“I do not cut my life up into days but my days into lives, each day, each hour, an entire life.”

— Juan Ramon Jiménez
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Sunday, June 3, 2007 marked our Cancer Center’s 14th Annual Survivor’s Walk. This celebration is our signature event. It provides an opportunity to reflect on the importance of our mission and to remember those whose lives were shortened by cancer. Each year, I am struck by the camaraderie and sense of community nurtured by this activity. A morning filled with emotion – a mixture of joy and sorrow. Always inspiring, each step a reminder of our patient’s courage and the significant challenges that remain.
David Cella, PhD, discovered his affinity for the field of psycho-oncology purely by accident. After receiving his doctorate in clinical psychology from Loyola University of Chicago, Dr. Cella applied for a fellowship with the pediatric psychiatry division of The New York Hospital, but was placed instead at Memorial Sloan-Kettering Cancer Center in New York. “Until that time,” he says, “I had always worked with people whose primary presenting problem was mental health, where many conditions are chronic and incurable.” Cella’s experience had taught him that most mental health conditions are chronic. Treatment could relieve his patient’s symptoms and problems, but not cure them.

The discovery that cancer patients, whose problems were specific to their situation, responded dramatically to the same tools that applied to psychiatric patients was both exciting and motivating to Cella. “It was like watching a drug that was moderately effective in your practice have a major impact in a new population,” he explains, “except, in this case the drug was psycho therapy.

Thirty years ago the prognosis for cancer patients was not as good as it is today. Few therapists worked with cancer patients, and many just, “accepted depression as coming with the territory,” says Cella. It was his mentor at Sloan Kettering, Jimmie Holland, MD, who first recognized the need to treat the emotional trauma experienced by many cancer patients and their families, and ultimately founded the field of psycho-oncology. “It was her program that
launched me into this work.”

Dr. Cella, a Professor of Psychiatry and Behavioral Science at Northwestern University’s Feinberg School of Medicine is also Cancer Control Program Leader at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and Executive Director of the Center on Outcomes, Research and Education at Evanston Northwestern Healthcare (ENH). Additionally, he is a Research Professor at the Institute for Healthcare Studies. Most recently, he was appointed Davis Family Chair of Outcomes Research, ENH.

As the principal investigator of the Statistical Coordinating Center for the NIH Roadmap Initiative to build a Patient Reported Outcome Measurement Information System (PROMIS), Dr. Cella’s current focus is on quality of life research. “What we’re doing,” he explains, “is standardizing the measurement of several major conditions that are important to people such as fatigue, pain, physical functioning, distress, depression, anxiety and social function.” Standardizing the concepts and the way they’re evaluated will allow researchers to apply the measures across different diseases—and within diseases across treatment settings and situations. Consequently, scientists will have a common metric and be able to discuss a fatigue score or a distress score in a common language. “Right now there are so many instruments and so many different ways to measure any given concept that it’s not possible to come to a conclusion about which is the best approach or which are the best sets of questions.” One main goal of the PROMIS initiative is to develop a set of publicly available computerized adaptive tests for the clinical research community, providing all investigators with common ground.

Dr. Cella is equally enthusiastic about his work on Neuro-QOL with the National Institute of Neurological Disorders and Stroke (NINDS) and the Toolbox effort with the National Institute on Aging (NIA) to expand this standardization effort into assessing motor, sensory and cognitive function. Along with PROMIS the all rely to some degree on repositories of questions known as item banks. Instead of cash questions are deposited into the item banks, and the more that’s learned about them the more valuable they become; particularly the ones that perform well. “We can go to someone and say, “These are the best performing questions if you want to measure fatigue,”” says Cella. Someone else may ask for a different subset of questions, or they may prefer to have the computer select the questions based on the answers to previous queries. He is confident that this functionality will be available publicly within a year. PROMIS, Neuro-QOL and Toolbox “are three large inter-related projects that we think can help deal with the Tower of Babel that is patient reported outcomes today.”

It is likely that Dr. Cella developed his interest in psychology growing up in Chicago as one of eight siblings and learning how to “fit into a large group and make sense of it.” Now, as the father of five children himself, he draws upon those skills on a daily basis.
In order to excel at his job, a foreign correspondent must be empathetic, tenacious and intensely curious. He should thrive on change and be motivated to share his knowledge with others. The qualities that made William Gradishar, MD, FACP, consider a career in journalism are the same ones that inspired him to pursue his interest in science and a career in medicine. “What we do is hard work,” says Gradishar. “That’s not unique to being a physician. It’s a learned skill to persevere, focus on a goal—and hopefully attain it.”

