that accompany treatments including: vomiting, nausea, xerostomia, neuropathy, immune function, insomnia, anxiety, depression, fatigue, hot flashes, constipation, and diarrhea. Minimal side effects are associated with acupuncture. Much evidence-based research bolsters acupuncture’s effectiveness in treating cancer patients. Along with many other studies, acupuncture has been found to be an effective treatment for aromatase inhibitor induced joint pain and stiffness. In 1997, the National Institutes of Health Acupuncture Consensus Panel determined acupuncture to be an effective treatment for nausea and vomiting in chemotherapy patients, a finding confirmed in a 2010 Cochrane review. Currently NIM and the Department of Social Sciences are conducting a research study to quantify acupuncture benefits for a variety of quality of life measures in cancer patients.

**Massage**
Massage is a type of manual therapy in which the practitioner uses his or her hands to manipulate soft tissue in order to produce global health improvement throughout the body. Many cancer patients can benefit greatly from massage therapy, as it aids in management of symptoms such as anxiety, pain, lymphedema, restlessness, insomnia, musculoskeletal discomfort, stress, and fatigue. A multi-site, randomized control trial conducted by Kutner et al. showed immediate, statistically significant results of decreased pain and improved mood in cancer patients after receiving massage. The study also suggested massage to be more effective than simple touch. Another randomized controlled trial in breast cancer patients undergoing chemotherapy found massage to decrease nausea. Massage has little to no adverse effects, and the few contraindications include open wounds, burns, or tumors. Massage acts as a great support to conventional care in reduce many symptoms, especially pain and anxiety.

**Energy Medicine**
Energy medicine is a broad field of practice where the practitioner manipulates putative universal healing energy to promote patient healing and wellness. Reiki, a form of energy medicine originating 2000 years ago in Japan, is a non-invasive, hands-on practice where the practitioner places his or her hands lightly on or above different parts of the body and allows energy to flow to areas of imbalance. Healing Touch is a similar form of energy medicine developed by Janet Mentgen, RN around 30 years ago. While these two forms of energy medicine are offered through the 360 program and NIM, all forms of energy medicine may help cancer patients with pain, anxiety, depression, nausea, as well as helping recovery and generating overall wellness. A study done on newly diagnosed patients with gynecologic cancers showed statistically significant results that Healing Touch improved pain, functioning, and overall vitality compared to a mock-treatment. There is very little risk of adverse side effects of energy based therapies.

**Naturopathic Medicine**
Naturopathic medicine is a medical system of healing available through the 360 program at NIM. Naturopathic medicine is based upon the body’s innate ability to heal itself and the belief the body is one interrelated system.
Naturopathic doctors focus on the underlying causes of diseases and collaborate with other physicians to find the best possible treatment for the patient. Often naturopathy includes diet, exercise, herbs, homeopathy, hydrotherapy, and counseling in adjunct to conventional treatment. Similar to many other integrative treatments, naturopathy helps manage symptoms and side effects from chemotherapy and radiation treatments. Naturopathy is often used in weight control, immune support, hot flashes, sleep issues, nerve pain, gastrointestinal symptoms, and anxiety and depression. By treating the patient as a whole and throughout patient education, naturopathy not only aims to heal the patient while receiving cancer treatments, but also prepares the patient to get back to daily life after disease.

Other services
Anxiety, stress, depression, and fatigue frequently accompany disease, and are especially prevalent in cancer patients. Coping with a serious disease such as cancer often leave patients distraught and emotionally overwhelmed. Although not offered through the 360 program, NIM does offer mind-body medicine classes to address the emotional and mental components of cancer. A May 2012 study on breast cancer patients who had undergone chemotherapy or radiation treatment showed a 40% decrease in fatigue scores.20 Mind-body medicine can serve as an extremely effective adjunct to cancer treatment, aiding in healing and supporting conventional treatment.

For patients seeking assistance in developing an integrative treatment plan before, during or after their conventional treatment is complete, NIM offers comprehensive physician consults by physicians fellowship-trained in integrative medicine.

Patient Care Symposium in Integrative Oncology
Northwestern Integrative Medicine and the Lurie Cancer Center presented the second biennial Integrative Oncology Patient Symposium on Saturday October 20th, 2012. Patients as well as clinical staff were invited to attend this free event, supported by philanthropy, to learn through informative talks on holistic approaches to health and participate in integrative workshops including mindfulness meditation, Traditional Chinese Medicine, mindful eating, nutrition, qi Gong, music therapy and yoga. The Keynote Speaker was Dr. D. Barry Boyd, Integrative Oncology Expert and Author of “The Cancer Recovery Plan: How to Increase the Effectiveness of your Treatment and Live a Fuller, Healthier Life” and “The Missing Link: Insulin and Cancer.”

Conclusion
The field of integrative oncology has been described as both a science and a philosophy that focuses on the complex health of people with cancer and proposes an array of approaches to accompany the conventional therapies of surgery, chemotherapy, molecular therapeutics, and radiotherapy to facilitate health.21 When symptoms stemming from conventional treatment as well as emotional and mental distress are addressed, the patient is better equipped for the challenges of their cancer journey. Engaging in an integrative approach can help patients and their families feel more empowered to make a difference in their outcome.

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Cancer Disparities Research Network: Improving Minority and Underrepresented Populations Access to and Involvement in Biospecimen Research

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Building on the principles of team science, the National Cancer Institute’s (NCI) Center to Reduce Cancer Health Disparities (CRCHD) funded the Geographic Management Program/Biospecimen Management Program (GMaP/BMaP) Network. This Network is a regional strategy to build critical “hubs” for the support and efficient management of cancer health disparities research, training and infrastructure programs. The goals of this five region initiative (Figure 1) are to advance the science of cancer health disparities in these regions; contribute to the next generation of cancer health disparities researchers; and achieve measurable reductions in cancer health disparities in these regions. BMaP, the biospecimen arm of this network strategy, under the leadership of Northwestern University, seeks to improve the participation of minority and marginalized populations in biospecimen research while also improving biospecimen scientists’ integration of minority and underserved populations into their research.

The Cancer Disparities Research Network (CDRN) (see Table 1 for CDRN Partners), originally convened as the Region Five GMaP/BMaP Network, brings together community-engaged researchers, NCI’s Continuing Umbrella of Research (CURE) trainees, basic scientists, biospecimen experts, pathologists, bioinformatics researchers, community health educators, community members and organizations. CDRN aims to create transdisciplinary teams of scientists not only...
working with each other in their own fields, but across disciplines combined with trainees and outreach to underrepresented communities to eradicate cancer disparities. CDRN has conducted a regional needs assessment to evaluate current practices, resources and needs of each participating institution using a community-engaged approach. The BMAP component of the assessment sought to assess minority biospecimen collection, biobanking practices, and education and outreach initiatives. This paper describes the development of the Cancer Disparities Research Network, presents key high level findings from the Comprehensive Needs Assessment’s Biospecimen Facility Survey and follow-up interviews with biospecimen facility administrators to describe a few of the opportunities for collaboration that can be leveraged to support cancer health disparities research.

