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 23 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.

“It always seems impossible until it’s done.”
— Nelson Mandela
LETTER FROM THE EDITOR

Steven T. Rosen, MD, FACP

The beginning of a new year, and of a new chapter in my career, offer the opportunity to step back and take stock of our collective accomplishments. The unique strengths of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University stem from our remarkable staff, clinicians and scientists, and exceptional programs spanning from basic science research, prevention and screening, to all aspects of treatment, to survivorship.

Dedicated in 1993 through a $10 million gift of endowment from Ann and Robert H. Lurie, the Lurie Cancer Center was awarded NCI designation that same year. The Lurie Cancer Center became an NCI-designated Comprehensive Cancer Center in 1997. This year we achieved our highest rating, an overall “Outstanding,” on the competitive renewal of our Cancer Center Support Grant (CCSG). Additional points of personal pride include:

- Securing seven Endowed Chairs in Cancer Research.
- Increasing NCI CCSG funding from $1.5 million to $4.9 million, annual external funding of Lurie Cancer Center members from $45.5 million to $175 million, and philanthropic support to $10.4 million annually.
- Accelerating the growth of clinical and research services, opening new state-of-the art outpatient clinics and tripling the number of inpatient oncology beds. The Lurie Cancer Center and its affiliated hospitals are the largest provider of cancer care in Illinois. The expanded breadth of our clinical trials include early phase, therapeutic, survivorship, and behavioral intervention studies.
- Augmenting significant basic, clinical, prevention and control, behavioral and population-based investigations with interactive research and training opportunities that bridge them, including Northwestern’s NCI-funded Center of Cancer Nanotechnology Excellence, Physical Sciences and Oncology Center, Breast and Prostate Cancer SPORES, and CURE (Continuing Umbrella of Research Experience) Summer Research Program.
- Serving as a founding member of the National Comprehensive Cancer Network and the Big Ten Cancer Research Consortium.
- Expanding the Cancer Survivors’ Celebration & Walk, held annually on National Cancer Survivors Day. With close to 4,000 participants, it is the largest survivorship event of its kind in the country.

I’m amazed and energized by the strides made in recent years—and the advances just keep coming. It has been a privilege to lead the Lurie Cancer Center to a position of national distinction among our academic cancer center peers. I am indebted to the Lurie Cancer Center team for their years of service and am confident it will continue to thrive as a result of their leadership.
Elizabeth Eklund, MD, Professor of Medicine at Northwestern University Feinberg School of Medicine, joined the family business, so to speak, when she became a physician-scientist. Her first cousin, twice removed, the late Warren Weaver, PhD, who once headed the Division of Natural Sciences at the Rockefeller Foundation, played a historic role in the scientific world. Shares Eklund, “He was the first person to coin the term ‘molecular biology’ in the scientific literature. An advocate for science, he felt that this new discipline or category of science [at the time], should be created and supported.”

Too young to become acquainted with her much older cousin Warren, Eklund nurtured her interests in the STEM (science, technology, engineering, and mathematics) fields thanks to her community. She grew up in Downers Grove, Illinois, the daughter of an Argonne National Laboratory IBM computer contractor father and artist mother. She says, “Argonne was nearby and like many of the ‘Argonne kids,’ I was exposed to science, engineering, and computer science at an early age because of our parents’ work.”

Clinically Attuned
Eklund set her sights on medicine and clinical research. She first earned a bachelor’s degree in chemical engineering at the University of Illinois at Champaign-Urbana before going on to medical school at Rush Medical College in Chicago. Although completing her family
practice training in 1986, she realized prior to graduation that she really was most interested in caring for cancer patients. “The outcomes for these individuals greatly depend on the experience and carefulness of their physicians,” says Eklund. “I was very impressed by the ability of hematology/oncology specialists to pull patients back from the brink in oftentimes desperate situations.”

So Eklund shifted gears to become a hematologist/oncologist and as soon as she finished one residency, she started another in internal medicine (required for the subspecialty) at the Mayo Clinic. Then at Indiana University in Indianapolis, she completed a fellowship in hematology/oncology in 1991 and finally a postdoctoral fellowship in molecular hematology in 1993. Her family medicine background, however, wasn’t all for naught. It has given her a broader perspective in an area of medicine where many patients, sadly, still succumb to their disease.

“Initially trained as a primary care physician, I appreciate the importance of not leaving patients and their families in the lurch when they aren’t responding to cancer treatment or ‘failed’ chemotherapy, as if it was somehow their fault,” explains Eklund. “It’s also provided me with a good understanding of knowing when we’ve exhausted all we can do. Sometimes in this specialty, it’s difficult to give up even when it might be in the best interests of the patient.”

Current Research

Advancing current treatment options for leukemia, Eklund focuses on investigating the molecular biology of leukemogenesis. Specifically, she has been working on identifying translational targets for novel therapeutic approaches for chronic myeloid leukemia (CML) and acute myeloid leukemia (AML).

Currently tyrosine-kinase inhibitors (TKI) are the first-line treatment for CML. While TKI therapeutics work wonders by increasing survival, they often can’t eliminate every leukemia stem cell. “These cells hide out in the bone marrow and resist normal cell death signals,” explains Eklund, who leads the Lurie Cancer Center’s Hematologic Malignancies Program. “So if you stop treatment, many patients often relapse.” Eklund and her colleagues hope to target these “sneaky” stem cells further downstream from TKI therapy. They’ve identified a promising peptide that they are now developing for therapeutic use.

Patients with AML usually receive high doses of chemotherapy to treat their cancer. Toxic and frequently not well tolerated, this current standard of care can result in remission for some people but generally most will relapse over time. Investigators believe, once again, that AML stem cells may be avoiding detection in the bone marrow and fibroblast growth factors (FGF) may also stimulate their growth.

Eklund has served as Chief of Hematology/Oncology for the Jesse Brown VA Medical Center since 2006. In the mid-1990s, she began her association with the Veteran’s Administration when she received her first VA grant as a junior faculty member at the University of Alabama in Birmingham. For Eklund, caring for the VA patient population provides a nice contrast to Northwestern’s Streeterville environment. She says, “The VA is particularly good for exposing our fellows to patients from different socio-economic classes. Also, because we don’t have to worry about whether our patients have insurance, we can focus on delivering the best care that we can.”

In addition to her research lab on campus, Eklund also maintains one at Jesse Brown.

Living in downtown Chicago, Eklund avails herself of all the city has to offer especially when it comes to cultural arts. She often spends her leisure time going to the theatre and museums.
Her large ears flapping, an angry elephant charges at a pack of hyenas to protect her defenseless calf. A leaping impala literally jumps out of the mouth of a hungry lioness. Recently picked up by international news outlets like Britain’s Daily Mail, these dynamic images of wildlife in Botswana are the work of photo buff Jayesh Mehta, MD, Professor of Medicine at Northwestern University Feinberg School of Medicine.

“After I completed my initial medical school studies, I thought about giving up medicine to become a photographer,” shares Mehta, Director of the Lurie Cancer Center’s Hematopoietic Stem Cell Transplant Program and Co-Deputy Director of the Comprehensive Transplant Center at Northwestern. “I had published some photos and won a competitive international prize but with a little hindsight, I am glad I stuck with medicine!”

Like his physician father, Mehta attended Bombay University, where he earned his MD degree in 1990. There he met his spouse, Seema Singhal, MD (see profile on page 7 for more about Dr. Singhal), who was a year behind him. Also similar to his dad, Mehta specialized in hematology/oncology, but in his own way—in the then emerging area of bone marrow transplantation. He says, “Training was absolutely not available in India. It was clear we had to go abroad.”
Becoming Transplant Experts
After completing a one-year fellowship program at Hadassah University in Jerusalem, Israel, Mehta and Singhal were ready to bring novel cancer treatments to patients. However, their homeland of India lacked the infrastructure to support such sophisticated techniques. Then, a series of opportunities and chance encounters guided the career direction of Mehta and his wife for the next eight years as they honed their skills and became renowned experts in stem cell transplantation and multiple myeloma.

From 1992 to 1996, they were senior registrars at the Royal Marsden Hospital in London; Mehta served as a Bone Marrow Transplant Coordinator, and Singhal, a fellow in the Department of Medical Oncology’s Leukemia and Myeloma Units. While pursuing their clinical and research interests, the couple came across an opportunity to do even more at the University of Arkansas in Little Rock. There Mehta became Chief of Allogeneic Stem Cell Transplantation and was one of the key investigators (Singhal was the other) involved in the exciting discovery of the drug thalidomide as a novel compound for combating cancer.

“We started two patients simultaneously on the drug,” recalls Mehta. “The program chief and I were jointly looking after one of them and Seema, the other. Her patient responded to the drug, which launched a whole new category of drug treatments for myeloma.”

Elevating Northwestern’s Stature
A Grand Rounds lectureship brought Mehta to Chicago and the Lurie Cancer Center for the first time in 1999. Although he didn’t know anyone at Northwestern, that soon changed when Lurie Cancer Center Director, Steve Rosen, MD, introduced himself. “He said, ‘Wonderful lecture. If you ever want a job, I have one here for you.”

While flattered, Mehta had just relocated to take a position as Director of the Myeloma and Lymphoma Program at the University of South Carolina in Columbia. Several months later, though, financial difficulties shut down the program. Says Mehta, “I called Dr. Rosen and said I don’t know if you remember me and right away he said, ‘I do. Would you like a job?’” This time, Mehta took him up on the offer. “Seema and I believed there was great potential to build something really nice at Northwestern.”

Indeed, that turned out to be the case. Since Mehta joined the Lurie Cancer Center in 2000, the Stem Cell Transplant program has grown from approximately 45 per year to become among the top 5-10 nationally in volume and types of transplants, averaging close to 280 annually. He remarks, “I credit our success to achieving good clinical outcomes for our patients and building bridges to people in the community.”

Beyond his clinical work, Mehta’s research interests include advancing treatment for plasma cell malignancies such as multiple myeloma; hematopoietic stem cell transplantation to fight opportunistic infections in immunocompromised patients; and the use of stem cells in organ transplantation. “Maintaining transplanted organs without rejection can be a major struggle,” explains Mehta. “If we could use allogeneic stem cells from the organ donor to induce tolerance in the recipient then we could possibly begin to withdraw immunosuppressive drugs and eliminate lifelong dependency on them.”

The occupational hazard of working in the same field as his spouse has been to dissuade the couple’s two sons, Neil, 21, and Aran, 14, from becoming physicians. Says Mehta, “We’ve been quite successful!” In the past several years, Mehta has renewed his passion for photography. In 2012 he entered a wildlife photography competition sponsored by the BBC and the London Natural History Museum. The venerable international contest often attracts over 50,000 submissions. Although Mehta didn’t win a prize, two of his photos—the angry elephant and the leaping impala—reached the finals.
Fanfare seems to accompany significant professional milestones for Seema Singhal, MD, Professor of Medicine at Northwestern University Feinberg School of Medicine. Ever since completing medical training in her native India, the renowned multiple myeloma expert has found her life to be a “bit of an adventure” with a little serendipity thrown in for good measure.

In March 1991 she and spouse Jayesh Mehta, MD, (see profile on page 5 for more about Dr. Mehta) arrived in the Middle East just days after the end of the First Gulf War. Pursuing a fellowship in bone marrow transplantation at Hadassah University Hospital in Jerusalem, the young couple flew to Egypt and entered Israel overland – crossing the Sinai and the Suez – with armored escort. In the immediate aftermath of the Gulf War, safety was a serious concern, recalls Singhal. In July 1996, while relocating from Europe to the United States to become Chief of Investigative Diagnostics and Director of the Stem Cell Laboratory at the University of Arkansas in Little Rock, she remembers traveling alongside throngs of people flying into Atlanta for the Summer Olympics. Then shortly after starting her first junior faculty position, she and her colleagues, quite by accident, discovered a new drug for the treatment of multiple myeloma: thalidomide.

“I have been very fortunate to witness history,” says Singhal, Director of the Lurie Cancer Center.
Center’s Multiple Myeloma Program. “For 15 minutes or so [before I told our program chief], I was the only person in the world who knew that thalidomide was active in myeloma, or any cancer for that matter.”

Once used to combat morning sickness, the medication gained notoriety in the late 1950s and early 1960s when it was found to cause birth defects. Although taken off the market in many countries, the drug was still licensed for use with certain diseases such as HIV. Thirty years later, thalidomide regained some traction for its antiangiogenic properties. For example, the father of angiogenesis research Judah Folkman, MD, believed thalidomide could stop new vessel growth in cancer, even “liquid” tumors such as those caused by multiple myeloma. In fact, he suggested the drug for a dying patient at Little Rock who had contacted Folkman and strongly lobbied for the opportunity to try antiangiogenesis therapy as a last ditch effort. Says Singhal, “Dr. Folkman had an early feeling thalidomide could be useful.”

An Exciting Discovery
Both Singhal and her husband had previous experience using thalidomide for its anti-inflammatory effect to combat graft-versus-host disease in bone marrow transplant patients. So they became the natural choice to lead the University of Arkansas’ clinical trial. On the same day, one hour apart, two patients were put on thalidomide. Unfortunately, it was not effective for the first individual, the one who originally pushed for its use, but it worked for Jimmy, one of Singhal’s patients.

“Jimmy had come to the end of the road and we were talking about hospice care,” says Singhal. “I suggested he try thalidomide and told him if nothing else, because the drug is a sedative, it would help him sleep well at night.” Jimmy went back to his home in Alabama with a supply of pills and Singhal took a family vacation to India, not expecting to see Jimmy again. Several weeks later, however, she returned to find that not only was Jimmy still alive, but he also was thriving on thalidomide as evidenced by his lab results. “He was having a stupendous response. You could see a vertical drop in his M protein, which had been very high.”

Word quickly spread. Multiple myeloma patients from around the world flocked to Little Rock to participate in Singhal’s clinical study. With a 30 percent positive response rate, thalidomide is a viable option for relapsed myeloma patients.

In a 1999 issue of the New England Journal of Medicine, Singhal, Mehta (as second author), and colleagues detailed the antitumor activity of thalidomide and its activity against advanced myeloma.

Offering new hope
Patients fighting multiple myeloma often face relapse and depend on the development of innovative therapeutics to keep them going. Lurie Cancer Center patients have access to the latest treatments for myeloma, thanks, in part, to Singhal’s clinical research efforts. At the beginning of her tenure at Northwestern in 2001, Singhal served as site PI for a study on the drug Velcade (bortezomib) that rapidly gained Food and Drug Administration approval. “We quickly became a referral center,” says Singhal. “This success established us as a place to go to for new therapies for myeloma.” Just this past November, a clinical trial was launched to test the efficacy of the promising monoclonal antibody Daratumumab.