Dr. Gradishar is Director of Breast Medical Oncology at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and Professor of Medicine at the Feinberg School of Medicine. He also serves as Chair of the Lynn Sage Breast Cancer Symposium, Director of the Hematology / Oncology Fellowship Training Program and Associate Director of the Lynn Sage Breast Cancer Program. After graduating from the University of Illinois Abraham Lincoln School of Medicine in 1982 and completing his residency in Internal Medicine at the Michael Reese Medical Center in 1986, Dr. Gradishar trained as a Hematology / Oncology Fellow at the University of Chicago Medical Center.

About half-way through his fellowship, Dr. Gradishar took a year off during the Soviet war in Afghanistan and followed his inner foreign correspondent to the Pakistan / Afghanistan border. Although he was still working in medicine, Gradishar faced new and disparate
challenges training Afghan insurgents how to return to the country and run primary care clinics. “It was a fascinating experience,” he relates. “It’s a very different mindset—tertiary care versus no care.”

It wasn’t any one individual who inspired Dr. Gradishar’s interest in cancer. “There are a number of people I’ve admired over the years who had attributes that I’ve tried to incorporate into how I interact with others and how I conduct my career,” he says. “I hope I’ve taken something away from each of them.”

Dr. Gradishar is encouraged by what he sees as a reinforced link between science and clinical medicine. “Increased understanding of the science has stimulated the effort to develop therapies that are more rational, targeted and, consequently, better tolerated and more effective,” he states. “That’s proved to be true with both breast cancer and hematologic malignancies. I believe that we’ll continue to see more rational drug design as we go forward.”

As a result of the new treatment options, Dr. Gradishar believes that people will come to understand that although they may not be cured of their disease, they have a chronic illness that they can manage. They can anticipate a long life and good quality of life despite a diagnosis of cancer. “I think we’ll begin to see in solid tumors what we’ve seen in hematologic malignancies over the last several years,” he says. “By developing more targeted therapies based on an understanding of biologic pathways we’ll be able develop drugs that uniquely fit each patient—to tailor therapy. It’s a phrase that’s been in use for the past decade, but there’s reason to believe that it’s now within the realm of possibility for many, many patients.”

Dr. Gradishar is actively preparing for the 9th Annual Lynn Sage Breast Cancer Symposium to be held September 27-30, 2007 at the Fairmont Chicago. He began the conference with Dr. V. Craig Jordan and Dr. Monica Morrow with the goal of developing a dominant meeting to educate practicing physicians about breast cancer. “It was an effort to harness our strengths here at Northwestern, build on our reputations and enlist people from across the country and around the world to serve as faculty. The meeting has grown each year, and we’re proud of it’s success.”

A Fellow of the American College of Physicians, Dr. Gradishar is also a member of the American Association for Cancer Research, the American Federation for Clinical Research, and the Association of Subspecialty Professors. He is the immediate past chair of the Oncology Training Program Committee of the American Society of Clinical Oncology (ASCO) as well as a member of ASCO’s Program Committee. He is a member of the Breast Cancer Core Committee of the Eastern Cooperative Oncology Group, the Committee on Cancer of the American College of Surgeons, the National Comprehensive Cancer Network (NCCN) Breast Cancer Guidelines Panel, and the NCCN Breast Cancer Prevention Panel. In addition, he serves as a consultant to the Oncology Drug Advisory Committee of the FDA, serves on several study sections nationally and internationally including: NIH, Komen Foundation, Avon Foundation, American Cancer Society, Alberta Cancer Board and the Imperial Cancer Fund. He is a member of editorial boards and reviewer for numerous journals, including Journal of the National Cancer Institute, Journal of Clinical Oncology, and Clinical Cancer Research. He has published extensively in the area of breast cancer therapeutics, with a focus on new endocrine therapy, chemotherapy and novel targeted therapies.

Dr. Gradishar and his wife are the parents of two boys and admits, “there isn’t a lot of free time.” For the past eight years the family has lived in a Frank Lloyd Wright house that vies for his attention as well. “There are always things in a 120 year old house that need working on, but it’s not a museum, it’s a home.”
Life before medical school is only a vague memory for Timothy Kuzel. Medicine wasn’t necessarily part of his plan, but when he received the letter accepting him into the combined college / medical school program (Inteflex) that would allow him to graduate from the University of Michigan in 6 years, everything fell into place. “It was just one of those things,” he recalls. “A door opens, a path unfolds and you say ‘I’ll go down that road for a while and see where it takes me.’”