Development of the Cancer Disparities Research Network Partnership
CDRN was established in the fall of 2009, initially bringing together twelve CRCHD-funded institutions committed to supporting the objectives of BMaP. Over the last two and half years, our membership has increased by 9 additional NCI-funded institutions. A Coordinating Committee (CC) composed of Principal Investigators (PIs) represented in the Region have provided the expertise to several core and elective areas, participated in the NCI-developed Readiness Assessment Tool (RAT), guided the development and implementation of the regional Comprehensive Needs Assessment Tool (CNAT), and established strategic direction for our partnership. In the spring of 2011, our membership also formalized our region’s network by establishing the name Cancer Disparities Research Network to ensure the sustainability of our efforts beyond the CRCHD funding period. The institutions represented in the network comprise 6 cancer centers, 3 minority-serving intuitions, and 12 academic partners. Region Five originally spanned the states of Minnesota, Illinois, Michigan, Ohio, New York, Pennsylvania, Massachusetts, New Jersey, since June 2012, the Region now includes: North and South Dakota, Iowa, Wisconsin, Indiana, Connecticut, and Rhode Island (Figure 1).
Comprehensive Needs Assessment- The Biospecimen Facility Survey

The CNAT was developed to identify strengths and weaknesses in order to establish short and long term objectives to identify opportunities for collaborative research. This regional assessment consisted of qualitative and quantitative data composed off our instruments: a Principal Investigator survey, PI semi-structured interviews, Biospecimen Facility survey, and Biospecimen Administrators semi-structured interviews. This paper will focus on the BMaP component of the assessment- the Biospecimen Facility survey and Biospecimen Administrators interviews. Fox Chase Cancer Center, our GMaP counterpart, was responsible for the oversight of the Principal Investigator survey and PI semi-structured follow-up interviews. The development of the biospecimen facility survey and biospecimen facility interview instruments was spearheaded by the biospecimen/ biobanking core leader and supported by investigators with considerable experience partnering with communities to collect minority biospecimens for research. During the months of March to May 2011, the Biospecimen Facility Survey was completed online by 10 biospecimen facilities. From July to October 2011, the biospecimen administrator interviews were conducted over the phone with eight institutions.

The Biospecimen Facility Survey sought to assess minority biospecimen collection, biobanking practices, specimens available for research, and education and outreach initiatives from the institutions’ core perspective. The biospecimen administrator’s interviews were designed to follow up on key themes highlighted on the survey and help us to identify opportunities and challenges for collaborative health disparities research. The Fox Chase Cancer Center and Northwestern University Institutional Review Boards approved this study.

To analyze the biospecimen facility survey data, descriptive statistics were conducted and frequencies were generated. Each interview was transcribed and reviewed to extract common themes across our sample.

Table 1: Cancer Disparities Research Network Membership

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<tr>
<th>Institutions</th>
<th>Principal Investigator &amp; Core/Elective Leaders</th>
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<tr>
<td>Boston University*</td>
<td>Tracy Battaglia, MD, MPH</td>
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<td>Cancer Institute of New Jersey**</td>
<td>Shawna Hudson, PhD</td>
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<td>City College of New York*</td>
<td>Karen Hubbard, PhD</td>
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<td>Columbia University****</td>
<td>Mary Beth Terry, PhD</td>
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<td>Dana Farber- Harvard Cancer Center*</td>
<td>Karen Emmons, PhD &amp; Karen Burns White, MS</td>
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<td>Fox Chase Cancer Center*</td>
<td>J. Robert Beck, MD &amp; Linda Fleisher, PhD, MPH</td>
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<td>Harvard University*</td>
<td>VishViswanath, PhD</td>
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<td>Karmanos Cancer Center*</td>
<td>Terrance L. Albrecht, PhD</td>
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<td>Lincoln University*</td>
<td>Delroy Louden, PhD &amp; Anna Hull, PhD</td>
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<td>Mayo Clinic Cancer Center*</td>
<td>Judith S. Kaur, MD</td>
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<td>Memorial Sloan-Kettering Cancer Center *</td>
<td>Tim Ahles, PhD &amp; Francesca Gany, MD, MS</td>
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<td>Northwestern University*</td>
<td>Steven Rosen, MD, Melissa Simon, MD, MPH, Julian Schink, MD, June McKay, MD, MPH, JD, MBA &amp; Raymond Bergan, MD</td>
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<td>Ohio State University*</td>
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<td>Pennsylvania State University***</td>
<td>Eugene Lengerich, VMD, MS</td>
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<td>Roswell Park Cancer Center**</td>
<td>Deborah Erwin, PhD</td>
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<td>University of Mass Boston*</td>
<td>Adán Colón-Carmona, PhD</td>
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<tr>
<td>University of Pennsylvania***</td>
<td>Timothy Rebbeck, PhD</td>
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<td>* Original Partner Institution; ** New Partner Institutions- January 2011; *** New Partner Institutions- May 2011; **** New Partner Institutions- Spring 2012</td>
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Findings from the Biospecimen Facility Survey demonstrated the breadth of types of cancer specimens collected across Region Five. Overall, a total of 36 cancer types are collected by our biospecimen facilities. The most common cancer types include: breast, colorectal, lung, prostate, gynecologic (uterus, ovary, etc.), pancreatic, liver cancer, bladder, melanoma, and skin other than melanoma. While the majority of the facilities reported collecting age, gender, race, medical history, and ethnicity, less than half collect the patient’s family health history, education level, household income, and primarily language spoken. There was a lack of standardization in basic specimen annotation and collection of race and ethnicity data. In order to harness the full potential of samples, detailed patient and clinical information needs to be associated with the specimen, including standard operating procedures, pathological status, demographics, medical and family history, and clinical outcomes data. This gap in standardized annotated data provides opportunities for collaboration across Region Five sites to share and standardize patient information tools.

In reference to the specimens that were collected and available for research, significant differences in biospecimen collection among minority populations were reported. Among the seven sites who reported data, specimens were collected from a total of 130,457 patients; 89% of specimens were from White patients (116,417) and 11% from non-White patients (13,969) (Table 2). Seventy percent of facilities (n=10) indicated that specimens would be available for research.

In terms of infrastructure, all facilities indicated the use of electronic annotation systems for biospecimen collection. The wide range of data systems/platforms used across the institutions, however, has garnered support for standardization of electronic annotation systems. Related issues such as data reporting, data sharing and mining, data accessibility, and network security are critical areas that will be addressed in the next phase of planning the CDRN biospecimen network as well. Since bioinformatics and data management are a central component of any biobank, we will closely collaborate with bioinformatics directors and managers to identify commonalities and data systems that can be integrated to address our needs.