In addition to research, Singhal juggles a busy clinical practice with her role as mom to two sons—one in college at Northwestern and the other in high school. While seeing patients is “like having 5,000 children with needs that come before your own,” Singhal wouldn’t trade the fulfillment she gets from her profession. “As oncologists, we get to see the best side of people.”
Lurie Cancer Center Receives “Outstanding” Rating and Core Grant Renewal from the NCI

The Lurie Cancer Center received its highest rating, an overall “Outstanding”, on the competitive renewal of its National Cancer Institute (NCI) Cancer Center Support Grant (CCSG), along with recommended funding of $24.9 million over five years. The grant award, which will run through 2018, provides essential support for the Lurie Cancer Center’s nine research programs and 15 shared research facilities.

The award follows a rigorous review process by the NCI, including a peer-review site visit in February. “This rating for the NCI Cancer Center Support Grant reflects the scope and strength of the work being done by our researcher’s, clinicians and staff members, said Steven T. Rosen, MD, Director of the Lurie Cancer Center. “We are honored by the NCI’s continued recognition of our commitment to collaboration and to discovering more effective ways to prevent, detect and treat cancer.”

Bilimoria Receives NCCN Young Investigator Award

Karl Bilimoria, MD, Assistant Professor in surgical oncology and medical social sciences at the Feinberg School of Medicine, has been named a 2013 Young Investigator by the National Comprehensive Cancer Network (NCNN).

Bilimoria will use the grant – $150,000 over two years – to work on research regarding the quality of care delivered to melanoma and breast cancer patients. “In particular, the project will look at ways to help hospitals improve how they determine whether the cancer has spread to the lymph nodes,” said Bilimoria, a member of the Lurie Cancer Center. “We will also be trying to define which patients would benefit most from having their lymph nodes checked for the spread of the cancer.”
Developmental Therapeutics Institute Brings More Early Phase Cancer Studies and New Treatments to Northwestern

There aren’t enough early phase clinical studies of new anti-cancer approaches in Chicago, forcing patients with hard-to-treat cancers to look elsewhere. That’s about to change with the establishment in July of the Northwestern Medicine Developmental Therapeutics Institute (NMDTI) launched by the Lurie Cancer Center.

An initial $10 million investment will bring many more phase 1, first-in-human, and early-phase clinical studies of new anti-cancer approaches to Chicago. Leading the new institute is Frank Giles, MD, an internationally known physician-scientist in the cancer developmental therapeutics field. He will shepherd the promising therapies developed in Northwestern’s own science labs – with their particular strengths, including nanoparticles – all the way to multi-site national or international clinical trials. Giles plans to bring more international collaboration in developmental therapeutics to Northwestern with physician-scientists he has relationships with in Asia, Canada, and Europe. He also will work more closely with pharmaceutical companies on Northwestern developmental therapeutics in cancer and other diseases that share targets with cancer.

“We have all of this concentration of science here and we need to be focused on when this reaches a tipping point for developing a new therapy,” Giles says.

Read more at nmdti.org

Renowned Neurosurgeon, Andrew Parsa, Joins Northwestern

Andrew Parsa, MD, PhD, an internationally-renowned neurosurgeon specializing in complex tumors of the brain and spine, has joined Northwestern Brain Tumor Institute and Northwestern University Feinberg School of Medicine as the Michael J. Marchese Professor and Chair of the Department of Neurological Surgery. “I am truly excited to embark upon this next stage of my career, which will allow me to impact neurosurgery more broadly,” Parsa said. “I will have a unique opportunity to positively shape the training of residents and the development of faculty in neurosurgery at one of the most respected institutions in the country.”

For the past decade, Parsa has been at the University of California San Francisco (UCSF), most recently as Professor, Vice Chair, and Reza and Georgianna Khatib Endowed Chair in Skull Base Tumor Surgery. Continuously supported by the NIH since 2002, Parsa’s research on brain tumor immunology has provided landmark insights, including the identification of a novel link between oncogenesis and immune-resistance in brain tumors. He is currently the study chair for the largest randomized brain tumor vaccine trial ever to be funded by the National Cancer Institute.
20th Annual Cancer Survivors’ Celebration & Walk and New 5K Was a Celebration to Remember!
The wind and rain was no match for the spirits of close to 4,000 cancer survivors & supporters who gathered in Grant Park on June 2, 2013 to walk, run and celebrate on National Cancer Survivors Day!

The 20th anniversary of the Lurie Cancer Center’s signature event was a celebration to remember. The addition of our first 5K got the morning off to a running start, and the walkers stayed warm by “twisting out cancer” with cancer survivor, Jenna Benn, and dancing along with special guest, Bonnie Hunt, who attended with 15 family members. “You’re all making an investment in your own Karma by being here today,” Hunt told the crowd. “I think we all know what it’s like... to hear the words, or to have someone in your family hear the words—you have cancer. The next sentence has to be ‘but there’s something we can do about it.’ We all want that hope.”

Please join us June 1, 2014 for the 21st Annual Cancer Survivors’ Celebration Walk & 5K.

View photos and videos from the Walk and 5K at cancer.northwestern.edu/walk
Scientists Discover Regulator That Drives Majority of Lymphoma

A multi-center collaboration that grew out of the lab of Jonathan Licht, MD, has revealed protein EZH2 to be a powerful regulatory molecule and key driver of B-cell lymphoma, a type of cancer in white blood cells. The study suggests that combining an inhibitor of EZH2 with other anti-tumor agents may offer a much-improved treatment option for up to 70 percent of adult lymphoma cases.

“Our findings also demonstrated that EZH2 is required for normal B-cell lymphocytes (white blood cells), and if deleted, the lymphocytes cease to develop at a certain stage,” said Licht, Johanna Dobe Professor of Hematology/Oncology at the Feinberg School of Medicine and Associate Director for Clinical Sciences Research at the Lurie Cancer Center.

B-cells produce antibodies within the body that fight invading microbes. B-cell lymphomas occur most frequently in older adults and in individuals with compromised immune systems.

“Our group was able to map what the mutated EZH2 does to a cell and correlate those findings in animal models with the human data of our collaborators in order to identify the whole program of gene expression that is being shut down,” said Licht.

Read more at cancer.northwestern.edu/regulator

Platanias Receives 2013 Milstein Award

Leonidas Platanias, MD, PhD, Deputy Director of Lurie Cancer Center, was a recipient of the 2013 Seymour & Vivian Milstein Award for Excellence in Interferon and Cytokine Research.

The Milstein Award, which represents the pinnacle of scientific achievement in cytokine and interferon research, is presented by the International Cytokine and Interferon Society to a leading biomedical research scientist who has made outstanding contributions in either a basic or applied field. Many Laureates have made seminal advancements that have enabled the successful treatment of disease or have the potential to lead to significant health benefits.

Platanias, the Jesse, Sara, Andrew, Abigail, Benjamin and Elizabeth Lurie Professor of Oncology, and Professor of Medicine at Northwestern University Feinberg School of Medicine, has focused his research efforts on the field of signal transduction in cancer for over 20 years; studying the mechanisms of signaling for cytokines and other ligands in malignant cells. In recent years, he has performed extensive work on the mechanisms of interferon signaling in malignancies and of arsenic trioxide signaling in leukemia. In addition, his laboratory has defined kinase elements as targets for the development of innovative therapeutic approaches in myeloid leukemias.

Read more at cancer.northwestern.edu/Milstein
New Chemo Drug Gentler on Fertility, Tougher on Cancer

A new gentler chemotherapy drug in the form of nanoparticles has been designed by Lurie Cancer Center scientists to be less toxic to a young woman’s fertility, but extra tough on cancer. This is the first cancer drug tested while in development for its effect on fertility using a novel in vitro test.

The scientists designed a quick new in vitro test that predicts the toxicity of a chemotherapy drug to fertility and can be easily used to test other cancer drugs in development as well as existing ones. Currently the testing of cancer drugs for fertility toxicity is a time and resource intensive process.

“Our overall goal is to create smart drugs that kill the cancer but don’t cause sterility in young women,” said Teresa Woodruff, PhD, a Co-Principal Investigator of the study and Chief of Fertility Preservation at the Feinberg School of Medicine. Woodruff and Thomas O’Halloran, PhD, also a Co-Principal Investigator and Director of the Chemistry of Life Processes Institute at Northwestern, and Associate Director for Basic Sciences Research at the Lurie Cancer Center, are a wife and husband team who developed and tested the drug.

Their intersecting interests — hers in fertility preservation, his in cancer drug development — percolated over dinner conversations and sparked the collaboration.

Read more at cancer.northwestern.edu/news/chemo-fertility

Lurie Cancer Center Named Center of Excellence in AYA Oncology

The Lurie Cancer Center has been designated a Change it Back National Center of Excellence in Adolescent and Young Adult Oncology. The Lurie Cancer Center is one of only two cancer centers in the nation to hold this honor, recognizing them as leaders in the field of Adolescent and Young Adult (AYA) cancer care. The award was presented at the annual conference of Critical Mass/The Young Adult Cancer Alliance. A member of Critical Mass since 2009, the Lurie Cancer Center formed a multidisciplinary working group to improve standards of care and outcomes for patients diagnosed with cancer between the ages of 15 and 39.

Read more at cancer.northwestern.edu/news
The Cancer Survivorship Institute at the Lurie Cancer Center

The Cancer Survivorship Institute at the Lurie Cancer Center is an interdisciplinary institute that brings together clinicians and scientists to stimulate and support exceptional cancer survivorship patient care and research programs. Our patient centered approach provides comprehensive supportive oncology services including psychosocial, rehabilitative, integrative and palliative care. Our specialized survivorship medical clinics address the unique needs of specific groups of cancer survivors. The Institute is closely aligned with the Lurie Cancer Center’s Cancer Control and Survivorship research program where an interdisciplinary team of researchers conducts various studies aimed at improving the lives of cancer patients, their families and caregivers.

There are approximately 14 million cancer survivors in the United States, and that number is expected to grow to nearly 18 million by 2022. “Despite advances in early detection and treatment, the chronicity of cancer and treatment-related symptoms present challenges that can compromise quality of life and health outcomes well beyond treatment,” says CSI Director, Frank Penedo, PhD. “The unique medical and psychosocial needs of cancer survivors should be managed in the context of a long-term comprehensive, holistic and evidence-based approach in conjunction with investigations spanning from basic mechanisms to translational and community research models. The CSI incorporates these clinical and research efforts seamlessly to improve the lives of cancer survivors, their families and the community.”

Read more at cancer.northwestern.edu/survivorship

Northwestern Part of Big Ten Cancer Research Consortium

Opponents on the football field, a group of eleven schools from the Big Ten athletic conference came together in Chicago last June to launch an ambitious new effort against a common foe: cancer. The Big Ten Cancer Research Consortium was created to transform cancer research through collaborative oncology trials that leverage the scientific and clinical expertise of each university.

“The consortium will benefit patients because researchers will work together to turn ideas into potential new treatments. I view this as the beginning of a broad spectrum of potential research, training, and care initiatives that will benefit our patients and society,” said Steven Rosen, MD, Director of the Lurie Cancer Center.

Newly developed clinical trials will be linked to molecular diagnostics, enabling researchers to understand what drives the cancers to grow and what might be done to stop them from growing. The consortium will also leverage geographical locations and existing relationships among cancer centers.

Read more at bigtencrc.org

Cancer Research Consortium
The Relationship of Single Strand Breaks in DNA to Breast Cancer Risk

Robert T. Chatterton, PhD*, Oukseub Lee, PhD*, Mathavi Sadavan*, Hong Hu, MD*, Jun Wang, PhD*, and Seema A. Khan, MD*

Sara Sukumar, PhD#, Vered Stearns, MD#, and Mary Jo Fackler, PhD#

Single-strand breaks (SSB) in DNA are discontinuities in one strand of the DNA and are usually accompanied by loss of a single nucleotide and by damaged 5’- or 3’-termini at the site of the break. If not repaired rapidly or appropriately, chromosomal SSBs pose a serious threat to genetic stability and cell survival. Of the different types of DNA damage that occur in cells, SSBs are the most common, arising at a frequency of thousands per cell per day. Obviously, the repair process is a major function of the cells and must occur continuously. SSB damage may occur by oxidative attack by endogenous reactive oxygen species (ROS), by adduct formation, by physical damage, or by deficiencies in repair mechanisms. Many sources of damage may be involved from chemical carcinogens to ionizing radiation to wound repair processes. They can also occur as a result of disintegration of the oxidized sugar or indirectly during DNA base-excision repair of oxidized bases, abasic sites, or bases that are damaged or altered in other ways. SSBs can also occur as a result of erroneous or abortive activity of cellular enzymes such as DNA topoisomerase. Caldecott lists 10 different types of chemical alterations in 3’- and 5’-termini that may occur.

The most common consequence of unrepaired SSBs in proliferating cells is the blockage or collapse of DNA replication forks during the S phase of the cell cycle, which may lead to double strand breaks (DSBs). However, the frequency of SSBs due to endogenous...
causes exceeds that of DSBs by three orders of magnitude. Repair of SSBs is a process that involves detection, DNA end processing, DNA gap filling and DNA ligation. The SSB sensor protein poly(ADP-ribose) polymerase 1 (PARP-1) is a common first step in detection of SSBs. It binds transiently to SSBs and is activated, producing several hundred ADP-ribose units in length, causing focal accumulation of SSB repair proteins including the X-ray repair cross-complementing protein 1 (XRCC1) which functions as a molecular scaffold that interacts with, stabilizes, and stimulates multiple enzymatic components of the SSB repair process. Transcription of the PARP-1 enzyme is not significantly upregulated in this process but its activity is greatly increased. Unlike repair of DSBs, SSB repair most probably operates throughout the cell cycle to rapidly detect and remove the majority of chromosomal SSBs.

Tumor suppressor proteins such as cyclin kinase inhibitor p21 that inhibit cell cycle progression are unlikely to be significantly associated with SSB repair. However, PARP-1 activity may be assessed by measuring expression of MTUS2/TIP150, a microtubule associated tumor suppressor, which is inhibited by PARP-1. Another gene product whose expression is increased by ROS, alkylating agents and abasic sites is APEX-1 endonuclease. Quantitative measurement of the expression of these genes may provide information on the occurrence of single strand breaks in DNA. Because many processes are involved in creating DNA breaks and repair, it is not a simple task to quantify the occurrence of DNA damage in cells by measurement of gene expression profiles. Indeed, many of the enzymes including PARP1 are regulated posttranslationally.

Participating in the protection from oxidative damage is nuclear respiratory factor 1 (NRF1). Nuclear respiration factor-1 (NRF-1) is a transcription factor that regulates the expression of nuclear-encoded mitochondrial genes that control transcription of the mitochondrial genome. NRF1 regulates a battery of antioxidant- and xenobiotic-metabolizing genes through the antioxidant response element (ARE). It also has been shown to increase expression of glutathione biosynthesis and other oxidative defense enzymes. We chose to measure this and superoxide dismutase (MnSOD2) as a means of assessing their influence in preventing SSB.

