Robert H. Lurie
Comprehensive Cancer Center
OF NORTHWESTERN UNIVERSITY

THE JOURNAL

WINTER 2008 VOLUME XII, NUMBER 2

"There is really nothing you must be.
And there is nothing you must do.
There is really nothing you must have.
And there is nothing you must know.
There is really nothing you must become.
However it helps to understand that fire burns,
and when it rains the earth gets wet"

— Japanese Zen Scroll

Winter 2008
Vol. XII

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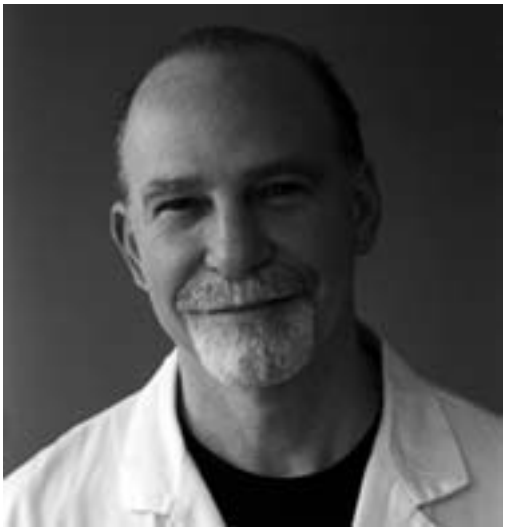
ISSN 1049-6026

LETTER FROM THE EDITOR

Steven T. Rosen, MD, FACP



The Lurie Cancer Center is fortunate to have the support and commitment of a number of remarkable Chicago-based foundations. These organizations have provided the critical resources necessary to advance our mission and ensure that we remain competitive with the finest institutions in the nation. Each group brings a unique personality, perspective and style to its philanthropic activities. The Chicago Baseball Cancer Charities (CBCC), Lynn Sage Cancer Research Foundation (LSCRF), Renee Israel Foundation and the H Foundation are the largest of our community partners. Their generosity and dedication have had a profound impact on the development and growth of our cancer center.

A volunteer organization comprised of former and current professional athletes, members of the Chicago sports media and the corporate community, **Chicago Baseball Cancer Charities** has raised over $11 million for cancer patient care, education and research programs at the Lurie Cancer Center. Funds are raised primarily though their annual All-Star Invitational Golf Outing where each foursome plays with a local celebrity. Their efforts support PhD training in cancer research through the Tumor Cell Biology track of the Feinberg School of Medicine's Integrated Graduate Program.

Dedicated to the courageous spirit of Lynn Sage, the **Lynn Sage Cancer Research Foundation** was established in 1985 by family and friends as a way to combat breast cancer. The foundation provides financial support for research, education and counseling programs relating to the treatment and prevention of breast cancer in partnership with Northwestern Memorial Hospital and the Lynn Sage Breast Cancer Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Since its inception, LSCRF has raised over $14 million.

The **Renee Israel Foundation** was established by her family in 2006 as a way to honor her memory. The foundation has donated $475,000 in the last three years to benefit breast cancer research at the Lurie Cancer Center.

Over the past six years, The **H Foundation**--comprised of a volunteer group of LaGrange, Illinois-based business owners and friends--has donated more than $1.7 million in philanthropic support to the Lurie Cancer Center. Most recently, their donation of $320,000 has enabled us to award "bridge" funding and incentive grants to scientists who are pursuing highly innovative and promising cancer studies.

Each organization was inspired by the challenges of an individual who was affected by cancer. Fostering research, clinical care, training and education is a common theme that unites each entity in a unique way. We are blessed by the sincere friendship and encouragement we have received from our partners. It is this dedication that inspires us to work towards a cure in the measure of each day.

NOTABLE CANCER CENTER MEMBER
William Catalona, MD

As a young medical student at Yale University, William Catalona, imagined life as a physician and anticipated how he would use his newly acquired skills to provide his patients with the best care possible. But Catalona now Professor of Urology at Northwestern University's Feinberg School of Medicine and Director of the Clinical Prostate Cancer Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, also wanted to make a contribution to medical science. "I was hoping I could give something back," he says.

Catalona approached one of his professors and was advised to choose a problem with a high rate of incidence that medicine had been struggling to solve without success. After exploring several options, Catalona homed in on the two most important problems facing prostate cancer patients at the time: late diagnosis and the unacceptable side effects of surgical treatment.

"Prostate cancer was the most common cancer in men and the second leading cause of cancer death," Catalona says. "The majority of those diagnosed already had metastases and a poor prognosis." One of the reasons for this was because the only available diagnostic test was a digital rectal exam. The exam was not only unpleasant for patients, but its accuracy was dependant on the expertise of the physician and varied widely depending on the individual doctor's skill and experience.

In addition, the surgical techniques then used to remove tumors resulted in impotence and often left patients incontinent as well, something many considered worse than the disease itself. So, starting in the 1980's, Catalona set out to address these two urgent problems—and eventually helped solve them both.

Dr. Catalona was the first to demonstrate that the Prostate-Specific Antigen (PSA) test, a simple blood test that involves little discomfort or inconvenience for the patient, could be used as a screening tool for prostate cancer, allowing doctors to detect the disease far earlier than they had been able to with the rectal exam alone.

Previously used as a monitoring test to determine whether a patient was responding to treatment, Catalona wondered if the PSA could also be used as a diagnostic tool. His research proved it could and his findings were published in *The New England Journal of Medicine* in 1991. Soon after, the PSA test became the gold standard for prostate cancer diagnosis, allowing physicians to detect the disease in its earliest stages for the first time. "With the PSA test, there has been a 75 percent reduction in the percentage of men with metastatic disease at the time of diagnosis since 1992," says Catalona. "And there has been a 37 percent decrease in age-specific death rates in the US alone."

Later that decade, Dr. Catalona also conducted the initial feasibility studies and headed the multi-institutional research program that led to the refinement of the PSA test, called the "free" PSA. This blood test, which came to market in 1997, allows physicians to better determine the level of antigen present in a patient's blood whose initial PSA results are just slightly elevated and fall within a "gray zone." This sensitive test helps doctors determine which patients should undergo a biopsy and which can skip the procedure.

Catalona was mentored by Patrick C. Walsh, the surgeon who developed the nerve-sparing radical prostatectomy, while he was a urology resident at the Johns Hopkins Hospital in Baltimore. This new technique, which preserved sexual function and helped patients avoid other devastating side effects associated with earlier surgeries, revolutionized prostate cancer treatment. Today, Catalona has become the foremost expert in the procedure, having performed more of them than any other surgeon—over 5,000 to date—treating patients from throughout the world.

Though the PSA tests and nerve-sparing surgery have moved detection and treatment forward, Catalona continues to look for new ways to save and improve lives by concentrating on cancer genetics. "There have got to be even better ways to diagnose and treat this disease," he says. "If we can unravel the genetics of cancer, we might come up with better diagnostics, treatments, and maybe even ways to prevent it."

Catalona is currently co-chair of a Specialized Program of Research Excellence (SPORE) grant at the Lurie Cancer Center that involves close collaboration with all other prostate cancer SPOREs (11, total). The principal goal of this research is to identify risk allele signatures for aggressive and non-aggressive cancers using DNA samples and patient histories. Researchers in the program are examining data collected from all participating institutions, including Northwestern University, the Mayo Clinic, the University of Chicago, and others to see if the alleles in patients with varying forms of aggressive or indolent tumors show different patterns, or "signatures." (The study is also dedicated to innovative therapeutics, cancer prevention, and ways to improve patients' quality of life.)

This focus of the SPORE project was first suggested by Catalona who, along with Jeffrey Gulcher, PhD, co-founder of the biopharmaceutical company deCODE Genetics, and other deCODE scientists, discovered and validated several risk alleles for prostate cancer. Using DNA samples and patient histories supplied by Catalona's patients, their research demonstrated that risk is associated with the "dose" of alleles an individual receives from their parents. (They also found that these alleles could make someone more susceptible to either prostate or breast cancer, depending on the patient's gender.) The deCODE genetics, Inc. research group, including Catalona as the principal North American collaborator published their findings in an article for *Nature Genetics* in 2006.

Catalona is also a part of the International Consortium for Prostate Cancer Genetics (ICPCG), a group of researchers working to

find out why prostate cancer is inherited in some families, as well as a multi-institutional study of a new tumor marker, called Pro-PSA, for which the researchers hope to gain FDA approval. He says preliminary studies show the marker may prove to be an even more accurate screening tool for prostate cancer than the PSA test.

In addition to his research efforts, Catalona runs the Urological Research Foundation, a fundraising organization established over 20 years ago to provide patient education and support research into the prevention, detection, and treatment of cancer and other diseases of the prostate.

Reflecting on his career as both a researcher and clinician, Catalona says he enjoys working in both arenas. "Seeing patients every day, getting to know them, and seeing what their biggest problems are allows me to focus on those areas in my research," he notes. He also savors the opportunity to help patients and families directly. "I really think it's important for patients to have doctors whom they can trust, who will be their advocates," he says. "Cancer patients and their families go through such a trying time and it's very, very gratifying when you can make this difficult experience nothing more than a bump in the road for them."

NOTABLE CANCER CENTER MEMBER
Richard Longnecker, PhD

An academic scientist's success is measured not only by his own accomplishments, but also "by what those he's trained have gone on to do," says Richard Longnecker, PhD. Longnecker, John Edward Porter Professor of Biomedical Research and past Director of the Integrated Graduate Program at Northwestern University's Feinberg School of Medicine and Director of the Viral Oncogenesis Basic Science Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, says training new scientists and mentoring them in their careers has been one of the most rewarding aspects of his work.

Longnecker's own career path began at the University of Michigan in Ann Arbor where he earned a bachelor's degree in cellular and molecular biology with honors in 1982, but he credits his mother, Jo, in encouraging him in his early "scientific experiments." At Michigan, he worked on the yeast cell cycle and was mentored by Professor John Pringle. It was at Michigan that Longnecker got interested in the regulation of cell growth and its relationship to cancer. Longnecker then went on to perform graduate work at the University of Chicago with Dr. Bernard Roizman working on Herpes Simplex Virus (HSV), taking a brief hiatus from cancer research, and earned his PhD in virology in 1987. His post-doctorate work (from 1988 to 1993) was performed at Harvard under yet another mentor, Dr. Elliott Keiff. At Harvard, Longnecker worked on Epstein-Barr virus, the first human virus associated with cancer. Thus, he was able to combine his love of virology with that of oncology. Longnecker credits his

early mentors with making him a better scientist and guiding him in his career.

Since joining Northwestern in 1993, Longnecker's primary research focus has been on the Epstein-Barr virus (EBV), which is associated with a variety of human cancers such as Burkitt's Lymphoma, Hodgkin's Lymphoma, and nasopharyngeal carcinoma. Research in the Longnecker laboratory focuses on several aspects of EBV pathogenesis. First, his laboratory is interested in the cancer association. Specifically, research is being conducted to understand the molecular basis of the ability of EBV to be an important part in the transition of a normal cell into a cancer cell.

Second, the laboratory is interested in understanding the ability of the virus to persist and remain latent in the human host. In this regard, the laboratory is developing animal models for EBV latent infections. These studies will be important in understanding the unique ability of EBV to remain latent in the human host and the disease syndromes associated with these latent infections. EBV, like all herpes viruses, is able to establish lifelong infections usually associated with this disease.

Finally, the Longnecker laboratory is investigating viral entry, assembly, and cellular genes that are required for viral entry. Overall, Longnecker hopes his studies will provide insight for the development of novel therapeutics for the treatment of EBV-related malignancies, an understanding of the virus life cycle, and an understanding of signal transduction and cell growth regulation in lymphocytes. Work on these fundamental aspects of EBV biology in his laboratory is supported by multiple NIH grants from both the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Disease (NIAD).

Dr. Longnecker also heads a research project to develop novel therapeutics for EBV-associated cancers, for which he recently won a NCI grant. Longnecker is working with Lurie Cancer Center members, Drs. Leo Gordon and Andrew Evens, to find treatments for a variety of hematopoietic cancers associated with EBV, such as EBV-associated Hodgkin's lymphoma and B cell proliferative disorders associated with HIV infection or immune suppression.

While Longnecker clearly loves delving into the how's and why's of basic science, he appreciates the opportunity his work with the Lurie Cancer Center has provided him to apply scientific discoveries to clinical practice and make a contribution to patient care. "It's gratifying to be able to extend scientific understanding to therapies that may directly benefit others," he says.

When he's not researching or teaching, Longnecker likes to spend time with his family. He and his wife, Megan McNerney, an MD-PhD, in the Department of Pathology at the University of Chicago, have a 12 month-old daughter, Elizabeth. While Longnecker says he used to spend his free time sailing, fishing, or playing tennis and golf, since Elizabeth arrived, he prefers spending time with her and his wife. "My daughter is my hobby now," he says.

In addition to the accomplishments noted above, some of Longnecker's other achievements include being a Regents Alumni Scholar at the University of Michigan; a Fellow, Special Fellow, and Scholar of the Leukemia Society of America; and an editorial board member for several journals including the *Journal of Virology*. He has served on multiple advisory committees, including those that review private foundation grants, as well as numerous NIH grant review committees. Despite his many personal accomplishments, however, Longnecker says it is his students' success that he is most proud of.

"My students and post-docs have done everything," he says. "Some are academic scientists, some work in the pharmaceutical industry, one runs a venture capital fund for biotechs, and others are actively involved in teaching at the high school and college levels getting young people excited about science." Longnecker emphasizes that careers in academia are no longer the only successful outcome for those pursuing a scientific occupation. "For one thing, there probably aren't enough positions for everyone," he says. "But, as long as they are using the skills they've gathered while working in the lab, there's a wide range of successful outcomes for them."

Though his student days are behind him, Longnecker says he is still learning, and still benefiting from mentors like Drs. Steve Rosen and Pat Spear at Northwestern. "Becoming a successful scientist requires nurturing throughout one's career," he says. "Whether it's helping you think about a question in a new way, working with you to finish a paper, or someone like Steve Rosen pointing you in the direction of new research opportunities. Mentorship means being a little bit of everything, even being just a friend."

NOTABLE CANCER CENTER MEMBER
Teresa Woodruff, PhD

Teresa Woodruff, Executive Director of Northwestern University's Institute for Women's Health Research and the Thomas J. Watkins Memorial Professor of Obstetrics and Gynecology at the Feinberg School of Medicine, says it was her mother's love of science that inspired her to pursue a career in the field. "She was always doing the most amazing things in her first grade class," says Woodruff, whose mother taught first grade in Kankakee, Illinois for over 30 years. "I was influenced very early by her passion for education and science."

While her initial goal was to follow in her mother's footsteps and become a first grade teacher herself, it wasn't long before Woodruff's interest in scientific research took over. While pursuing her bachelor's degree at Olivet Nazarene University in Bourbonnais, she says she "soon realized it was research that captured my energies and interests." After receiving her B.A. in chemistry & zoology in 1985, Woodruff went on to Northwestern University where, in 1989, she earned her PhD in biochemistry, molecular biology, and cell biology.

Dr. Woodruff was asked to head the Institute for Women's Health Research (IWHR) when it opened one year ago. With its goal of accelerating the rate of scientific discoveries that impact women's health, the Institute fosters research by developing a wide range of coordinated projects and encouraging

collaboration among researchers in a number of different disciplines. The IWHR reports directly to the Dean of the Feinberg School of Medicine, rather than a specific department, in order to facilitate this multidisciplinary approach.

"Northwestern is world-renowned for its excellence in reproductive science," says Woodruff. "And the Institute helps us apply those scientific discoveries to clinical practice across women's health." The Institute is an umbrella organization that supports the research community by creating opportunities for studying the sex differences in a range of medical disciplines, accelerates the translation of research into practice, trains women's health experts and engages the community through its Women's Health Registry (whr.northwestern.edu). It serves as a central depository of the research and program information that impacts women's health throughout Northwestern University and its affiliated clinical partners.

After serving as Basic Science Director for the Lurie Cancer Center for a number of years, Dr. Woodruff became the chief of the newly created Division of Fertility Preservation in the Department of Obstetrics and Gynecology. "While they are live-saving, cancer treatments can limit or destroy a young patient's ability to conceive children," say Woodruff. "Because cancer treatments have improved, life expectancy for young cancer patients has increased leading to the urgent need to preserve fertility now for later use."

Dr. Woodruff recently won a $21 million National Institute of Health (NIH) Roadmap Grant to study fertility preservation in young cancer patients and provide information and support to patients coping with a variety of medical, psychological, and social issues surrounding cancer treatment and fertility. The program, called The Oncofertility Consortium, is facilitating collaboration within disciplines and among institutions in order to encourage creative approaches to these problems. (Dr. Woodruff coined the term, "oncofertility," to describe this new field.)

To help this growing cadre of patients, Northwestern University's Feinberg School of Medicine and the Lurie Cancer Center are working together to develop new technologies that allow patients to conceive after cancer treatment. These multidisciplinary projects include one of Dr. Woodruff's own projects to preserve and grow human follicles. The study involves harvesting follicles from ovaries of those donated by eligible cancer patients and coaxing those follicles to mature into eggs. It is hoped that when the patient is ready to conceive, the frozen tissue can be thawed and the follicles matured for the patients use.

The Oncofertility Consortium involves close collaboration with several other institutions around the country and Woodruff says she is especially proud of the role the Lurie Cancer Center has played. "Once we developed the network of activity here at the Cancer Center, it became clear that this was something other institutions could copy — and begin delivering this new kind of care to their patients, too" she says. Over the past year, she adds, Northwestern University researchers have provided the templates for their clinical research, including many of their protocols, to 50 other institutions around the country. "So many clinicians were looking for ways to provide these services to their cancer patients and just didn't have the roadmap to get that done. So we've provided it, and now have this magnificent network that works together in a very altruistic way to develop technologies that help preserve fertility in young cancer patients."

The Northwestern team has also created a Website, www.myoncofertility.org, to disseminate information about its Consortium efforts as well as a site created especially for patients, their partners and parents.

Woodruff says that the ability to directly impact patients' lives is the most rewarding aspect of her work. "Scientists often talk about the ability to take something from the bench to the bedside, but we are actually doing that here," she says. "Seeing the kind of work that we have developed in the mouse being adapted to human cells and then used to treat patients is a remarkable aspect of what we're doing."

Had she not become a scientist, Woodruff says she would have have been a first grade teacher or played cello for the ELO (Electric Light Orchestra). "My fallback is music," she says with a smile. Fortunately, for thousands of young cancer patients, as well as women of all ages facing a variety of health concerns, Woodruff decided to pursue her first passion of scientific research instead.

$7.5 Million NCI Grant Award to Vadim Backman

Lurie Cancer Center member, **Vadim Backman, PhD**, who has developed optical technology shown to be effective for the early detection of colon cancer has received a $7.5 million grant over five years from the National Cancer Institute to further study an instrument that potentially could become a routine colon cancer screening test.

Colon cancer, the second-leading cause of cancer deaths in the United States, can be easily treated if detected early. But no existing population-wide screening test can accurately predict the presence of the disease with adequate sensitivity. Backman, principal investigator for the grant and professor of biomedical engineering at Northwestern's McCormick School of Engineering and Applied Science, believes the technology he has developed could lead to the first such test. A major part of the NCI grant is to validate the technology being developed for an inexpensive, non-invasive test for routine colon cancer screening, and have it ready for use.

In the future, it is possible that the simple test would be conducted by a primary care physician during an annual exam. Only patients with abnormal results would go on to have the more invasive and expensive colonoscopy.

The clinical trials will include two studies. The first study of 1,000 patients will be to finalize the technology to be used in the test (making sure it can be used clinically and is practical) and to define the technology's prediction rules; the second will be a double-blind study of 3,000 patients. The screening test, which does not require bowel preparation, will be done in patients about a week before a colonoscopy. Each person will have a colonoscopy even if the results from the screening test are negative in order to correlate the screening results with the colonoscopy results. "Our hope is that similar to how the routine pap smear drastically reduced deaths from cervical cancer, this new technology could do the same when it comes to colon cancer," said Backman.

Backman's optical technique takes advantage of certain light scattering effects and is minimally invasive. The method can detect abnormal changes in cells lining the colon long before those changes can be seen under a microscope, and even before polyps form.