Among biospecimen facilities, multiple levels of collaboration and capacity to support collaborative research projects exist. These collaborations include partnerships with community-engaged researchers and G/BMaP partners to collect specimens for research collaboration. With regards to outreach and education, few education and outreach programs are aimed at promoting biospecimen collection in minority populations. At our second annual meeting, CDRN members voted to address this gap by agreeing to participate in a formative evaluation and adaptation of the Cancer 101 Biospecimens/Biobanking module. This community education module is focused on improving minority and underserved populations’ understanding of biospecimen research. Our effort to address this gap perfectly co-aligns with NCI’s Office of Biorepositories and Biospecimen Research’s strategic priority focused on the development of education communication tools and resources. In addition, there is encouraging evidence that racial and ethnic minorities in the U.S. are as willing as non-Hispanic whites to participate in health research. We will build on these findings and seek to strengthen relationships with our cancer centers, NCI Community Cancer Centers Program, and communities to provide information and resources to communities.

Overall, biospecimen facility directors and administrators reported barriers that limit their facilities from collaborating on collection programs. Despite these barriers, they expressed a high desire to work in partnership to collect additional specimens and/or share samples and viewed this collaboration as valuable resource for their institutions. For future collaborations, facilities indicated that it is necessary to identify which institutions or principal investigators have various interests to help identify expertise

<table>
<thead>
<tr>
<th>Race/Ethnicity*</th>
<th>Number of distinct patients</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>White</td>
<td>116,417</td>
<td>89%</td>
</tr>
<tr>
<td>African American</td>
<td>9,840</td>
<td>8%</td>
</tr>
<tr>
<td>Asian</td>
<td>1,920</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Latino</td>
<td>1,648</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>American Indian</td>
<td>466</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Native Hawaiian</td>
<td>95</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

*Race and ethnicity were not collected as two separate variables.

Table 2: Race/Ethnicity groups represented in Region Five Biospecimen Facilities (n=130,386).
and capacity for how we can contribute. One respondent indicated that, “Once we identify the main goals of each initiative; we can see how we can contribute and avoid redundancies. Complement strengths and weaknesses of the region. What we can do better and expedite, get things done that are complementary.” CDRN will build on the existing programs and the expertise of our community-engaged researchers to collect minority specimens both within their institutions and in community settings.

As a convenience sample, these data do not represent the entire biospecimen collection efforts of Region Five; however, they do shed important light on minority specimen collection efforts. Furthermore, for feasibility purposes, biospecimen facilities were asked to provide information that was easily accessible at the time of survey completion. Finally, these data only represent the opinions of academicians, researchers, and biospecimen facility leaders. In order to advance the science of cancer disparities, our next steps will include the community voice.

Next Steps and Future Direction for CDRN’s BMaP efforts

The CNAT’s Biospecimen Facility Survey and follow-up interviews yielded valuable information regarding Region Five’s current and potential capacity to collect and biobank minority biospecimens. Our Coordinating Committee has facilitated building relationships with biospecimen facilities and connecting us with biospecimen stakeholders to identify strengths and barriers to minority biospecimen collection and biobanking. The willingness among biospecimen facilities to collaborate shows promise for actively engaging community partners with biospecimen facilities in the next phase of development. CDRN can enhance the work of our respective facilities and research, including a willing to share specimens, best practices, and foster research ideas.

Similar to other community-engaged partnerships, building a multi-disciplinary regional research network and broadening our partnership involves many challenges. We have learned that considerable time and efforts are required to develop trusting relationships with stakeholders, such as biospecimen facility administrators, pathologists and basic scientists, with whom our Network does not have a previous history of collaboration. Utilizing our community-engaged approach, in the last year, we have conducted site visits at our partners’ institutions to formally meet pathology directors, facility administrators, biospecimen researchers, clinical trials administrators, and community-health educators, among others, to glean the expertise of the institutions and discuss opportunities and barriers for collaboration. Through these meetings, we have heard a resounding willingness to collaborate and a desire to meet other biospecimen stakeholders to set the stage for collaborative relationships. These site meetings will provide the platform to develop a regional BMaP road map intended to facilitate collaborative biospecimen research, education, and training in cancer health disparities across our region in tandem with our Region Five GMAP partner that will set the stage for the third annual Region Five GMaP/BMaP meeting.

Drawing upon our findings from the regional needs assessment and interviews, we will develop and pilot test a communication tool that bridges the interface of biospecimen study recruiters (e.g. clinical trial recruiters) with the patient, especially patients from underrepresented populations. The Cancer 101 Biospecimen/Biobanking pilot data will inform the communication tool. The goals of this communication tool are to: 1) support and optimize the study discussion and consent process, 2) lead to participation of more underrepresented and minority populations in trials, 3) help support biospecimen trial recruiters to improve minority and underrepresented population recruitment, and 4) empower the patient and increase satisfaction with trial participation.

Our immediate next steps are to continue to promote minority biospecimen collection efforts, and identify and invite the critical partners from the new states that joined Region Five, which include North and South Dakota, Iowa, Wisconsin, Indiana, Connecticut, and Rhode Island. We will also seek to build relationships with the CRCHD funded NCI Community Cancer Centers Program and incorporate community organizations into our network. A Community Advisory Committee has been proposed for CDRN to serve as an advisory capacity to CDRN’s BMaP efforts. This advisory committee will advise on all elements related to minority biospecimen collection efforts, including to help identify,
define, and address specific socio-cultural factors that intertwine with biospecimen collection and evaluate the perception of biobanking research among multi-ethnic communities. Lastly, Northwestern University will host our third annual Region Five GMaP/BMaP meeting in April 2013 that will bring together a broad group of biospecimen stakeholders to identify collaborative research opportunities.

References


Shared Resource Core Facilities

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.

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 Informatics Core Facility
Director: Warren Kibbe, PhD
312.695.1334 or wakibbe@northwestern.edu

The Cancer Informatics Core Facility provides microarray design and analysis support, including methylation arrays, SNP arrays, and gene expression arrays, support for investigators performing next generation sequencing, clinical research informatics services, as well as custom web-based database development for basic science and clinical projects.

Cell Imaging Core Facility
Director: Teng-Leong Chew, PhD
312.503.2841 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.

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 quadripole 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.
Clinical Research Office
Director: Timothy Kuzel, MD
Administrative Director: Renee Webb
312.695.1301 or tkuzel@northwestern.edu
r-riphenburg@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, neuro-oncology, surgical oncology, and chemoprevention.

Developmental Therapeutics Core
Director, Andrew Mazar, PhD
847.467.0942 or a-mazar@northwestern.edu

The Developmental Therapeutics Core is a university-wide shared resource dedicated to providing a full suite of fee-for-service tumor biology and translational support services including in vitro and in vivo assessment of drug activity and mechanism of action, exploratory drug development activities such as pharmacokinetics and toxicology, consultation and project management and clinical trial support.