If the presence of single strand DNA breaks could be quantified directly, that should provide a means of detecting a process which puts cells at high risk of developing cancer. A quantitative procedure has been devised based on nick translation for this purpose.

Methods

Subjects. Single strand breaks and associated genetic and epigenetic parameters in random fine needle aspirates of the breast (rFNA) were studied in 172 of 388 total subjects. None of the women had clinically apparent breast cancer. The 5-year Gail estimated risk ranged from 0.5 to 5.5, median 1.4; the median lifetime Gail risk was 12.5 (5.6 to 28.3). The median BMI was 28.2 (18.7 to 51.3) and the median Masood score was 13 (0 to 18). Random fine-needle aspiration was conducted as described by Fabian et al. Breast density was determined from digital mammograms as the percentage occupied by dense, non-fatty tissue. Material from ten passes of the needle were transferred to Cytolyt (Hologic Corp.) and frozen at -80 °C for methylome analysis, and that from an additional 10 passes were transferred to phosphate-buffered saline (PBS) for the nick translation procedure.

Nick translation procedure. The rFNA sample in 15 ml of phosphate-buffered saline was centrifuged, the mixed cell precipitate was lysed, and DNA was extracted using a kit from Norgen Biotek Corp. The initial flow-through was saved for protein analyses. RNA and DNA are then sequentially eluted. DNA was measured by absorbance at 260/280 nm; the range of amounts was 0.014 to 6.82 µg (median, 0.76 µg). Only samples with absorbance ratios between 1.5 and 2.3 were used. A total of 200 ng of DNA was used for the nick translation assay. Calf thymus DNA was used as a quality control preparation and aliquots were assayed with each batch of patient samples. 3H-dCTP was obtained from Perkin Elmer. The specific activity was 60.8 µCi/mmol; 110,000 cpm was added to each DNA sample in 50 mM Tris-HCl buffer containing 50 mM MgCl₂, pH 7.8, with a mixture of triphosphodeoxynucleotides (50 pmol). Five units of DNA polymerase 1 from E. coli were added, and the samples were incubated at 15° C for 120 min. The reaction was stopped by heating at 65° C for 10 min. 3H-dCTP that was incorporated into DNA was separated from unincorporated 3H-dCTP on a 14 x 80 mm Sephadex G50 column with 0.1 M
Tris-HCl buffer, pH 8.6. The incorporation of $^3$H-dCTP reached a maximum at 30 min, and the incorporation was linear with time to more than two hours. Concordance of interassay quality control samples was 0.96.

Quantification of gene expression levels. RNA (100 ng), purified from rFNA, was reverse transcribed. qPCR reactions were carried out using the TaqMan OpenArray (Applied Biosystems) for MTUS2, XRCC1, APEX1, SOD2, and NRF1. Expression levels of the target genes were normalized to the average expression of GAPDH and HPRT1.

DNA methylation procedure. Quantitation of DNA methylation was conducted by QM-MSP from cell lysates assessing the cumulative methylation level of eleven cancer-specific genes (AKR1B1, FZD10, TM6SF1, GAS5C, ALX1, CCND2, RARB, RASSF1A, TWIST1, TMEFF2, and SCGB3A1/HIN1) and a cumulative methylation index (CMI) was calculated as described previously.

Cytological analysis. rFNA samples were examined for cytological features associated with breast cancer as described by Masood.

Statistics. SSB, Lifetime Gail, Percent breast density, CMI, and Masood score were converted to natural log values for normalization. Pearson correlation coefficients without correction for multiple comparisons are presented. Data were also analyzed by a backward stepwise regression procedure. Expression of mRNA was not normalized by log transformation, and so differences between tertiles were tested by the non-parametric Kolmogorov-Smirnov procedure. All statistical analyses were conducted with SYSTAT software.

Results
Incorporation of nucleotides into DNA ranged from 0.03 to 8.59 pmol/µg DNA. The median amount was 0.63 pmol/µg DNA. There was a negative association with BMI and a positive association with lifetime Gail model (Table 1). The association was similar in specimens from pre- and postmenopausal women. Although the correlation of CMI with SSB levels was not significant, it contributed to the estimate of SSB levels. SSB was significantly related to BMI, Lifetime Gail risk estimates, and CMI by multiple regression analysis with standard coefficients of -0.292, 0.239, and 0.132, respectively, at stage three were significant at the P<0.001 level.

The association of SSB level with gene products associated with base-excision repair was tested. The association by tertiles is shown in Table 2. Although suppression of MTUS2 may have provided a means of assessing PARP1 activity, it was not detectable in most samples. APEX1 was consistently negatively associated with SSB but was not significant. There was a difference in XRCC1 between the first and second tertiles of SSB levels approaching significance and that

<table>
<thead>
<tr>
<th>Measure</th>
<th>Premenopausal</th>
<th></th>
<th>Postmenopausal</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>p</td>
<td>r</td>
<td>p</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.295</td>
<td>0.020</td>
<td>-0.349</td>
<td>0.003</td>
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<tr>
<td>Percent breast density</td>
<td>0.038</td>
<td>&gt;0.20</td>
<td>0.337</td>
<td>0.005</td>
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<tr>
<td>Lifetime Gail model</td>
<td>0.251</td>
<td>0.041</td>
<td>-0.013</td>
<td>&gt;0.20</td>
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<tr>
<td>CMI</td>
<td>0.174</td>
<td>0.179</td>
<td>0.156</td>
<td>0.201</td>
</tr>
<tr>
<td>Masood score</td>
<td>0.010</td>
<td>&gt;0.20</td>
<td>0.044</td>
<td>&gt;0.20</td>
</tr>
</tbody>
</table>

Table 1: Association of single strand breaks (SSB) with other measures of risk (N = 170)

<table>
<thead>
<tr>
<th>Gene product</th>
<th>Percent difference between tertiles (significance)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 v 2</td>
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<tr>
<td>MTUS2</td>
<td>0 (0.848)</td>
</tr>
<tr>
<td>XRCC1</td>
<td>-31 (0.082)</td>
</tr>
<tr>
<td>APEX1</td>
<td>-30 (0.940)</td>
</tr>
<tr>
<td>NRF1</td>
<td>-69 (0.324)</td>
</tr>
<tr>
<td>SOD2</td>
<td>-48 (0.607)</td>
</tr>
</tbody>
</table>

Table 2: Significance of fold change in mRNA from GAPDH by tertiles of SSB (P, two-sided)
between the first and third tertiles was \( P = 0.025 \). Because oxidative processes may lead to SSBs, we also examined the relationship between tertiles of SSB and the gene products of \( \text{NRF1} \) and \( \text{SOD2} \). Both of these were significantly negatively associated with the occurrence of SSBs.

**Discussion**

DNA damage occurs in response to reactive oxygen species generated from endogenous processes such as the cytotoxic activities of the immune system and from exogenous sources. SSBs can occur directly by disintegration of the oxidized sugar or indirectly during base-excision repair of oxidized bases, abasic sites, or bases damaged on other ways. The repair of oxidized bases by base excision repair (BER) is a constant process independent of the cell cycle and is a highly efficient process; less than 0.1\% of SSBs go on to form double strand breaks in DNA\(^1\). The nick translation procedure used in the present study measures quantitatively the existence of unrepaired SSBs at the time the biopsies are obtained. The incorporation of \(^3\)H-dCTP is given per \( \mu \)g of total DNA in the specimen. Thus, the proportion of parenchymal tissue in the sample is less in women with a higher BMI, assuming the fat and connective tissue cells are present in greater proportion with higher BMI, and the level of SSB per gram is less (Table 1). As may be expected, the percent breast density in postmenopausal women was highly significantly associated with the SSB level. The lack of a significant correlation in the premenopausal women is surprising because the risk associated with breast cancer is not limited to older women\(^8\). However, the timing of the mammogram in the life of the patient in relation to the occurrence of a change in detectable DNA damage may be a factor. In contrast, the lifetime Gail risk estimate was associated with SSB level only in the premenopausal women. Since age itself is a major component of the estimate, this may limit the association with ongoing events in the breast. CMI is a cumulative expression of the methylation level of a number of genes that are associated with breast cancer. While the cumulative index was not significantly associated with the SSB level, evaluation of individual gene methylation patterns in relation to SSB level may prove to be interesting, and CMI contributed to the significance of the multiple regression relating other measures of risk to the SSB level. The cytomorphology of the fine-needle aspirates, classified according to Masood\(^5\) were not associated with the level of SSB. While the associations with several measures of breast cancer risk are not consistently high, there are sufficient indications that the level of DNA damage measured as SSB is associated with breast cancer. The fact that it does not reproduce any of the other measures in an indication that the information obtained is, to a reasonable degree, independent of the other measures.

To determine whether the procedure for measuring SSBs is consistent with functions associated with the DNA damage response, we measured expression of two genes involved in DNA base-excision repair, XRCC1 and APEX1 and one (MTUS2) associated with initiation of repair (Table 1). Because the variables were not normalized by a log transformation, we employed a non-parametric method to evaluate the associations. The SSB data was arrayed in tertiles from smallest to largest. The concordance of the expression level of each of the gene produces with the tertiles of SSBs was tested by the K-S statistical procedure. MTUS2 was not expressed in significant levels for detection, so decreases in the expression of this gene, which has been associated with PARP1 replication\(^1\), could not be measured. XRCC1 could be easily measured in these samples, and was 31\% lower in SSB tertile 2 than in tertile 1 despite the increase in SSB level between tertiles. This trend continued between tertiles 2 and 3, and the 80\% difference between the first and third tertiles of SSB was significant at the \( p = 0.025 \) level. It is clear that increased levels of SSB were associated with lower expression levels of this enzyme. Expression of APEX1 was also negatively associated with the SSB level to a lesser degree and did not reach significance.

These results suggest that lower expression levels of the base-excision repair enzymes may have been responsible for the greater occurrence of SSBs, with XRCC1 being more limiting than APEX1. Studies of polymorphisms of these genes also suggest that base-excision repair is more susceptible to alterations in XRCC1 than to alterations in APEX1\(^9,10\).

The expression of NRF1 and SOD2 were also measured to assess the potential protective effect of these antioxidant factors on the occurrence of SSBs. Lower expression of both of these genes was associated with significantly higher levels of SSBs indicating, as expected, that higher
levels of antioxidant activity help to prevent the formation of SSBs.

In summary, a procedure for measuring SSBs in biopsy specimens of the breast has been devised. The levels of SSBs measured by the nick translation technique are associated with other measures of breast cancer risk, but appear to provide estimates of risk that are not redundant with existing measures. Preliminary results suggest that both the level of expression of base-excision repair genes and the level of antioxidants available to the cells reduce the levels of SSBs.

References


NU-NEIGHBORS’ Partnership: Collaborating with a Minority Serving Institution of Higher Education to Reduce Cancer Health Disparities

Melissa A. Simon, MD, MPH*; Emily Malin, MSW*; Moira Stuart, PhD*; Marian Gidea, PhD*; Anuj Mubayi, PhD*; Brian Hitsman, PhD*; Christina Ciecierski, PhD*; David Victorson, PhD*; Jennifer Banas, MPH, MSEd, EdD; Tracy Luedke, PhD*; Shaan Trotter, MSc*; Tammi Dobbins, BS*; David Cella, PhD*

The National Cancer Institute (NCI) defines “cancer health disparities” as adverse differences in cancer incidence, cancer prevalence, cancer death, cancer survivorship, and burden of cancer or related health conditions that exist among specific population groups in the US. In an effort to address the rise in cancer disparities over the past couple of decades, NCI created the Partnerships to Advance Cancer Health Equity (PACHE) program, which offers unique funding mechanisms that support collaborations between Minority Serving Institutions (MSIs) and NCI-designated Cancer Centers. The program allows each institution to submit separate but complementary grant applications that support the partnership. The applications are simultaneously reviewed, but awarded separately to the respective institutions, allowing for the MSI and the CC to enter an equal and mutually beneficial partnership.

The Feasibility Studies for Collaborative Interaction for Minority Institution/Cancer Center Partnership (P20) planning grants are one of the mechanisms offered through the program. The P20 acts an incubator for the planning and implementation of MSI and CC collaborations in one or more of the target areas of cancer-related research, training, career development, education, and/or outreach, with the ultimate goal that the partnerships will use the preliminary data from these studies to apply for further competitive grant funding.
I. Development of the NU NEIGHBORS’ Partnership

In 2010, the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (RHLCCC-NU) embarked on its first P20 application with Northeastern Illinois University (NEIU) to form a community-engaged research partnership called NU-NEIGHBORS. NEIU is fully accredited public university that serves more than 12,000 students and is the only four-year Hispanic Serving Institution in the Midwest. NEIU engages community-based organizations and reaches its students on five campuses in communities around Chicago that face high numbers of health disparities. In fact, being only 8.7 miles apart from each other in the city of Chicago, the NU-NEIGHBORS’ Partnership is at a geographic advantage to address the well-documented cancer health disparities that exist in this area. The collaboration leverages the strengths and cancer expertise of the private research-intensive institution (RHLCCC-NU) with those of the public teaching-intensive institution (NEIU). For the initial P20 submissions, faculty members from both sites completed a faculty match matrix that connected faculty members together based on their identified cancer health disparities research interests. This exercise ended with four pairs of inter-institutional faculty members to pursue potential research pilot projects under the P20 grant.

To enable a competitive joint proposal, the RHLCCC-NU invested in the partnership by providing seed funding for two of the inter-institutional faculty pairs, for the purpose a pre-pilot and partnership-building phase to foster and support their research projects. Facilitated by the RHLCCC-NU’s Office of Equity and Minority Health, the institutions met several times to create a more substantial and meaningful partnership that dramatically strengthened the proposed P20 applications. In 2011, the partnership received a $1.2 million from NCI’s Center to Reduce Cancer Health Disparities. The NU-NEIGHBORS’ Partnership embarked on a four-year initiative under the leadership of Drs. Melissa Simon (Associate Professor and Vice Chair of Clinical Research of Obstetrics and Gynecology at NU), David Cella (Professor and Chair of the Department of Medical Social Sciences at NU), Moira Stuart (Associate Professor of Health, Physical Education, Recreation & Athletics at NEIU), Marian Gidea (Professor of Mathematics at NEIU) and Anuj Mubayi (Assistant Professor of Applied Mathematics at NEIU).

The partnership addresses cancer health disparities through three aims. First, it seeks to facilitate and foster opportunities for skills training, education, and mentorship amongst faculty and students. Second, it seeks to build capacity for inter-institutional cancer disparities research projects. Third, it seeks to build a pipeline of students from underrepresented backgrounds interested in pursuing education, research, and careers in the social science and health fields. To date, many of these expectations are successfully underway (see Table 1).