Nanodiamond Drug Device Could Transform Cancer Treatment

A Northwestern University research team has developed a promising nanomaterial-based biomedical device that could be used to deliver chemotherapy drugs locally to sites where cancerous tumors have been surgically removed.

The flexible microfilm device, which resembles a piece of plastic wrap and can be customized easily into different shapes, has the potential to transform conventional treatment strategies and reduce patients' unnecessary exposure to toxic drugs. The device, which takes advantage of nanodiamonds, an emergent technology, for sustained drug release, "could be used to treat a localized region where residual cancer cells might remain after a tumor is removed," says Dean Ho, assistant professor of biomedical engineering and mechanical engineering at Northwestern's McCormick School of Engineering and Applied Science, who led the research.

The researchers demonstrated that the device releases the chemotherapy agent Doxorubicin in a sustained and consistent manner -- a requirement of any implanted device for localized chemotherapy. If a surgical oncologist, for example, was removing a tumor from the breast or brain, the device could be implanted in the affected area as part of the same surgery. This approach, which confines drug release to a specific location, could mitigate side effects and complications from other chemotherapy treatments.

"Several surgeons at Northwestern's Feinberg School of Medicine, as well as other medical schools and hospitals, are very interested in the device because it is biocompatible and provides such stable and consistent drug release," says Ho, a member of the Lurie Cancer Center.

In their study, Ho and his colleagues embedded millions of tiny drug-carrying nanodiamonds in the FDA-approved polymer parylene. Currently used as a coating for implants, the biostable parylene is a flexible and versatile material resembling plastic wrap. A substantial amount of drug can be loaded onto clusters of nanodiamonds, which have a high surface area. The nanodiamonds then are put between extremely thin films of parylene, resulting in a device that is minimally invasive.

To test the device's drug release performance, the researchers used Doxorubicin, a chemotherapeutic used to treat many types of cancer. They found the drug slowly and consistently released from the embedded nanodiamond clusters for one month, with more Doxorubicin in reserve, indicating a more prolonged release (several months and longer) was possible. The device also avoided the "burst" or massive initial release of the drug, a common disadvantage with conventional therapy.

In control experiments, where the drug was present but without the nanodiamonds, virtually all of the drug was released within one day. By adding the drug-laden nanodiamonds to the device, drug release was instantly lengthened to the months-long timescale.

In addition to their large surface area, nanodiamonds have many other advantages that can be utilized in drug delivery. They can be functionalized with nearly any type of therapeutic. They can be suspended easily in water, which is important for biomedical applications. The nanodiamonds, each being four to six nanometers in diameter, are minimally invasive to cells, biocompatible and do not cause inflammation, a serious complication. And they are very scalable and can be produced in large quantities.

The architecture of the device is amenable to housing small molecule, protein, antibody or RNA- or DNA-based therapeutics. This gives the technology the potential to impact a range of treatment strategies where implanted, long-term drug release is needed.

Ho and his research group previously pioneered the application of nanodiamonds for systemic drug-carrying applications. This new work successfully transitions the nanodiamonds from basic materials to serving as a foundation for device manufacturing.

In the area of localized chemotherapy, the team hopes that this technology will bring new levels of treatment efficacy that can complement injected chemotherapy to reduce dosages and decrease devastating side effects. Because of the proven biocompatibility and massively parallel deposition capabilities of parylene, the researchers are engaged with pre-clinical trials of the nanodiamond-embedded parylene.

Lurie Cancer Center Team Honored for Contributions to caBIG

A team from the Robert H. Lurie Comprehensive Cancer Center of Northwestern University was honored for significant accomplishments and contributions at the cancer Biomedical Informations Grid (caBIG) Annual Meeting 2008 Recognition Awards ceremony in Washington D.C.

Pan Du, Gilbert Feng, Dong Fu, Warren Kibbe, Simon Lin, Eric Odulio, Rhett Sutphin, Renee Webb, and Sean Whitaker were presented with the caBIG Delivering Results Award in recognition of superior use of caBIG applications and the use of shared data from caGrid to address specific research questions.

Additionally, Rhett Sutphin and Sean Whitaker received the caBIG™ Teamwork Award for their work with the caBIG™ Clinical Trials Suite Team. Dong Fu, Warren Kibbe and Andrew Winter were also presented with the caBIG™ Teamwork Award for their efforts with the Prostate SPORE Informatics Team.

Overseen by the National Cancer Institute for Biomedical Informatics and Information Technology, caBIG was conceived to address the needs of all constituencies in the cancer community—researcher, clinicians, patients—to share data and knowledge, simplify collaboration, speed research to get diagnostics and therapeutics from bench to bedside faster and more cost-effectively, and ultimately realize the potential of Personalized Medicine. caBig also addresses a critical problem facing both basic and clinical researchers today—an explosion of data that requires new approaches for collection, management and analysis.

David Mahvi Named Hines Professor of Surgery

David M. Mahvi, MD, who joined Northwestern University's Feinberg School of Medicine in July as Chief of Gastrointestinal and Oncologic Surgery, has been named the James R. Hines Professor in Surgery.

Mahvi, a member of the Lurie Comprehensive Cancer Center, is at the forefront of research in pancreatic, liver and hepatobiliary diseases, and he has developed an international reputation as an expert in the field of gastrointestinal malignancies. He has investigated gene therapy for the treatment of cancer and has developed several devices to treat liver cancer.

His clinical interests include the surgical treatment of upper gastrointestinal malignancies (liver, pancreas and stomach) and liver tumor ablation for colorectal cancers.

Mahvi has published more than 100 manuscripts in peer-reviewed journals and authored eight book chapters. His recent publications have focused on biomedical engineering and cancer.

Mahvi serves on the editorial board of Annals of Surgery and is a member of numerous professional societies, including the American

College of Surgeons, the American Surgical Association, the Society of Surgical Oncology and the Society for Surgery of the Alimentary tract, of which he is president elect.

He was a professor of surgery at the University of Wisconsin–Madison and a member of the University of Wisconsin Comprehensive Cancer Center.

Gail L. Gamble, MD, Named Medical Director of Cancer Rehabilitation Program

Gail L. Gamble, MD, has been appointed Medical Director of the Rehabilitation Institute of Chicago's (RIC) Cancer Rehabilitation Program, bringing cancer rehabilitation expertise acquired over more than 20 years at the Mayo Clinic. Founded on the belief that patients overcoming cancer hope for more than just survival, the RIC's Cancer Rehabilitation Program is focused on improving the abilities that increase the quality of life and on helping patients to thrive.

As Medical Director, Dr. Gamble will collaborate with the Lurie Cancer Center, Northwestern University's Feinberg School of Medicine, and Northwestern Memorial Hospital to advance RIC's patient care program, education and clinical research. She will develop and recruit additional top medical and scientific talent to the Cancer Rehabilitation Program. She is the past president of the American Academy of Physical Medicine and Rehabilitation, a previous member of the Advisory Committee to the National Center of Medical Rehabilitation Research (NIH), and a member of the Physical Medicine and Rehabilitation Residency Review Committee(RRC)of the Accreditation Council for Graduate Medical Education (ACGME).

New Website Helps Cancer Patients Explore Fertility Preservation

When a woman, man or teenage girl or boy is diagnosed with cancer, there is only a brief window of time to learn about options for preserving his or her fertility before treatment. Cancer therapy often has irreversible effects on a patient's fertility.

But it hasn't been simple for patients and their families to get information. Oncofertility — the intersection of oncology and reproductive medicine — is a new, rapidly advancing field, and many physicians aren't familiar with the latest developments.

Northwestern University has launched a new interactive Web site, http://www.MyOncofertility.org, to meet that growing need. The site teaches patients about the potential effect of cancer and treatments on their fertility, options to preserve their fertility and offers resources for discussing these issues with their doctors.

The site is an educational project of the national Oncofertility Consortium of Northwestern University's Feinberg School of Medicine. The consortium is headed by Lurie Cancer Center member, Teresa Woodruff, PhD, chief of the Feinberg School's fertility preservation division and the Thomas J. Watkins Professor of Obstetrics and Gynecology. The consortium is a $21-million research, clinical and education program targeting fertility threats posed by cancer treatment.

The multi-media web site includes more than 200 expert videos and survivor stories. Visitors can get answers to their questions from leading Northwestern physicians and scientists and hear how other cancer survivors and their families made decisions about fertility preservation in the face of a cancer diagnosis.

Increased Microvascular Blood Supply as a Potential Biomarker of Field Carcinogenesis in the Colon

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Colonoscopy utilization, regarded as the gold standard for colorectal cancer (CRC) screening, has reduced CRC incidence by 65-90% through identification and removal of adenomatous polyps (1). Despite colonoscopy's unequivocal benefit, several lines of evidence suggest a significant number of adenomas are missed during endoscopic examination. It is estimated that ~5% of CRC patients have received a negative colonoscopy within the five years prior to diagnosis (2) while tandem colonoscopy studies have demonstrated a ~ 22% miss rate in expert hands (3). Moreover, results from CT colography suggest a miss rate up to 12% of advanced adenomas (4). These findings underscore the need for improved methods of polyp detection.

One possible method of adenoma detection relies on the field effect concept of colon carcinogenesis. The field effect proposes that the environmental and genetic milieu resulting in a focal lesion should be detectable in the histologically normal mucosa remote from the lesion itself. Biochemical, genetic, and proteomic studies have corroborated the field effect in the colon but present biomarkers lack the accuracy requisite for clinical practice (5-7).

We have recently developed a novel optical technology known as four-dimensional elastic light scattering fingerprinting (4D-ELF) which allows for accurate and depth-selective quantification of microvascular blood content (8, 9). Increased blood supply (primarily through angiogenesis) is a hallmark of

Figure 1. *(A) Frontal view of the probe. (B&C) Photographs of the probe demonstrating size compatibility with an endoscope.*

tumorigenesis. Recent data confirms the increased blood supply occurring as early as the small adenoma and aberrant crypt foci stage (10, 11). While these studies suggest an increased blood supply to a given lesion, negligible attention has been dedicated to the blood supply in the uninvolved mucosa of patients with neoplasia. Using 4D-ELF, we have illustrated that mucosal microvascular blood content was increased in the histologically normal mucosa of two experimental models of colonic neoplasia: the azoxymethane (AOM)-treated rat and the MIN mouse (8). This early increase in blood supply (EIBS) was preceded by the development of both adenomas and aberrant crypt foci. A distinguishing feature of our optical approach is that it commissions only the capillary network of the mucosal layer to be interrogated, avoiding contamination from deeper blood vessels that are not expected to be diagnostic in early carcinogenesis. Indeed, while Western blot analysis for hemoglobin has confirmed our findings in the animal models, it has exhibited much less sensitivity than 4D-ELF due to possible contamination from larger blood vessels.

More recently, we have simplified the 4D-ELF benchtop instrument into an endoscopically compatible fiber-optic probe. This has enabled us to investigate EIBS *in vivo* on a cohort of 222 patients undergoing screening colonoscopy (12). Representative results from this *in vivo* study are presented.

Methods

Design of endoscopically-compatible fiber-optic probe for microvascular blood supply measurement

The probe design, depicted in Fig. 1, consists of three fibers positioned in an equilateral triangle with a gradient refractive index (GRIN) lens and two polarizing sheets oriented perpendicular to each other placed in front of the fibers. One fiber serves to illuminate the tissue with white light while the remaining two fibers collect light scattered back from the tissue surface. The lens collimates the incident light and focuses light scattered from tissue onto the collection fibers. The two thin film polarizer sheets polarize the incident light and allow independent collection of light polarized parallel to the incident beam (co-polarized signal $I_{||}$) and light polarized perpendicular to the incident beam (cross-polarized signal $I^{\perp}$) The collection fibers couple to a spectrometer which records signal intensity as a function of wavelength for later analysis. One key aspect of the design permits depth-selectivity via polarization gating (13-15). The differential polarization signal $\Delta I = I_{||} - I^{\perp}$, co-polarized signal $I_{||}$, and cross-polarized signal $I^{\perp}$ probe progressively deeper tissue depths. Furthermore, altering the physical design of the probe (i.e. lens focal length, fiber diameter, inter-fiber spacing), regulates the penetration depth. After evaluating several probe configurations, we determined the optimal design most suitable for sampling the mucosal microvasculature (depth ~ 100 μm). Studies in the laboratory showed the penetration depths of the ΔI, $I_{||}$, and $I^{\perp}$ signals are ~100±35 μm, 130±40 μm, and 170±30 μm, respectively. We employed the finalized probe design in our *in vivo* studies

In vivo Studies

Patients undergoing screening colonoscopy at Evanston Hospital were recruited under the auspices of the Institutional Review Board of Evanston-Northwestern Healthcare. Approximately 10 probe measurements were taken from random sites of the visually normally mucosa in the cecum, mid-transverse, and rectum. If a polyp was detected during colonoscopy, additional measurements were

taken directly on the polyp, < 10 cm away from the polyp, and 10-30 cm proximal and distal to the polyp site. Based on endoscopic and pathological findings, patients were classified into three groups: advanced adenoma, non-advanced adenoma, and no neoplasia (no adenoma found).

Spectroscopic determination of blood content

Blood content was calculated from the probe measurements using Beer's law to exploit the unique absorption features of oxyhemoglobin (OHb) and deoxyhemoglobin (DHb) in the visible wavelength range (16). Under the constraints of Beer's Law, the collected light intensity is proportional to the tissue scattering signal and has an inverse exponential relationship with the absorber concentration in tissue. We have assumed the scattering signal from tissue (signal from tissue if it were devoid of absorbers) has a form of the smooth second order polynomial absent of any characteristic hemoglobin features. Applying Beer's Law and this assumption, a least squares optimization algorithm computes the concentrations of OHb and DHb that best fit each measured spectrum.

Results

Patient characteristics

We recruited a total of 222 patients with 175 having no neoplasia, 35 having non-advanced adenomas, and 12 having advanced adenomas. Age, gender, tobacco and alcohol history did not differ significantly between the no neoplasia and adenoma groups.

EIBS is depth localized

The polarization-gating property of the probe allows hemoglobin concentration (OHb + DHb) to be measured from the three penetration depths described previously. For each depth, hemoglobin concentrations from patients without any adenoma were compared with the corresponding concentrations from the uninvolved mucosa of patients harboring an adenoma. It was identified that patients having an adenoma had statistically significant elevated levels of hemoglobin at 100 μm but not at the other two deeper penetration depths (Fig. 2). The depth of 100 μm corresponds to the pericryptal network underlying the epithelium and our study suggests that only this network of blood vessels, which comprises only a fraction of total colonic blood supply is involved in EIBS.

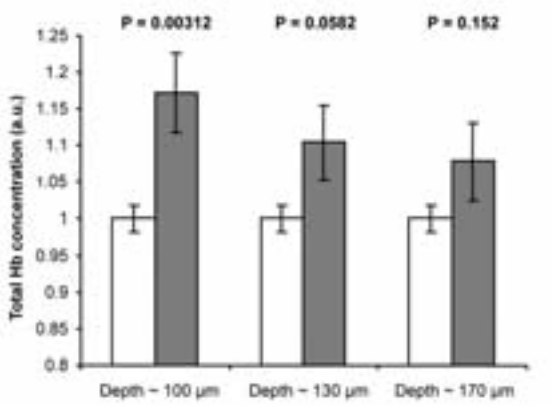

Figure 2. *Total hemoglobin concentration readings taken from the uninvolved mucosa within 30 cm of an adenoma compared with corresponding readings from patients without neoplasia for three different penetration depths. The ~100 m depth provided the greatest distinction with progressively lower effect sizes at 130 m, and ~170 m respectively. Increase in blood supply is localized to superficial tissue layers.*

EIBS mirrors proximity to adenomatous lesions

To assess the spatial variation of blood concentration with respect to adenoma location, we have focused on measurements from 100 μm since EIBS was localized to this depth. Measurements were taken on the adenomatous polyp, < 10 cm away from the polyp, within 30 cm of the polyp, and > 30 cm from the polyp. Figure 3 shows a clear spatial gradient of hemoglobin concentration with respect to adenoma location. The magnitude of hemoglobin concentration increase relative to controls was greatest directly at the adenoma site (~ 75%) and gradually diminished with increasing distance from the adenoma location. The uninvolved mucosa < 10 cm and < 30 cm away from the adenoma also showed statistically significant elevated levels of hemoglobin relative to patients without neoplasia (ANOVA P-value < 0.001).

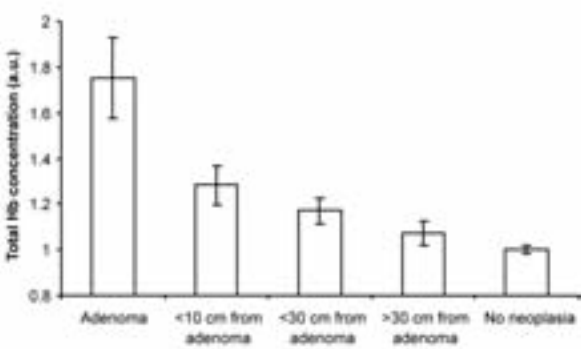

Figure 3. *Total hemoglobin concentration levels (depth ~ 100 μm) mirrored the distance away from adenomatous lesions.*

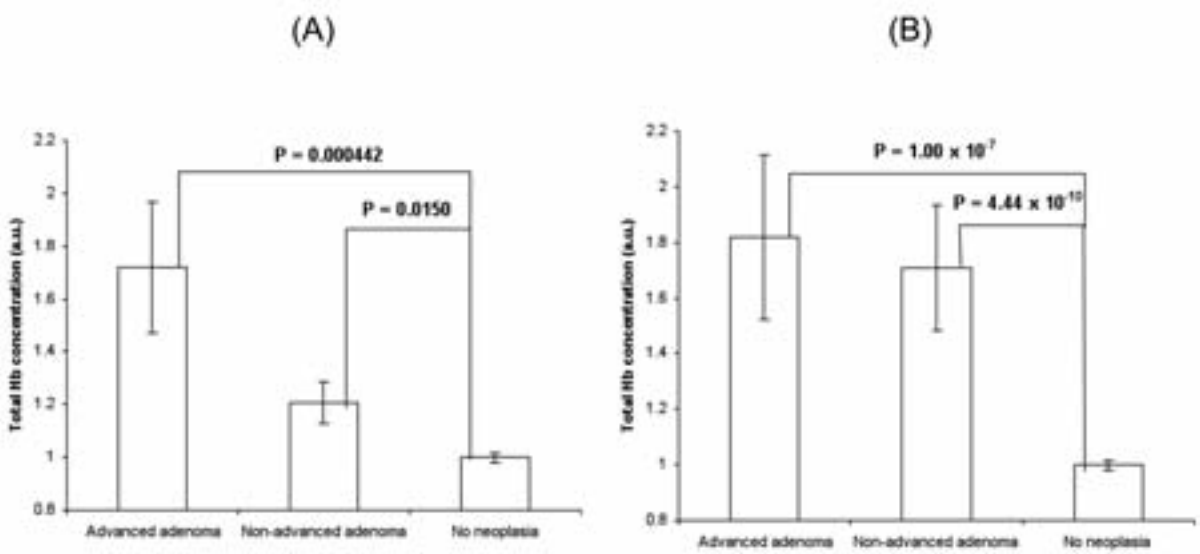

Figure 4. *Total hemoglobin concentration readings (depth ~ 100 μm) taken from the polyp site in (A) and from within < 10 cm of the polyp site in (B) for advanced and non-advanced adenomas. Advanced adenomas had greater effect sizes than non-advanced adenomas indicating that EIBS is correlated with polyp severity.*

EIBS correlates with polyp size and histology

Adenomas were classified as advanced if polyp size exceeded 10 mm, or the presence of 25% villous features or high grade dysplasia. We found that both advanced and non-advanced adenomas gave rise to EIBS but that the effect was greater for advanced adenomas as shown in Fig. 4. Hyperplastic polyps, generally thought to be innocuous, possessed increased hemoglobin levels at the polyp site but not in the uninvolved mucosa. EIBS is therefore specific to clinically relevant lesions.

Conclusion

In summary, our *in vivo* study has demonstrated that microvascular blood content is elevated in the uninvolved mucosa of patients who harbor neoplasia. This discovery has both clinical and biological implications. The presence of EIBS could provide a "red flag" to the endoscopist during procedures. In addition, the spatial gradient associated with EIBS could aid endoscopists in localizing hard to detect polyps, particularly flat and depressed lesions and those polyps obscured by folds in the colonic mucosa. We plan to validate our results in multi-center trials on a larger set of patients.