Flow Cytometry Facility
Director: Charles Goolsby, PhD
312.908.1294 or c-goolsby@northwestern.edu

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 mult-parametric, multilaser 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: Nadereh 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.

High Throughput Analysis Laboratory Facility
Director: Eric Weiss, PhD
847.491.5643 or elweiss@northwestern.edu

The High Throughput Analysis Laboratory 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.

Keck Biophysics Facility
Director: Amy Rosensweig, PhD
847.467.5301 or amyr@northwestern.edu

The Keck Biophysics Facility is a unique resource that provides researchers with 24-hour access to a collection of state of the art instruments for biophysical and biochemical characterization of macromolecules and their interactions. Services include use of fluorimeters, spectrometers, microcalorimeters, imagers, light scattering instruments, SPR and HPLC systems.
Medicinal & Synthetic Chemistry Core  
Director: Karl Scheidt, PhD  
847.467.2629 or scheidt@northwestern.edu  

The Medicinal & Synthetic Chemistry Core is a university-wide resource that provides researchers access to chemistry services and expertise to advance their biomedical research. Services include molecular modeling and cheminformatics, custom chemical synthesis, hit-to-lead development, and compound purification using advanced LC-MS techniques.

Molecular and Translational Imaging Core Facility  
Director, Chicago Facility: Andrew Larson, PhD  
Director, Evanston Facility: Thomas Meade, PhD  
312.926.3499 or a-larson@northwestern.edu  
312.908.9595 or tmeade@northwestern.edu  

The Molecular and Translational Imaging Core is a university-wide shared resource dedicated to providing researchers with an efficient pipeline for developing, testing and imaging new diagnostics and therapeutics. The imaging core offers investigators access to a wide array of state of the art imaging modalities including: MRI, IVIS for in vivo bioluminescence and fluorescence imaging, optical imaging, and partial wave spectroscopy. These unique capabilities are central to the advancement of efforts to understand and integrate cellular architecture, flow of information, regulation, and communication across length scales and their impact on tumorigenesis, metastasis, and response to treatment.

Mouse Histology and Phenotyping Laboratory  
Director: Warren G. Tourtellotte, MD, PhD, FCAP  
Co-Director: Lin Li, MD, MS  
Facility Manager: Donna Emge, HT (ASCP)  
312.503.2679 (Histology), 312-503-2695 (Phenotyping and Immunohistochemistry) or MHPL@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 they can involve a systemic overview of all major organ systems to identify phenotypes. The lab provides a full range of histology, immunohistochemistry and phenotyping services. In addition, pathologist consultation will allow the development of strategies to elucidate phenotypes 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, MA  
312.503.9804 or e-hahn@northwestern.edu  

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, including special attention to literacy and cultural diversity; serves as a central resource for state-of-the-science instruments and measurement methods; and provides in-house research support services for the translation, collection and psychometric analysis of outcomes and survey data.

Pathology Core Facility  
Director: Peter Kulesza, MD, PhD  
Associate Director: Julie Karpus  
312.908.5546 or p-kulesza@northwestern.edu  
j-karbus@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
312.503.0848 or a-mondragon@northwestern.edu
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 LS-CAT beamlines at Sector 21 of the Advanced Photon Source, at Argonne National Laboratory. 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: Rajeshwar Awatramani, PhD
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 led 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.

Nanocytology of rectal colonocytes to assess risk of colon cancer based on field cancerization.


**Abstract**

Developing a minimally invasive and cost-effective prescreening strategy for colon cancer is critical because of the impossibility of conducting colonoscopy on the entire at-risk population. The concept of field carcinogenesis, in which normal-appearing tissue away from a tumor has molecular and, consequently, nanoarchitectural abnormalities, offers one attractive approach to identify high-risk patients. In this study, we investigated whether the novel imaging technique partial wave spectroscopic (PWS) microscopy could risk-stratify patients harboring precancerous lesions of the colon, using an optically measured biomarker (L(d)) obtained from microscopically normal but nanoscopically altered cells. Rectal epithelial cells were examined from 146 patients, including 72 control patients, 14 patients with diminutive adenomas, 20 patients with nondiminutive/nonadvanced adenomas, 15 patients with advanced adenomas/high-grade dysplasia, 12 patients with genetic mutation leading to Lynch syndrome, and 13 patients with cancer. We found that the L(d) obtained from rectal colonocytes was well correlated with colon tumorigenicity in our patient cohort and in an independent validation set of 39 additional patients. Therefore, our findings suggest that PWS-measured L(d) is an accurate marker of field carcinogenesis. This approach provides a potential prescreening strategy for risk stratification before colonoscopy.


Incorporation of Adjuvant Therapy into the Multimodality Management of Gastrointestinal Stromal Tumors of the Stomach in the United States.


**Abstract**

**BACKGROUND:** Gastrointestinal stromal tumors (GIST) treatment changed considerably with introduction of imatinib in 2001 and reports of early successes. However, little is known about imatinib incorporation into practice. Our objective was to examine the integration of adjuvant systemic therapy into...
GIST management. METHODS: Patients with gastric GIST were identified (n = 4508) from the National Cancer Data Base (2001-2007). Separate regression models were developed to examine factors associated with adjuvant and neoadjuvant therapy use. RESULTS: A total of 3050 patients underwent surgical resection. From 2001-2003 to 2006-2007, use of adjuvant therapy increased from 29 to 47% (P < 0.001). Patients were less likely to receive adjuvant therapy if tumors were <3 cm, low grade, had negative margins, were treated at low-volume centers, or were diagnosed during 2001-2003 (P < 0.01). Adjuvant systemic therapy for lesions <3 cm also increased (17 to 25%, P = 0.001). For high-risk GISTs, adjuvant therapy use increased from 41 to 58% overall, with increases of 46 to 70% at high-volume centers and 40 to 48% at low-volume centers (P < 0.001). Neoadjuvant therapy increased from 0 to 8%; patients were more likely to receive neoadjuvant treatment if their tumor was >6 cm, treated at high-volume centers, or were diagnosed during 2006-2007 (P < 0.001). CONCLUSIONS: Adjuvant systemic therapy use for GISTs was increasing and widespread prior to FDA approval of adjuvant imatinib, suggesting that contemporaneous advances in management of advanced GIST were being simultaneously and rapidly translated into the adjuvant setting. As relatively costly therapies are integrated into practice, more robust tracking systems are needed to monitor the incorporation of new treatments.


Soy Isoflavone Supplementation for Breast Cancer Risk Reduction: A Randomized Phase II Trial.