Today, Timothy Kuzel, MD, is the Director of the Clinical Research Office for the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and Professor of Medicine in the Division of Hematology/Oncology at Northwestern University’s Feinberg School of Medicine. He joined the faculty in 1990, after completing medical school at the University of Michigan and his residency/fellowship at the McGaw Medical Center of Northwestern University.

The decision to specialize in hematology / oncology was more deliberate. Dr. Merrill Keyes and Dr. Leo Gordon were among the faculty that impressed Dr. Kuzel with their bedside manner and their knowledge. The types of diseases, the science, and how much was yet to be learned all led him to believe that oncology was a “field that had real opportunities to evolve in the coming years,” and he has not been disappointed. “What we’ve learned and the ability to apply it therapeutically has been staggering,” he says, and believes the
ability to synthesize designer molecules to inhibit specific targets and cells may be the most promising concept of the past decade.

Dr. Kuzel singles out Gleevec, a therapy that affects the molecular cause of Chronic Myeloid Leukemia (CML), with pioneering the ability to target “so exquisitely a single protein that can perturb a cell so greatly.” He is gratified to see such effective drugs being introduced with increasing regularity and looks forward to seeing similar targeted strategies become available for a wider range of cancers. “It’s clearly the discovery process that excites me about oncology,” says Kuzel. “Taking basic science concepts and figuring out a way we can apply them at the bedside,” is the beginning, but it’s “learning from the results and then going back to the lab to try to improve upon them” that is the most stimulating.

An anomaly in the sense that he treats both liquid and solid tumors, Dr. Kuzel cannot be defined by any one label. In addition to his work with genitourinary (GU) malignancies, which encompass cancers of the prostate, bladder, kidney, and testis, he also works with melanomas, non-melanomatous skin cancers, and skin lymphomas. Cutaneous T-cell lymphoma (CTCL) has been a major research focus for Dr. Kuzel. “The research principles that I utilize with that group of patients are really the same ones that I draw on for my GU and melanoma work,” he says. He tries to identify a basic question based on the biology of a disease, and then looks for a therapeutic modality that will act on a weakness in that disease. Dr. Kuzel has successfully been able to apply the knowledge he gained from his extensive CTCL research to the biologic therapies he is currently using for kidney cancer and melanoma. His wide range of interests effect Dr. Kuzel’s teaching style as well. “The fellows, residents, and medical students can come to a morning clinic with me and see six different diseases. It is never monotonous.”

Cancer Center Director, Steve Rosen, MD was the first to stimulate Dr. Kuzel’s lifelong interest in CTCL. “I started working with him when I was a second year fellow and it was a wonderful decision. Steve has been a tremendous inspiration to me and a mentor throughout,” he says.

Currently, Dr. Kuzel serves as the leader for the Clinical Research Core of the prostate cancer SPORE. In collaboration with Dr. Chung Lee, he has co-authored papers on TGF-beta resistance based cellular therapy for prostate cancer patients. He is also a co-investigator with Dr. Lee on his SPORE pilot research project and will be responsible for treating all prostate cancer patients in the clinical protocol. He has previously been the principal investigator on NIH funded translational projects in the field of anti-angiogenesis. Dr. Kuzel is also an active member of the Eastern Cooperative Oncology Group and has served on a number of peer review panels for NCI and NIH programs and grant applications.

Although Dr. Kuzel enjoys golf and tennis, he readily acknowledges, “Trying to keep my children happy is my biggest hobby.” He has coached soccer teams for both his children and helped out with basketball and softball, as well. Now that his daughter is focused on ballet, he admits to a few limitations. “I can applaud and videotape performances. That’s about all I can do for now.”
CANCER CENTER NEWS

CENTER OF EXCELLENCE AWARD
The Cancer Center has been named a Center of Excellence (COE) by Fertile Hope, a non-profit organization that assists cancer patients faced with infertility. The Cancer Center is the fifth medical center in the country to receive the designation as part of the Fertile Hope Center of Excellence Program, the first program of its kind to address fertility preservation and parenthood options. Although nearly 90% of patients diagnosed with cancer during their reproductive years are at risk for infertility, studies have shown that less than 10% of oncologists are informing all eligible patients about their risks and options.

Dr. Teresa Woodruff, PhD, Associate Director, Robert H. Lurie Comprehensive Cancer Center of Northwestern University and Executive Director, Institute for Women’s Health Research at Northwestern’s Feinberg School of Medicine has spearheaded this effort and presented her work at the three-day series of educational programs on fertility preservation hosted by the Cancer Center in November.