<table>
<thead>
<tr>
<th>Outcomes</th>
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<tr>
<td>Institutional conference/event poster presentations</td>
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<tr>
<td>Inter-institutional guest faculty lectures</td>
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<tr>
<td>Courses created to incorporate cancer health disparities topics</td>
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<table>
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<tr>
<th>Trainees</th>
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<tr>
<td>Graduate students</td>
<td>3</td>
</tr>
<tr>
<td>Junior investigators</td>
<td>6</td>
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<tr>
<td>Total number of trainees</td>
<td>35</td>
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</table>

Table 1: Outcomes of the NU-NEIGHBORS’ Partnership
II. Shared Governance, Policies, Procedures and Evaluations

Receiving the funds to build a partnership enables but does not guarantee success. Both institutions came to the table from different academic climates and cultures. The strengths of the partnering institutions and their academic acumen set the foundation for creating a unique approach for a disease focused collaboration. To assure trust, shared decision-making, expectations, and communication, the partnership established a shared governance model that collectively created shared policies, procedures, and partnership evaluation.

As a means of maintaining clear and formal communication, the partnership holds monthly meetings between its administrative staff, faculty researchers and pilot teams. The governance structure includes an Internal Advisory Committee (IAC) and Community Steering Committee (CSC) that meets quarterly to help guide and advise the institutions through the partnership process.

The IAC is comprised of senior leaders from RHLCCC-NU and NEIU, agreed to ensure the entire NEIU/RHLCCC-NU collaboration would meet the outlined goals and objectives. The IAC reviews and supports the partnership’s research pilot projects, faculty mentoring plans and education proposals. The IAC is comprised of the partnership’s four Principal Investigators, Drs. Steve Rosen (Director of LCCC-NU), Richard McGee (NU School of Medicine’s Associate Dean for Faculty Recruitment and Professional Development), and NEIU’s Deans Wamucii Njogu (College of Arts and Sciences) and Maureen Gillette (College of Education).

Both academic institutions identified common community partners who aligned with the mission, vision and goals of the collaborative. Next, they invited a number community members to join the NU-NEIGHBORS’ CSC to set priorities for the partnership, establish mechanisms for community engagement, report the partnership’s findings to the community, and advise the partnership on future grant applications. The CSC is currently comprised of a breast cancer advocate and survivor, the executive director of the Chicago Hispanic Health Coalition, a Chicago public health professional and a recent NEIU graduate.

Collectively the NU-NEIGHBORS’ governance bodies decided that any funded research and educational pilots would need to have their projects and faculty mentoring plans reviewed on an annual basis. The partnership also agreed to complete an iterative needs assessment and curricular modifications throughout the four-year project timeline. Process and outcomes evaluations focus on approaches to filling gaps related to cancer health disparities in NEIU curricula and programming targeting NEIU and NU student and faculty cancer disparity research and faculty career development. Furthermore, the partnership assesses the funded pilot projects in their abilities to secure more competitive funding and publish novel findings.

III. Outcomes and Next Steps

As the partnership enters its third year of funding, it supports two research pilot projects. The first project it titled “MAESTRA: Managing Adverse Events and Symptoms with novel Technologies and Real-time Assessment.” Drs. David Victorson (NU Department of Medical Social Sciences) and Jennifer Banas (NEIU Department of Health, Physical Education, Recreation & Athletics), are the Co-Principal Investigators of this study which leverages eHealth-based culturally tailored symptom management interventions to reduce unnecessary symptoms and health inequities among Hispanic cancer patients. The study proposes to develop and evaluate an information technology-enabled symptom management support tool for Hispanic/Latino men and women who have received cancer treatment. This bilingual tool can assist this underserved population by providing culturally and personally matched symptom management support and education. Use of this type of novel approach can increase patient engagement, self-efficacy and ultimately access to supportive care and health promotion, which can lead to minimized costs. This research will build capacity for novel symptom management approaches and health promotion research.

The pilot team is also working to assist the NEIU’s Bachelor of Arts in Health and Wellness Program through its beginning steps of seeking external accreditation as a public health degree program. The team is collaborating with the program to emphasize and incorporate topics of health disparities and research throughout existing and new course content.

Brian Hitsman, PhD, of NU Department of Preventive Medicine, and Christina Ciecierski,
PhD, of NEIU Department of Economics are the Co-Principal Investigators on the second funded pilot titled, “Sociodemographic Disparities in Cancer Risk Behaviors Among US College Students.” The team’s research focuses on understanding the complex interrelationships among cancer-risk behaviors in college students and the extent to which behavior clustering varies by race, ethnicity and socioeconomic status. The team is working with Joseph Kang, PhD, of NU Department of Preventive Medicine, to analyze data from the American College Health Association’s National College Health Assessment. The data involves 450,000 students from across 395 two-year and four-year public and private colleges and universities. An important aspect of their research is to identify campus-level characteristics that explain any disparities in cancer risk behaviors.

Specific to NEIU’s campus and students, the pilot team is also working Marian Gidea, PhD, and Anuj Mubayi, PhD, of NEIU’s Department of Mathematics to tease apart individual and environmental effects of health behavior by developing and analyzing an agent-based model. The model will help understand the impact of dynamic structure and social behavior of students on the coevolution of alcohol and tobacco use by campus community over time. The research incorporates mechanisms specific to NEIU’s campus like social contexts, resilience to initiation and peer influences. The eventual goal is to incorporate other health behaviors in the modeling framework and identify risks associated with cancer over temporal and spatial scale in the NEIU student population.

The pilot team has already been engaged in influencing smoking policies on NEIU’s campus and expects that their findings will help them obtain independent grant funding to develop and evaluate campus-based interventions that address multiple unhealthy behaviors that are targeted to racial/ethnic minority groups.

The NU-NEIGHBORS’ Partnership received funding from RHLCCC-NU to fund a formal trainee program during the summer titled the Cancer Health Disparities Research Program. The competitive program was offered to all NEIU undergraduate students interested in pursuing careers in social science, basic science, and health care. The program accepted four NEIU undergraduate students to work on an eight-week long research project that addressed topics of cancer health disparities. The research-intensive experience provided students with an overview of health disparities, cancer health disparities and research methods. Students participated in weekly seminars, journal clubs, and faculty lectures and were encouraged to become engaged with community health organizations and events. Students were also provided with ongoing mentoring and career advice. The end of the experience culminated in a moderated oral presentation of each individual student’s research project.

The P20 is also funding Drs. Tracy Luedke (Associate Professor of Anthropology at NEIU) and Melissa Simon to create a visible and valuable space for health disparities education, training and research across the two institutions. This work has involved multiple institutional leadership, faculty and student level discussions to ascertain the optimal way of creating a cohesive place for all activities around health disparities to be catalogued, fostered and supported.

In sum, the NU-NEIGHBORS’ Partnership has brought considerable attention to the topic of health disparities and community engaged work across both institutions. This partnership has fostered several academic- and community-related outputs that will have direct impact on improving cancer disparities. We look forward to continuing to grow this partnership and leverage the lessons learned to positively influence and encourage other cross-institutional partnerships.

References
The Molecular Aging Program (MAP) is proposed to be a multi-departmental research and educational program facilitating collaborations between clinical, translation, and basic research investigators in different scientific areas with an interest in the processes that govern aging. This program is structured around the idea that the organismal and cellular processes that direct aging are mechanistically connected to human illnesses that have previously been shown to have a strong statistical connection to increasing age. This proposed program addresses one of the NIH Road Map’s Strategic Plans in the area of ‘investigating aging processes.’ The Northwestern University program, housed within the Department of Medicine, is divided into four scientific areas: (1) carcinogenesis or tumor cell resistance, (2) neurodegenerative models, (3) insulin resistance, and (4) cardiovascular disease. These human illnesses share a great deal of common and overlapping cellular factors that when dys-regulated appear to play a role, at least in some significant part, in the aberrant pathological molecular and biochemical processes resulting in a disease permissive phenotype.
Aging refers to the accumulation of biological, physical, psychological, and social changes in an organism over time. Aging is a physiological process that affects all species including humans but may also reflect cultural and societal changes over time. Around 100,000 people die every day from age-related causes worldwide. Aging is a very complex process and cannot be simply defined; however, it seems clear that longevity (a statistically probability of how long someone may live) and aging (a collection of physical changes such as graying hair, thinning skin, etc) are directly linked. In addition, the pathological effects of aging can be divided into separate classifications as well. For example, universal aging – defined as aging characteristics that occur in every member of a species – and statistical or probabilistic aging – defined as a pathologically phenotype that will occur in specific members of a species, such diabetes and cancer.

Recent studies in mice and lower organisms (like nematodes and yeast) suggest that lifespan (or longevity) can be extended in experimental settings, and the genetic manipulation of specific proteins in these primitive species have been shown to either extend or shorten lifespan. Interestingly, the mammalian homologs of these proteins have been identified and also appear, at least in some part, to play a physiological role in either directly determining lifespan (longevity) or aging related illnesses such as diabetes, cancer, etc. Based on these results, it is now hypothesized that longevity and other aspects of aging are determined by cellular genetics. In addition, and by extension, this hypothesis suggests that the proteins of these genes may be molecular biological targets for the development of new therapeutic strategies for the treatment of age-related human illnesses in pre-clinical studies with mice and potentially in patients.

As one might guess, these seminal scientific discoveries have generated a great deal of interest in finding ways to reverse or significantly slow down the process of aging using these newly discovered aging or potentially anti-aging proteins as molecular targets. In this regard, the proposed NU program currently contains 57 members from 12 departments, including $35 million dollars in grant monies. In addition, a new seminar series has already begun with programmatic goals to:

1. Bring together investigators with interest in molecular aging in order to share data and increase collaboration.
2. Provide a platform for regular conferences that focus on molecular aspects of aging with both internal and external speakers.
3. Apply for collaborative grants among several investigators who have mutual interest in the field of molecular aging.
4. Eventually advance the program into a center of excellence within the University.

One might ask why an aging program is of importance to a medical school, including the Northwestern University Feinberg School of Medicine (NUFSOM). To put this into perspective, as baby boomers begin to turn just over sixty years of age and become eligible to receive Social Security benefits, it is estimated that over the next twenty years America will experience an increase in retirees from 45 million to nearly 80 million. In addition as the baby boomers reach age 62, their life expectancies are about 20 years for men and 23 years for women, and these age estimates are increasing each year. This increase in retirees raises a series of critical questions in regards to health care as well as health care related research. Therefore, it is proposed that a more comprehensive understanding of these mechanisms is of fundamental importance for successful implementation of intervention strategies targeting the decline or loss of homeostasis during aging and as manifested in numerous age-associated disorders which diminishing quality of life in the elderly. The initial areas of emphasis proposed by the MAP – carcinogenesis, neurodegenerative disease, insulin resistance, and cardiovascular disease – were chosen with the growth of the aging American population in mind and are seen as key investigative opportunities.

As such, the MAP has two initial goals. The first is to build a collaborative community that will foster the development of new coordinated research projects that simultaneously address several interrelated areas of the biology of aging. To begin to address this, MAP has initiated a new lecture series meeting the second Wednesday of each month at which each laboratory presents their research that is mechanistically connected to aging. In the future these lecture series will also include invited external speakers who have national and
international reputations as leaders in health related scientific research in the field of aging biology and how aging directly affects human related illnesses. This aspect of the program is intended to foster potential collaborations between like-minded researchers who have a common interest in the processes that govern aging and how these processes could be used to prevent and/or develop new therapeutic strategies for age-related human illnesses.

The second short term goal of this proposed program is to use the collaborations that might emerge from our new seminar series to foster fresh programmatic initiatives to obtain funding for both training grants as well as other basic, translational, and pre-clinical programmatic grants. While this aspect of the program is still developing, there are several specific programmatic areas that are being considered: (1) animal models that may identify and develop new molecular targets and/or therapeutic strategies for the treatment of age related illnesses; (2) in vivo and in vitro research to determine the underlying mechanisms and causes of cardiovascular disease; (3) basic and translational investigation of age-related changes in the endocrine system that may underlie such human illnesses as insulin resistance (or type II diabetes); (4) metabolic dys-regulation in relation to aging as well as other illnesses; (5) stem cell biology and how specific stem cells and stem cell niches during aging play a causative role in both aging and age-related illnesses; and (6) musculoskeletal biology that investigates muscle, bone and cartilage that may have negative effects on the health of the elderly. While this program is still in its early stages of development and growth, this new program has the potential to develop into a robust and productive collaborative research community.
Late Chemoradiation Treatment-Related Swallow Effects in HNC Patients

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Over the past 20 years, it has become clear that radiotherapy used as treatment for head and neck cancer (HNC) can cause changes in the oropharyngeal swallow. When combined with concurrent chemotherapy, the radiation effect is strengthened. This concurrent combination can cause worsening of swallowing problems.\(^1\)\(^-\)\(^8\) In an attempt to reduce adverse effects of treatment including impairment to swallowing, Intensity-Modulated Radiation Therapy (IMRT) has been designed to minimize radiation doses to structures related to swallow and thus to improve oropharyngeal swallow post chemoradiation with IMRT while curing the patient’s tumor. There is particular interest in applying IMRT techniques to reduce the dose to structures specifically related to swallowing function, especially the pharyngeal constrictors, supraglottic larynx and glottic larynx.\(^9\)\(^-\)\(^12\)

This study investigated the relationship in swallowing problems from pre-radiation treatment to 12 months post-chemoradiation treatment and radiation doses administered to specific head and neck structures during the chemoradiation treatment.

Methods
Forty (40) patients with HNC receiving chemoradiation with IMRT were included in this study. The radiographic study known as the Modified Barium Swallow (MBS)\(^13\) was recorded for each patient at pre-treatment and at 12 months post-treatment. The radiation
doses in centigray (cGy) to multiple laryngeal and adjacent structures at the time of IMRT were measured. Radiation doses were reported for each of the following structures and substructures:

1. epiglottis: suprahyoid epiglottis, infrahyoid epiglottis
2. supraglottic larynx: epiglottis, arytenoid cartilages, aryepiglottic folds
3. larynx: supraglottic larynx, glottic larynx, subglottic larynx, thyroid cartilage, cricoid cartilage

Two of the most frequent swallowing disorders demonstrated by patients treated with chemoradiation are reduced tongue base retraction and delayed triggering of the pharyngeal swallow. We examined the patients’ MBS studies both at baseline and at 12 months post-treatment completion to document the presence of these two disorders.

The mean dose to each structure of interest was calculated for each patient. The mean doses were summarized for two patient subgroups, A & B using the mean and standard error of the mean. Subgroup A included patients who demonstrated a swallow disorder prior to chemoradiation (i.e. baseline) and continued to demonstrate it at 12 months post completion of chemoradiation. Subgroup B included patients who demonstrated a swallow disorder at baseline but did not continue to have the disorder at 12 months post completion of chemoradiation. Subgroups were compared statistically using the Wilcoxon Rank Sum Test.