Abstract
Soy isoflavone consumption may protect against breast cancer development. We conducted a phase IIIB trial of soy isoflavone supplementation to examine its effect on breast epithelial proliferation and other biomarkers in the healthy high-risk breast. One hundred and twenty-six consented women underwent a random fine-needle aspiration (rFNA); those with 4,000 or more epithelial cells were randomized to a double-blind 6-month intervention of mixed soy isoflavones (PTIG-2535) or placebo, followed by repeat rFNA. Cells were examined for Ki-67 labeling index and atypia. Expression of 28 genes related to proliferation, apoptosis, and estrogenic effect was measured using quantitative reverse transcriptase PCR. Hormone and protein levels were measured in nipple aspirate fluid (NAF). All statistical tests were two-sided. Ninety-eight women were evaluable for Ki-67 labeling index. In 49 treated women, the median Ki-67 labeling index was 1.18 at entry and 1.12 post intervention, whereas in 49 placebo subjects, it was 0.97 and 0.92 (P for between-group change: 0.32). Menopausal stratification yielded similar results between groups, but within premenopausal soy-treated women, Ki-67 labeling index increased from 1.71 to 2.18 (P = 0.04). We saw no treatment effect on cytologic atypia or NAF parameters. There were significant increases in the expression of 14 of 28 genes within the soy, but not the control group, without significant between-group differences. Plasma genistein values showed excellent compliance. A 6-month intervention of mixed soy isoflavones in healthy, high-risk adult Western women did not reduce breast epithelial proliferation, suggesting a lack of efficacy for breast cancer prevention and a possible adverse effect in premenopausal women.


Communicating About Chemotherapy-Induced Nausea and Vomiting: A Comparison of Patient and Provider Perspectives.


Abstract
Despite recent progress, chemotherapy-induced nausea and vomiting (CINV), especially delayed CINV, continues to be a problem. Delayed CINV is underestimated and perceived differently by providers and patients. Communication between providers and patients about this side effect may help improve outcomes. This study identifies
patients’ and providers’ perceptions of management and barriers to quality CINV care. Provider and patient versions of a Nausea and Vomiting Management Barriers Questionnaire were developed to address potential barriers. Providers and patients were given opportunities to add detail in open-ended questions. Providers were recruited through the NCCN and the Oncology Nursing Society mailing lists. Patients who received at least 2 cycles of chemotherapy and experienced CINV were recruited through a consortium of advocacy groups. Both providers (n = 141) and patients (n = 299) completed the survey. Providers (41%) and patients (42%) agreed medication side effects were a concern, but more patients (63%) than providers (36%) tried to limit the number of medications taken (P < .0001). Many providers (67%) spontaneously reported barriers to managing CINV, with financial and patient-related factors among the most common. Few patients (10%) reported cost as a barrier, but 37% endorsed the desire “to be strong by not complaining.” Barriers to communication and quality care of CINV differ between caregivers and patients. Addressing misconceptions and establishing mutually consistent goals will lead to more effective overall care.

Parker, J. B.; Palchaudhuri, S.; Yin, H.; Wei, J.; Chakravarti, D.

A Transcriptional Regulatory Role of THAP11-HCF-1 Complex in Colon Cancer Cell Function.


Abstract
The recently identified Thanatos associated protein (THAP) domain is an atypical zinc-finger motif with sequence specific DNA binding activity. Emerging data suggest THAP proteins may function in chromatin dependent processes including transcriptional regulation but the roles of most THAP proteins in normal and aberrant cellular processes remain largely unknown. In this work, we identify THAP11 as a transcriptional regulator differentially expressed in human colon cancer. Immunohistochemical analysis of human colon cancers revealed increased THAP11 expression in both primary tumors and metastases. Knockdown of THAP11 in SW620 colon cancer cells resulted in a significant decrease in cell proliferation and gene expression profiling in these cells identified a novel gene set comprised of 80 differentially expressed genes, 70% of which were de-repressed by THAP11 knockdown. THAP11 was found to physically associate with the transcriptional co-regulator HCF-1 (Host cell factor-1) and recruit HCF-1 to target promoters. Importantly, THAP11 mediated repression and chromatin association requires HCF-1 while HCF-1 recruitment at these genes requires THAP11. Collectively, these data provide the first characterization of THAP11 dependent gene expression in human colon cancer cells and suggests THAP11/HCF-1 complex may be an important transcriptional and cell growth regulator in human colon cancer.


Cdc42-interacting protein 4 promotes breast cancer cell invasion and formation of invadopodia through activation of N-WASp.

Cancer Research 70:8347-8356.

Abstract
In the earliest stages of metastasis, breast cancer cells must reorganize the cytoskeleton to affect cell shape change and promote cell invasion and motility. These events require the cytoskeletal regulators Cdc42 and Rho, their effectors such as N-WASp/WAVE, and direct inducers of actin polymerization such as Arp2/3. Little consideration has been given to molecules that shape the cell membrane. The F-BAR proteins CIP4, TOCA-1, and FBP17 generate membrane curvature and act as scaffolding proteins for activated Cdc42 and N-WASp. We found that expression of CIP4, but not TOCA-1 or FBP17, was increased in invasive breast cancer cell lines in comparison with weakly or noninvasive breast cancer cell lines. Endogenous CIP4 localized to the leading edge of migrating cells and to invadopodia in cells invading gelatin. Because CIP4 serves as a scaffolding protein for Cdc42, Src, and N-WASp, we tested whether loss of CIP4 could result in decreased N-WASp function. Interaction between CIP4 and N-WASp was epidermal growth factor responsive, and CIP4 silencing by small interfering RNA caused decreased tyrosine
phosphorylation of N-WASp at a Src-dependent activation site (Y256). CIP4 silencing also impaired the migration and invasion of MDA-MB-231 cells and was associated with decreased formation of invadopodia and gelatin degradation. This study presents a new role for CIP4 in the promotion of migration and invasion of MDA-MB-231 breast cancer cells and establishes the contribution of F-BAR proteins to cancer cell motility and invasion.


Identification of Regulators of Polyploidization Presents Therapeutic Targets for Treatment of AMKL.


Abstract
The mechanism by which cells decide to skip mitosis to become polyploid is largely undefined. Here we used a high-content image-based screen to identify small-molecule probes that induce polyploidization of megakaryocytic leukemia cells and serve as perturbagens to help understand this process. Our study implicates five networks of kinases that regulate the switch to polyploidy. Moreover, we find that dimethylfasudil (diMF, H-1152P) selectively increased polyploidization, mature cell-surface marker expression, and apoptosis of malignant megakaryocytes. An integrated target identification approach employing proteomic and shRNA screening revealed that a major target of diMF is Aurora kinase A (AURKA). We further find that MLN8237 (Alisertib), a selective inhibitor of AURKA, induced polyploidization and expression of mature megakaryocyte markers in acute megakaryocytic leukemia (AMKL) blasts and displayed potent anti-AMKL activity in vivo. Our findings provide a rationale to support clinical trials of MLN8237 and other inducers of polyploidization and differentiation in AMKL.


Pilot neoadjuvant trial in HER2 positive breast cancer with combination of nab-paclitaxel and lapatinib.