Biologically, EIBS is a promising marker of field carcinogenesis. The presence of both a diffuse and localized augmentation of blood supply demonstrated by the spatial gradient parallels findings on other field effect markers. For example, several genomic (cyclooxygenase 2, osteopontin) (7) and immunohistochemical (cytochrome C oxidase subunit I) (17) markers are diffusely present in the colonic mucosa of patients harboring neoplastic lesions while others such as carcinoembryonic antigen diminish steeply with distance (18).

Angiogenesis has been shown to be an essential step in carcinogenesis and occurs with early adenomas and aberrant crypt foci (10, 11). Given these findings, we hypothesize that EIBS plays an important role in early tumorigenesis. Increased microvascular blood content would be expected to maintain a hyperprofilerative epithelium, a defining feature of early carcinogenesis. Currently, the biological mechanisms driving EIBS is not firmly understood. There is some evidence that nitric oxide (19), cyclooxeganase (COX-2) (20), and/or, vascular endothelial growth factor (VEGF) (21) may be mediators of EIBS in the mucosa adjacent to neoplastic lesions. Interestingly, drugs targeting these possible EIBS mediators demonstrate effective chemopreventive ability (20, 22-24). Further elucidation of the mechanisms of EIBS may lead to enhanced angio-preventive strategies.

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Targeting a Novel Embryonic Pathway In Melanoma and Breast Cancer

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Metastatic cancer cells resemble stem cells in their ability to self-renew and to derive a diverse progeny. Moreover, the phenotype of both stem cells and cancer cells is profoundly influenced by the microenvironment. During embryogenesis, precursor cells are specified to particular fates through the autocrine or paracrine delivery of signaling molecules, and during cancer progression malignant cells similarly release and receive cues that promote tumor growth and metastasis. There also exists a convergence between cancer cells and stem cells in the molecular messengers that they implement to regulate self-renewal, proliferation and cell fate. These factors, classically associated with developmental processes, include members of the Notch, Wingless (Wnt), and Transforming Growth Factor Beta (TGF-β) superfamilies (1-7). Particularly noteworthy is our recent finding involving Nodal, an embryonic morphogen belonging to the TGF- superfamily (4), which represents a new therapeutic target in aggressive melanoma and breast carcinoma. Nodal is a pivotal regulator of embryonic stem cell fate, and has recently been shown by our laboratory to play an instrumental role in the maintenance of melanoma and breast carcinoma tumorigenicity and plasticity. For example, over-expression of Nodal prevents hESC differentiation (8), and inhibiting Nodal signaling in metastatic melanoma and breast carcinoma results in decreased colony formation in soft agar concomitant with a marked abrogation of tumor formation in orthotopic mouse models.

The multipotent phenotype of metastatic cancer cells permits them to respond to cues normally restricted to developmental processes (1). Hence, we have hypothesized that embryonic microenvironments, which are inherently permissive to normal stem cell differentiation, may be harnessed to reprogram (*i.e.* redifferentiate) cancer cells toward a more benign phenotype. In support of this concept, embryonic microenvironments have been shown to inhibit the tumorigenicity of a variety of cancer cell lines (1, 9-11). For example, by injecting metastatic teratocarcinoma cells into a mouse blastocyst, Mintz and colleagues demonstrated that the mouse embryonic microenvironment can reprogram teratocarcinoma cells to a non-tumorigenic phenotype capable of differentiating into normal tissues (11). More recently, extracts derived from zebrafish embryos were shown to inhibit proliferation and induce apoptosis in a number of cancer cell types (12), and we have demonstrated that exposure of metastatic melanoma cells to an embryonic zebrafish microenvironment, prior to gastrulation, results in their reprogramming toward a non-tumorigenic phenotype (13). Remarkably, although still present after a three-month period of observation, melanoma cells exposed to this embryonic microenvironment lay dormant and unable to form tumors (13). Similarly, we have shown that metastatic melanoma cells transplanted into developing chick embryos are capable of following neural crest migration pathways, resulting in a loss of tumorigenicity and the acquisition of a neural crest-like phenotype (10).

In order to elucidate the mechanisms by which embryonic microenvironments reprogram cancer cells to a more differentiated, less aggressive phenotype, so that novel humanized therapeutic modalities may be discovered, we developed an *in vitro* 3-D model to investigate the capacity of human embryonic stem cell (hESC)-derived factors to epigenetically influence metastatic cancer cells (1, 14). Utilizing this approach we previously determined that exposure of melanoma cells to the hESC microenvironment results in the re-expression of melanocyte-specific markers (illustrative of redifferentiation), as well as a reduction in invasive potential (1, 14). However, the molecular underpinnings of the reprogramming potential of the hESC microenvironment remained elusive. In our most recent study we have discovered that the hESC microenvironment suppresses the tumorigenic phenotype of human metastatic melanoma and breast carcinoma cells, and that this effect is exclusive to hESCs and not other stem cell types (*e.g.* derived from amniotic fluid, cord blood, or adult bone marrow). Mechanistically, the hESC microenvironment specifically neutralizes the aberrant expression of the embryonic morphogen Nodal in metastatic melanoma and breast carcinoma cells, reprogramming them to a less aggressive phenotype exemplified by diminished clonogenicity and tumorigenicity (with apoptosis). Moreover, we uncovered hESC-secreted Lefty (an inhibitor of the Nodal signaling pathway) as an important mediator of these phenomena. The microenvironment of hESCs provides a novel and previously unexplored entity for the regulation of aberrantly expressed embryonic morphogen(s) by aggressive tumor cells and the development of tumor-suppressive therapies.

The incidence of melanoma is rising at an alarming rate in the U.S. with metastatic melanoma having a cure rate of less than 15% and a median survival of 6-9 months. Breast carcinoma, particularly the multipotent, plastic, dedifferentiated phenotype, represents the single most frequent malignant disease affecting women. Its reported incidence has continuously increased during the past four decades largely due to increased screening and improved diagnostic accuracy. Although progress in early diagnosis and novel treatment strategies has led

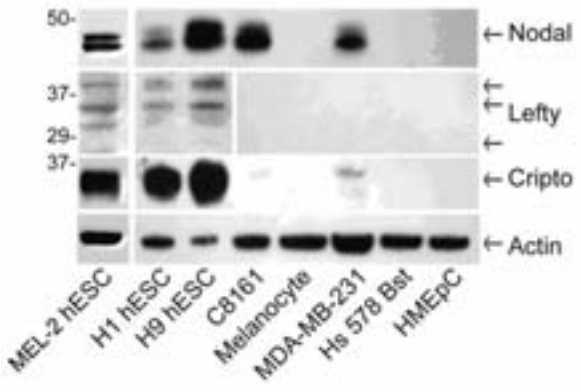

Figure 1. *Nodal expression correlates with a plastic phenotype in embryonic stem cells and metastatic tumor cells. Western blot analyses of Nodal, Lefty and Cripto in: MEL-2, H1 and H9, human embryonic stem cells (hESCs); C8161, human metastatic melanoma cells; normal human melanocytes; MDA-MB-231, human metastatic breast carcinoma cells; Hs 578 Bst, normal human myoepithelial cells; and HMEpC, normal human mammary epithelial cells. Actin is used as a loading control.*

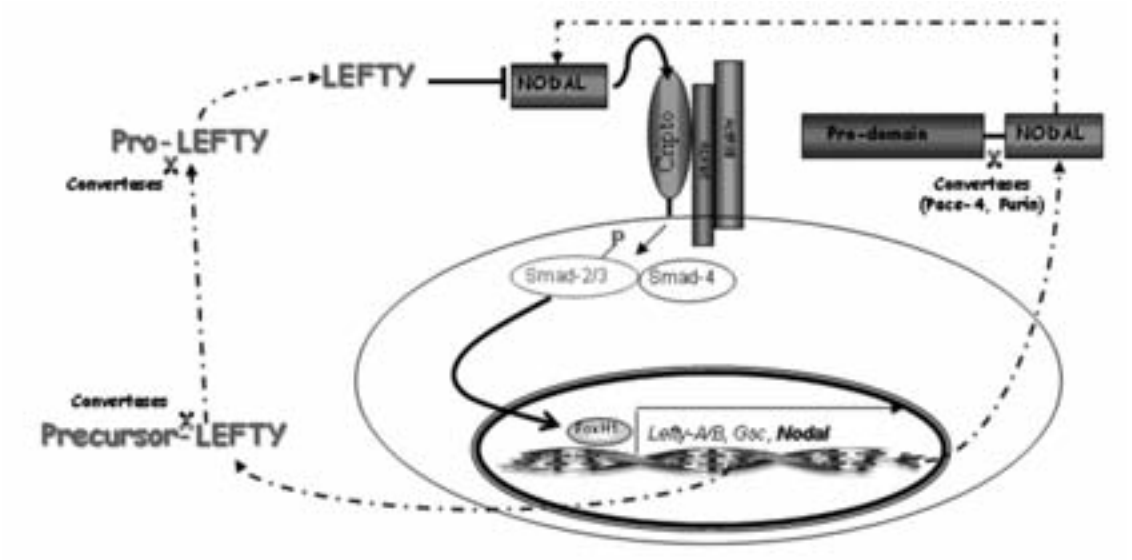

Figure 2. *Nodal signaling pathway in normal stem cells.*

- *Nodal propagates its signal by binding to Cripto-1 and heterodimer complexes between type I (ALK 4/7) and type II (ActRIIB) activin-like kinase receptors.*
- *Assembly of this complex results in the phosphorylation and activation of ALK 4/7 by ActRIIB, followed by the ALK 4/7-mediated phosphorylation of Smad-2 and possibly Smad-3, association with Smad-4 and then translocation to the nucleus where it regulates gene expression through an association with transcription factors such as FoxH1, and Mixer -- stimulating the transcription of Nodal and Lefty A/B.*
- *Cripto-1 directly associates with ALK 4 (with its CFC domain) and Nodal (with its EGF domain) for Nodal signaling.*
- *Nodal can bind to and activate ALK 7 in the absence of Cripto-1.*
- *Nodal (precursor form) can bind to ALK 4 in a Cripto-1 independent manner.*
- *Lefty A/B control Nodal signaling by spatially and temporally restricting the Nodal-mediated activation of ALK 4/7.*

to increased survival in affected women, breast cancer still represents the leading cause of death among U.S. women. Most of the deaths from these two cancers are caused by complications due to disease recurrence and metastatic spread. Therefore, more attention should be devoted to early detection biomarkers for disease progression and novel pathways to target that are specific to this deadly tumor cell phenotype.

Characterization of Nodal signaling pathway members in human normal cells, metastatic cancer cells, human embryonic stem cells and other stem cell types.

Given the commonality of plasticity shared by aggressive cancer cells and stem cells, as well as the role of Nodal in the maintenance of both pluripotency and tumorigenicity, we have determined the expression of key components of the Nodal signaling pathway in select normal, neoplastic and stem cell types. Western blot analyses revealed that in a manner similar to hESCs (MEL-2, H1 and H9), metastatic melanoma (C8161) and breast carcinoma (MDA-MB-231) cells express Nodal protein at approximately 48 kDa (Fig.1). This is in contrast to corresponding normal cell types [melanocytes, myoepithelial cells (Hs 578 Bst) and primary human mammary epithelial cells (HMEpC)], in which Nodal was not detected. A preliminary validation of Nodal expression by immunohistochemistry was performed using human melanoma and breast TMAs (tissue microarrays), and suggested a positive correlation between Nodal expression and melanoma and breast carcinoma progression. In normal stem cells, Nodal propagates its signal (please refer to the signaling pathway scheme in Fig. 2) by binding to a receptor complex comprised of Cripto and a heterodimer of type I (ALK 4/7) and type II (ActRIIB) activin-like kinase receptors. Genetic studies in zebrafish and mice have determined that Cripto, an Epidermal Growth Factor–Cripto-1/FRL1/cryptic (EGF-CFC) family member, directly associates with ALK 4 and Nodal and that these associations facilitate the ability of Nodal to propagate its signal (16, 17). Using Western blot analysis and immunofluorescence microscopy, we determined that hESCs uniformly express high levels of Cripto at approximately 35 kDa. However, only a very low to absent level of Cripto was heterogeneously expressed in metastatic human

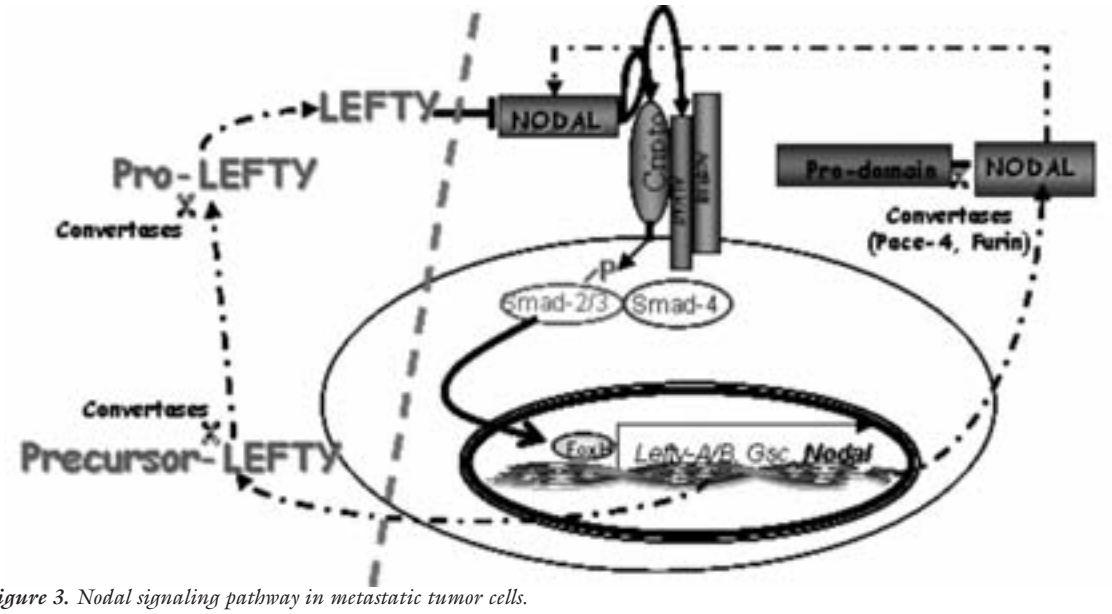

Figure 3. *Nodal signaling pathway in metastatic tumor cells.*

- *In the absence of Lefty, Nodal can propagate its signal in a Cripto-dependent or Cripto-independent manner, as described in the legend for Figure 2.*
- *Without Lefty to regulate Nodal, Nodal signaling is further stimulated by a feed forward mechanism.*

melanoma (C8161) and breast carcinoma (MDA-MB-231) cells, suggesting Nodal signaling in a Cripto-independent manner, possibly via direct binding to ALK 4/7.

Nodal signaling pathway in metastatic tumor cells.
The Lefty proteins (Lefty-A, Lefty-B), divergent members of the TGF- superfamily, spatially and temporally antagonize Nodal in embryological systems (18). Moreover, the Lefty genes are downstream targets of Nodal signaling, thereby providing a powerful negative-feedback loop for this pathway (19). Using Western blot analysis we determined that, in accordance with previously published accounts of Lefty protein processing patterns, hESCs express Lefty protein at approximately 42, 34 and 28 kDa (Fig. 1). In contrast, Lefty is not expressed by metastatic breast carcinoma and melanoma cells or by corresponding normal somatic cell types (Fig. 1). These data indicate that Nodal is expressed in an unregulated manner in metastatic tumor cells, which presents a challenge as well as a new therapeutic opportunity (Fig. 3). In order to visualize the localization of Lefty and Nodal in hESC colonies and their microenvironment, we performed immunofluorescence localization with confocal microscopy. Utilizing this methodology, we determined that Lefty protein localizes to the areas where hESCs are in contact with the underlying matrix, and that hESC-derived Lefty permeates into this microenvironment. This is in contrast to Nodal protein, which localizes to the surface of hESC colonies, and is secreted into the media (15).

Given the significant observation that like hESCs, cancer cells express Nodal, while unlike hESCs, they do not express Lefty, we hypothesized that hESC-derived Lefty and possibly other tumor-suppressive factors found in hESC conditioned matrices (CMTX), may inhibit Nodal signaling in cancer cells (please see the model shown in Fig. 4). We further proposed that by neutralizing Nodal in the cancer cells, the hESC microenvironment will reprogram these tumor cell types toward a less tumorigenic phenotype, which we have demonstrated *in vitro* and *in vivo* (15).

Future directions and clinical insights.
Our long-term goal is to understand the molecular mechanisms underlying the bi-directional communication between tumor cells and their microenvironment that ultimately result in cell fate determinations, plasticity, metastasis and drug resistance. Our short term goals are to validate Nodal as a new biomarker for disease progression in human tumor tissues with matching serum samples, and to use orthotopic mouse models to determine whether Nodal serves as a novel therapeutic target. Our rationale for conducting these studies is that there is a paucity of information regarding the biological significance of Nodal expression in cancer, and our data indicate the existence of an unregulated Nodal signaling pathway resulting

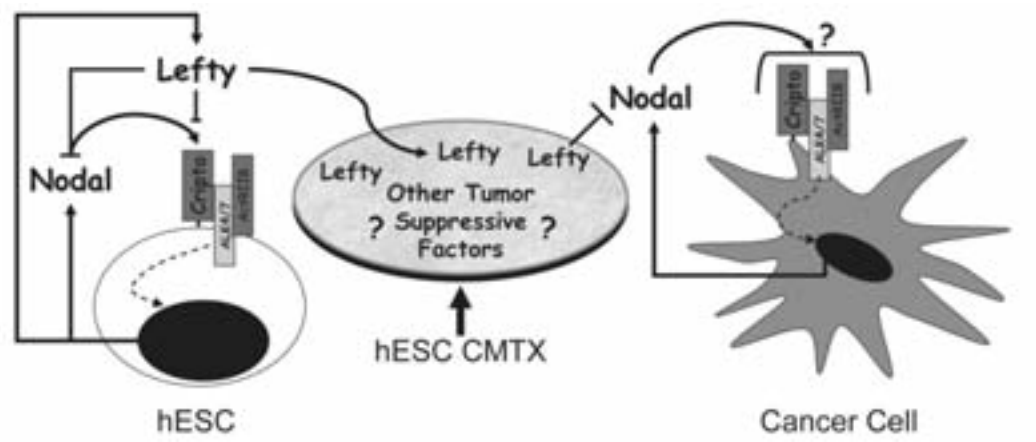

Figure 4. *Putative signaling model outlining how hESCs may reprogram metastatic cancer cells by inhibiting Nodal signaling. Nodal initiates a signaling cascade by binding to a receptor complex consisting of Cripto, type I (ALK 4/7) and type II (ActRIIB) activin-like kinase receptors and is regulated via a positive feedback loop. hESCs also secrete Nodal inhibitors, including Lefty, which is up-regulated in response to Nodal but antagonizes the Nodal signaling pathway by interacting with Nodal and/or Cripto. Like hESCs, cancer cells also express Nodal while unlike hESCs they do not express Lefty. HESC-derived Lefty (found in hESC conditioned matrices (CMTX) may inhibit Nodal signaling in cancer cells and promote their reprogramming toward a less malignant phenotype. Other tumor suppressive factors may also be deposited by the hESCs.*

in tumor cell plasticity that can be reprogrammed by exposure to Lefty, Nodal's inhibitor, or by genetically down-regulating Nodal. Targeting Nodal in experimental models will generate crucial insights into the design of new therapeutic strategies (initiating a Phase I clinical trial) to inhibit the progression of melanoma and breast carcinoma, and possibly other cancers, exhibiting an aggressive plastic phenotype.

Grateful acknowledgements:
This research is supported by grants from the National Cancer Institute CA59702 and CA121205 and philanthropy. The work was primarily performed by Lynne-Marie Postovit, Elisabeth A. Seftor, Naira V. Margaryan, Dawn A. Kirschmann, and Richard E.B. Seftor.