NEW NCCN CHAIR IS AL B. BENSON III, MD
Al B. Benson III, MD, Associate Director for Clinical Investigations at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and Professor of Medicine at Northwestern University’s Feinberg School of Medicine in Chicago, Illinois, has been elected to the position of Chairman of the Board of the National Comprehensive Cancer Network (NCCN).

Dr. Benson is recognized internationally as a leading expert in the treatment of colon, rectal and other GI cancers. He has conducted research and written extensively about biologics, cancer therapy and cancer prevention. “I am excited and honored to accept this new role at NCCN,” Dr. Benson stated. “With the combined expertise of our 21 Member Institutions, we will continue to make great contributions to oncology and to patients whom we serve.”
CANCER SURVIVORS’ CELEBRATION & WALK WAS “A DAY OF JOY”

On Sun. June 3, National Cancer Survivors Day, over 700 cancer survivors along with friends and family members gathered in Chicago’s Grant Park for the Robert H. Lurie Cancer Center of Northwestern University’s signature event – the 14th Annual Cancer Survivors’ Celebration and Walk. 24 states were represented by the more than 3,500 people who came out to celebrate together. Before the walkers stepped off, Allen Lichter, MD, Executive Vice President and Chief Executive Officer of the American Society of Clinical Oncology (ASCO) spoke to participants about the significance of research and breakthroughs discussed at this year’s annual meeting.

Calling it a “day of joy”, Chicago’s first lady, Maggie Daley, was among the cancer survivors who chose to walk, surrounded by friends and family, including the Mayor. Following the walk and picnic, many left a personal message of love, support or remembrance on the Dedication Wall. “Today there are so many wonderful drugs, so many really worthwhile treatments, that many of us who might not have survived 10 years ago really are making progress,” Mrs. Daley told the assembled crowd. Each survivor present, she concluded, “is a reminder about the possibilities and hopefulness.”
Viruses have an extensive and fascinating interrelationship with cancer and biomedical research. It has been demonstrated that diverse viruses can initiate and perpetuate genetic and physiologic alterations that lead to cancer. Viruses have also been instrumental as tools for probing cellular mechanisms that control cell growth and metabolism and have revealed the myriad means by which these mechanisms can become corrupted in cancer. The recent FDA approval of a cervical cancer vaccine that prevents infection by the human papillomavirus (HPV) has brought about increased public awareness of the connections between virus infections and cancer. The mass media marketing campaigns for the HPV vaccine have implied that many people were previously unaware of the roles viruses play in oncogenesis. Here, we briefly summarize some of the roles that viruses have played in cancer, in cancer research, and in the development of cancer therapeutics.

Viruses in Cancer Research: A Nobel Pursuit
The first connections that established cancer could be caused by a virus were made by studying spontaneous chicken tumors known as sarcomas. Dr. Peyton Rous demonstrated in 1911 that non-cellular extracts of these solid tumors could induce similar cancers in unaffected chickens (Rous, 1911). Despite the overwhelming evidence from this work and many other laboratories implicating the Rous sarcoma virus in cancer transmission, the idea that a virus might be the causative agent of
cancer was not widely supported for the next 40 years. Nonetheless, Rous’ work was finally recognized by the Nobel Prize in 1966 “for his discovery of tumor-inducing viruses”.

During the period between 1940 and the 1950’s many laboratories began to use viruses to study the basic principles of genetics and molecular biology. The study of bacteriophage, viruses that infect bacteria, provided an early experimental model of basic life processes that was fundamental to the early investigations of molecular genetics and in determining the transmission modes and coding strategies of genetic information. This field of phage investigation was pioneered by legendary researchers such as Max Delbrück, Salvador Luria, and Alfred Hershey. Delbrück and Luria developed the study of phage genetics and replication to include more modern biochemical and quantitative studies. In 1952, Hershey and his team resolved the ongoing debate regarding the nature of the genetic material by testing the roles of phage protein and DNA in the transmission of traits. They discovered that the phage genetic information is encoded by the viral DNA, and not the protein, but that the phage protein was essential as the method of gene delivery (Hershey and Chase, 1952). Hershey further applied methods of quantitative genetics and recombination to map the relative positions of phage genes. For these seminal contributions “concerning the replication mechanism and the genetic structure of viruses”, Delbrück, Luria, and Hershey shared the 1969 Nobel Prize.

Analysis of bacteriophage DNA was also used to determine the basis of gene organization and the control of gene expression. In 1958 François Jacob and Jacques Monod combined information from genetic analysis of phage lysogeny and the inducible biosynthesis of β-galactosidase to reveal the mechanisms underlying not only the transfer of genetic information but also critical aspects of the means by which the host bacteria regulate protein synthesis (Pardee et al., 1958). Their analysis led them to develop new concepts in gene expression including messenger RNA, regulatory genes, coordinately controlled genetic operons, and the duality of allosteric proteins. These experiments resulted in a Nobel Prize awarded to Jacob, Monod, and André Lwoff in 1965 “for their discoveries concerning genetic control of enzyme and virus synthesis”.