Abstract
Lapatinib, a dual kinase inhibitor against epidermal growth factor receptor (EGFR) and human epidermal receptor two (HER2) has shown efficacy in treating HER2 positive breast cancer. Nanoparticle albumin bound (nab) paclitaxel was developed to reduce toxicities from paclitaxel and improve its efficacy. Thirty patients with stage I-III HER2 positive breast cancer were treated in the neoadjuvant setting with lapatinib 1,000 mg/day and nab-paclitaxel 260 mg/m(2) every 3 weeks for four cycles. The primary end point of the trial was clinical response rate (cRR) with secondary end points including pathologic complete response rate (pCR), tolerability of the combination, and marker response. The cRR was 82.8% (24 patients) with six (20.7%) patients having complete clinical response, 18 (62.1%) having partial clinical response, and five (17.2%) stable disease. A pCR was observed in five of the 28 patients (17.9%). The most frequent grade 2 toxicities were neuropathy in nine patients (30%), fatigue in seven patients (23.3%), rash in 11 patients (36.7%), and bone pain in 10 patients (33.3%). There was no significant drop in the left ventricular ejection fraction (LVEF). Of the tissue markers examined, we were not able to find a predictor of response. The combination of lapatinib and nab-paclitaxel was well tolerated and provided good efficacy in women with HER2 positive breast cancer. This combination offers an alternative non-anthracycline-containing regimen for women with HER2 positive breast cancer.
Grippo, P. J.; Fitchev, P. S.; Bentrem, D. J.; Melstrom, L. G.; Dangi-Garimella, S.; Krantz, S. B.; Heiferman, M. J.; Chung, C.; Adrian, K.; Cornwell, M. L.; Flesche, J. B.; Rao, S. M.; Talamonti, M. S.; Munshi, H. G.; Crawford, S. E.

Concurrent PEDF deficiency and Kras mutation induce invasive pancreatic cancer and adipose-rich stroma in mice.


**Abstract**

**Background and Aims:** Pigment epithelium-derived factor (PEDF), a non-inhibitory SERPIN with potent antiangiogenic activity, has been recently implicated in metabolism and adipogenesis, both of which are known to influence pancreatic cancer progression. Increased pancreatic fat in human pancreatic tumour correlates with greater tumour dissemination while PEDF deficiency in mice promotes pancreatic hyperplasia and visceral obesity. Oncogenic Ras, the most common mutation in pancreatic ductal adenocarcinoma (PDAC), has similarly been shown to promote adipogenesis and premalignant lesions.

**Methods:** In order to determine whether concurrent loss of PEDF is sufficient to promote adipogenesis and tumorigenesis in the pancreas, the authors ablated PEDF in an EL-Kras(G12D) mouse model of non-invasive cystic papillary neoplasms. **Results:** EL-Kras(G12D)/PEDF deficient mice developed invasive PDAC associated with enhanced matrix metalloproteinase (MMP)-2 and MMP-9 expression and increased peripancreatic fat with adipocyte hypertrophy and intrapancreatic adipocyte infiltration (pancreatic steatosis). In support of increased adipogenesis, the stroma of the pancreas of EL-Kras(G12D)/PEDF deficient mice demonstrated higher tissue levels of two lipid droplet associated proteins, tail-interacting protein 47 (TIP47, perilipin 3) and adipose differentiation-related protein (ADRP, Pperilipin 2), while adipose triglyceride lipase, a key factor in lipolysis, was decreased. In patients with PDAC, both tissue and serum levels of PEDF were decreased, stromal TIP47 expression was higher and tissue VEGF to PEDF ratio was increased (p<0.05). **Conclusions:** These data highlight the importance of lipid metabolism in the tumour microenvironment and identify PEDF as a critical negative regulator of both adiposity and tumour invasion in the pancreas.


Expression of RORγt marks a pathogenic T-regulatory cell subset in human colon cancer.

_Science Translational Medicine_ (in press).

**Abstract**

There is much controversy about the role of T-regulatory cells (Treg) in human colon cancer (CC). High densities of tumor-infiltrating Treg can predict better or worse clinical outcomes depending on the study. Accordingly, in mouse models of cancer, Treg can suppress inflammation and protect the host, can suppress T-cells and protect the tumor, or even have direct cancer-promoting attributes. These different effects are a result of the presence of different Treg subsets. We report the preferential expansion in human CC of a Treg subset with potently T-cell suppressive, but compromised anti-inflammatory properties, which are distinguished from Treg that abound in healthy donors by their co-expression of Foxp3 and RORγt. Treg with similar attributes were found to be expanded in mouse models of hereditary polyposis. Ablation of RORγt gene, when specifically directed to Foxp3+ cells, stabilized Treg anti-inflammatory functions, suppressed inflammation, improved polyp-specific immune surveillance, and severely attenuated polyposis. Ablation of IL6, IL23, IL17, or TNFα were protective but significantly less than loss of RORγt. Surprisingly, loss of IL17A had a dual effect, as mice had fewer polyps but continued to have RORγt+ Treg and developed invasive cancer. Thus, we conclude that RORγt has a central role in determining the balance between protective relative to pathogenic Treg in CC, and that the quality of Treg regulates inflammation, potency of immune surveillance, and severity of disease outcome.
MMSET stimulates myeloma cell growth through microRNA-mediated modulation of c-MYC.


Abstract
Multiple myeloma (MM) represents the malignant proliferation of terminally differentiated B cells, which, in many cases, is associated with the maintenance of high levels of the oncoprotein c-MYC. Overexpression of the histone methyltransferase MMSET (WHSC1/NSD2), due to t(4;14) chromosomal translocation, promotes the proliferation of MM cells along with global changes in chromatin; nevertheless, the precise mechanisms by which MMSET stimulates neoplasia remain incompletely understood. We found that MMSET enhances the proliferation of MM cells by stimulating the expression of c-MYC at the post-transcriptional level. A miRNA profiling experiment in t(4;14) MM cells identified miR-126(*) as an MMSET-regulated miRNA predicted to target c-MYC mRNA. We show that miR-126(*) specifically targets the 3'-untranslated region (3'-UTR) of c-MYC, inhibiting its translation and leading to decreased c-MYC protein levels. Moreover, the expression of this miRNA was sufficient to decrease the proliferation rate of t(4;14) MM cells. Chromatin immunoprecipitation analysis showed that MMSET binds to the miR-126(*) promoter along with the KAP1 co-repressor and HDACs, and is associated with heterochromatic modifications, characterized by increased trimethylation of H3K9 and decreased H3 acetylation, leading to miR-126(*) repression. Collectively, this study shows a novel mechanism that leads to increased c-MYC levels and enhanced proliferation of t(4;14) MM, and potentially other cancers with high MMSET expression.