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Adult Survivors of Childhood Cancer and Their Parents: Experiences With Survivorship and Long-term Follow-up

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Survival rates for childhood cancers are approaching 80% due in part to advances in multimodal treatments and clinical trials.[1] Currently, one in every 640 adults aged 20 to 39 years in the United States is a survivor of childhood cancer.[2,3] Nationally, there were 270,000 childhood cancer survivors in 1997 with increasing numbers each year. As a group, survivors are a vulnerable population that require specialized long-term follow-up (LTFU) care throughout their life.[2,4] The risk for "late effects" and the development of chronic health conditions related to their prior cancer treatment is well established. [5–7] The largest of these studies included 10,397 adult survivors treated in the 1970s and 1980s who were enrolled in the Childhood Cancer Survivor Study.[8] Results revealed that 30 years after the cancer diagnosis the cumulative incidence of at least 1 chronic health condition was 73.4% (95% CI, 69.0-77.9) and the cumulative incidence for severe, disabling, or life-threatening conditions or death due to a chronic condition was 42.4% (95% CI, 33.7-51.2).[6] An equally concerning finding was the fact that these chronic health conditions increase over time and do not appear to plateau at any certain age.[6]

It is important to note that the effects of a traumatic event such as a childhood cancer extend beyond the survivor to the family system.[9] Little is known about the concerns, perceptions, and needs of the parents as their children enter adulthood, gain independence

over medical follow-up decisions while facing the threat of additional health conditions. Illness uncertainty is a significant predictor of adjustment outcomes among parents of children with chronic illness such as childhood cancer. This can lead to symptoms of depression and anxiety and general psychologic distress in both the parents and cancer patient.[10–12] Several studies have documented the presence of posttraumatic stress symptoms in both adult survivors of childhood cancer and their parents.[13–16] Posttraumatic stress is important because of the associated functional limitations, psychologic comorbidities, and the possible adverse impact on the survivor's willingness to obtain follow-up care.[13,14]

Transitioning survivors into adult-oriented healthcare that addresses their unique follow-up needs as cancer survivors has proven to be a challenge.[17] However, parental involvement may be important to continued involvement in follow-up care as an adult survivor. Ressler et al[18] noted that parental attendance with an adult offspring was 3 times as high for adult survivors seen in a cancer survivor clinic as patients seen in either a primary care or subspecialty internal medicine clinic. Most parents attending with their child who was an adult survivor admitted that they did not accompany their other adult children to their doctors' appointments but that there was a unique bond created by the cancer experience which did not diminish with increasing age of their children.[18] Virtually no other studies have explored the role of parents in their adult child's cancer follow-up care or survivorship.

The aims of this cross-sectional, descriptive study were to compare the perspectives of adult childhood cancer survivors and their parents in terms of: (1) parental involvement in the survivor's healthcare, (2) thoughts and discussion about their own or their son's/daughter's childhood cancer, (3) concern about the survivor's current health status, and (4) perceived benefits of follow-up care. The study focuses upon a group of childhood cancer survivors who have successfully transitioned to a comprehensive LTFU program for adult survivors of childhood cancer and their parents.

MATERIALS AND METHODS

Study Design

This cross-sectional, descriptive study consisted of a standardized semistructured telephone interview with adult survivors of childhood cancer and one of their parents (except in 1 case where both parents completed the interview simultaneously). The information used in this study was obtained with full Institutional Review Board approval and the explicit consent of the survivors and verbal consent from their parent(s) most involved in their care once the survivor was contacted.

Participants

The pool of potential participants consisted of all survivors seen in the clinic at least 1 time since the inception of the survivor program in 2001. Survivors were excluded if they had been diagnosed with brain tumors or had received cranial radiation exceeding 2400 cGy, as these patients frequently experience side effects from treatment (eg, speech disorders, cognitive impairments), which would make a telephone interview extremely difficult for them to complete. Seventy-four percent of the patients were treated at and referred from the children's hospital, which is affiliated with this adult program. The remaining 26% were referred to this program by various means such as self-referral, other Children's Oncology Group (COG) institutions, and Internet survivor resources. Ninety-one percent of patients interviewed indicted that they were current patients of the survivor program at the time of the study. The program for adult survivors of childhood cancer was in existence for approximately 4 years when this study took place. The survivor program includes medical surveillance and testing, physical examinations, patient education in a ''one on one'' setting in clinic as well as access to support groups and education events. Coordination of care is provided by the nurse and doctor who also facilitate subspecialty access as needed for specialized management of late effects. All demographic information was abstracted from each patient's electronic medical record.

Procedure

The LTFU nurse coordinator mailed a 1-page letter to the 102 eligible survivors, explaining the purpose of the study, which was to examine the relationship between the survivor and their parent(s) in terms of the survivor's healthcare and follow-up. All survivors included in this study had previously signed a written informed consent to be contacted for possible participation in research projects. Survivors were able to opt out of this study by telephoning or emailing the clinic nurse coordinator. Two survivors emailed in response

Survivor Questions	Parent Questions
1. Within the past year how often have you thought about your childhood cancer? 1 not at all, 2 occasionally 3 fairly often, 4 all the time	1. Within the past year how often have you thought about (child's name) childhood cancer? 1 not at all, 2 occasionally, 3 fairly often, 4 all the time
2. Specifically focusing on your parents, within the past year how often have you and your parent(s) talked about your childhood cancer? 1 not at all, 2 occasionally, 3 fairly often, 4 all the time	2. Within the past year how often have you and (child's name) talked about his/her childhood cancer? 1 not at all, 2 occasionally, 3 fairly often, 4 all the time
3. On a 4-point scale, how concerned are you about your present state of health? 1 not concerned at all, 2 slightly concerned, 3 moderately concerned, 4 very concerned	3. On a scale from 1 to 4, how concerned are you about (child's name) present state of health? 1 not concerned at all, 2 slightly concerned, 3 moderately concerned, 4 very concerned
4. What benefits do you think you have received from being in the LTFU Program? (open ended)	4. What benefits do you think (child's name) has received from being in the LTFU program? (open ended)
5. Are you currently receiving follow-up care through the LTFU Program? "Yes"/"no"	5. What is most important to you now regarding (child's name) followup care? (open ended)
6. Have your parents regularly attended the LTFU program with you? "Yes"/"no"	6. Are you currently involved with helping manage your son's/daughter's health care? "Yes"/"no"
Why do you think your parent(s) did or did not attend with you? (open-ended)	

TABLE 1. *Survivor and Parent Questions*

to the letter and declined to participate. An undergraduate communication student at a major university in the Midwest region of the United States contacted remaining survivors by telephone. The students were participating in a research course and had completed Human Subjects Training in addition to formal training in standardized interviewing techniques. Students practiced reading the questionnaires to one another, and were critiqued by their peers and the researchers regarding their abilities to ask questions clearly and word-for-word. Appropriate probing strategies were also reviewed and practiced by each student. Upon completion of training, each student received a randomly assigned group of survivors to contact via telephone. A maximum of 3 telephone attempts were made on 3 separate days and at different times of the day. Once a survivor was reached by telephone, the study details were provided and verbal consent to participate was obtained. Survivors were given the option of completing the interview at that time or scheduling a more convenient day and time. Survivors who completed the interview were asked permission to contact the parent who was most involved in their pediatric cancer care to conduct a similar interview. Survivors provided contact information for that parent who was telephoned to complete a similar interview. Parents were telephoned a maximum of 3 times. Interviews were completed using the same procedure that was employed with the survivors. All telephone interviews were recorded using a digital voice recorder and the content was subsequently transcribed for analysis.

Protocol/Questions

This manuscript describes responses to a set of questions that were a part of a larger interview. Six questions were asked to survivors and 6 questions were asked to the survivor's parents. As shown in Table 1 both survivor and parent interviews were comprised of 3 closed-ended questions with a 4-point response format (ie, 1=not at all, 2=occasionally, 3=fairly often, and 4=all the time). The survivor interview also included 2 dichotomous questions (yes/no) of which 1 had an openended follow-up and an

Benefits Identified by Survivors	Benefits Identified by Parents
Comprehensive care/late effects care themes	Comprehensive care/late effects care themes
Comprehensive Care	Health maintenance
Access to subsepcialiests	Best care possible/best doctors
1 doctor who knows all history	
Late effects focus	
Continued late effects care	
Psychosocial care	
Team approach	
Personal attention/relationship with the nurse themes	Personal attention/relationship with the nurse themes
Personal attention/relationship	Personal attention/relationship
Nurse (familiar)	Made to feel comfortable
Health Maintenance themes	Unsure/not involved in their care themes
Maintain health	Unsure
Medical surveillance	Parent not involved with their care
Long-term health	
General medicine	
Access to MD	
Keeps me going to a doctor	
Access to resources/education themes	Knowing they are not alone/networking themes
Resources	Happy they are not alone with medical issues
Education on late effects/health	Networking with other survivors
Health-related "Peace of Mind" themes	Research for self and other survivors themes
Security related to health	Involved in research to help others
Peace of mind	To help other survivors
Networking themes	Resources/education themes
Provides a connection	Access to medical resources
Network with survivors	Access to support resources
	Access to patient education
Saved my life themes	Making child responsible for healthcare themes
Saved my life	It makes my child be responsible

TABLE 2*. A List of Themes and Categories Identified in Survivor and Parent Responses to "What Benefits do You Think You Have (Your Child has) Received From Being in the LTFU Program?"*

additional open-ended question, whereas the parent interview had 1 dichotomous question and 1 open-ended questions.

Content Analysis Procedures

Responses to all open-ended questions were coded and analyzed using constant comparative analysis with no prespecified criteria or themes.[19,20] Constant comparative analysis is a core method of analysis underlying the grounded theory approach to qualitative research. Constant comparative analysis is an iterative process of understanding qualitative data whereby responses are broken into smaller segments or themes. Those themes are then coded into larger categories. Constant comparisons are made between responses to look for similarities or differences that may suggest boundaries on the thematic categories or require new themes and categories. As described by Tesch,[21] the goal is to identify conceptual similarities, refine the discriminative power of the themes, and identify patterns across responses.

In this study, the first phase of analyses of openended questions involved identifying a list of themes that appeared in the responses to each question. This was completed independently by 2 authors who read the interview transcripts in their entirety and created lists of themes. The 2 authors met to discuss the themes that emerged without reference to the actual transcripts and agreed upon a smaller list of broad themes. This list of themes was entered into an excel spreadsheet along with an identification number for each survivor. The second phase of analyses involved having the 2 reviewers read the transcripts a second time and independently code each response with the agreed upon themes. Codes were recorded in the excel spreadsheet. The

third phase involved collapsing themes with common elements into larger categories. Table 2 lists all of the categories and underlying themes that were identified in the analysis of the open-ended question asking survivors and their parents about perceived benefits from being in a LTFU program. Each response was given an additional code based upon whether the 2 authors agreed or disagreed upon the category. Overall agreement across the 4 openended questions was high with an interrate reliability of 0.95. Disagreements were discussed until consensus was reached. This same process was completed separately for the survivors' interviews and the parents' interviews.

Quantitative Analyses

Analysis of variance was used to compare thedemographic characteristics and age at diagnosis in 3 groups defined by their level of participation in the study as follows: (1) survivors who participated with a parent, (2) survivors who completed the larger survey without a parent, and (3) survivors who could not be contacted. This comparison was performed to understand if any group differed in terms of demographic characteristics (ie, age, martial status). Questions with a 4-point response format were analyzed using paired samples t test to compare survivors' and parents' responses.

RESULTS

Survivors' Interviews

Of the 102 eligible survivors, 2 declined to participate, 46 could not be located, and 54 (53%) were successfully interviewed. One audio-recorded interview was excluded due to technical problems. Of the remaining 53 survivors with interviews, parent interviews were obtained on 42 survivors. Eleven survivors completed the interview without a parent participating. This study reports upon the 42 survivor-parent dyads where data were collected from both the survivor and parent (in 1 case both parents simultaneously participated in 1 interview).

An initial analysis was conducted to identify differences in general demographic characteristics across 3 groups that were defined by their level of participation in the study (ie, 42 survivors who completed the interview with a parent, 11 survivors who completed an interview without a parent, and 48 survivors who did not participate in the research or declined. The survivor whose interview was excluded due to technical problems was not included in this analysis). There were no differences between these 3 groups on sex, highest level of education, age, age at diagnosis, years since diagnosis, or current living situation (results not shown). The survivors that completed the interview without a parent were more likely to be married (P=0.03) than either the dyads or the survivors who did not participate. Hispanic/Latino survivors were less likely to participate than White or African American survivors (P=0.02).

N=42	N	%
Sex		
Male	17	40.5
Female	25	59.5
Race/ethnicity		
White	37	88.1
Other	5	11.9
Marital status		
Single	26	61.9
Married	16	38.1
Education		
High school degree, GED or less	10	23.9
College degree	32	76.1
Employment status		
Student	7	16.7
Employed part-time	5	11.9
Employed full-time	27	64.3
Unemployed	3	7.1
Type of cancer		
Hodgkin disease	13	31.0
Non-Hodgkin lymphoma	5	11.9
Leukemias	10	23.8
Neuroblastoma	3	7.1
Sarcoma	4	9.5
Rhabdomyosarcoma	3	7.1
Wilm tumor	4	9.5
	Mean (SD)	**Range**
Survey age, y	28.8 (6.0)	20-45
Diagnosis age, y	10.1 (5.2)	1-21
Time since diagnosis, y	18.3 (7.0)	7-35

TABLE 3. *Demographics of Survivors*

**GED indicates general equivalency diploma.*

The demographic characteristics of the survivors included in this study are summarized in Table 3. The average age of the survivors was 28.8 years (range: 20 to 45) and the average time since diagnosis was 18.3 years (range: 7 to 35). The sample was largely White, college educated, and employed full time. Twenty-four percent (10/42) had at least 1 child (range: 1 to 3) of their own.

Reason Why Parents Attended Category*	Survivors,(N) %	Reasons Why Parents did not Attend Category*	Survivors, (N) %
Parents were concerned and interested	10 (63.0)	The survivor's age now	19 (73.0)
Provide emotional support	7 (44.0)	Parents live too far/out of town	15 (58.0)
Parents were "used to" attending	6 (38.0)	The survivor's responsibility	6 (23.0)
In case a new health problem arose	2 (13.0)	The survivor never asked them to	2 (8.0)
Survivors asked them to attend	2 (13.0)	Parents just never have attended with the survivor	1 (4.0)
Help with the transfer	1 (6.0)	Their parent's age 1	(4.0)

TABLE 4. *Survivor's Responses to "Why do You Think Your Parent(s) Attended With You?" N= 16. "Why do You Think They did not Attend With You?" N= 26*

**Some survivors provided more than 1 response.*

We asked survivors if their parents regularly attended the follow-up clinic with them and reasons why or why not. Thirty-eight percent (16/42) reported that their parent attended with them. As shown in Table 4 the top 3 reasons why survivors thought that their parents attended their annual follow-up visit with them were: parents were concerned and interested in what went on at the appointment (10/16), parents provided emotional support (7/16), and parents were just "used to coming with them" (6/16). Patients whose parents did not attend their annual follow-up visit with them (26/42) were asked, "Why do you think they did not attend with you?" The top 3 reasons included: the patient's age now (19/26), parents live too far or out of town (15/26), and survivors healthcare was their own responsibility (6/26) (Table 4). Twenty of the 26 survivors who attended without a parent (6 survivors were not asked this question by the interviewers) were asked whether or not they communicated with parents about their medical visits. Interestingly, 17 of the 20% or 85% of survivors reported that they did have follow-up communication with their parents about the clinic visit and about results from medical tests.

Parents' Interviews

We are reporting on 42 parents who completed interviews with 38 mothers, 3 fathers, and 1 with both parents. Fifty percent (21) of parents indicated that they were currently involved with or helped manage their son or daughter's healthcare. Parents who reported having been involved in managing their child's healthcare had younger children (mean=26.2 y vs. 31.6 y; Pr0.005) with more recent dates of diagnosis (mean=16.0 vs. 20.7 y; Pr0.05) than parents who reported that they were not involved in their child's healthcare. To understand more about parents' health-related concerns for their adult children, we asked them "What is most important to you now regarding (name's) follow-up care?" Results from the 38 parents who answered this question (4 parents were not asked) include: that they get yearly check-ups, necessary tests 61% (23), late effects care, preventative care with the right doctors 29% (11), that the parent can have a "piece of mind" knowing their child is cancer free 11% (4), and that their child maintains a good quality of life 11% (4).

Survivor-parent Dyad Results

Three similar closed-ended questions were asked of each survivor-parent dyad:

1. "Within the past year how often have you thought about your childhood cancer (your child's cancer)?" 1=not at all to 4=all of the time.

2. "How concerned are you about your (your child's) present state of health?" 1=not at all to 4=very concerned.

3. "Within the last year how often have you and your parents (child) talked about your (their) childhood cancer?" 1=not at all to 4=all of the time.

Results showed that parents reported thinking about the cancer more often than their child reported (45% vs. 25%), reported being more concerned with their child's health status than their child reported (41% vs. 26%), and talked about the cancer more often than their child reported (22% vs. 12%). None of these differences reached a statistically significant level in paired samples t test.

Forty-two survivors were asked by the interviewer "What benefits do you think you have received from being in the long-term follow-up (LTFU) program?" The 3 most common perceived benefits for survivors were: comprehensive care/late effects care 43% (18), personal attention/relationship with the nurse 43% (18), and health maintenance 33% (14) (Table 5). Forty of the parents were asked

Benefit Category Patients,	N	(%)	Benefit Category Parents,	N	(%)
Comprehensive care/late effects care	18	(43.0)	Comprehensive/late effects care	18	(45.0)
Personal attention/relationship with the nurse	18	(43.0)	Personal attention/relationship with the nurse	8	(20.0)
Health maintenance	14	(33.0)	Unsure/not involved in their care	8	(20.0)
Access to resources/education	12	(29.0)	Knowing they are not alone/networking	5	(13.0)
Health-related "peace of mind"	7	(17.0)	Research for self and other survivors	5	(13.0)
Networking	5	(12.0)	Resources/education	4	(10.0)
Research	1	(2.0)	Health-related "peace of mind"	4	(10.0)
"'Saved my life"	1	(2.0)	Making child responsible for healthcare	1	(3.0)

TABLE 5. *Survivor's Responses to "What Benefits do You Think You Have Received From Being in the LTFU Program?" *N = 42. Parent's Responses to "What Benefits do You Think (Child) has Received From Being in the LTFU Program?" *N = 40*

**76% of survivors mentioned more than 1 benefit and 30% of parents mentioned more than 1 benefit.*

"What benefits do you think (your child) has received from being in the LTFU program?" Two parents were not asked this question. The 3 most common perceived benefits included: comprehensive/late effects care 45% (18), personal attention, made to feel comfortable 20% (8), and knowing that their child was not alone in dealing with their healthcare issues 13% (5). An additional 20% (8) mentioned that they were not sure of any benefits from the late effects program because they were not involved in their child's care.

DISCUSSION

This study is among the first to describe parental involvement and concern with the health status and healthcare of adult childhood cancer survivors from both the survivor and parent perspectives. Results revealed that 38% of adult survivors reported having a parent regularly accompany them to their annual follow-up visit. These results can be contrasted with Ressler's study that found 66% of adult survivors were accompanied to their clinic visits by a parent.[18] Interestingly, the mean age was similar across the 2 samples. Survivors in our study were a mean of 28.8 years old (range: 20 to 45) compared with Ressler with a mean age of 25.0 years (range: 19 to 43). A few factors may have contributed to the difference in findings. The current study was conducted within a clinic designed for adult childhood cancer survivors and located within an adult-focused medical center. Ressler's study was based within a specialized clinic providing care to pediatric and adult cancer survivors. It is possible that parental attendance with adult survivors in Ressler's study was normalized by the presence of parents with children. In addition, the geographic distance between where survivors and their parents reside may play a role. Ressler's study reported that 62.8% of the sample lived within 10 miles of their parents and 20.9% lived more than 50 miles away from their parents. In our study, of the 26 survivors whose parents did not attend clinic with them, 58% (15) indicated that their parents lived too far away to accompany them to the visit. Both studies identified a subgroup of childhood cancer survivors who maintained close parental involvement in their healthcare into adulthood.