Results
The frequency of occurrence of reduced tongue base retraction in the 40 patients at baseline and 12 months is reported in Table 1. Nine patients demonstrated the reduced tongue base retraction at baseline and at 12 months. Eleven patients had the disorder at baseline but not at 12 months. Six patients did not show the problem at baseline but did show the problem at 12 months. Fourteen patients did not have a reduction in tongue base at any point during that 12-month period.

There were two patient subgroups of interest who had reduced tongue base motion in swallowing. Subgroup A is the group of 9 patients who had the tongue base retraction problem both before and at 12 months post treatment. Subgroup B consists of the 11 patients who had the tongue base retraction problem before their chemoradiation but did not have it at 12 months post treatment. The difference in swallow function profiles raises the question, “Was IMRT dose to different structures in the larynx and pharynx related to the difference in swallow function as defined by these two subgroups?”

Table 2 summarizes the age, gender, and tumor characteristics of the two patient groups. The two groups did not differ significantly on age, gender, or location of tumor. The most frequent location of tumor was oropharyngeal.

We hypothesized that those patients who had a swallowing problem pre-treatment and no problem at 12 months post-treatment either received less radiation than those in whom the swallowing problem remained, or received more radiation possibly obtaining greater tumor control, thereby resulting in fewer swallowing problems at 12 months.

Table 3 presents the radiation doses to structures of interest for the two subgroups. The tongue base extends down to behind the epiglottis and to the top of the larynx. IMRT dose tended to be higher in patients who did not have tongue base problems at 12 months post tumor treatment (subgroup B). Results were statistically significant at p<.05 for the glottic larynx, cricoid cartilage, thyroid cartilage, and subglottic larynx. Doses to the

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>9</td>
</tr>
<tr>
<td>B</td>
<td>11</td>
</tr>
</tbody>
</table>

Table 2: Age, gender, and tumor characteristics of subgroup A (patients who demonstrated reduced tongue base retraction at baseline and at 12 months post completion of chemoradiation with IMRT) and subgroup B (patients who demonstrated reduced tongue base retraction at baseline but not at 12 months post completion of chemoradiation with IMRT).

<table>
<thead>
<tr>
<th></th>
<th>Subgroup A</th>
<th>Subgroup B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>mean age (sem)</td>
<td>54.2 (3.7)</td>
<td>55.8 (2.7)</td>
<td>0.76</td>
</tr>
<tr>
<td>% male</td>
<td>89%</td>
<td>64%</td>
<td>0.32</td>
</tr>
<tr>
<td>% oropharyngeal</td>
<td>78%</td>
<td>45%</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Table 1: Presence of the Swallow Disorder “Reduced Tongue Base Retraction” at baseline and 12 months post-completion of chemoradiation with IMRT.
epiglottis and supraglottic laryngeal structures were not significantly different between the two groups.

Delay in the triggering of the pharyngeal swallow is also a frequent and potentially debilitating swallow disorder after treatment for HNC. Table 4 summarizes the occurrence of this swallow disorder in the 40 patients. Eleven of the patients had a delay in triggering the swallow both at baseline and at 12 months. Sixteen had the problem at baseline but not at 12 months. Two patients did not have the problem at baseline but did at 12 months post treatment. Eleven patients did not have a delayed swallow at either time point.

The two subgroups of interest in relation to the delayed pharyngeal swallow are the 11 who had the problem at both time points (subgroup A) and the 16 patients who had the delayed swallow before the chemoradiation treatment but did not have it at 12 months post-treatment (subgroup B). Our interest was to determine whether the IMRT dose to different structures in these two groups related to the occurrence of delayed pharyngeal swallow.

Patients in subgroups A and B did not differ significantly in mean age, gender, or percentage with oropharyngeal tumor location (Table 5).

Table 6 indicates that none of the IMRT doses to the structures of interest were significantly different between patients whose delayed pharyngeal swallow remained at 12 months as compared to those who had no delay in the pharyngeal swallow at 12 months.

Conclusions

Patients with reduced tongue base retraction at pre-treatment who did not have this problem at 12 months post-treatment received higher doses of radiation to laryngeal structures than did patients in whom the problem persisted at 12 months post-treatment completion. Higher radiation doses may have resulted in more effective tumor control, resulting in amelioration of reduced tongue base movement during swallowing.

The delayed pharyngeal swallow was not affected by doses to the region of the base of tongue and larynx. It is likely that doses in the posterior oral cavity must be examined in more detail in order to understand effects of IMRT on the delay in triggering of the pharyngeal swallow.

---

**Table 3:** Mean (se) radiation dose in cGy to structures of interest for subgroup A (patients who demonstrated reduced tongue base retraction at baseline and at 12 months post completion of chemoradiation with IMRT) and subgroup B (patients who demonstrated reduced tongue base retraction at baseline but not at 12 months post completion of chemoradiation with IMRT).

<table>
<thead>
<tr>
<th>Structure</th>
<th>Subgroup A</th>
<th>Subgroup B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>9</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>oral cavity</td>
<td>6612 (185)</td>
<td>6339 (251)</td>
<td>0.57</td>
</tr>
<tr>
<td>epiglottis</td>
<td>6724 (219)</td>
<td>7091 (227)</td>
<td>0.24</td>
</tr>
<tr>
<td>suprahypoid epiglottis</td>
<td>7146 (167)</td>
<td>7177 (205)</td>
<td>0.73</td>
</tr>
<tr>
<td>infrahyoid epiglottis</td>
<td>6146 (313)</td>
<td>6856 (280)</td>
<td>0.06</td>
</tr>
<tr>
<td>supraglottic larynx</td>
<td>6313 (280)</td>
<td>6941 (245)</td>
<td>0.16</td>
</tr>
<tr>
<td>arytenoid cartilage</td>
<td>5871 (363)</td>
<td>6598 (269)</td>
<td>0.10</td>
</tr>
<tr>
<td>aryepiglottic folds</td>
<td>6475 (261)</td>
<td>6968 (228)</td>
<td>0.31</td>
</tr>
<tr>
<td>glottic larynx</td>
<td>5597 (376)</td>
<td>6582 (291)</td>
<td>0.05*</td>
</tr>
<tr>
<td>subglottic larynx</td>
<td>5316 (330)</td>
<td>6330 (245)</td>
<td>0.04*</td>
</tr>
<tr>
<td>thyroid cartilage</td>
<td>6159 (248)</td>
<td>6850 (206)</td>
<td>0.04*</td>
</tr>
<tr>
<td>cricoid cartilage</td>
<td>5570 (290)</td>
<td>6397 (228)</td>
<td>0.04*</td>
</tr>
</tbody>
</table>

**Table 4:** Presence of the Swallow Disorder “Delayed Pharyngeal Swallow” at baseline and 12 months post-completion of chemoradiation with IMRT.

<table>
<thead>
<tr>
<th>Baseline</th>
<th>12 months</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>11</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>16</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>11</td>
</tr>
</tbody>
</table>

**Table 5:** Age, gender, and tumor characteristics of subgroup A (patients who demonstrated delayed pharyngeal swallow at baseline and at 12 months post completion of chemoradiation with IMRT) and subgroup B (patients who demonstrated reduced delayed pharyngeal swallow at baseline but not at 12 months post completion of chemoradiation with IMRT).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subgroup A</th>
<th>Subgroup B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>mean age (sem)</td>
<td>52.4 (4.3)</td>
<td>54.6 (3.4)</td>
<td>0.54</td>
</tr>
<tr>
<td>% male</td>
<td>73%</td>
<td>88%</td>
<td>0.37</td>
</tr>
<tr>
<td>% oropharyngeal</td>
<td>82%</td>
<td>81%</td>
<td>0.99</td>
</tr>
</tbody>
</table>

**Table 6:** Mean (se) radiation dose in cGy to structures of interest for subgroup A (patients who demonstrated reduced tongue base retraction at baseline and at 12 months post completion of chemoradiation with IMRT) and subgroup B (patients who demonstrated reduced tongue base retraction at baseline but not at 12 months post completion of chemoradiation with IMRT).
It is unclear the amount of dose reduction or increase that will facilitate more nearly normal swallowing. Thus, at this time the effect of IMRT on swallow function is based upon speculation and needs further research.

References


<table>
<thead>
<tr>
<th>Subgroup</th>
<th>A</th>
<th>B</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of patients</td>
<td>11</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>oral cavity</td>
<td>6703 (142)</td>
<td>6469 (192)</td>
<td>0.66</td>
</tr>
<tr>
<td>epiglottis</td>
<td>6917 (189)</td>
<td>6986 (165)</td>
<td>0.73</td>
</tr>
<tr>
<td>suprathyroid epiglottis</td>
<td>7237 (143)</td>
<td>7171 (136)</td>
<td>0.81</td>
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<tr>
<td>infrathyroid epiglottis</td>
<td>6469 (286)</td>
<td>6532 (213)</td>
<td>0.99</td>
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<tr>
<td>supraglottic larynx</td>
<td>6548 (239)</td>
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<td>0.88</td>
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<tr>
<td>arytenoid cartilage</td>
<td>6041 (329)</td>
<td>5892 (275)</td>
<td>0.66</td>
</tr>
<tr>
<td>aryepiglottic folds</td>
<td>6683 (221)</td>
<td>6706 (179)</td>
<td>0.92</td>
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<tr>
<td>glottic larynx</td>
<td>5812 (336)</td>
<td>5912 (278)</td>
<td>0.88</td>
</tr>
<tr>
<td>subglottic larynx</td>
<td>5532 (316)</td>
<td>5498 (324)</td>
<td>0.88</td>
</tr>
<tr>
<td>thyroid cartilage</td>
<td>6401 (218)</td>
<td>6515 (171)</td>
<td>0.81</td>
</tr>
<tr>
<td>cricoid cartilage</td>
<td>5789 (285)</td>
<td>5680 (270)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Table 6: Mean (se) radiation dose in cGy to structures of interest for subgroup A (patients who demonstrated delayed pharyngeal swallow at baseline and at 12 months post completion of chemoradiation with IMRT) and subgroup B (patients who demonstrated reduced delayed pharyngeal swallow at baseline but not at 12 months post completion of chemoradiation with IMRT).
The American Association of Cancer Research (AACR) has released its second Annual Report on Cancer Survivorship in the United States. According to the report, as of January 2012, there were 13.7 million cancer survivors living in the United States with an expected growth to 18 million by 2022. With this increasing number of cancer survivors, the ability of the oncologist to provide ongoing surveillance is challenged by time constraints, financial limitations, and reimbursement issues. Furthermore, each cancer patient travels with unique physical and psychological needs mandating that survivorship plans consider prevention, early detection, diagnosis, treatment, advance directives, and end of life care.

Cancer Survivorship: An Emerging Health Care Priority
The Institute of Medicine (IOM) released a report in 2006 titled From Cancer Patient to Cancer Survivor: Lost in Translation. This report ignited interest in developing post cancer treatment care and clinics to target and address the needs of patients living with cancer. A key recommendation from this report was a call for the development of survivorship care plans (SCPs) for each patient. SCPs are personalized documents provided at the end of treatment and are designed to improve the communication and coordination of care between healthcare providers as patients transition from oncology treatment to primary care.
The IOM recommends that the following elements be included in SCPs: diagnostic tests and results, tumor characteristics, dates of treatment initiation and completion, types of treatment used, including agents and dosages, indicators of treatment response and toxicities, psychosocial, nutritional, and other supportive services provided, contact information, and identification of a key coordinator of care. Of equal importance is inclusion of information regarding follow up needs, such as the projected course of the disease, recommended screening, and information about possible late and long term effects of treatment. While the screening and follow up recommendations populate these guidelines and are of particular importance to Primary Care Providers (PCPs), information detailing late and long term effects of cancer treatment, which patients seek, has been lacking and has resulted in patient dissatisfaction and disenchantment.²

Endorsed by the American Society of Clinical Oncology (ASCO) and The American College of Surgeons Commission on Cancer³, SCPs have been favorably rated by PCPs who reported that SCPs assisted them in providing long term care to their patients with cancer and increased their understanding of late and long term treatment effects and surveillance requirements. Oncologists,⁴ however, have raised concerns about the feasibility of SCPs, noting that time constraints hamper their ability to provide complete and effective care plans. Furthermore, the time devoted to SCPs is not reimbursable and there is no clear recommendation as to who should take ownership for SCPs completion and for reviewing them with patients and, if necessary, their families. SCPs undoubtedly require time, financial resources, and institutional commitment, and in the present healthcare payment environment are low on the list of priorities. Consequently, despite the wide support for expanded use of SCPs among patients, oncologists, and PCPs, fewer than half of National Cancer Institute (NCI) cancer centers provide their patients with these plans.³

Transitions
Survivorship is a period of transition and is rarely faced alone. It encompasses the time from diagnosis through the balance of life and includes family, friends, and caregivers. Survivorship presents growing challenges for the oncologist, the patient, and the patient’s PCP as the patient living with cancer transitions from treatment to surveillance and long term supportive care. Considerations, such as long term follow up care, management of long term and late effects of cancer and its treatment, cancer rehabilitation, and health promotion and prevention are paramount. Furthermore, unexpected psychological and psychosocial issues during the survivorship period are compounding.

Most of the work related to SCPs has been developed in the pediatric population. The Children’s Oncology Group (COC) has developed the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers.⁵ These guidelines are regularly updated and serve as a resource for clinicians who provide ongoing care to survivors of childhood malignancies. Recommendations related to the screening and management of potential late and long term effects of the pediatric cancer treatment are made. On the contrary, established and evidence based guidelines are yet to be developed in the management and monitoring of long term effects of cancer therapy in adult cancer survivors. The absence of established consensus regarding standards of care, clinical practice guidelines, or quality of care measurements in the senior adult population remains an obstacle to the wide-spread institution of survivorship plans for this cohort.

Senior Adult Survivors
It has become increasingly apparent in the care domain of the geriatric cancer survivor that adult cancer survivorship guidelines and standards of care are critical to the establishment of effective, meaningful, and purposeful survivorship care plans. As individuals age, their risk of developing cancer increases and many of the genetic processes contributing to aging play a role in cancer development. For example, telomere shortening, a major theory of aging, has been linked to both the natural progression of aging as well as the development of numerous types of cancers.⁶ Not surprisingly, 61% of new cancer diagnoses occur in individuals age 65 years and older. As in all other patient populations, increasing numbers of geriatric patients are surviving cancer, with those over the age of 65 estimated at 6.5 million and projected to increase as the aging population explodes.⁷ Interestingly, many of these survivors have one or more comorbid illnesses.
A population based study by Kendal et al to evaluate the complex interplay between age and mortality on different types of cancers found that for biologically aggressive cancers, deaths attributable to the cancer itself exceeded deaths from comorbidities. However, for the other 70% of cancer types deaths due to comorbidities far outnumbered those attributed to cancer. These results underscore the importance of comprehensive planning and assessment of senior adult cancer survivors, many of whom are grappling with other serious illnesses.