Abstract
Glycosyltransferases catalyze the reaction between an activated sugar donor and an acceptor to form a new glycosidic linkage. Glycosyltransferases are responsible for the assembly of oligosaccharides in vivo and are also important for the in vitro synthesis of these biomolecules. However, the functional identification and characterization of new glycosyltransferases is difficult and tedious. This paper describes an approach that combines arrays of reactions on an immobilized array of acceptors with an analysis by mass spectrometry to screen putative glycosyltransferases. A total of 14,280 combinations of a glycosyltransferase, an acceptor and a donor in four buffer conditions were screened, leading to the identification and characterization of four new glycosyltransferases. This work is notable because it provides a label-free method for the rapid functional annotation of putative enzymes.

Ban, L.; Pettit, N.; Li, L.; Stuparu, A. D.; Cai, L.; Chen, W.; Guan, W.; Han, W.; Wang, P. G.; Mrksich, M.

Discovery of glycosyltransferases using carbohydrate arrays and mass spectrometry.

Murphy, A. B.; Kelley, B.; Nyame, Y. A.; Martin, I. K.; Smith, D. J.; Castaneda, L.; Zagaja, G. J.; Hollowell, C. M.; Kittles, R. A.

Predictors of Serum Vitamin D Levels in African American and European American Men in Chicago.


Abstract
Vitamin D deficiency is epidemiologically linked to prostate, breast, and colon cancer. When compared with European American (EA) men, African American (AA) men have increased risk of prostate cancer, but few studies evaluate vitamin D status in AA men. The authors evaluate the biological and environmental predictors of vitamin D deficiency in AA and EA men in Chicago, Illinois, a low ultraviolet radiation environment. Blood samples were collected from 492 men, aged between 40 and 79 years, from urology clinics at three hospitals in Chicago, along with demographic and medical information, body mass index, and skin melanin content using a portable narrow-band reflectometer. Vitamin D intake and ultraviolet radiation exposure were assessed using validated questionnaires. The results demonstrated that Black race, cold season of
blood draw, elevated body mass index, and lack of vitamin D supplementation increase the risk of vitamin D deficiency. Supplementation is a high-impact, modifiable risk factor. Race and sunlight exposure should be taken into account for recommended daily allowances for vitamin D intake.


Topical delivery of siRNA-based spherical nucleic acid nanoparticle conjugates for gene regulation.


**Abstract**

Topical application of nucleic acids offers many potential therapeutic advantages for suppressing genes in the skin, and potentially for systemic gene delivery. However, the epidermal barrier typically precludes entry of gene-suppressing therapy unless the barrier is disrupted. We now show that spherical nucleic acid nanoparticle conjugates (SNA-NCs), gold cores surrounded by a dense shell of highly oriented, covalently immobilized siRNA, freely penetrate almost 100% of keratinocytes in vitro, mouse skin, and human epidermis within hours after application. Significantly, these structures can be delivered in a commercial moisturizer or phosphate-buffered saline, and do not require barrier disruption or transfection agents, such as liposomes, peptides, or viruses. SNA-NCs targeting epidermal growth factor receptor (EGFR), an important gene for epidermal homeostasis, are > 100-fold more potent and suppress longer than siRNA delivered with commercial lipid agents in cultured keratinocytes. Topical delivery of 1.5 μM EGFR siRNA (50 nM SNA-NCs) for 3 wk to hairless mouse skin almost completely abolishes EGFR expression, suppresses downstream ERK phosphorylation, and reduces epidermal thickness by almost 40%. Similarly, EGFR mRNA in human skin equivalents is reduced by 52% after 60 h of treatment with 25 nM EGFR SNA-NCs. Treated skin shows no clinical or histological evidence of toxicity. No cytokine activation in mouse blood or tissue samples is observed, and after 3 wk of topical skin treatment, the SNA structures are virtually undetectable in internal organs. SNA conjugates may be promising agents for personalized, topically delivered gene therapy of cutaneous tumors, skin inflammation, and dominant negative genetic skin disorders.


Autophagic degradation of the BCR-ABL oncprotein and generation of antileukemic responses by arsenic trioxide.


**Abstract**

We provide evidence that arsenic trioxide (As(2)O(3)) targets the BCR-ABL oncprotein via a novel mechanism involving p62/SQSTM1-mediated localization of the oncprotein to the autolysosomes and subsequent degradation mediated by the protease cathepsin B. Our studies demonstrate that inhibitors of autophagy or cathepsin B activity and/or molecular targeting of p62/SQSTM1, Atg7 or cathepsin B result in partial reversal of the suppressive effects of As(2)O(3) on BCR-ABL expressing leukemic progenitors, including primitive leukemic precursors from chronic myelogenous leukemia (CML) patients. Altogether, these findings indicate that autophagic degradation of BCR-ABL is critical for the induction of the antileukemic effects of As(2)O(3) and raise the potential for future therapeutic approaches to target BCR-ABL expressing cells by modulating elements of the autophagic machinery to promote BCR-ABL degradation.

Klaic, L.; Morimoto, R. I.; Silverman, R. B.


**Abstract**

The natural product celastrol (1) possesses numerous beneficial therapeutic properties and affects numerous cellular pathways. The mechanism of action and cellular target(s) of celastrol, however, remain unresolved. While a number of studies have proposed that the
activity of celastrol is mediated through reaction with cysteine residues, these observations have been based on studies with specific proteins or by in vitro analysis of a small fraction of the proteome. In this study, we have investigated the spatial and structural requirements of celastrol for the design of suitable affinity probes to identify cellular binding partners of celastrol. Although celastrol has several potential sites for modification, some of these were not synthetically amenable or yielded unstable analogs. Conversion of the carboxylic acid functionality to amides and long-chain analogs, however, yielded bioactive compounds that induced the heat shock response (HSR) and antioxidant response and inhibited Hsp90 activity. This led to the synthesis of biotinylated celastrols (23 and 24) that were used as affinity reagents in extracts of human Panc-1 cells to identify Annexin II, eEF1A, and beta-tubulin as potential targets of celastrol.


ACR Appropriateness Criteria(R) Definitive Therapy for Early-Stage Cervical Cancer.


Abstract

OBJECTIVES: The definitive treatment of early-stage cervical cancer involves multidisciplinary decision making. This expert panel was convened to reach consensus on the selection of appropriate therapies based on patient and disease characteristics at presentation. METHODS: The American College of Radiology Appropriateness Criteria are evidence-based guidelines for specific clinical conditions that are reviewed every 2 years by a multidisciplinary expert panel. The guideline development and review include an extensive analysis of current medical literature from peer reviewed journals and the application of a well-established consensus methodology (modified Delphi) to rate the appropriateness of imaging and treatment procedures by the panel. In those instances where evidence is lacking or not definitive, expert opinion may be used to recommend imaging or the treatment. RESULTS: Three clinical variants were developed to represent common scenarios in the treatment of early-stage cervical cancer. Group members reached consensus on the appropriateness of therapeutic options. This process yielded numerical ratings and descriptive commentary. CONCLUSIONS: This manuscript represents the consensus opinion of an expert panel based on a survey of all available medical literature. This manuscript may be used to inform the clinical decision making of physicians involved in the treatment of early-stage cervical cancer.