Our comparison of survivors' responses with their parents' responses to similar questions revealed that in general, the parent thought more about the child's cancer, talked to the child more often about the cancer, and was more concerned than the survivor was about the survivor's present state of health. Although the differences were not statistically significant, there may be clinical significance when treating the "whole" survivor (ie, the survivor, their family, and their support systems). The parents' demonstration of a high level of concern about their child's health status and recurrent thoughts regarding their child's prior cancer coincide with Ginsberg's description of obstacles when childhood cancer survivors are transitioning to adult care. She reports that parents of childhood cancer survivors can exhibit a heightened perception of disease severity and over protectiveness of the young adult.[11,22] This may be related to the uncertainty the parent's feel in terms of their child's medical status and future health and may be a symptom of posttraumatic stress disorder.[13–16]

Interestingly, when we asked the survivors and parents about perceived benefits from being followed in the LTFU program for adult survivors of childhood cancer they both responded with "comprehensive/late effects care" as their most frequent perceived benefit. Not surprisingly, as most survivors in this study

were active patients in the LTFU program, 95% perceived at least 1 benefit from being in the program for follow-up care. Those who did not see a benefit would be less likely to seek care in a LTFU program. Similarly, 80% of parents mentioned benefits that they perceived their child was receiving from the LTFU program. Twenty percent of parents were unable to list benefits or indicated they were not involved in their child's healthcare as a reason for not understanding the benefits. Other top benefit responses survivors' gave included access to resources, knowing that they were not alone, and the opportunity to network with other adult survivors. Zebrack et al[23] reported in a modified Delphi panel study, that adult survivors of childhood cancer participating in his study ranked the importance of opportunities to meet other young adult survivors at a higher level than healthcare professionals participating in the study did. Also, the survivors ranked those opportunities higher than the importance of support from their family and friends.[23] The opportunities to meet new friends, share stories and resources can benefit the survivors by enhancing their self-concept and social and emotional well-being.[24,25] If networking with other survivors is important then future studies should assess the needs of these survivors and their parents to discover the type of networking events and opportunities they would most likely attend. Examples of opportunities for networking/sharing resources may include hospital or support agency education symposiums, camps for children, adolescents and young adult survivors, and cancer survivor walks that the survivor and their family can attend.

In the current study, the majority of parents remained an important source of support to most survivors whether that involved accompanying them to their appointments or communication about the appointment and test results after the visit. These findings need to be evaluated further in future studies with a larger cohort of adult survivors and their parents. One of the limitations of this study was that it involved a single site cohort participating, which reflected 1 model of adult follow-up care, which takes place in cancer center in an adult medical setting. Interviewing a sample of adult survivors obtained from several sites that represented various models of cancer follow-up programs for these survivors (ie, formal LTFU programs vs. primary care setting) would be interesting to assess in terms of differences in the findings.[26,27] Also, it is likely that overall parent participation in follow-up visits in our clinic may be higher than we report in this study because we excluded survivors who were treated for brain tumors and with cranial XRT over 2400 cGy. This group of survivors is known to have more treatment related effects and is at increased risk for cognitive difficulties making them more likely to be dependent on parents.[28,29]

As more children are surviving cancer into young adulthood the number of survivors requiring LTFU care continues to rise. Adult survivors of childhood cancer are followed in a variety of different medical settings for their health issues, some of which are better prepared to provide the risk-based care they need.[30] Providing education for the survivor and their family beginning in the early stages of survivor care (usually in a children's hospital) is crucial for their success as a long-term cancer survivor.[31,32] Pediatric oncology health professionals will support their patients and their families into young adulthood if they provide anticipatory guidance to the patient regarding how to access the medical care they need as they mature into adulthood. This will better prepare them to obtain the appropriate late effects care they need, feel as though they have the ability to take charge of their medical issues and have their parents support them as needed.

ACKNOWLEDGMENT

The authors thank Kathy Meeske, PhD, for her guidance in preparing this manuscript.

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The Use of Transcatheter Intraarterial Perfusion (TRIP) MRI to Monitor Chemoembolization of Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is the 8th leading cause of cancer death in the US (1). Cirrhosis secondary to chronic viral hepatitis or alcohol abuse is the single most important risk factor for HCC (2) and accounts for HCC's multi-focal nature. Surgical resection and liver transplantation are the sole potentially curative HCC treatments, but only 10-15% of patients are surgical candidates (3). Hence, most other systemic and regional therapies offer palliation rather than cure.

Interventional radiologists currently treat HCC under x-ray digital subtraction angiographic (DSA) guidance with transcatheter arterial chemoembolization (TACE). TACE involves the injection of cytotoxic chemotherapy, along with a combination of emulsified poppyseed oil (Ethiodol) and particles, to reduce tumor perfusion. The ideal endpoint of TACE, i.e. how much chemoembolic material to deliver, is unknown. Injection of too little chemoembolic material into the tumor's arterial blood supply will incompletely treat the tumor. Injection of too much material can harm the patient by a) reducing function in adjacent liver uninvolved with tumor and b) inducing expression of angiogenic growth factors that might counter-productively promote tumor growth. The fundamental role of perfusion during TACE on clinical outcomes is unknown. This role could not previously be answered because there has been no objective and reproducible intra-procedural method to measure serial perfusion changes during TACE.

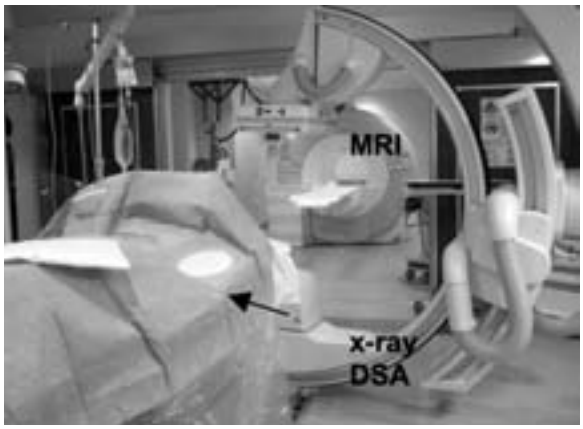

Figure 1. *MR-IR hybrid x-ray DSA/MRI suite at Northwestern Memorial Hospital. Moving table (arrow) allows easy transfer of patients between x-ray DSA and MRI during interventional procedures.*

To address this gap in knowledge, we developed an innovative magnetic resonance imaging (MRI) technique to quantify perfusion. This technique, termed transcatheter intraarterial perfusion (TRIP)-MRI, permits serial monitoring of perfusion levels during TACE. In this article, we will present our translational research experience using TRIP-MRI to monitor the treatment of HCC with TACE.

Magnetic Resonance-Interventional Radiology (MR-IR) Monitoring of Therapy

MR-IR suites (4) that combine x-ray DSA with adjacent MRI scanners permit intra-procedural monitoring of HCC therapies. The concept is to use x-ray guidance for catheter placement because of its high spatial resolution (0.1 mm^2) and to use MRI because of its capacity to monitor the functional effect of therapy. MRI's ability to help identify tumor perfusion altered anticipated catheter position from DSA in 40%-50% of patients undergoing transcatheter hepatic artery therapies (4, 5). While these combined MR-IR suites were initially limited to a few research institutions, they are increasing in prevalence. For instance, Siemens (Erlangen, Germany) recently installed or has pending orders for 7 – 10 new MR-IR suites in N. America (Christine Lorenz, PhD, personal communication). In early 2006, Northwestern Memorial Hospital became one of the first hospitals in the world to apply such a unit (Fig. 1) to the clinical setting of TACE.

Dynamic Contrast Enhanced Tumor Perfusion Imaging

Dynamic contrast enhanced (DCE)-MRI is the conventional MRI technique used to measure tumor perfusion. It uses IV bolus injection of gadolinium-based (Gd) contrast agent, followed by repeated rapid sampling of T1-weighted (T1-w) images to measure the time course of signal change. Gd shortens tissue T1 thereby increasing signal intensity within T1-w images. Perfusion parameters are then calculated from time-curves depicting these dynamic signal intensity changes after Gd administration. However, conventional IV-bolus DCE-MRI approaches are not generally suitable for serial intra-procedural perfusion measurements due to a) limitations upon cumulative contrast dose and b) the typically long contrast wash-out times (>1hr) required between serial measurements.

Advantages of TRIP-MRI for Monitoring TACE

TRIP-MRI can overcome the limitations of conventional DCE-MRI. TRIP-MRI differs from DCE-MRI because TRIP-MRI uses intraarterial (IA) injections of Gd directly through the hepatic artery catheter, while DCE-MRI uses standard IV injections of Gd. Because TRIP-MRI uses IA injections of tiny amounts of Gd (4-10 mL of 20% diluted Gd solution, equivalent to 1-2 mL of full-strength Gd), serial injections can be performed during TACE without having to wait > 1 hr for the 20 mL of full-strength Gd to wash-out from DCE-MRI. Also, the catheter-based IA injections can verify the distribution of injected chemoembolic material, in some cases showing that the tumor will not be adequately targeted in the current catheter position. We have recently improved our TRIP-MRI technique from acquiring a temporal series of liver slices to a series of liver volumes (i.e. moving from 2D to 4D TRIP-MRI), thereby overcoming potential partial volume effects from 2D imaging. We have also developed a method that now offers assessment of absolute perfusion levels across patients, rather than relative changes within the same patient. These perfusion changes can be correlated with clinical outcomes and be used to validate DSA treatment endpoints.

The benefits of employing quantitative TRIP-MRI during TACE can be viewed within the context of the fourth Biomedical Imaging Research Opportunities Workshop (BIROW IV) held in Bethesda, MD in 2006 (6). Co-sponsored by 24 separate imaging societies, BIROW IV lauded the development of 4D image-guided interventional techniques that could be used during the procedure to validate treatment endpoints (6).

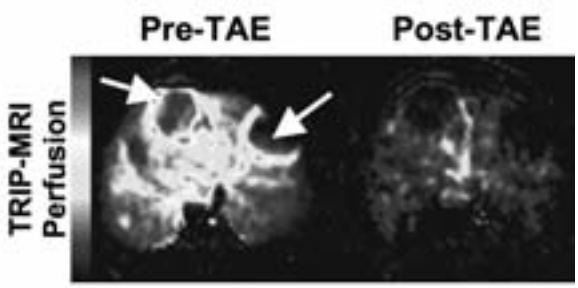

Figure 2. *TRIP-MRI perfusion maps depicting reduction to rabbit VX2 liver tumor perfusion following transcatheter arterial embolization (TAE) procedure (2 liver tumors, arrows, both tumors centrally necrotic).*

Pre-Clinical TRIP-MRI Studies

The fundamental principle of TRIP-MRI is to measure the dynamic enhancement of a volume of liver tissue over time and convert this information into a perfusion metric. Tumor signal intensity is converted to T1, which is then converted to Gd concentration for quantitative perfusion measurements using pharmacokinetic modeling. There are a number of both quantitative and semi-quantitative perfusion parameters that can be estimated with pharmacokinetic modeling of the Gd tracer uptake. The term 4D TRIP-MRI indicates that a volume of liver (3 spatial dimensions) is repeatedly imaged over time (1 time dimension) to assess changes in perfusion during TACE.

To develop and refine the TRIP-MRI technique, we have performed experiments in > 150 rabbits (7-11), most with surgically implanted VX2 carcinoma liver tumors. These pre-clinical studies in rabbit VX2 liver tumors included experiments in which we showed the benefit of using IA (TRIP-MRI) over IV (DCE-MRI) injections of contrast agent (7); devised 4D TRIP-MRI as a rapid volumetric imaging method and confirmed its accuracy using fluorescent microspheres (Fig. 2, (12, 13)); and demonstrated that embolization induces tumor angiogenesis by staining for increased HIF-1 expression(9, 14). The initial rabbit studies led us to file a patent application for the use of TRIP-MRI as an intra-procedural technique to monitor perfusion reductions during TACE.

Clinical TRIP-MRI Studies

In a series of subsequent studies, we have successfully translated our innovative TRIP-MRI techniques into the clinical arena. For the clinical use of TRIP-MRI, interventional radiologists position catheters within the hepatic artery using conventional x-ray guidance. Patients are then transferred to the adjacent MRI unit for pre-TACE TRIP-MRI. After undergoing TACE, they then receive an immediate follow-up TRIP-MRI scan to detect the change in perfusion.

Using the MR-IR unit at NMH, we were the first group to clinically implement TRIP-MRI to detect semi-quantitative perfusion changes during TACE, correlating findings with available liver explant specimens(15). In an initial cohort of 13 HCC TACE sessions using TRIP-MRI, mean perfusion reduction was 74.6%±24.8% ($p<0.013$) (15). In a subsequent cohort of 7 patients using 4D TRIP-MRI (16), we showed that TACE reduced intra-procedural tumor perfusion by roughly 50%. Maps showing localized perfusion differences can be constructed. Fig. 3 shows sample images and perfusion maps in HCC patients. These perfusion maps revealed clear perfusion differences over the injected angiographic territory pre and post TACE (greater perfusion depicted with color red, while lesser perfusion depicted with color blue).

Our preliminary results suggest that perfusion need not be entirely eliminated to achieve a successful response to therapy. For instance, in 3 available liver explants, complete tumor necrosis was seen in 2 patients after perfusion reductions of 93% and 84% (Fig. 4), while viable HCC was seen in 1 patient with perfusion reduction of 5%.

In a separate clinical study in 15 patients (17), we compared the reproducibility of interventional radiologists in classifying angiographic endpoints. We found that there was only moderate reproducibility between interventional radiologists using subjective

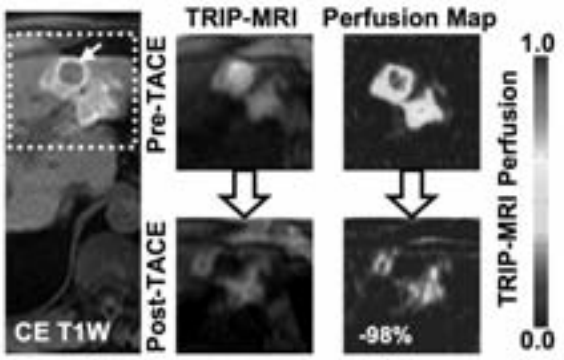

Figure 3. *TRIP-MRI in patient with HCC. Anatomic contrast-enhanced T1-weighted (CE T1W) image depicts HCC position. Pre/post-TACE TRIP-MRI and functional perfusion maps show significant reductions in perfusion.*

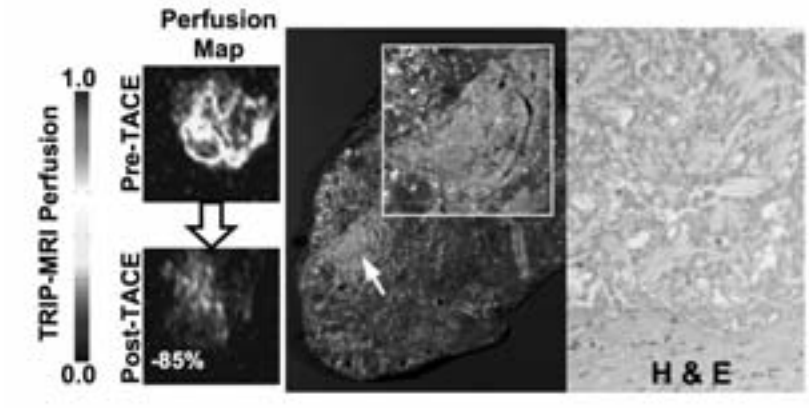

Figure 4. *TRIP-MRI functional perfusion maps before and after TACE show reduction in right-lobe HCC perfusion (left). Gross specimen depicts position of treated HCC (arrow) with follow-up H&E staining at pathology confirming complete necrosis (right).*

angiographic endpoints, with kappa = 0.46 ±0.12. However, there was no correlation between these subjective angiographic endpoints and objective reductions in tumor perfusion using TRIP-MRI (r = 0.16 for one interventional radiologist and 0.02 for the other two).

Perfusion Mismatch Technique to Exclude Collateral Tumor Supply to Treated HCC

At least 26 different collateral artery pathways can develop following occlusion of hepatic artery supply (18). These collateral pathways can serve as the only arterial supply to HCC or as additional conduits supplying portions of the tumor. Collaterals are most commonly seen in large HCC or tumors near the dome of the liver (19-21), or from multiple previous TACE sessions (22, 23). It is essential to identify these collaterals during TACE, or else the tumor might not be treated in its entirety. Because conventional planar DSA does not provide soft tissue contrast, it can be difficult to exclude the presence of these collaterals without considerable time, ionizing radiation, and iodinated contrast agent dose.

To identify these potential collaterals, we devised a perfusion mismatch technique that combines TRIP- and DCE-MRI. The technique requires an additional DCE-MRI scan using 0.1 mmol/kg IV Gd injection after completion of post TACE TRIP-MRI scan. This separate IV injection of Gd identifies whether any residual portion of tumor is still enhancing. If so, this indicates that collateral vessels are present and should be sought out within the IR unit at the time of the next treatment session (Fig. 5). If not, TACE can be confidently terminated with knowledge that no collaterals are present. In an initial clinical study(24), we demonstrated that this perfusion mismatch technique reliably identifies whether there is collateral supply to treated HCC during MR-IR monitored TACE and that the prevalence of this mismatch occurred in 2/8 patients (25%).

Limitations

There are several limitations to using TRIP-MRI. First, the clinical technique requires the use of MR-IR units, which are currently available only within advanced tertiary care

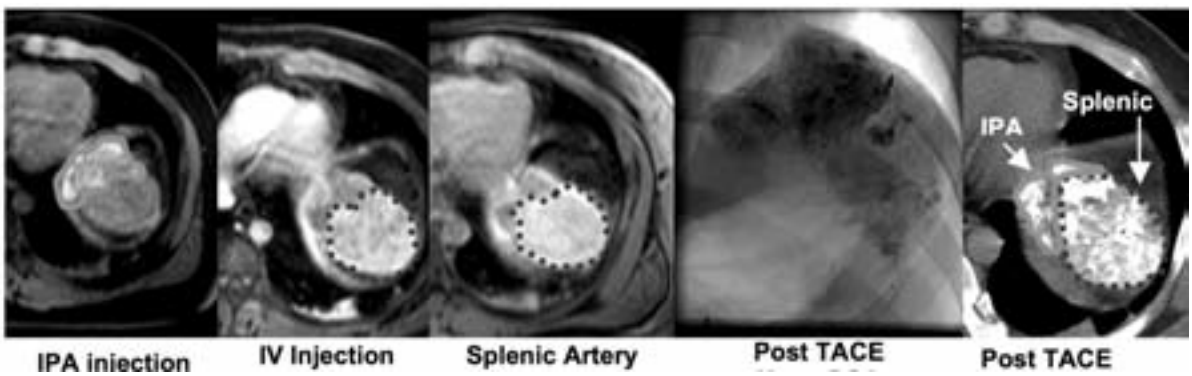

Figure 5. *TRIP-MRI via left inferior phrenic artery (IPA) injection shows that medial portion of tumor (solid orange outline) would be targeted with catheter in this position. After IPA TACE, DCE-MRI with IV Gd injection shows that larger, more lateral portion of tumor still enhances (within dashed blue outline). Follow-up TRIP-MRI performed via splenic artery collateral injection shows similar tumor enhancement as IV DCE-MRI. This verifies that lateral portion of tumor is supplied by splenic artery collateral and can be successfully targeted with catheter in this position. X-ray angiogram following superselective TACE shows Ethiodol retention within large left lobe tumor. Immediate follow-up non-contrast CT scan verifies Ethiodol distribution within the tumor.*

university medical centers. Second, TRIP-MRI prolongs procedure time in patients undergoing TACE by approximately 1 hour. However, we think that the benefits (verification of tumor targeting, measurement of functional changes in tumor perfusion) easily outweigh the added time required for imaging. Third, TRIP-MRI should not be performed in patients with glomerular filtration rates of <30 mL/min/1.73 m^2 because of the risk of inducing contrast-induced nephrogenic systemic fibrosis (25).

Future Directions and Conclusion

TRIP-MRI is a useful technique to monitor patients with hepatocellular carcinoma who are undergoing chemoembolization. It can assess changes in tumor perfusion as a functional biomarker for endpoint determination. Ongoing technical development projects seek to improve the accuracy and reproducibility of our TRIP-MRI methods and ultimately permit more rigorously quantitative tissue perfusion measurements. Future clinical studies will correlate TRIP-MRI monitored perfusion endpoints during TACE to long-term patient response. In both pre-clinical and clinical studies we are exploring additional applications for TRIP-MRI including intra-procedural monitoring of uterine fibroid embolization as well as drug and/or radiopharmaceutical delivery to both pancreatic and liver tumors.