The IOM’s call for the inclusion of survivorship care plans in the standard of care for cancer survivors poses a unique challenge for the geriatric population. Without question, the SCP for a geriatric patient will be visually and content distinctive from that of a younger cancer survivor. Specifically, older patients present with problems and concerns independent of their cancer and cancer treatment, such as comorbid illnesses, and these must be taken into consideration when drafting a SCP. With this in mind, the Comprehensive Geriatric Assessment (CGA) can serve as a tool for guiding survivorship care and developing effective SCPs for the senior adult population.

The Comprehensive Geriatric Assessment
The major components of the CGA include medical assessment, assessment of functional capacity, psychological assessment, including assessment of mood and cognition, social assessment and environmental assessment, including home safety evaluation, plus advanced care preferences. For example, in older patients with high-risk myelodysplastic syndrome or acute myeloid leukemia, the CGA, along with the geriatric depression scale (GDS-9), was found to be useful in identifying treatment-related issues. The assessment tool was recommended for inclusion in routine clinical outcomes analysis and the authors recommended its use when making decisions about treatment and regimen intensity.

Senior Oncology Outcomes Advocacy and Research (SOAR) Program
We recently launched the Senior Oncology Outcomes Advocacy and Research (SOAR) Program at the Robert H. Lurie Comprehensive Cancer Center under a grant from the Coleman Foundation. SOAR is a multifaceted program aimed at improving the overall health outcomes for older individuals living with cancer and is strategically positioned to address the needs of the aging baby boomer generation living with cancer. One of SOAR’s foci will be the development of SCPs for older individuals, taking into consideration the spectrum of comorbid illnesses attendant to aging and the intersection of physiologic organ systems changes with pathologic changes exerted by cancer. Sensory impairment (vision and hearing loss, neuropathy, loss of postural balance), cognitive impairment, and functional decline are several of the core constructs that will be explored and addressed.

Individualization of SCPs is important
Individualized models of care work best for aging patients. One size does not fit all. SCPs will succeed through collaboration with multiple stakeholders, chief of whom will be the patient. The geriatric patient is not an aging child, but rather a unique human being with peculiar physiologic changes that must be addressed when cancer treatment is being contemplated and survivorship plans drafted. It is well settled that any core geriatric survivorship care plan must embrace not only physical concerns, but also psychosocial, cognitive, spiritual, cultural, and community concerns. As such, the Comprehensive Geriatric Assessment should serve as the framework for an effective survivorship care plan.

Conclusion
The next decade will be a true test of the efficacy and fidelity of Survivorship Care Plans. With the aging tsunami and age-related physiologic changes affecting major organ systems, differentiating between cancer-related effects and age-related effects will be challenging. The provision of excellent survivorship care will therefore rest with a multidisciplinary care team of geriatricians, mid-level geriatrics providers, oncologists, geriatric social workers, and patient advocates working in concert to mitigate these effects. Finally, research focusing on SCPs across cancers more prevalent among aging populations and on culturally competent patient centric SCPs is needed to inform the development of robust models of cancer survivorship for the geriatric patient. The SOAR program stands ready to lead in this effort.

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: Ramana Davuluri, PhD
Administrative Director: Abby Consentino-Boehm
312.503.2306 or a-consentino-boehm@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 tchew@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 multi-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 Genta.

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 amy@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*  
*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: Stephen Rohan, MD*  
*Associate Director: Efstathaia Bakou*  
*312.503.1159 or s-rohan@northwestern.edu*  
*e-bakou@northwestern.edu*

The Pathology Core Facility has three main components: research histology, specimen procurement and protocol review. The research histology component provides all of the tissue processing and histology services typically performed in a clinical laboratory but it is specifically dedicated to the needs of the Northwestern University research community in general and the Cancer Center research community in particular. The Pathology Core Facility is unique in that it has the capability and flexibility to address specific research protocol needs. The tissue procurement component of the Pathology Core Facility has two main functions: (1) human tissue and fluid procurement, storage and distribution and (2) quality assurance and protection of research subjects. The tissue procurement component addresses the growing need for human tissue and serves as an “honest broker” with HIPAA covered entities in an effort to expedite research activities, particularly in the use of human biological materials and associated data.
Structural Biology Facility  
*Director:* Alfonso Mondragon, PhD  
*Facility Manager:* Pamela Focia, PhD  
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focia@northwestern.edu

The facility is essential for the research programs of investigators who are studying the relationship between macromolecular structure and function, or who are using protein structure as the starting point for structure-based drug design. The Structural Biology Facility is a unique resource at Northwestern University that capitalizes on the extensive expertise of a large group of users and regular access to the synchrotron radiation X-ray source at the 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  
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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.
Trifilio, Steven; Zhou, Zheng; Mehta, Jayesh; Czerniak, Colleen; Pi, Judy; Greenberg, Deborah; Koslosky, Molly; Pantiru, Mihaela; Altman, Jessica

Idarubicin appears equivalent to dose-intense daunorubicin for remission induction in patients with acute myeloid leukemia.


**Abstract**

Daunorubicin has historically been considered the anthracycline of choice at many cancer centers for the treatment of acute myeloid leukemia (AML). Drug shortages have required the substitution of daunorubicin with idarubicin. Randomized studies have shown idarubicin (10-12mg/m2) to be comparable or superior to standard dose daunorubicin (45-60mg/m2) for achieving complete remission (CR). Whether these results can be extrapolated to dose-intense daunorubicin (90mg/m2), recently shown to improve CR rates when compared to standard daunorubicin doses remains uncertain. This observational study was conducted at Northwestern Memorial Hospital (NMH) to compare CR rates. The results suggest idarubicin is equivalent to daunorubicin, and for some subsets of patients, idarubicin may have superior CR rates.

Bilimoria, Karl Y; Chung, Jeanette; Ju, Mila H; Haut, Elliott R; Bentrem, David J; Ko, Clifford Y; Baker, David W

Evaluation of Surveillance Bias and the Validity of the Venous Thromboembolism Quality Measure.


**Abstract**

**IMPORTANCE** Postoperative venous thromboembolism (VTE) rates are widely reported quality metrics soon to be used in pay-for-performance programs. Surveillance bias occurs when some clinicians use imaging studies to detect VTE more frequently than other clinicians. Because they look more, they find more VTE events, paradoxically worsening their hospital’s VTE quality measure performance. A surveillance bias may influence VTE measurement if (1) greater hospital VTE prophylaxis adherence fails to result in lower measured VTE rates, (2) hospitals with characteristics suggestive of higher quality (eg, more accreditations) have greater VTE prophylaxis adherence rates but worse VTE event rates, and (3) higher hospital VTE imaging utilization use rates are associated with higher measured VTE event rates. **OBJECTIVE** To examine whether a surveillance bias influences the validity of reported VTE rates. **DESIGN, SETTING, AND PARTICIPANTS**
2010 Hospital Compare and American Hospital Association data from 2838 hospitals were merged. Next, 2009-2010 Medicare claims data for 954,926 surgical patient discharges from 2786 hospitals who were undergoing 1 of 11 major operations were used to calculate VTE imaging (duplex ultrasonography, chest computed tomography/magnetic resonance imaging, and ventilation-perfusion scans) and VTE event rates. MAIN OUTCOMES AND MEASURES The association between hospital VTE prophylaxis adherence and risk-adjusted VTE event rates was examined. The relationship between a summary score of hospital structural characteristics reflecting quality (hospital size, numbers of accreditations/quality initiatives) and performance on VTE prophylaxis and risk-adjusted VTE measures was examined. Hospital-level VTE event rates were compared across VTE diagnostic imaging rate quartiles and with a quantile regression. RESULTS Greater hospital VTE prophylaxis adherence rates were weakly associated with worse risk-adjusted VTE event rates ($r^2 = 4.2\%$; $P = .03$). Hospitals with increasing structural quality scores had higher VTE prophylaxis adherence rates (93.3% vs 95.5%, lowest vs highest quality quartile; $P < .001$) but worse risk-adjusted VTE rates (4.8 vs 6.4 per 1000, lowest vs highest quality quartile; $P < .001$). Mean VTE diagnostic imaging rates ranged from 32 studies per 1000 in the lowest imaging use quartile to 167 per 1000 in the highest quartile ($P < .001$). Risk-adjusted VTE rates increased significantly with VTE imaging use rates in a stepwise fashion, from 5.0 per 1000 in the lowest quartile to 13.5 per 1000 in the highest quartile ($P < .001$). CONCLUSIONS AND RELEVANCE Hospitals with higher VTE prophylaxis rates but worse risk-adjusted VTE rates. Increased hospital VTE event rates were associated with increasing hospital VTE imaging use rates. Surveillance bias limits the usefulness of the VTE quality measure for hospitals working to improve quality and patients seeking to identify a high-quality hospital.

Moy, Irene; Lin, Zhihong; Rademaker, Alfred W; Reierstad, Scott; Khan, Seema A; Bulun, Serdar E


Abstract
Aromatase inhibitors (AIs) are the most effective class of drugs in the endocrine treatment of breast cancer, with an approximate 50% treatment response rate. Our objective was to determine whether intratumoral expression levels of estrogen-related genes are predictive of AI responsiveness in postmenopausal women with breast cancer. Primary breast carcinomas were obtained from 112 women who received AI therapy after failing adjuvant tamoxifen therapy and developing recurrent breast cancer. Tumor ERalpha and PR protein expression were analyzed by immunohistochemistry (IHC). Messenger RNA (mRNA) levels of 5 estrogen-related genes-AKR1C3, aromatase, ERalpha, and 2 estradiol/ERalpha target genes, BRCA1 and PR-were measured by real-time PCR. Tumor protein and mRNA levels were compared with breast cancer progression rates to determine predictive accuracy. Responsiveness to AI therapy-defined as the combined complete response, partial response, and stable disease rates for at least 6 months-was 51%; rates were 56% in ERalpha-IHC-positive and 14% in ERalpha-IHC-negative tumors. Levels of ERalpha, PR, or BRCA1 mRNA were independently predictive for responsiveness to AI. In cross-validated analyses, a combined measurement of tumor ERalpha and PR mRNA levels yielded a more superior specificity (36%) and identical sensitivity (96%) to the current clinical practice (ERalpha/PR-IHC). In patients with ERalpha/PR-IHC-negative tumors, analysis of mRNA expression revealed either non-significant trends or statistically significant positive predictive values for AI responsiveness. In conclusion, expression levels of estrogen-related mRNAs are predictive for AI responsiveness in postmenopausal women with breast cancer, and mRNA expression analysis may improve patient selection.

Ono, Masanori; Yin, Ping; Navarro, Antonia; Moravek, Molly B; Coon, John S 5th; Druschitz, Stacy A; Serna, Vanida Ann; Qiang, Wenan; Brooks, David C; Malpani, Saurabh S; Ma, Jiajia; Ercan, Cihangir Mutlu; Mittal, Navdha; Monsivais, Diana; Dyson, Matthew T; Yemelyanov, Alex; Maruyama, Tetsuo; Chakravarti, Deabrata; Kim, J Julie; Kurita,
Takeshi; Gottardi, Cara J; Bulun, Serdar E

Paracrine Activation of WNT/Beta-catenin Pathway in Uterine Leiomyoma Stem Cells Promotes Tumor Growth.


**Abstract**

Uterine leiomyomas are extremely common estrogen and progesterone-dependent tumors of the myometrium and cause irregular uterine bleeding, severe anemia, and recurrent pregnancy loss in 15-30% of reproductive-age women. Each leiomyoma is thought to arise from a single mutated myometrial smooth muscle stem cell. Leiomyoma side-population (LMSP) cells comprising 1% of all tumor cells and displaying tumor-initiating stem cell characteristics are essential for estrogen- and progesterone-dependent in vivo growth of tumors, although they have remarkably lower estrogen/progesterone receptor levels than mature myometrial or leiomyoma cells. However, how estrogen/progesterone regulates the growth of LMSP cells via mature neighboring cells is unknown. Here, we demonstrate a critical paracrine role of the wingless-type (WNT)/beta-catenin pathway in estrogen/progesterone-dependent tumorigenesis, involving LMSP and differentiated myometrial or leiomyoma cells. Estrogen/progesterone treatment of mature myometrial cells induced expression of WNT11 and WNT16, which remained constitutively elevated in leiomyoma tissues. In LMSP cells cocultured with mature myometrial cells, estrogen-progesterone selectively induced nuclear translocation of beta-catenin and induced transcriptional activity of its target gene AXIN2, leading to the proliferation of LMSP cells. This effect could be blocked by a WNT antagonist. Ectopic expression of inhibitor of beta-catenin and T-cell factor 4 in LMSP cells, but not in mature leiomyoma cells, blocked the estrogen/progesterone-dependent growth of human tumors in vivo. We uncovered a paracrine role of the WNT/beta-catenin pathway that enables mature myometrial or leiomyoma cells to send mitogenic signals to neighboring tissue stem cells in response to estrogen and progesterone, leading to the growth of uterine leiomyomas.

Cassidy, Justin J; Jha, Aashish R; Posadas, Diana; Giri, Ritika; Venken, Koen JT; Ji, Jingran; Jiang, Hongmei; Bellen, Hugo J; White, Kevin P; Carthew, Richard W

miR-9a Minimizes the Phenotypic Impact of Genomic Diversity by Buffering a Transcription Factor.


**Abstract**

Gene expression has to withstand stochastic, environmental and genomic perturbations. For example, in the latter case, 0.5-1% of the human genome is typically variable between any two unrelated individuals. Such diversity might create problematic variability in the activity of gene regulatory networks, and ultimately, in cell behaviors. Using multigenerational selection experiments, we find that for the proneural network, the effect of genomic diversity is dampened by miR-9a-mediated regulation of senseless expression. Reducing miR-9a regulation of the Senseless transcription factor frees the genomic landscape to exert greater phenotypic influence. Whole genome sequencing identified genomic loci that potentially exert such effects. A larger set of sequence variants, including variants within proneural network genes, exhibit these characteristics when miR-9a concentration is reduced. These findings reveal that microRNA-target interactions may be a key mechanism by which the impact of genomic diversity on cell behavior is dampened.

Sullivan LB, Martinez-Garcia E, Nguyen H, Mullen AR, Dufour E, Sudarshan S, Licht JD, Deberardinis RJ, Chandel NS.

The Proto-oncometabolite Fumarate Binds Glutathione to Amplify ROS-Dependent Signaling.