Multiple Behavior Changes in Diet and Activity: A Randomized Controlled Trial Using Mobile TechnologyBehavior Changes in Diet and Activity.


Abstract

BACKGROUND: Many patients exhibit multiple chronic disease risk behaviors. Research provides little information about advice that can maximize simultaneous health behavior changes. METHODS: To test which combination of diet and activity advice maximizes healthy change, we randomized 204 adults with elevated saturated fat and low fruit and vegetable intake, high sedentary leisure time, and low physical activity to 1 of 4 treatments: increase fruit/vegetable intake and physical activity, decrease fat and sedentary leisure, decrease fat and increase physical activity, and increase fruit/vegetable intake and decrease sedentary leisure. Treatments provided 3 weeks of remote coaching supported by mobile decision support technology and financial incentives. During treatment, incentives were contingent on using the mobile device to self-monitor and attain behavioral targets; during follow-up, incentives were contingent only on recording. The outcome was standardized, composite improvement on the 4 diet and activity behaviors at the end of treatment and at 5-month follow-up. RESULTS: Of the 204 individuals randomized, 200 (98.0%)
completed follow-up. The increase fruits/vegetables and decrease sedentary leisure treatments improved more than the other 3 treatments ($P < .001$). Specifically, daily fruit/vegetable intake increased from 1.2 servings to 5.5 servings, sedentary leisure decreased from 219.2 minutes to 89.3 minutes, and saturated fat decreased from 12.0% to 9.5% of calories consumed. Differences between treatment groups were maintained through follow-up. Traditional dieting (decrease fat and increase physical activity) improved less than the other 3 treatments ($P < .001$). **CONCLUSIONS:** Remote coaching supported by mobile technology and financial incentives holds promise to improve diet and activity. Targeting fruits/vegetables and sedentary leisure together maximizes overall adoption and maintenance of multiple healthy behavior changes.

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McMillen, B. D.; Aponte, M. M.; Liu, Z.; Helenowski, I. B.; Scholtens, D.M.; Buttin, B. M.; Wei, J.J.

Expression analysis of MIR182 and its associated target genes in advanced ovarian carcinoma.


**Abstract**

BRCA1/BRCA2 mutations are common and the hallmarks of high-grade serous ovarian carcinoma. We found that MIR182, a negative BRCA1 regulator, is significantly overexpressed in high-grade serous ovarian carcinoma. To examine whether overexpression of MIR182 and its target genes, including BRCA1, HMGA2 (high-mobility group A2), FOXO3 and MTSS1, are associated with high-grade serous ovarian carcinoma tumor types and clinical outcome, we studied MIR182 by in situ hybridization and its target gene expression by immunohistochemistry in 117 cases of advanced ovarian cancer. We found that high-grade serous ovarian carcinoma had significantly higher MIR182 ($P=0.0003$) and HMGA2 ($P=0.04$) expression, and significantly lower BRCA1 ($P<0.0001$) and FOXO3 ($P<0.001$) expression than normal controls. MIR182 is significantly correlated with MTSS1 expression ($r=0.31$; $P<0.001$), whereas other target genes did not show a significant correlation with MIR182, indicating a complicated regulatory mechanisms of these genes in high-grade serous ovarian carcinoma. Among the examined MIR182 target genes, only HMGA2 was significantly associated with serous type carcinomas ($P<0.01$), ascites ($P<0.01$) and high death rate ($P=0.02$). FOXO3 expression was associated with lower-stage disease ($P=0.04$) and solid growth pattern ($P=0.03$). MIR182 expression is significantly higher in high-grade serous ovarian carcinoma than in fallopian tubes.
The Robert H Lurie Comprehensive Cancer Center of Northwestern University

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PROFESSIONAL EDUCATION PROGRAMS

Throughout the year, the Lurie Cancer Center offers professional education programs related to various cancer specialties.

Listed below are some of the programs planned for 2013. To view an up-to-date list of educational opportunities with details and online registration, visit cancer.northwestern.edu or call 312.695.1304.

Breast Cancer Review:
*Updates from the 2012 San Antonio Breast Cancer Symposium*
January 11, 2013
Chair: William Gradishar, MD

Gastrointestinal Malignancies: 2013 Update of Clinical Care
February 22, 2013
Chair: Mary Mulcahy, MD

Hematology Update: Coverage from ASH Conference
March 8, 2013
Chair: Steven Rosen, MD

Northwestern Brain Tumor Institute CME Symposium
March 23, 2013
Chairs: James Chandler, MD, and Jeffrey Raizer, MD

20th Annual Cancer Survivors’ Celebration & Walk
June 2, 2013

Reception: ASCO Annual Meeting
June 2, 2013

8th Annual Pain and Palliative Care Conference
June 13, 2013
Chair: Judith Paice, PhD, RN
PATIENT AND PUBLIC 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.

To view an up to date list of programs with details and online registration, visit cancer.northwestern.edu or call 312.695.1304

20th Annual Cancer Survivors’ Celebration & Walk
Sunday, June 2, 2013

Sunday, June 2, 2013 marks the 20th anniversary of the Lurie Cancer Center’s signature event, the Cancer Survivors’ Celebration & Walk. Held each year on National Cancer Survivors Day, the community awareness event draws close to 4,000 participants—bringing cancer survivors, family and friends together with the physicians, scientists and health professionals who support them. The non-competitive walk begins in Grant Park and continues along Chicago’s lakefront.

No pledges are required to take part in the walk and activities for the family including, a picnic, t-shirt, music, entertainment, an opportunity to sign the Dedication Wall and more. There are exciting new additions planned for this year’s program as we celebrate this milestone, and the strides being made in cancer treatment and research.

ONGOING PROGRAMS

Cancer Connections
An opportunity for patients, families and caregivers to learn about tools, techniques and services they can use to reenergize during and after cancer treatment. Workshops led by Lurie Cancer Center Supportive Oncology team members are offered on a wide range of topics.

Gilda’s Club Chicago at the Lurie Cancer Center
Lurie Cancer Center patients and families have on-site access to a variety of programs and activities offered by Gilda’s Club Chicago. Designed to be fun, informative, and to help reduce stress, all of the activities are offered free of charge.
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, Ann & Robert H. Lurie Children’s 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 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 NCI-designated Comprehensive Cancer Centers in the nation. In addition, the Lurie Cancer Center is a founding member of the National Comprehensive Cancer Network (NCCN), an alliance of 21 of the world’s leading cancer centers dedicated to improving the quality and effectiveness of care provided to patients with cancer.

The Lurie Cancer Center acknowledges and thanks the Lea Charitable Trust for their support and encouragement. A generous donation from the Lea Charitable Trust provides partial support for the publication of The Journal.

“Few will have the greatness to bend history itself, but each of us can work to change a small portion of events, and in the total of all those acts will be written the history of this generation. It is from numberless diverse acts of courage and belief that human history is shaped.”

— Robert F. Kennedy