Acknowledgements:

The authors wish to acknowledge grant support from NIH R01 CA126809-01A2 and R01 CA134719-01; the Society of interventional Radiology Foundation; and the Rosenberg Family Cancer Research Fund.

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The CORE of the Outcomes Measurement and Survey Core

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The Outcomes Measurement and Survey Core (OMSC) is a shared resource of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Because CORE has a large staff of scientists, research assistants, bilingual study interviewers, database programmers and statisticians, the OMSC can efficiently provide consultation and research support services, as well as assist investigators in assembling an experienced research team. Self-report data refers to any data obtained directly from a patient, provider or other respondent. In many cases this information is not directly observable and can only be obtained by asking the person directly, e.g., health status, knowledge and attitudes. In cancer research, important and commonly measured patient-

reported outcomes (PRO) include symptom burden, health-related quality of life and treatment satisfaction. We serve as a central resource for state-of-the-science instruments and survey methods, and provide in-house research support services for the collection of outcomes and survey data.

The OMSC is housed within the Center on Outcomes, Research and Education (CORE) at NorthShore University HealthSystem (formerly Evanston Northwestern Healthcare). Because CORE has a large staff of scientists, research assistants, bilingual study interviewers, database programmers and statisticians, the OMSC can efficiently provide consultation and research support services, and can also assist you in assembling an experienced research team.

Following are descriptions of the resources and services available from the OMSC along with illustrative projects that have been supported.

Outcomes Measurement Library

The OMSC has a large library of questionnaires and reference material, some of which is on our website: (http://apps.basic.northwestern.edu/omc/default.cfm). The OMSC assists interested researchers by helping them find the most appropriate tools for their particular needs, including relevant publications and/or translations.

Development of Surveys and Questionnaires

Questionnaires are valuable tools for collecting data in research studies. But as OMSC Director Elizabeth Hahn, MS, and Kathleen Yost, PhD, stress in their MPH course Survey Design and Methodology (PH 438), there is a lot more to creating a questionnaire than simply writing questions on a piece of paper. The wording of the questions, how they are ordered and even the formatting can affect the quality of the data collected. Following is a general description of the steps one might take in developing a questionnaire:

The first step is to clarify the purpose and ultimate use of the questionnaire data (e.g., descriptive, analytic). The next step is to outline all of the topic areas that need to be covered (e.g., demographics, health behaviors, family history). If a topic area is unique or has not been previously studied, it may be necessary at this stage to conduct qualitative research such as focus groups or semi-structured interviews in a small sample from the population of interest to identify themes that can be used to guide the creation of new questions. If the topic area is more general, existing surveys are identified and reviewed to determine whether questions measuring a topic of interest already exist. Provided there are no copyright restrictions on the source material, these existing questions are included in the questionnaire and additional questions are written, where needed. A panel of reviewers with expertise in the various topics covered in the questionnaire should review a draft version to ensure that the content is appropriate and can fulfill the purpose of the questionnaire.

An often overlooked, but essential step in questionnaire development is the pretest, in which questions - including existing questions borrowed from other sources - are tested in a small sample from the population of interest. The purpose of the pretest is to assess the quality of the questions. For example, the pretest provides an opportunity to determine if there are any questions that are difficult to comprehend, offensive, or not relevant to the participants. An in-person debriefing interview is a common method used in pretesting. The participant first completes the questionnaire, then a trained interviewer conducts the interview by going over the entire questionnaire and probing about each question. If the population of interest is culturally diverse, the pretest sample should reflect that. In this case, the debriefing interview could include probes to specifically determine whether questions are being interpreted similarly by different cultural groups. Pretesting is also an opportunity to assess instruction and formatting to determine whether the respondent can easily navigate through the questionnaire. Questions might be discarded or reworded based on the information obtained in the pretest. Ideally, any questions that were changed should be pretested again.

The next step is to administer the questionnaire to another sample from the population of interest in order to assess the reliability and validity of the questions. This sample is larger than the one used in the pretest. Questions that are judged to be without value can be dropped or revised, but if they are, their validity must be reassessed. Thus, questionnaire design is a fairly iterative process. If the questions are found to be reliable and valid, the questionnaire is ready for use as a data collection tool in a research study.

An optional step that might take place at this point is translating the questionnaire into other languages. A rigorous translation methodology should be followed that includes forward translation into the target language and back translation into English. The translated questions are not necessarily literal translations; rather, it is more important that they capture the meaning of the questions. The final step in translation is to conduct a pretest in a sample of native speakers of the target language. The pretest should include a debriefing interview or some other methodology for assessing the quality of the translation.

Faculty and staff in the OMSC have assisted several Lurie Cancer Center members in developing and formatting their questionnaires. We have also helped Lurie Cancer Center members to set up questionnaire administration procedures and to analyze data collected via questionnaires.

Focus Groups

Qualitative research methods are especially useful for exploration and discovery about either topics or groups of people that are poorly understood. Focus groups are group interviews and discussions designed to generate a rich understanding of participants' experiences and beliefs and that are guided by a moderator. Questions are asked or discussion topics are posed in an interactive group setting where participants are free to talk with other group members. The groups are typically comprised of six to eight individuals who share some interest/characteristic in common (e.g., same diagnosis, live in same neighborhood). The moderator is a well-trained professional who works from a set of discussion topics that have been carefully determined in advance by the investigator(s). In academic research, focus groups serve four primary purposes: generating research questions, exploring research design issues, for purposes of collecting qualitative data, and to aid in data analysis or interpretation. Focus groups can be especially helpful in research when there are gaps between people to bridge, when investigating complex behavior and motivations, and in understanding diversity (Morgan, 1998).

The OMSC has recently conducted focus groups in support of two Lurie Cancer Center initiatives. The lab of Teresa Woodruff, PhD, has developed novel methods that promote immature ovarian follicle growth in vitro. Based on this technology, the Lurie Cancer Center has developed a new program in oncofertility in partnership with the Division of Fertility Preservation in the Department of Obstetrics and Gynecology. The mission of the program is to develop and apply new technologies that can preserve and extend fertility options for young women and girls with a cancer diagnosis. As part of the exploration of extending the options to young girls, OMSC investigators collaborated with Dr. Woodruff's research staff to qualitatively evaluate the attitudes of adult survivors of childhood cancer and their parents about accessing fertility preservation options at a young age. OMSC investigators facilitated four focus groups: two with adult women who were diagnosed and treated for cancer as adolescents and two with their parents, with the purpose of exploring and comparing the attitudes towards fertility and fertility preservation among and between the survivors and parents. The qualitative results from those groups have now been published (Neiman et al., 2007).

A second research initiative utilizing focus groups was Rex Chisholm, PhD's, NuGene grant, which is exploring whether biorepositories developed at institutions with robust electronic medical records could provide samples and phenotypes derived from EMRs that would produce quality samples for genome wide association studies. Although a number of studies have assessed public opinion regarding informed consent and uses of genetic data, attitudes toward consent processes for high-throughput genomic-wide technologies and widespread sharing of data are not known. Potential concerns among relevant stakeholders have not been formally assessed. Therefore, as a part of this study, a community consultation process, which involved focus groups conducted with biorespository participants and the general public, was implemented to elicit feedback and opinions from a diverse group of community members. The goal of these groups was to gain a better understanding about biorepository participants' and the public's views toward generating, analyzing, and sharing genetic research findings in order to produce greater insight into and contribute to best practices of conducting genetic research. OMSC investigators facilitated the three public focus groups, and NUGene staff facilitated the biorepository participant groups. Those data are currently undergoing analysis.

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HOPE Study

The Helping Obtain Palliative Excellence (HOPE) clinical research program is an inter-campus inter-disciplinary collaboration among clinical research investigators from the Lurie Cancer Center, NorthShore University HealthSystem, Northwestern Memorial Hospital (NMH)) and OMSC researchers. David Cella, PhD, and Lynne Wagner, PhD, from CORE obtained funding to support the HOPE study, with the primary goals of implementing a symptom screening tool as recommended by the National Comprehensive Cancer Network (NCCN) and characterizing the symptom management services patients received. The HOPE team included Judy Paice, PhD, RN, FAAN, Jamie Von Roenn, MD, Joshua Straus, MD, and Cameron Muir, MD, from NMH and Daniel Shevrin, MD, Bobbi Marks, RN and George Carro, RpH, from NorthShore University HealthSystem and A.H. Peterman, PhD, from the University of North Carolina. The HOPE team identified priority cancer-related symptoms (fatigue, pain, emotional distress, and appetite loss) based on prevalence and impact on health-related quality of life and developed a screening tool for the rapid identification of patients with clinically significant target symptoms. This year, the HOPE researchers published two papers that addressed communication about and identification of these important symptoms (Butt et al., 2008a; 2008b).

At baseline and two monthly follow-ups, the HOPE researchers asked a diverse sample of patients with solid tumor or lymphoma (n = 99) about their fatigue, pain and distress, their treatment for these symptoms, and their satisfaction with treatment via standardized questionnaires and semi-structured interviews. At least half of the sample experienced some fatigue, pain, or distress at each timepoint. HOPE researchers found that patients and providers do communicate about fatigue, pain and distress, and at least 75% of patients found these discussions helpful when they occurred. This suggests that improved symptom identification and communication may optimize the detection of those at risk of morbidity and decreased quality of life due to excess symptom burden (Butt et al, 2008a).

Symptom identification may be improved with psychometrically sound screening tools. NCCN clinical practice guidelines for fatigue and distress recommend further evaluation of patients with scores > 4: however, this cut-off score had not been established empirically. To evaluate the usefulness of a single item screening for fatigue, pain, distress and anorexia, the HOPE team administered a self-report screening instrument to 597 ambulatory outpatients with solid tumors within the first 12 weeks of chemotherapy. Patients rated the severity of each symptom on a 0 to 10 scale, at its worst over the past 3 days, with higher ratings associated with higher symptom levels. From this sample, 148 patients also completed a more comprehensive assessment of these symptoms. Two criteria were used to determine optimal cut-off scores on the screening items: (1) the sensitivity and specificity of each screening item to predict clinical cases using receiver operating characteristics (ROC) analysis and (2) the proportion of patients at each screening score who reported that some relief of the target symptom would significantly improve their life. Optimal cut-off scores ranged from 4 - 6 depending on the target symptom (area under the curve range = 0.68 – 0.88). The HOPE team reported that use of single item screening instruments for fatigue, pain, distress and anorexia may assist and improve routine clinical assessment in ambulatory oncology practice (Butt et al, 2008b).

3 Butt, Z., Wagner, L. I., Beaumont, J. L., Paice, J. A., Straus, J. L., Peterman, A. H., Carro, G., Von Roenn, J. H., Shevrin, D., & Cella, D. (2008a). Longitudinal screening and management of fatigue, pain, and emotional distress associated with cancer therapy. Supportive Care in Cancer, 16, 151-159.

4 Butt, Z., Wagner, L. I., Beaumont, J. L., Paice, J. A., Peterman, A. H., Shevrin, D., Von Roenn, J. H., Carro, G., Straus, J. L., Muir, J. C., & Cella, D. (2008b). Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice. Journal of Pain and Symptom Management, 35, 20-30.

Development and Validation of Eleven Symptom Indexes to Evaluate Response to Chemotherapy for Advanced Cancer

Although clinical researchers and practicing oncologists acknowledge the importance of patient-reported outcomes such as health-related quality of life (HRQL) for patients undergoing cancer treatment, there is considerable confusion about how to interpret

HRQL information, the clinical meaningfulness of HRQL scores and how to translate them into treatment decisions.

The importance of symptom control in cancer has been widely recognized due to the high prevalence of physical and psychological symptoms as well as the impact of these symptoms on HRQL. Indeed, for patients with advanced disease, where life expectancy is reduced and curative options are limited, relief of physical symptoms and maintenance of function become primary objectives of medical intervention. In evaluating the efficacy of new chemotherapeutic agents, the ability to demonstrate the amelioration of symptoms specific to a given tumor may represent efficacy in achieving a meaningful patient outcome. However, the FDA Oncology Drug Advisory Committee subcommittee on HRQL has asserted that any claims made about HRQL need to be as specific as possible; assessment of symptoms represent a reasonable place to start in working toward a focused assessment of HRQL.

Recent guidance from the FDA discusses patient-reported outcomes as endpoints in clinical trials. Using methods consistent with this guidance, with support provided by grants from 15 pharmaceutical companies, this study developed 11 new symptom indexes for patients with advanced cancer. The primary objective was to identify patients' highest priority cancer symptoms for 11 advanced cancers, to compare their priority ratings with those of oncology experts, and to construct indexes utilizing the combined input of physicians, nurses and patients to assess these symptoms and concerns. 533 patients were recruited from Robert H. Lurie Comprehensive Cancer Center and 4 other NCCN member institutions, in addition to 4 local non-profit social service organizations. Diagnoses included the following primary cancers: bladder, brain, breast, colorectal, head/neck, hepatobiliary/pancreatic, kidney, lung, lymphoma, ovarian and prostate. Physician experts from NCCN institutions, including the Lurie Cancer Center, were surveyed to differentiate symptoms that were predominantly disease-based from those that were predominantly treatment-induced. As a co-investigator on the study, Dr. Jamie Von Roenn's expertise in symptom management in advanced cancer was vital to the success of this study.

Priority symptoms were assessed using surveys of items derived from the well-established FACT-G and 11 FACT tumor-specific scales. We evaluated input from patients and international oncology experts to determine which disease-related symptoms/concerns are agreed upon as most important to monitor in advanced cancers. Patients also had the opportunity to add items not present on the surveys. Items endorsed most frequently by both patients and medical experts were retained on the new symptom indexes. Physician expert input was obtained from 91 oncologists as to which symptoms are considered to be disease-related versus treatment-related.

The resulting NCCN/FACT symptom indexes comprise 16-24 items, depending on tumor site. Symptoms and concerns receiving the most consistent endorsement across diseases included lack of energy (fatigue), ability to enjoy life, worry condition will worsen, nausea, ability to sleep well, contentment with quality of life and pain. This study produced 11 symptom indexes that reflect the highest priorities of people affected by these 11 advanced cancers and the experienced perspective of the people who provide their medical treatment. Each index includes three subscales: Disease-Related Symptoms (DRS), Treatment Side-Effects (TSE) and general Function and Well-Being (FWB).

Using patient-centered, validated outcome measures such as these may help clinical researchers evaluate the effectiveness of noncurative therapy on the symptoms that matter most to people with these advanced cancers. Beyond the clinical value of such indexes, they may also contribute significantly to satisfying regulatory requirements for a standardized tool to evaluate drug efficacy with respect to symptomatology.

Study findings were presented at the 2007 annual meetings of the American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer (MASCC). Several manuscripts are now available or in press:

5 Butt, Z., Rosenbloom, S. K., Abernethy, A. P., Beaumont, J. L., Paul, D., Hampton, D., Jacobsen, P. B., Syrjala, K., Von Roenn, J. H., & Cella, D. (2008). Fatigue is the most important symptom for advanced cancer patients who have had chemotherapy. Journal of the National Comprehensive Cancer Network, 6(5), 448-455.

6 Pickard, A.S., Kohlmann, T., Janssen, M.F., Bonsel, G.

Rosenbloom, S. & Cella, D. (2007). Evaluating equivalency between response systems: Application of the Rasch model to a 3-level and 5-level EQ-5D. Medical Care, 45, 812-819.

7 Pickard, A.S., De Leon, M.C., Kohlmann, T., Cella, D., & Rosenbloom, S. (2007). Psychometric comparison of the standard EQ-5D to a 5 level version in cancer patients. Medical Care, 45(3), 259-263.

8 Abernethy, A.P., Podnos, Y., Rosenbloom, S., Cella, D. (2007). Advance cancer patients' endorsement of constipation as a distressing symptom [Abstract]. Supportive Care in Cancer, 15, 716.

9 Rao, D., Butt, Z., Rosenbloom, S., Robinson, D., Von Roenn, J., Kuzel, T.M., Cella, D. (In press). A comparison of the Renal Cell Carcinoma Symptom Index (RCC-SI) and the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). Journal of Pain and Symptom Management.

10 Rosenbloom, S.K., Yount, S.E., Yost, K.J., Hampton, D., Paul, D., Abernethy, A.P., Jacobsen, P.B., Syrjala, K., Von Roenn, J.H., & Cella, D. (In press). Development and validation of eleven symptom indices to evaluate response to chemotherapy for advanced cancer: Measurement compliance with regulatory demands. In I. Farquhar, K. Summers and A. Sorkin (Eds.), The Value of Innovation: Impacts on Health, Life Quality, and Regulatory Research. Oxford: Elsevier.

Summary of PRO Tool Development with Mario Lacouture, MD

The OMSC provides cancer center members with scientific consultation on the assessment of patient-reported outcomes (PRO), including cancer- and treatment-related symptoms. As new anti-cancer treatments emerge and become widely used in clinical practice, the systematic collection of PRO data can contribute to our comprehensive understanding of treatment-related symptom burden and associated impact on health-related quality of life (HRQL). Collaborating with the Director of the Lurie Cancer Center's Dermatologic Care Center, Mario Lacouture, MD, the OMSC has supported the empirical investigation of HRQL effects of epidermal growth factor receptor inhibitor (EGFRI)-associated dermatologic toxicities. Dr. Lynne Wagner is a co-investigator on this study, working closely with Dr. Lacouture (with ongoing consultation from other OMSC members Hahn, Yost, and Beaumont) on the design of his research study to develop a PRO measure to assess dermatologic symptoms and HRQL.

In accordance with recommendations from the FDA on the development of instruments to assess PROs, we systematically collected qualitative data from 20 cancer patients who experienced EGFRI-associated dermatologic toxicities and 12 expert clinicians. Interviews were conducted, transcribed and analyzed with the assistance of medical students, residents and fellows under the supervision of Drs. Wagner and Lacouture. Results from these interviews were published in a special issue of Oncology (Wagner & Lacouture, 2007) and have been presented at ASCO (Witherspoon et al. 2008) and at an ONS satellite symposium on rash management (Wagner, 2007). Dr. Lacouture has collaborated with the Multinational Association of Supportive Care in Cancer (MASCC) to bring together international experts to form a MASCC Skin Toxicity Study Group, which met in Chicago in November 2007. During this meeting, Dr. Wagner chaired the Quality of Life working group where a draft of the newly developed PRO measure was discussed.

This collaboration has yielded a 38-item instrument, the Functional Assessment of Side effects to Therapy–EGFRI (FAST-EGFRI). The OMSC will continue to provide Dr. Lacouture with consultation on follow-up research to validate this measure and utilize the instrument in clinical trials. Currently, Drs. Lacouture and Wagner are collaborating with investigators from the Southwest Oncology Group (SWOG) on the design of a clinical trial to include the FAST-EGFRI as a secondary endpoint. We anticipate continued refinement of this patient-reported outcomes measure as additional EGFRI agents become available.

11 Wagner, L.I. & Lacouture, M. (2007). Clinical psychologist's perspective on dermatologic toxicities associated with EGFR inhibitors: Impact on health-related quality of life and implications for clinical management of psychological sequelae. Oncologist, 21, 34-36.

12 Witherspoon, J.N., Wagner, L., Rademaker, A., West, D., Rosenbaum, S., & Lacouture, M.E. (2008). Correlation of patient factors and NCI-Common Terminology criteria for adverse events (CTCAE) v 3.0 grading with dermatology-related quality of life (QOL) in patients with EGFR inhibitor induced rash. Poster presented at the 44th Annual Meeting of the American Society of Clinical Oncology.

Conclusion

The OMSC is a unique resource for the Lurie Cancer Center which provides consultation and support for research that involves self-report data in culturally diverse populations.

For more information contact: Elizabeth Hahn. email: e-hahn@northwestern.edu

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 Cancer Center and support the Cancer Center's mission to foster basic and translational research in the mechanisms and treatment of cancer.

Bioinformatics Core Facility

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

The Bioinformatics Core Facility provides analysis, support and design for microarrays, proteomics, clinical trial informatics as well as custom web-based database development for basic science and clinical projects.