**Abstract**

The tricarboxylic acid cycle enzyme fumarate hydratase (FH) has been identified as a tumor suppressor in a subset of human renal cell carcinomas. Human FH-deficient cancer cells display high fumarate concentration and ROS levels along with activation of HIF-1.
The underlying mechanisms by which FH loss increases ROS and HIF-1 are not fully understood. Here, we report that glutamine-dependent oxidative citric acid cycle metabolism is required to generate fumarate and increase ROS and HIF-1 levels. Accumulated fumarate directly bonds the antioxidant glutathione in vitro and in vivo to produce the metabolite succinated glutathione (GSF). GSF acts as an alternative substrate to glutathione reductase to decrease NADPH levels and enhance mitochondrial ROS and HIF-1 activation. Increased ROS also correlates with hypermethylation of histones in these cells. Thus, fumarate serves as a proto-oncometabolite by binding to glutathione which results in the accumulation of ROS.

Chen, Yolande; Aardema, Jorie; Kale, Sayali; Whirsch, Zakary; Awomolo, Arinola; Blanchard, Elisabeth; Chang, Brian; Myers, David; Ju, Lining; Tran, Reginald; Reece, David; Christensen, Hilary; Boukour, Siham; Debili, Najet; Strom, Ted; Rawlings, David; Vazquez, Francisco; Voth, Gregory; Zhu, Cheng; Kahr, Walter; Lam, Wilbur; Corey, Seth

Loss of the F-BAR Protein CIP4 Reduces Platelet Production by Impairing Membrane-Cytoskeleton Remodeling.


Abstract
Megakaryocytes generate platelets through extensive reorganization of the cytoskeleton and plasma membrane. Cdc42 interacting protein 4 (CIP4) is an F-BAR protein that localizes to membrane phospholipids through its BAR domain and interacts with Wiskott-Aldrich Syndrome Protein (WASP) via its SRC homology 3 domain. F-BAR proteins promote actin polymerization and membrane tubulation. To study its function, we generated CIP4-null mice that displayed thrombocytopenia similar to that of WAS(-/-) mice. The number of megakaryocytes and their progenitors was not affected. However, the number of proplatelet protrusions was reduced in CIP4-null, but not WAS(-/-), megakaryocytes. Electron micrographs of CIP4-null megakaryocytes showed an altered demarcation membrane system. Silencing of CIP4, not WASP, expression resulted in fewer proplatelet-like extensions.

Fluorescence anisotropy studies showed that loss of CIP4 resulted in a more rigid membrane. Micropipette aspiration demonstrated decreased cortical actin tension in megakaryocytic cells with reduced CIP4 or WASP protein. These studies support a new biophysical mechanism for platelet biogenesis whereby CIP4 enhances the complex, dynamic reorganization of the plasma membrane (WASP independent) and actin cortex network (as known for WASP and cortical actin) to reduce the work required for generating proplatelets. CIP4 is a new component in the highly coordinated system of megakaryocytic membrane and cytoskeletal remodeling affecting platelet production.

Shah, Chirag; Bei, Ling; Wang, Hao; Platnias, Leonidas; Eklund, Elizabeth

The Leukemia-Associated Mll-Ell Oncoprotein Induces Fibroblast Growth Factor 2 (Fgf2)-dependent Cytokine Hypersensitivity in Myeloid Progenitor Cells.


Abstract
The subset of acute myeloid leukemias (AML) with chromosomal translocations involving the MLL gene have poor prognosis (referred to as 11q23-AML). The MLL-fusion proteins that are expressed in 11q23-AML facilitate transcription of a set of HOX genes, including HOXA9 and HOXA10. Since Hox proteins are transcription factors, this suggests the possibility that Hox target genes mediate the adverse effects of MLL-fusion proteins in leukemia. Identifying such Hox target genes might provide insights to the pathogenesis and treatment of 11q23-AML. In the current study, we found that Mll-Ell (an MLL-fusion protein) induced transcriptional activation of the FGF2 gene in a HoxA9 and HoxA10 dependent manner. FGF2 encodes Fibroblast Growth Factor 2 (also referred to as basic Fibroblast Growth Factor). Fgf2 influences proliferation and survival of hematopoietic stem cells and myeloid progenitor cells, and increased Fgf2-expression has been described in AML. We determined that expression of Mll-Ell in myeloid progenitor cells resulted in autocrine production of Fgf2, and Fgf2-dependent cytokine hypersensitivity. Therefore, our results implicated increased Fgf2-expression...
in progenitor proliferation and expansion in 11q23-AML. Since small molecule inhibitors of Fgf-receptors are in human clinical trials, this suggested a potential therapeutic approach to this treatment refractory leukemia.

Huang W; Bei L; Eklund EA.

Fas-Associated Phosphatase 1 (Fap1) Influences βcatenin Activity in Myeloid Progenitor Cells Expressing the Bcr-abl Oncogene.


Abstract
Increased betacatenin activity correlates with leukemia stem cell (LSC) expansion and disease progression in chronic myeloid leukemia (CML). We previously found that expression of the CML-related, Bcr-abl oncoprotein in myeloid progenitor cells increases expression of Fas associated phosphatase 1 (Fap1). This resulted in Fap1-dependent resistance to Fas-induced apoptosis in these cells. Fap1 also interacts with the Adenomatous Polyposis Coli (Apc) protein, but the functional significance of this interaction is unknown. Apc participates in a complex that includes Glycogen synthase kinase beta (Gsk3beta) and betacatenin. Assembly of this complex results in phosphorylation of betacatenin by Gsk3beta, which facilitates betacatenin ubiquitination and degradation by the proteasome. In the current study, we found increased association of Fap1 with the Apc complex in Bcr-abl+ myeloid progenitor cells. We also found Fap1-dependent inactivation of Gsk3beta, and consequent stabilization of betacatenin, in these cells. Consistent with this, Bcr-abl+ cells exhibited a Fap1-dependent increase in betacatenin activity. Our studies identified Fap1-dependent Gsk3beta-inactivation as a molecular mechanism for increased betacatenin activity in CML.

Hitsman, Brian; Papandonatos, George D; McChargue, Dennis E; Demott, Andrew; Herrera, Maria Jose; Spring, Bonnie; Borrelli, Belinda; Niaura, Raymond

Past Major Depression and Smoking Cessation Outcome: a Systematic Review and Meta-Analysis Update.


Abstract
AIMS: To update our prior meta-analysis that showed past major depression (MD+) to be unrelated to smoking cessation outcome [Hitsman et al. J Consult Clin Psychol 2003; 71:657-63]. METHODS: Eligible trials included 14 from our original review and 28 identified through an updated systematic review (2000-2009). We coded for assessment of past MD, exclusion for recent MD episode (MDE; /=6 months) abstinence were estimated and combined using random effects. Two-way interaction models of past MD with study methodology and treatment factors were used to evaluate hypothesized moderators of the past MD-abstinence association. RESULTS: MD+ smokers had 17% lower odds of short-term abstinence (n=35, OR=0.83, 95% CI=0.72-0.95, p=0.009) and 19% lower odds of long-term abstinence (n=38, OR=0.81, 95% CI=0.67-0.97, p=0.023) than MD- smokers after excluding the sole study of varenicline because of its antidepressant properties. The association between past MD and abstinence was affected by methodological (recent MDE exclusion, type of MD assessment) and treatment (CBT modality) factors. CONCLUSIONS: Past major depression has a modest adverse effect on abstinence during and after smoking cessation treatment. An increased focus on the identification of effective treatments or treatment adaptations that eliminate this disparity in smoking cessation for MD+ smokers is needed.

Freaney, Jonathan E; Kim, Rebecca; Mandhana, Roli; Horvath, Curt M

Extensive Cooperation of Immune Master Regulators IRF3 and NFkappaB in RNA Pol II Recruitment and Pause Release in Human Innate Antiviral Transcription.


Abstract
Transcription factors interferon regulatory factor 3 (IRF3) and nuclear factor kappaB (NFkappaB) are activated by external stimuli, including virus infection, to translocate to the nucleus and bind genomic targets important for immunity and inflammation. To investigate
RNA polymerase II (Pol II) recruitment and elongation in the human antiviral gene regulatory network, a comprehensive genome-wide analysis was conducted during the initial phase of virus infection. Results reveal extensive integration of IRF3 and NFκB with Pol II and associated machinery and implicate partners for antiviral transcription. Analysis indicates that both de novo polymerase recruitment and stimulated release of paused polymerase work together to control virus-induced gene activation. In addition to known messenger-RNA-encoding loci, IRF3 and NFκB stimulate transcription at regions not previously associated with antiviral transcription, including abundant unannotated loci that encode novel virus-inducible RNAs (nviRNAs). These nviRNAs are widely induced by virus infections in diverse cell types and represent a previously overlooked cellular response to virus infection.

Wang, Jun; Scholtens, Denise; Holko, Michelle; Ivancic, David; Lee, Oukseub; Hu, Hong; Chatterton, Robert T Jr; Sullivan, Megan E; Hansen, Nora; Bethke, Kevin; Zalles, Carola M; Khan, Seema A

Lipid Metabolism Genes in Contralateral Unaffected Breast and Estrogen Receptor Status of Breast Cancer.


Abstract
Risk biomarkers that are specific to estrogen receptor (ER) subtypes of breast cancer would aid the development and implementation of distinct prevention strategies. The contralateral unaffected breast of women with unilateral breast cancer (cases) is a good model for defining subtype-specific risk because women with ER-negative (ER-) index primaries are at high risk for subsequent ER-negative primary cancers. We conducted random fine needle aspiration of the unaffected breasts of cases. Samples from 30 subjects [15 ER-positive (ER+) and 15 ER- cases matched for age, race and menopausal status] were used for Illumina expression array analysis. Findings were confirmed using quantitative real-time PCR (qRT-PCR) in the same samples. A validation set consisting of 36 subjects (12 ER+, 12 ER- and 12 standard-risk healthy controls) was used to compare gene expression across groups. ER- case samples displayed significantly higher expression of 18 genes/transcripts, 8 of which were associated with lipid metabolism on gene ontology analysis (GO: 0006629). This pattern was confirmed by qRT-PCR in the same samples, and in the 24 cases of the validation set. When compared to the healthy controls in the validation set, significant overexpression of 4 genes (DHRS2, HMGCS2, HPGD and ACSL3) was observed in ER- cases, with significantly lower expression of UGT2B11 and APOD in ER+ cases, and decreased expression of UGT2B7 in both subtypes. These data suggest that differential expression of lipid metabolism genes may be involved in the risk for subtypes of breast cancer, and are potential biomarkers of ER-specific breast cancer risk.


The Histone Methyltransferase MMSET/WHSC1 Activates TWIST1 to Promote an Epithelial-Mesenchymal Transition and Invasive Properties of Prostate Cancer.


Abstract
Epigenetic deregulation of gene expression has a role in the initiation and progression of prostate cancer (PCa). The histone methyltransferase MMSET/WHSC1 (Multiple Myeloma SET domain) is overexpressed in a number of metastatic tumors, but its mechanism of action has not been defined. In this work, we found that PCa cell lines expressed significantly higher levels of MMSET compared with immortalized, non-transformed prostate cells. Knockdown experiments showed that, in metastatic PCa cell lines, dimethylation of lysine 36 and trimethylation of lysine 27 on histone H3 (H3K36me2 and H3K27me3, respectively) depended on MMSET expression, whereas depletion of MMSET in benign prostatic cells did not affect chromatin modifications. Knockdown of MMSET in DU145 and PC-3 tumor cells decreased cell proliferation, colony formation in soft agar and strikingly diminished cell migration and invasion. Conversely, overexpression of MMSET in immortalized, non-transformed RWPE-1 cells promoted cell migration and invasion, accompanied by
an epithelial-mesenchymal transition (EMT). Among a panel of EMT-promoting genes analyzed, TWIST1 expression was strongly activated in response to MMSET. Chromatin immunoprecipitation analysis demonstrated that MMSET binds to the TWIST1 locus and leads to an increase in H3K36me2, suggesting a direct role of MMSET in the regulation of this gene. Depletion of TWIST1 in MMSET-overexpressing RWPE-1 cells blocked cell invasion and EMT, indicating that TWIST1 was a critical target of MMSET, responsible for the acquisition of an invasive phenotype. Collectively, these data suggest that MMSET has a role in PCa pathogenesis and progression through epigenetic regulation of metastasis-related genes.

Peck, Clara Bien; Affinati, Alison H; Ramsey, Kathryn Moynihan; Kuo, Hsin-Yu; Yu, Wei; Sena, Laura A; Ilkayeva, Olga; Marcheva, Biliana; Kobayashi, Yumiko; Omura, Chiaki; Levine, Daniel C; Bacsik, David J; Gius, David; Newgard, Christopher B; Goetzman, Eric; Chandel, Navdeep S; Denu, John M; Mrksich, Milan; Bass, Joseph


Abstract
Circadian clocks are self-sustained cellular oscillators that synchronize oxidative and reductive cycles in anticipation of the solar cycle. We demonstrate that the clock transcription feedback loop produces cycles of NAD+ biosynthesis, ATP production, and mitochondrial respiration through modulation of mitochondrial protein acetylation to synchronize oxidative metabolic pathways with the 24-hour fasting and feeding cycle. Circadian control of the activity of the NAD+-dependent deacetylase sirtuin 3 (SIRT3) generated rhythms in the acetylation and activity of oxidative enzymes and respiration in isolated mitochondria, and NAD+ supplementation restored protein deacetylation and enhanced oxygen consumption in circadian mutant mice. Thus, circadian control of NAD+ bioavailability modulates mitochondrial oxidative function and organismal metabolism across the daily cycles of fasting and feeding.

Krov, Sai Archana; Swindell, Elden P; O’Halloran, Thomas V; Nguyen, S. T.


Abstract
Polymer nanoparticles (PNPs) possessing a high density of drug payload have been successfully stabilized against aggregation in biological buffers after amine modification, which renders these PNPs positively charged. The resulting charge-stabilized PNPs retain their original narrow particle size distributions and well-defined spherical morphologies. This stabilization allows these PNPs to have an improved anti-proliferative effect on MDA-MB-231-Br human breast cancer cells compared to non-functionalized PNPs. As a non-cytotoxic control, similar surface-modified PNPs containing cholesterol in place of doxorubicin did not inhibit cell proliferation, indicating that the induced cytotoxic response was solely due to the doxorubicin release from the PNPs.