Biostatistics Core Facility

Director: Alfred Rademaker, PhD
312.908.1970 or rademaker@northwestern.edu

The Biostatistics Core Facility provides biostatistical and data management support including such services as: data analysis, clinical trial design, database design and management, design and analysis of clustered data, diagnostic screening tests, protocol preparation, and sample size determination

Cancer Therapeutics and Diagnostic Screening Core Facility

Director: Eric Weiss, PhD
Managing Director: Chi-Hao Luan, PhD
847-491-5643 or luanch@northwestern.edu

The Cancer Therapeutics and Diagnostic Screening Core Facility helps investigators design, validate, and conduct diverse high throughput assays. These can be virtually any assay with a photometric readout, such as absorbance, luminescence, and fluorescence polarization. The facility has recently added capability for high throughput microscopy, including sophisticated software for analysis of large image databases. Additionally, the facility provides access to advanced platforms for large scale liquid handling, plasmid preparation, generations and manipulation of arrayed microbial strains, and protein affinity purification.

Cell Imaging Core Facility

Director: Teng-Leong Chew, PhD
312.503.4445 or t-chew@northwestern.edu

The Cell Imaging Facility offer state-of-the art instrumentation and services for the study of biological processes at the tissue, cellular and subcellular levels. The facility's services include light, fluorescence, confocal, and electron microscopy, microinjection, digitally controlled temperature stage for live cell observation, computerized image analysis, and digital image manipulation.

Clinical Research Office

Director: Timothy Kuzel, MD
Administrative Director: Renee Webb
312.908.4026 or t-kuzel@northwestern.edu
r-ripenburg@northwestern.edu

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

Mary Beth Donnelley Clinical Pharmacology Core Facility

Director: Michael Avram, PhD
312.908.0638 or mja190@northwestern.edu

The Donnelley Clinical Pharmacology Core Facility was established to provide investigators with pharmacokinetic support for clinical studies, including Phase I and Phase II clinical trials, of cancer chemotherapeutic agents and analgesics. Support includes optimizing the design, conduct, analysis, and interpretation of the pharmacokinetic portion of the proposed clinical study. Chemotherapeutic and analgesic concentrations in body fluids are measured using a state-of-the-art Agilent high performance liquid chromatography system linked to an Applied Biosystems API 3000 triple 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.

Flow Cytometry Facility

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

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

Genomics Core Facility

Director: Nadereh Jafari, PhD
312.503.3702 or n-jafari@northwestern.edu

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

Keck Biophysics Facility

Director: Jonathan Widom, PhD
847.491.7610 or j-widom@northwestern.edu

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

Monoclonal Antibody Facility

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

The Monoclonal Antibody Facility provides investigators access to the technology for the efficient creation of hybridoma cell lines and the production of monoclonal antibodies from these cell lines. These services include immunization of animals, somatic cell fusions, cloning and screening of hybridomas, subcloning and establishment of antibody producing cell lines, and production of active antibodies from hybridoma lines. In addition to

providing these services, the facility provides consultation and training for investigators interested in establishing any of these activities in their own research laboratory or using monoclonal antibodies in their research.

Mouse Phenotyping Core Facility

Director: Warren G. Tourtellotte, MD
Facility Manager: Donna Emge
312.503.2679

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

Outcomes Measurement and Survey Core

Director: Elizabeth Hahn, PhD
224.364.7373 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, serve as a central resource for state-of-the-art instruments and measurement methods, and provides in-house research support services for the collection of outcomes data.

Pathology Core Facility

Director: Ximing Yang, MD, PhD
Facility Manager: Adekunle Raji
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a-raji@northwestern.edu

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

Structural Biology Facility

Director: Alfonso Mondragon, PhD
Facility Manager: Pamela Focia, PhD
312.503.0848 or a-mondragon@northwestern.edu
focia@northwestern.edu

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

Transgenic and Targeted Mutagenesis Laboratory

Director: Warren Tourtelotte, MD, PhD
Director of Core Operations: Lynn T. Doglio, PhD
312.503.0088 or warren@northwestern.edu
l-doglio@northwestern.edu

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

Altman, Jessica K; Yoon, Patrick; Katsoulidis, Efstratios; Kroczynska, Barbara; Sassano, Antonella; Redig, Amanda J; Glaser, Heather; Jordan, Alison; **Tallman, Martin S**; Hay, Nissim; **Platanias, Leonidas C**

Regulatory effects of mammalian target of rapamycin-mediated signals in the generation of arsenic trioxide responses.

The Journal of biological chemistry (2008) 283:1992-2001.

Abstract
Arsenic trioxide (As(2)O(3)) is a potent inducer of apoptosis of leukemic cells in vitro and in vivo, but the mechanisms that mediate such effects are not well understood. We provide evidence that the Akt kinase is phosphorylated/activated during treatment of leukemia cells with As(2)O(3), to regulate downstream engagement of mammalian target of rapamycin (mTOR) and its effectors. Using cells with targeted disruption of both the Akt1 and Akt2 genes, we found that induction of arsenic trioxide-dependent apoptosis is strongly enhanced in the absence of these kinases, suggesting that Akt1/Akt2 are activated in a negative feedback regulatory manner, to control generation of As(2)O(3) responses. Consistent with this, As(2)O(3)-dependent pro-apoptotic effects are enhanced in double knock-out cells for both isoforms of the p70 S6 kinase (S6k1/S6k2), a downstream effector of Akt and mTOR. On the other hand, As(2)O(3)-dependent induction of apoptosis is diminished in cells with targeted disruption of TSC2, a negative upstream effector of mTOR. In studies using primary hematopoietic progenitors from patients with acute myeloid leukemia, we found that pharmacological inhibition of mTOR enhances the suppressive effects of arsenic trioxide on leukemic progenitor colony formation. Moreover, short interfering RNA-mediated inhibition of expression of the negative downstream effector, translational repressor 4E-BP1, partially reverses the effects of As(2)O(3). Altogether, these data provide evidence for a key regulatory role of the Akt/mTOR pathway in the generation of the effects of As(2)O(3), and suggest that targeting this signaling cascade may provide a novel therapeutic approach to enhance the anti-leukemic properties of As(2)O(3).

Bennett, Charles L; Silver, Samuel M; Djulbegovic, Benjamin; Samaras, Athena T; Blau, C Anthony; Gleason, Kara J; Barnato, Sara E; Elverman, Kathleen M; Courtney, D Mark; **McKoy, June M**; Edwards, Beatrice J; Tigue, Cara C; Raisch, Dennis W; Yarnold, Paul R; Dorr, David A; **Kuzel, Timothy M**; **Tallman, Martin S**; Trifilio, Steven M; West, Dennis P; Lai, Stephen Y; Henke, Michael

Venous thromboembolism and mortality associated with recombinant erythropoietin and darbepoetin administration for the treatment of cancer-associated anemia.

JAMA : the journal of the American Medical Association (2008) 299:914-924.

Abstract
CONTEXT: The erythropoiesis-stimulating

agents (ESAs) erythropoietin and darbepoetin are licensed to treat chemotherapy-associated anemia in patients with nonmyeloid malignancies. Although systematic overviews of trials have identified venous thromboembolism (VTE) risks, none have identified mortality risks with ESAs. OBJECTIVE: To evaluate VTE and mortality rates associated with ESA administration for the treatment of anemia among patients with cancer. DATA SOURCES: A published overview from the Cochrane Collaboration (search dates: January 1, 1985-April 1, 2005) and MEDLINE and EMBASE databases (key words: clinical trial, erythropoietin, darbepoetin, and oncology), the public Web site of the US Food and Drug Administration and ESA manufacturers, and safety advisories (search dates: April 1, 2005-January 17, 2008). STUDY SELECTION: Phase 3 trials comparing ESAs with placebo or standard of care for the treatment of anemia among patients with cancer. DATA EXTRACTION: Mortality rates, VTE rates, and 95% confidence intervals (CIs) were extracted by 3 reviewers from 51 clinical trials with 13 611 patients that included survival information and 38 clinical trials with 8172 patients that included information on VTE. DATA SYNTHESIS: Patients with cancer who received ESAs had increased VTE risks (334 VTE events among 4610 patients treated with ESA vs 173 VTE events among 3562 control patients; 7.5% vs 4.9%; relative risk, 1.57; 95% CI, 1.31-1.87) and increased mortality risks (hazard ratio, 1.10; 95% CI, 1.01-1.20). CONCLUSIONS: Erythropoiesis-stimulating agent administration to patients with cancer is associated with increased risks of VTE and mortality. Our findings, in conjunction with basic science studies on erythropoietin and erythropoietin receptors in solid cancers, raise concern about the safety of ESA administration to patients with cancer.

Mirzoeva, S.; Kim, N. D.; Chiu, K.; Franzen, C. A.; **Bergan, R. C.**; **Pelling, J. C.**

Inhibition of HIF-1 alpha and VEGF expression by the chemopreventive bioflavonoid apigenin is accompanied by Akt inhibition in human prostate carcinoma PC3-M cells.

Molecular carcinogenesis (2008)

Abstract

Progression of cancer leads to hypoxic solid tumors that mount specific cell signaling responses to low oxygen conditions. An important objective of anti-cancer therapy is the development of new drugs that suppress hypoxic responses in solid tumors. Apigenin is a natural flavone that has been shown to have chemopreventive and/or anti-cancer properties against a number of tumor types. However, the mechanisms underlying apigenin's chemopreventive properties are not yet completely understood. In this study, we have investigated the effects of apigenin on expression of hypoxia-inducible factor-1 (HIF-1) in human metastatic prostate PC3-M cancer cells. We found that hypoxia induced a time-dependent increase in the level of HIF-1alpha subunit protein in PC3-M cells, and treatment with apigenin markedly decreased HIF-1alpha expression under both normoxic and hypoxic conditions. Further, apigenin prevented the activation of the HIF-1 downstream target gene vascular endothelial growth factor (VEGF). We then showed that apigenin inhibited expression of HIF-1alpha by reducing stability of the protein as well as by reducing the level of HIF-1alpha mRNA. We also found that apigenin inhibited Akt and GSK-3beta phosphorylation in PC3-M cells. Further experiments demonstrated that constitutively active Akt blunted the effect of apigenin on HIF-1alpha expression. Taken together, our results identify apigenin as a bioflavonoid that inhibits hypoxia-activated pathways linked to cancer progression in human prostate cancer, in particular the PI3K/Akt/GSK-3 pathway. Further studies on the mechanism of action of apigenin will likely provide new insight into its applicability for pharmacologic targeting of HIF-1alpha for cancer therapeutic or chemopreventive purposes. (c) 2008 Wiley-Liss, Inc.

Meeks, Joshua J; Thaxton, C Shad; Loeb, Stacy; Roehl, Kimberly A; Helfand, Brian T; **Catalona, William J**

Comparison of prostate specific antigen velocity in screened versus referred patients with prostate cancer.

The Journal of urology (2008) 179:1340-1343.

Abstract

PURPOSE: Despite the tremendous stage

migration associated with prostate cancer screening to our knowledge it remains unproven whether prostate specific antigen based screening decreases prostate cancer specific mortality. Recent studies have shown that prostate specific antigen velocity more than 2 ng/ml per year in the year before diagnosis is associated with a significantly greater risk of prostate cancer specific mortality after treatment. This may serve as a surrogate marker for prostate cancer outcomes. We compared the prostate specific antigen velocity profile between patients with prostate cancer in whom the tumor was detected in a formal screening study and those who were referred for treatment. MATERIALS AND METHODS: We evaluated prostate specific antigen velocity in 1,101 men from a prostate cancer screening study and in 368 not enrolled in a screening study who were referred for treatment. All patients underwent radical prostatectomy for clinically localized disease and had multiple preoperative prostate specific antigen measurements to calculate prostate specific antigen velocity. RESULTS: Median prostate specific antigen velocity before diagnosis was significantly higher in referred vs screened men (1.35 vs 0.68 ng/ml per year, p <0.0001). In addition, a significantly greater proportion of referred patients had prostate specific antigen velocity more than 2 ng/ml per year (38% vs 17%, p <0.0001). On multivariate analysis using prostate specific antigen, clinical stage and biopsy Gleason score screened vs referred status was a significant independent predictor of prostate specific antigen velocity more than 2 ng/ml per year (p <0.0004). CONCLUSIONS: Prostate specific antigen velocity more than 2 ng/ml per year has been linked to a significantly greater risk of prostate cancer specific mortality. Patients who underwent serial screening had a more favorable prostate specific antigen velocity profile at diagnosis, suggesting that screen detected prostate cancer may be more likely to be cured with definitive therapy.

Butt, Zeeshan; **Wagner, Lynne I**; Beaumont, Jennifer L; **Paice, Judith A**; Peterman, Amy H; Shevrin, Dan; **Von Roenn, Jamie H**; Carro, George; Straus, Joshua L; Muir, J Cameron; **Cella, David**

Use of a single-item screening tool to detect clinically significant fatigue, pain, distress, and anorexia in ambulatory cancer practice.

Journal of pain and symptom management (2008) 35:20-30.

Abstract
Fatigue, pain, distress, and anorexia are four commonly encountered symptoms in cancer. To evaluate the usefulness of a single-item screening for these symptoms, 597 ambulatory outpatients with solid tumors were administered a self-report screening instrument within the first 12 weeks of chemotherapy. Patients rated the severity of each symptom on a 0-10 scale, at its worst over the past three days, with higher ratings associated with higher symptom levels. From this sample, 148 patients also completed a more comprehensive assessment of these symptoms. Two criteria were used to determine optimal cut-off scores on the screening items: 1) the sensitivity and specificity of each screening item to predict clinical cases using receiver-operating characteristics analysis and 2) the proportion of patients at each screening score who reported that some relief of the target symptom would significantly improve their life. Optimal cut-off scores ranged from 4 to 6 depending on the target symptom (area under the curve range=0.68-0.88). Use of single-item screening instruments for fatigue, pain, distress, and anorexia may assist routine clinical assessment in ambulatory oncology practice. In turn, such assessments may improve identification of those at risk of morbidity and decreased quality of life due to excess symptom burden.

Guzy, Robert D; Sharma, Bhumika; Bell, Eric; **Chandel, Navdeep S**; **Schumacker, Paul T**

Loss of the SdhB, but Not the SdhA, subunit of complex II triggers reactive oxygen species-dependent hypoxia-inducible factor activation and tumorigenesis.

Molecular and cellular biology (2008) 28:718-731.

Abstract
Mitochondrial complex II is a tumor suppressor comprised of four subunits (SdhA, SdhB, SdhC, and SdhD). Mutations in any of these should disrupt complex II enzymatic activity, yet defects in SdhA produce bioenergetic deficiency while defects in SdhB, SdhC, or SdhD induce tumor formation. The mechanisms underlying

these differences are not known. We show that the inhibition of distal subunits of complex II, either pharmacologically or via RNA interference of SdhB, increases normoxic reactive oxygen species (ROS) production, increases hypoxia-inducible factor alpha (HIF-alpha) stabilization in an ROS-dependent manner, and increases growth rates in vitro and in vivo without affecting hypoxia-mediated activation of HIF-alpha. Proximal pharmacologic inhibition or RNA interference of complex II at SdhA, however, does not increase normoxic ROS production or HIF-alpha stabilization and results in decreased growth rates in vitro and in vivo. Furthermore, the enhanced growth rates resulting from SdhB suppression are inhibited by the suppression of HIF-1alpha and/or HIF-2alpha, indicating that the mechanism of SdhB-induced tumor formation relies upon ROS production and subsequent HIF-alpha activation. Therefore, differences in ROS production, HIF proliferation, and cell proliferation contribute to the differences in tumor phenotype in cells lacking SdhB as opposed to those lacking SdhA.

Chiu, B. C.; Dave, B. J.; Ward, M. H.; Fought, A. J.; **Hou, L.**; Jain, S.; **Gapstur, S.**; **Evens, A. M.**; Zahm, S. H.; Blair, A.; Weisenburger, D. D.

Dietary factors and risk of t(14;18)-defined subgroups of non-Hodgkin lymphoma.

Cancer causes & control : CCC (2008)

Abstract
OBJECTIVE: To evaluate the associations between diet and non-Hodgkin lymphoma (NHL) according to t(14;18) status, one of the most common chromosomal abnormalities in NHL, as t(14;18)-positive NHL represents a genetically more homogeneous group than NHL overall. METHODS: We determined the presence of the t(14;18)(q32;q21) by fluorescence in situ hybridization in 172 of 175 tumor blocks from a population-based, case-control study conducted in Nebraska during 1983-1986. Information on the frequency of consumption as an adult of 30 food items was derived from the parent case-control study. Dietary factors in 60 t(14;18)-positive and 87 t(14;18)-negative cases were compared with 1,075 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using polytomous logistic regression. RESULTS: The risk of t(14;18)-positive NHL for the highest versus the lowest approximate tertile of intake was elevated for milk (OR = 2.2; 1.0-5.0) and dietary nitrite (OR = 2.8; 1.3-6.1), whereas coffee consumption was inversely associated with risk (OR = 0.4; 0.2-0.7). We also found inverse associations between the intake of fish (OR = 0.5; 0.3-1.0) and carotene (OR = 0.5; 0.2-0.9) and risk of t(14;18)-negative NHL. There was no association between the intake of meats, vegetables, protein, or vitamin C and risk of either t(14;18)-positive or t(14;18)-negative NHL. CONCLUSION: We observed differences in associations between diet and t(14;18)-defined subgroups of NHL. These findings should be interpreted cautiously because of the small sample.

Evens, Andrew M; **Winter, Jane N**; Hou, Nanjiang; Nelson, Beverly P; **Rademaker, Alfred**; Patton, David; **Singhal, Seema**; Frankfurt, Olga; **Tallman, Martin S**; **Rosen, Steven T**; **Mehta, Jayesh**; **Gordon, Leo I**

A phase II clinical trial of intensive chemotherapy followed by consolidative stem cell transplant: long-term follow-up in newly diagnosed mantle cell lymphoma.

British journal of haematology (2008) 140:385-393.

Abstract
Mantle cell lymphoma (MCL) is associated with high relapse rates and poor survival when treated with conventional chemotherapy, with or without rituximab. We report the long-term follow-up of a phase II clinical trial using a new intensive multiagent chemotherapeutic regimen [cyclophosphamide, teniposide, doxorubicin and prednisone (CTAP) alternating with vincristine and high-dose methotrexate and cytarabine (VMAC)] in newly diagnosed MCL. Following 4-6 cycles of CTAP/VMAC induction, patients aged < or =65 years proceeded to consolidative autologous haematopoietic stem cell transplantation (auto-HSCT), while patients < or =55 years who had a HLA-identical sibling received allogeneic-HSCT (busulfan/cyclophosphamide conditioning for both). Twenty-five untreated MCL patients enrolled on the protocol between 1997 and 2002. Among evaluable patients, overall response rate (ORR) was 74% following

induction chemotherapy. Seventeen patients received HSCT (autologous-13/allogeneic-4). On intent-to-treat analysis, ORR for patients who received consolidative HSCT was 100% (complete remission 76%). Therapy was well-tolerated with 4% treatment-related mortality (including HSCT). The 5-year event-free-survival (EFS) and overall survival (OS) for all patients was 35% and 50% respectively. Furthermore, at 66-months median follow-up, the 5-year EFS and OS for patients who received consolidative auto-HSCT was 54% and 75% respectively. Patients who received auto-HSCT had improved outcomes compared to no auto-HSCT (EFS P = 0.001; OS P = 0.0002). CTAP/VMAC induction followed by consolidative auto-HSCT for newly diagnosed MCL is associated with high ORR and durable survival.

Evens, A. M.; **Schumacker, P. T.**; Helenowski, I. B.; Singh, A. T.; Dokic, D.; Keswani, A.; Kordeluk, E.; Raji, A.; **Winter, J. N.**; Jovanovic, B. D.; Holmgren, A.; Nelson, B. P.; **Gordon, L. I.**

Hypoxia inducible factor-alpha activation in lymphoma and relationship to the thioredoxin family.

British journal of haematology (2008) 141:676-680.

Abstract
Hypoxia inducible factors (HIFs) activate oncogenic pathways, while thioredoxins (Trx), including Trx1 and Trx reductases-1 and -2 (TrxR1 and TrxR2), promote HIF-alpha stabilization. In immunoblotting studies in lymphoma cell lines we found that Raji and SUDHL4 cells exhibited normoxic HIF-2alpha protein stabilization. Five cell lines showed increased TrxR1 expression, while only Namalwa, HF1 and SUDHL4 had Trx1 and TrxR2 activation. Tissue microarrays in diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) identified different HIF expression among histological subgroups (e.g. 44% DLBCL vs. 11% of FL cases with moderate-to-high expression of HIF-1alpha and HIF-2alpha, P = 0.0017). These data demonstrate that HIF and the thioredoxin family are abnormally activated in lymphoma.

Gerami, Pedram; Rosen, Steve; **Kuzel, Timothy**; Boone, Susan L; **Guitart, Joan**

Folliculotropic mycosis fungoides: an aggressive variant of cutaneous T-cell lymphoma.

Archives of dermatology (2008) 144:738-746.

Abstract
OBJECTIVES: To study the clinical features, therapeutic responses, and outcomes in patients with folliculotropic mycosis fungoides (FMF) and to compare our single-center experience of 43 patients with the findings from the Dutch Cutaneous Lymphoma Group. SETTING: A single-center experience from the Northwestern University Multidisciplinary Cutaneous Lymphoma Group. PATIENTS: Forty-three patients with FMF were included in the study and compared with 43 age- and stage-matched patients with classic epidermotropic mycosis fungoides (MF) with similar follow-up time. RESULTS: Folliculotropic mycosis fungoides showed distinct clinical features, with 37 patients having facial involvement (86%) and only 6 having lesions limited to the torso (14%). The morphologic spectrum of lesions is broad and includes erythematous papules and plaques with follicular prominence with or without alopecia; comedonal, acneiform, and cystic lesions; alopecic patches with or without scarring; and nodular and prurigolike lesions. Sixty-five percent of patients had alopecia, which in 71% of cases involved the face. Severe pruritus was seen in 68% of patients. In general, patients responded poorly to skin-directed therapy and in almost all cases required systemic agents to induce even a partial remission, including patients with early-stage disease. Overall survival was poor. Patients with early-stage disease (< or =IIA) had a 10-year survival of 82%, which took a steep drop off to 41% by 15 years. Patients with late-stage disease (> or =IIB) had an outcome similar to those patients in the control group with conventional epidermotropic MF of a similar stage. CONCLUSIONS: The morphologic spectrum of clinical presentation for FMF is broad and distinct from those in conventional MF. This is at least partially attributed to the ability of FMF to simulate a variety of inflammatory conditions afflicting the follicular unit. The disease course is aggressive, and many patients, including those with early disease, show a poor outcome particularly between 10 and 15 years after the initial onset of disease. Response to skin-directed therapy is poor even in early-stage

disease, and our best results were seen with psoralen plus UV-A (PUVA) therapy with oral bexarotene or PUVA with interferon alfa. These findings corroborate those of the Dutch Cutaneous Lymphoma Group and further validate the classification of FMF as a distinct entity.

Postovit, Lynne-Marie; Margaryan, Naira V; **Seftor, Elisabeth A**; **Kirschmann, Dawn A**; Lipavsky, Alina; Wheaton, William W; Abbott, Daniel E; **Seftor, Richard E B**; **Hendrix, Mary J C**

Human embryonic stem cell microenvironment suppresses the tumorigenic phenotype of aggressive cancer cells.

Proceedings of the National Academy of Sciences of the United States of America (2008) 105:4329-4334.

Abstract
Embryonic stem cells sustain a microenvironment that facilitates a balance of self-renewal and differentiation. Aggressive cancer cells, expressing a multipotent, embryonic cell-like phenotype, engage in a dynamic reciprocity with a microenvironment that promotes plasticity and tumorigenicity. However, the cancer-associated milieu lacks the appropriate regulatory mechanisms to maintain a normal cellular phenotype. Previous work from our laboratory reported that aggressive melanoma and breast carcinoma express the embryonic morphogen Nodal, which is essential for human embryonic stem cell (hESC) pluripotency. Based on the aberrant expression of this embryonic plasticity gene by tumor cells, this current study tested whether these cells could respond to regulatory cues controlling the Nodal signaling pathway, which might be sequestered within the microenvironment of hESCs, resulting in the suppression of the tumorigenic phenotype. Specifically, we discovered that metastatic tumor cells do not express the inhibitor to Nodal, Lefty, allowing them to overexpress this embryonic morphogen in an unregulated manner. However, exposure of the tumor cells to a hESC microenvironment (containing Lefty) leads to a dramatic down-regulation in their Nodal expression concomitant with a reduction in clonogenicity and tumorigenesis accompanied by an increase in apoptosis. Furthermore, this ability to suppress the tumorigenic phenotype is directly associated with the secretion of Lefty, exclusive to hESCs, because it is not detected in other stem cell types, normal cell types, or trophoblasts. The tumor-suppressive effects of the hESC microenvironment, by neutralizing the expression of Nodal in aggressive tumor cells, provide previously unexplored therapeutic modalities for cancer treatment.

Grugan, K. D.; Ma, C.; **Singhal, S.**; **Krett, N. L.**; **Rosen, S. T.**

Dual regulation of glucocorticoid-induced leucine zipper (GILZ) by the glucocorticoid receptor and the PI3-kinase/AKT pathways in multiple myeloma.

The Journal of steroid biochemistry and molecular biology (2008) 110:244-254.

Abstract
Glucocorticoids (GCs) are effective therapeutics commonly used in multiple myeloma (MM) treatment. Clarifying the pathway of GC-induced apoptosis is crucial to understanding the process of drug resistance and to the development of new targets for MM treatment. We have previously published results of a micro-array identifying glucocorticoid-induced leucine zipper (GILZ) as GC-regulated gene in MM.1S cells. Consistent with those results, GCs increased GILZ in MM cell lines and patient samples. Reducing the levels of GILZ with siRNA decreased GC-induced cell death suggesting GILZ may mediate GC-killing. We conducted a screen to identify other pathways that affect GILZ regulation and report that inhibitors of PI3-kinase/AKT enhanced GILZ expression in MM cell lines and clinical samples. The combination of dexamethasone (Dex) and LY294002, wortmannin, triciribine, or AKT inhibitor VIII dramatically up regulated GILZ levels and enhanced apoptosis. Addition of interleukin-6 (IL-6) or insulin-like growth factor (IGF1), both which activate the PI3-kinase/AKT pathway and inhibit GC killing, blocked up regulation of GILZ by GC and PI3-kinase/AKT inhibitors. In summary, these results identify GILZ as a mediator of GC killing, indicate a role of PI3-kinase/AKT in controlling GILZ regulation and suggest that the combination of PI3-kinase/AKT inhibitors and GCs may be a beneficial MM treatment.

Logemann, Jeri A; Pauloski, Barbara Roa; **Rademaker, Alfred W**; Lazarus, Cathy L; Gaziano, Joy; Stachowiak, Linda; Newman, Lisa; MacCracken, Ellen; Santa, Daphne; **Mittal, Bharat**

Swallowing disorders in the first year after radiation and chemoradiation.

Head & neck (2008) 30:148-158.

Abstract
BACKGROUND: Radiation alone or concurrent chemoradiation can result in severe swallowing disorders. This manuscript defines the swallowing disorders occurring at pretreatment and 3 and 12 months after completion of radiation or chemoradiation. METHODS: Forty-eight patients (10 women and 38 men) participated in this study involving videofluorographic evaluation of oropharyngeal swallow at the 3 time points. RESULTS: At baseline, patients had some swallow disorders, probably related to presence of their tumor. At 3 months posttreatment, frequency of reduced tongue base retraction, slow or delayed laryngeal vestibule closure, and reduced laryngeal elevation increased from baseline. Some disorders continued at 12 months posttreatment. Functional swallow decreased over time in patients treated with chemoradiation, but not those treated with radiation alone. DISCUSSION: Chemoradiation results in fewer functional swallowers than radiation alone at 12 months posttreatment completion.

Cilliers, Renee; Song, Ying; Kohlmeir, Ellen K; Larson, Andrew C; **Omary, Reed A**; **Meade, Thomas J**

Modification of embolic-PVA particles with MR contrast agents.

Magnetic resonance in medicine : official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine (2008) 59:898-902.

Abstract
We report the synthesis and characterization of polyvinyl alcohol (PVA) embolic particles modified with a clinically approved magnetic resonance (MR) contrast agent. PVA particles are used during transcatheter arterial embolization (TAE) procedures and this minimally invasive technique is a widely employed treatment for inoperable tumors. The PVA particles are injected into tumor vessels and prevent blood flow which results in tumor attenuation. An accurate assessment of the endpoint of embolization is critical to successful TAE procedures. Recent reports suggest that 20% of endpoint determination of TAE procedures by angiographic techniques are erroneous. Real time, in vivo imaging of the embolic particles would overcome this limitation. The contrast-modified PVA particles described here show an 80% decrease in T(1) relaxation times compared to unmodified particles. Images of particles in capillary tubes of similar size to catheters used in TAE procedures are clearly visible by MRI.

Park, Sung Yong; Lytton-Jean, Abigail K R; Lee, Byeongdu; Weigand, Steven; Schatz, George C; **Mirkin, Chad A**

DNA-programmable nanoparticle crystallization.

Nature (2008) 451:553-556.

Abstract
It was first shown more than ten years ago that DNA oligonucleotides can be attached to gold nanoparticles rationally to direct the formation of larger assemblies. Since then, oligonucleotide-functionalized nanoparticles have been developed into powerful diagnostic tools for nucleic acids and proteins, and into intracellular probes and gene regulators. In contrast, the conceptually simple yet powerful idea that functionalized nanoparticles might serve as basic building blocks that can be rationally assembled through programmable base-pairing interactions into highly ordered macroscopic materials remains poorly developed. So far, the approach has mainly resulted in polymerization, with modest control over the placement of, the periodicity in, and the distance between particles within the assembled material. That is, most of the materials obtained thus far are best classified as amorphous polymers, although a few examples of colloidal crystal formation exist. Here, we demonstrate that DNA can be used to control the crystallization of nanoparticle-oligonucleotide conjugates to the extent that different DNA sequences guide the assembly of the same type of inorganic nanoparticle into

different crystalline states. We show that the choice of DNA sequences attached to the nanoparticle building blocks, the DNA linking molecules and the absence or presence of a non-bonding single-base flexor can be adjusted so that gold nanoparticles assemble into micrometre-sized face-centred-cubic or body-centred-cubic crystal structures. Our findings thus clearly demonstrate that synthetically programmable colloidal crystallization is possible, and that a single-component system can be directed to form different structures.

Trott, Amy; West, James D; Klaic, Lada; Westerheide, Sandy D; **Silverman, Richard B**; **Morimoto, Richard I**; Morano, Kevin A

Activation of Heat Shock and Antioxidant Responses by the Natural Product Celastrol: Transcriptional Signatures of a Thiol-targeted Molecule.

Molecular biology of the cell (2008) 19:1104-1112.

Abstract
Stress response pathways allow cells to sense and respond to environmental changes and adverse pathophysiological states. Pharmacological modulation of cellular stress pathways has implications in the treatment of human diseases, including neurodegenerative disorders, cardiovascular disease, and cancer. The quinone methide triterpene celastrol, derived from a traditional Chinese medicinal herb, has numerous pharmacological properties, and it is a potent activator of the mammalian heat shock transcription factor HSF1. However, its mode of action and spectrum of cellular targets are poorly understood. We show here that celastrol activates Hsf1 in Saccharomyces cerevisiae at a similar effective concentration seen in mammalian cells. Transcriptional profiling revealed that celastrol treatment induces a battery of oxidant defense genes in addition to heat shock genes. Celastrol activated the yeast Yap1 oxidant defense transcription factor via the carboxy-terminal redox center that responds to electrophilic compounds. Antioxidant response genes were likewise induced in mammalian cells, demonstrating that the activation of two major cell stress pathways by celastrol is conserved. We report that celastrol's biological effects, including inhibition of glucocorticoid receptor activity, can be blocked by the addition of excess free thiol, suggesting a chemical mechanism for biological activity based on modification of key reactive thiols by this natural product.

Deng, Jie; Virmani, Sumeet; Young, Joseph; Harris, Kathleen; **Yang, Guang-Yu**; **Rademaker, Alfred**; **Woloschak, Gayle**; **Omary, Reed A**; Larson, Andrew C

Diffusion-weighted PROPELLER MRI for quantitative assessment of liver tumor necrotic fraction and viable tumor volume in VX2 rabbits.

Journal of magnetic resonance imaging : JMRI (2008) 27:1069-1076.

Abstract
PURPOSE: To test the hypothesis that diffusion-weighted (DW)-PROPELLER (periodically rotated overlapping parallel lines with enhanced reconstruction) MRI provides more accurate liver tumor necrotic fraction (NF) and viable tumor volume (VTV) measurements than conventional DW-SE-EPI (spin echo echo-planar imaging) methods. MATERIALS AND METHODS: Our institutional Animal Care and Use Committee approved all experiments. In six rabbits implanted with 10 VX2 liver tumors, DW-PROPELLER and DW-SE-EPI scans were performed at contiguous axial slice positions covering each tumor volume. Apparent diffusion coefficient maps of each tumor were used to generate spatially resolved tumor viability maps for NF and VTV measurements. We compared NF, whole tumor volume (WTV), and VTV measurements to corresponding reference standard histological measurements based on correlation and concordance coefficients and the Bland-Altman analysis. RESULTS: DW-PROPELLER generally improved image quality with less distortion compared to DW-SE-EPI. DW-PROPELLER NF, WTV, and VTV measurements were strongly correlated and satisfactorily concordant with histological measurements. DW-SE-EPI NF measurements were weakly correlated and poorly concordant with histological measurements. Bland-Altman analysis demonstrated that DW-PROPELLER WTV and VTV measurements were less biased from histological measurements than the

corresponding DW-SE-EPI measurements. CONCLUSION: DW-PROPELLER MRI can provide spatially resolved liver tumor viability maps for accurate NF and VTV measurements, superior to DW-SE-EPI approaches. DW-PROPELLER measurements may serve as a noninvasive surrogate for pathology, offering the potential for more accurate assessments of therapy response than conventional anatomic size measurements. J. Magn. Reson. Imaging 2008. (c) 2008 Wiley-Liss, Inc.

Iwamoto, Fabio M; Omuro, Antonio M; **Raizer, Jeffrey J**; Nolan, Craig P; Hormigo, Adilia; Lassman, Andrew B; Gavrilovic, Igor T; Abrey, Lauren E

A phase II trial of vinorelbine and intensive temozolomide for patients with recurrent or progressive brain metastases.

Journal of neuro-oncology (2008) 87:85-90.

Abstract
PURPOSE: To investigate the efficacy and safety of the combination of vinorelbine and intensive temozolomide for recurrent or progressive brain metastases from solid tumors. METHODS: Patients > or =18 years of age and with Karnofsky performance scale (KPS) > or = 60, adequate organ function and progressive or recurrent brain metastases were eligible. This was a phase II trial with 28-day cycles using temozolomide (150 mg/m(2), days 1-7 and 15-21) and vinorelbine 25 or 30 mg/m(2)on days one and eight. The primary endpoint was objective radiographic response. RESULTS: Thirty-eight patients (15 men, 23 women) with a median age of 57 years (range, 39-75) and median KPS of 80 were enrolled. The primary tumor sites were lung (n = 20), breast (n = 11), colorectal (n = 2), kidney (n = 2), bladder (n = 1), endometrium (n = 1), head and neck (n = 1). Prior therapies included chemotherapy (97%), whole-brain radiation therapy (79%), brain metastasis resection (53%) and stereotatic radiosurgery (47%). Objective radiographic response rate was 5% (one complete response and one minor response); five patients had stable disease, 29 progressive disease and two patients were not evaluable. Twenty-nine patients (76%) have died and the median follow-up of survivors was six months. Median progression-free and overall survivals were 1.9 and 5 months, respectively. Grade 3/4 toxicities were mainly hematological and two patients discontinued the study due to myelosuppression. CONCLUSIONS: In this heavily pretreated population of patients with brain metastases, adding vinorelbine and increasing the intensity of temozolomide do not improve response rates compared to previous studies with single-agent temozolomide at standard doses.

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CONTINUING MEDICAL EDUCATION PROGRAMS

Throughout the year, the Robert H. Lurie Comprehensive Cancer Center of Northwestern University offers Continuing Medical Education (CME) programs on various cancer specialties. Below is a list of programs for 2009. For specific dates, locations or more information about these programs, visit cancer.northwestern.edu or call the Lurie Cancer Center at 312.695.1304.

Continuing Trends in Leukemia, Lymphoma and Myeloma (Post ASH)
January 16, 2009
Robert H. Lurie Medicial Research Center
Chair: Steven Rosen, MD

San Antonio Review/NCCN Breast Cancer Guidelines
January 30, 2009
Northwestern Memorial Hospital, 3rd floor
Chair: William Gradishar, MD

Pain and Palliative Care Conference
March 13, 2009
Northwestern Memorial Hospital, 3rd floor
Chair: Judy Paice, RN, PhD

6th International Chicago Lymphoma Symposium
April 17-18, 2009
The Mid-America Club, Chicago
Chairs: Andrew Evens, DO and
Sonali Smith, MD (University of Chicago)

H Foundation Basic Science Symposium
May 15, 2009
Robert H. Lurie Medical Research Center
Chairs: Kathleen Green, PhD and
Carole LaBonne, PhD

8th International Association for the Study of Pain Research Symposium
June 4-5, 2009
Robert H. Lurie Medical Research Center
Chair: Judy Paice, RN, PhD

20th Annual Scientific Poster Session
June 17, 2009
Robert H. Lurie Medical Research Center

Onco-Biotechnology Summit
September 10-11, 2009
Robert H. Lurie Medical Research Center
Chair: Alicia Loeffler, PhD

11th Annual Lynn Sage Breast Cancer Symposium
October 1-October 4, 2009
Fairmont Hotel
Chair: William Gradishar, MD

International Conference on Differentiation Therapy
November 11-14, 2009
Hyatt Regency Chicago
Chairs: Martin Tallman, MD and
Jonathan Licht, MD

COMMUNITY EVENTS / PATIENT PROGRAMS

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

Girlfriends Night Out (Health Education)
January 27, 2009
Prentice Women's Hospital, 3rd floor

16th Annual Cancer Survivors' Celebration and Walk
June 7, 2009
Grant Park

Lynn Sage Breast Cancer Town Hall Meeting
October 4, 2009
Fairmont Hotel
Chair: William Gradishar, MD

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ARTHUR AND GLADYS PANCOE LIFE SCIENCES PAVILION

The Robert H. Lurie Comprehensive Cancer Center of Northwestern University is the focus of cancer research, treatment and education at Northwestern University. The Lurie Cancer Center coordinates and integrates the University's cancer and cancer-related activities and unites scientists, clinicians and educators in the fight against cancer. The Lurie Cancer Center's administrative offices and many of its basic science research activities are at Northwestern University's Feinberg School of Medicine on the Chicago campus. Additional offices and basic science research labs are located on the Evanston campus. Clinical research is conducted at the Feinberg School of Medicine's various affiliated teaching hospitals: Northwestern Memorial Hospital, Children's Memorial Hospital, the Rehabilitation Institute of Chicago and Jesse Brown VA Medical Center.

First established at Northwestern University in 1974, the Cancer Center was invigorated in 1989 when Ann Lurie and Robert H. Lurie made a commitment to endow an institution dedicated to research and advancement in the battle against cancer. In 1991, the Cancer Center was dedicated as the Robert H. Lurie Cancer Center of Northwestern University. This title was modified in 1998, when the National Cancer Institute (NCI) awarded the Cancer Center the highly competitive "comprehensive" designation. Today, the Robert H. Lurie Comprehensive Cancer Center of Northwestern University stands among the country's leaders as one of only 41cancer centers in the nation to hold this NCI distinction.

The 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.

The Journal of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University is published twice a year and is distributed to members of the Cancer Center; to Northwestern University faculty and staff whose work is related to cancer; to selected oncologists and oncology nurse clinicians; and to officials of academic cancer centers and community cancer programs in the United States and abroad. Please address correspondence to the editor, Steven T. Rosen, MD, Genevieve E. Teuton Professor of Medicine and Director, Robert H. Lurie Comprehensive Cancer Center of Northwestern University; 303 E. Superior St., Chicago, IL 60611. Mailing information and inquiries should be directed to The Journal's managing editor.

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