Crane, Courtney A; Han, Seunggu J; Ahn, Brian; Oehlke, Jessica; Kivett, Valerie; Fedoroff, Anne; Butowski, Nicholas; Chang, Susan M; Clarke, Jennifer; Berger, Mitchel S; McDermott, Michael W; Prados, Michael D; Parsa, Andrew T


Abstract
PURPOSE: Cancer immunotherapy offers hope of a highly specific nontoxic adjuvant treatment. Heat shock protein peptide complexes (HSPPCs) found in cancer cells carry tumor-specific antigenic proteins and can facilitate adaptive and innate immune responses. Here we show that peptides bound to a 96 kD chaperone protein (HSP-96) from brain tissue containing glioblastoma multiforme (GBM) can be used to
safely immunize patients with recurrent GBM. EXPERIMENTAL DESIGN: Multimodality immunomonitoring was completed on 12 patients with recurrent GBM before and after immunization with an autologous HSPPC vaccine derived from surgically resected tumor. Clinical endpoints included safety assessments and overall survival. RESULTS: No adverse events attributable to the vaccine were found. Testing of peripheral blood leukocytes before and after vaccination revealed a significant peripheral immune response specific for the peptides bound to HSP-96, in 11 of the 12 patients treated. Brain biopsies of immune responders after vaccination revealed focal CD4, CD8, and CD56 IFN-γ positive cell infiltrates, consistent with tumor site specific immune responses. Immune responders had a median survival of 47 weeks after surgery and vaccination, compared with 16 weeks for the single nonresponder. CONCLUSIONS: These data provide the first evidence in humans of individual patient-specific immune responses against autologous tumor derived peptides bound to HSP-96.

Penedo, Frank J; Benedict, Catherine; Zhou, Eric S; Rasheed, Mikal; Traeger, Lara; Kava, Bruce R; Soloway, Mark; Czaja, Sara; Antoni, Michael H

Association of Stress Management Skills and Perceived Stress with Physical and Emotional Well-Being Among Advanced Prostate Cancer Survivors Following Androgen Deprivation Treatment.


Abstract
Advanced prostate cancer (APC) is associated with disruptions that compromise health related quality of life (HRQOL). Treatment often includes androgendeprivation therapy (ADT), which results in a range of side effects (e.g., fatigue, urinary dysfunction) that further impact HRQOL. Despite these challenges, there are limited evaluations of the impact of stress and stress management skills on HRQOL among APC survivors on ADT. This study evaluated relationships among stress, stress management skills, and HRQOL, and it was hypothesized that better stress management skills would relate to greater physical and emotional well-being by mitigating perceived stress levels. Participants (N = 77) were 69.7 years old (SD = 9.8), 18.6 months post-treatment (SD = 17.5), and ethnically diverse (65% Non-Hispanic White, 13% Hispanic, 21% African-American). Measures included the Measure of Current Status for stress management skills, the Perceived Stress Scale for perceived stress, and the Medical Outcomes Study-Short Form (MOS SF-36; physical functioning and emotional well-being subscales) for HRQOL. Direct effects and mediation models were evaluated to determine the relationships between perceived stress, stress management skills, and HRQOL domains, controlling for relevant covariates. Stress management skills and perceived stress were significantly associated with physical functioning (β = .24, p < .05 and β = -.43, p < .01, respectively) and emotional well-being (β = .35, p < .01 and β = -.64, p < .01, respectively). Regression analyses supported the hypothesis that reduced perceived stress mediated the relationship between stress management skills and both physical functioning and emotional well-being. These results demonstrate that one way stress management skills may impact HRQOL is by lessening ongoing perceptions of stress.

Mitra AK, Zillhardt M, Hua Y, Tiwari P, Murmann AE, Peter ME, Lengyl E.

MicroRNAs Reprogram Normal Fibroblasts into Cancer-Associated Fibroblasts in Ovarian Cancer.


Abstract
Cancer-associated fibroblasts (CAF) are a major constituent of the tumor stroma, but little is known about how cancer cells transform normal fibroblasts into CAFs. microRNAs (miRNA) are small noncoding RNA molecules that negatively regulate gene expression at a posttranscriptional level. Although it is clearly established that miRNAs are deregulated in human cancers, it is not known whether miRNA expression in resident fibroblasts is affected by their interaction with cancer cells. We found that in ovarian CAFs, miR-31 and miR-214 were downregulated, whereas miR-155 was upregulated when compared with normal or tumor-adjacent fibroblasts. Mimicking this deregulation by transfecting miRNAs
and miRNA inhibitors induced a functional conversion of normal fibroblasts into CAFs, and the reverse experiment resulted in the reversion of CAFs into normal fibroblasts. The miRNA-reprogrammed normal fibroblasts and patient-derived CAFs shared a large number of upregulated genes highly enriched in chemokines, which are known to be important for CAF function. The most highly upregulated chemokine, CCL5, (C-C motif ligand 5) was found to be a direct target of miR-214. These results indicate that ovarian cancer cells reprogram fibroblasts to become CAFs through the action of miRNAs. Targeting these miRNAs in stromal cells could have therapeutic benefit.

Mehrotra, Swarna; Sharma, Bhumika; Joshi, Sonali; Kroczynska, Barbara; Majchrzak, Beata; Stein, Brady L; McMahon, Brandon; Altman, Jessica K; Licht, Jonathan D; Baker, Darren P; Eklund, Elizabeth A; Wickrema, Amittha; Verma, Amit; Fish, Eleanor N; Platanias, Leonidas C

Essential Role for the Mnk-Pathway in the Inhibitory Effects of Type I Interferons on Myeloproliferative Neoplasm (MPN) Precursors.


Abstract

The mechanisms of generation of the antineoplastic effects of interferons (IFNs) in malignant hematopoietic cells remain to be precisely defined. We examined the activation of Type I IFN-dependent signaling pathways in malignant cells transformed by Jak2V617F, a critical pathogenic mutation in myeloproliferative neoplasms (MPNs). Our studies demonstrate that during engagement of the Type I IFN receptor (IFNAR) there is activation of Jak-Stat pathways and also engagement of Mnk kinases. Activation of Mnk kinases is regulated by the MeK/Erk pathway and is required for the generation of IFN-induced growth inhibitory responses, but Mnk kinase activation does not modulate IFN-regulated Jak-Stat signals. We demonstrate that in order for Type I IFNs to exert suppressive effects in malignant hematopoietic progenitors from patients with Polycythemia Vera (PV), induction of Mnk kinase activity is required, as evidenced by studies involving pharmacological inhibition of Mnk or siRNA-mediated Mnk knock-down. Altogether, these findings provide evidence for key and essential roles of the Mnk kinase pathway in the generation of the antineoplastic effects of Type I IFNs in Jak2V617F-dependent MPNs.

Mavrommatis E; Arslan AD; Sassano A, Hua Y; Kroczynska B; Platanias LC.

Expression and Regulatory Effects of Murine Schlafen (sfln) Genes in Malignant Melanoma and Renal Cell Carcinoma.


Abstract

There is emerging evidence that the IFN-inducible family of Slfn genes and proteins play important roles in cell cycle progression and control of cellular proliferation, but the precise functional roles of different mouse Slfn members in the regulation of tumorigenesis remain unclear. In the present study, we undertook a systematic analysis on the expression and functional relevance of different mouse Slfn genes in malignant melanoma and renal cell carcinoma cells. Our studies demonstrate that several mouse Slfn genes are up-regulated in response to IFN treatment of mouse melanoma and renal cell carcinoma cells, including Slfn1, Slfn2, Slfn4, Slfn5, and Slfn8. Our data show that Slfn2 and Slfn3 play essential roles in the control of mouse malignant melanoma cell proliferation and/or anchorage-independent growth, suggesting key and non-overlapping roles for these genes in the control of malignant melanoma tumorigenesis. In renal cell carcinoma cells, in addition to Slfn2 and Slfn3, Slfn5 also exhibits important antineoplastic effects. Altogether, our findings indicate important functions for distinct mouse Slfn genes in the control of tumorigenesis and provide evidence for differential involvement of distinct members of this gene family in controlling tumorigenesis. They also raise the potential of future therapeutic approaches involving modulation of expression of members of this family of genes in malignant melanoma and renal cell carcinoma.
Abstract
Rising costs and a workforce talent shortage are two of the health care industry’s most pressing challenges. In particular, serious illnesses often impose significant costs on individuals and their families, which can place families at an increased risk for multigenerational economic deprivation or even an illness-poverty trap. At the same time, family caregivers often acquire a wide variety of health care skills that neither these caregivers nor the health care industry typically use. As these skills are marketable and could be paired with many existing medical certifications, this article describes a possible “path toward economic resilience” (PER) through a program whereby family caregivers could find meaningful employment using their new skills. The proposed program would identify ideal program candidates, assess and supplement their competencies, and connect them to the health care industry. We provide a set of practical steps and recommended tools for implementation, discuss pilot data on the program’s appeal and feasibility, and raise several considerations for program development and future research. Our analysis suggests that this PER program could appeal to family caregivers and the health care industry alike, possibly helping to address two of our health care system’s most pressing challenges with one solution.


Integrating Technology Into Standard Weight Loss Treatment: A Randomized Controlled Trial.

Spherical Nucleic Acid Nanoparticle Conjugates as an RNAi-Based Therapy for Glioblastoma.
Abstract

Glioblastoma multiforme (GBM) is a neurologically debilitating disease that culminates in death 14 to 16 months after diagnosis. An incomplete understanding of how cataloged genetic aberrations promote therapy resistance, combined with ineffective drug delivery to the central nervous system, has rendered GBM incurable. Functional genomics efforts have implicated several oncogenes in GBM pathogenesis but have rarely led to the implementation of targeted therapies. This is partly because many “undruggable” oncogenes cannot be targeted by small molecules or antibodies. We preclinically evaluate an RNA interference (RNAi)-based nanomedicine platform, based on spherical nucleic acid (SNA) nanoparticle conjugates, to neutralize oncogene expression in GBM. SNAs consist of gold nanoparticles covalently functionalized with densely packed, highly oriented small interfering RNA duplexes. In the absence of auxiliary transfection strategies or chemical modifications, SNAs efficiently entered primary and transformed glial cells in vitro. In vivo, the SNAs penetrated the blood-brain barrier and blood-tumor barrier to disseminate throughout xenogeneic glioma explants. SNAs targeting the oncoprotein Bcl2Like12 (Bcl2L12)-an effector caspase and p53 inhibitor overexpressed in GBM relative to normal brain and low-grade astrocytomas-were effective in knocking down endogenous Bcl2L12 mRNA and protein levels, and sensitized glioma cells toward therapy-induced apoptosis by enhancing effector caspase and p53 activity. Further, systemically delivered SNAs reduced Bcl2L12 expression in intracerebral GBM, increased intratumoral apoptosis, and reduced tumor burden and progression in xenografted mice, without adverse side effects. Thus, silencing antiapoptotic signaling using SNAs represents a new approach for systemic RNAi therapy for GBM and possibly other lethal malignancies.


Biomimetic, Synthetic HDL Nanostructures for Lymphoma.


Abstract

New therapies that challenge existing paradigms are needed for the treatment of cancer. We report a nanoparticle-enabled therapeutic approach to B-cell lymphoma using synthetic high density lipoprotein nanoparticles (HDL-NPs). HDL-NPs are synthesized using a gold nanoparticle template to control conjugate size and ensure a spherical shape. Like natural HDLs, biomimetic HDL-NPs target scavenger receptor type B-1, a high-affinity HDL receptor expressed by lymphoma cells. Functionally, compared with natural HDL, the gold NP template enables differential manipulation of cellular cholesterol flux in lymphoma cells, promoting cellular cholesterol efflux and limiting cholesterol delivery. This combination of scavenger receptor type B-1 binding and relative cholesterol starvation selectively induces apoptosis. HDL-NP treatment of mice bearing B-cell lymphoma xenografts selectively inhibits B-cell lymphoma growth. As such, HDL-NPs are biofunctional therapeutic agents, whose mechanism of action is enabled by the presence of a synthetic nanotemplate. HDL-NPs are active in B-cell lymphomas and potentially, other malignancies or diseases of pathologic cholesterol accumulation.


Ensuring Comprehensive Assessment of Urinary Problems in Prostate Cancer Through Patient-Physician Concordance.

Urologic Oncology (2013) In process.

23522840; 10.1016/j.urolonc.2012.09.006

Abstract

OBJECTIVES: To examine the concordance between clinicians and men diagnosed with prostate cancer on a clinician-derived pathophysiological classification of the following self-reported urinary complications: storage (irritative), voiding (obstructive), and leakage/incontinence. MATERIALS AND METHODS: Fourteen urology experts classified 37 urinary function questionnaire items into 3 primary
conceptual dimensions (e.g., storage [irritative], voiding [obstructive] and urinary leakage/incontinence) that would best reflect each item’s content. In addition, 218 patient participants provided responses to the 37 items. Using classifications by experts to develop the conceptual framework, the structure was tested using confirmatory factor analyses with patient data. RESULTS: Expert consensus was achieved in the classification of 31 out of 37 items. Using the 3-factor conceptual framework and patient data, the fit indices for the overall correlated factor model suggested an acceptable overall model fit. The analyses of the separate domains showed acceptable fit for the storage/irritative domain and the leaking/incontinence domain. The dimensionality of the voiding/obstructive domain was too difficult to estimate. CONCLUSIONS: Our analysis found items that conceptually and psychometrically support 2 constructs (leaking/incontinence and storage/irritative). The consistency of this support between the groups suggests a clinical relevance that is useful in treating patients. We have conceptual support for a third hypothesis (voiding/obstructive), although there were too few items to assess this psychometrically. Relative motivating factors of bother and urinary complaints were not addressed and remain an unmet need in this field.
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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 2014. To view an up-to-date list of educational opportunities with details and online registration, visit cancer.northwestern.edu or call 312.695.1304.

Staffileno Head and Neck Cancer Dental Symposium
January 17, 2014
Chairs: Mark Agulnik, MD, Mark Hutten, DDS, Bharat Mittal, MD, Harold Pelzer, MD, DDS, and Samir Sejpal, MD

Breast Cancer Review: Updates from the 2013 San Antonio Breast Cancer Symposium
February 14, 2014
Chair: William Gradishar, MD

Post-ASH Review: Current Trends in Hematologic Malignancies
February 28, 2014
Chair: Leo Gordon, MD

Gastrointestinal Malignancies: 2014 Update of Clinical Care
March 7, 2014
Chair: Mary Mulcahy, MD

21st Annual Cancer Survivors’ Celebration Walk & 5K
June 1, 2014

Reception: ASCO Annual Meeting
June 1, 2014

H Foundation Basic Science Symposium
June 2014

9th Annual Pain and Palliative Care Conference
June 12, 2014
Chair: Judith Paice, PhD, RN

16th Annual Lynn Sage Breast Cancer Symposium
October 9-12, 2014
Chair: William Gradishar, MD
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

21st Annual Cancer Survivors’ Celebration & Walk
Sunday, June 1, 2014

Sunday, June 1, 2014 marks the 21st 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. A timed 5K race before the Walk was added in 2013, and will be even bigger and better this year.

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 of Chicago, 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 23 of the world’s leading cancer centers dedicated to improving the quality and effectiveness of care provided to patients with cancer.

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“It always seems impossible until it’s done.”
— Nelson Mandela