The success of bacteriophage genetics and development of techniques for mammalian cell culture naturally led to the study of animal viruses in cultured cells. The study of animal viruses revealed many details of virus replication relevant to disease processes and vaccine development. Importantly, these studies also revealed fundamental principles governing mammalian cell growth and metabolism. One interesting group of viruses, Retroviruses, were found associated with a variety of animal tumor sources. During their life cycle, these viruses convert their RNA genome into DNA that gets incorporated into the host’s chromatin. The enzyme responsible for the RNA to DNA conversion, reverse transcriptase, was simultaneously isolated and characterized by David Baltimore and Howard Temin. The ability to convert RNA into DNA in vitro had broad implications for biomedical research, enabling cellular mRNAs to be copied into cDNA in vitro to produce an intermediate that could be propagated and amplified in bacteria, and expressed in vitro or in vivo from plasmid DNA. This discovery and the ability to make cDNA copies of any RNA enabled the development of modern molecular biology and remains an essential element at the core of biomedical research including the study of aberrant gene regulation during neoplastic transformation. For their “discoveries concerning the interaction between tumor viruses and the genetic material of the cell”, Temin and Baltimore shared a Nobel Prize with Renato Dulbecco in 1975.

Reverse transcription of the viral genetic material into DNA enables the viral genome, including oncogenes, to become integrated into the chromosomal DNA of the host cells. Investigations of the Rous sarcoma virus by Michael Bishop and Harold Varmus enabled them to demonstrate the true origin of oncogenes. Their research came to the remarkable conclusion that the oncogenes expressed by the virus originated as a normal cellular gene that had been acquired during latent virus replication in the host cell chromosome and was carried along afterwards (Stehelin et al., 1976). The cellular gene was found to have an essential function controlling cell growth and division. The original discoveries of cellular oncogenes led to an intensive search for further similar genes, and over 40 such genes were identified, greatly increasing our understanding of the
mechanisms involved in carcinogenesis and the complex systems which govern the normal growth of cells. These researchers were also honored by the Nobel Prize in Medicine or Physiology in 1989 "for their discovery of the cellular origin of retroviral oncogenes".

Animal viruses continue to play significant roles in revealing the basic processes and cellular functions that when dysfunctional can contribute to cancer. For example, analysis of the herpes simplex virus (HSV) VP16 protein, a potent transcriptional regulator, has been instrumental in determining many aspects of the mechanism of gene transcription by RNA polymerase II. Study of the cancer causing DNA viruses in the Papovavirus and Adenovirus families revealed several cellular mechanisms underlying transformation. For example, the simian virus 40 (SV40) enhancer represented the first identified regulatory sequence for mammalian gene expression and is considered a model for cellular enhancers. The Papovaviruses, by virtue of their proteins known as T (for tumor) antigens were found to interfere with cellular systems that typically suppress cancer. The SV40 T antigen was found to interact with a 53 kilodalton cellular factor, and this protein, known as p53, is one of the most frequently inactivated loci in human cancers (Lane et al., 1985). The Adenovirus early proteins, E1A and E1B were similarly found to interact with and inactivate p53 (Yew and Berk, 1992) and another cellular protein implicated in retinoblastoma termed Rb (Whyte et al., 1988) that controls cellular proliferation.

Viruses Can Cause Cancer: Tell a Friend
In addition to the numerous contributions to virology research and our understanding of cancer biology and basic principles, several viruses have been identified as causative agents in human cancers. HPV consists of several subtypes with distinct pathological consequences. While infection with HPV types 6 and 11 can cause genital warts, they are not associated with increased cancer risks. HPV types 16, 18, 33, and 35 are linked to cervical cancer, causing intraepithelial neoplasia and invasive cervical cancer with significant mortality and increased risk for cancers of the vulva, anus, and bladder (Roden and Wu, 2006). The fact that cervical cancer is the second largest cause of cancer deaths in women worldwide prompted intense investigations into therapeutics and vaccine development (Roden and Wu, 2006). In June 2006, the United States Food and Drug Administration approved a preventive quadrivalent HPV recombinant vaccine manufactured by Merck named Gardasil® (www.gardasil.com). This vaccine is comprised of a mixture of virus-like particles expressing the major capsid protein (L1) of HPV types 6, 11, 16 and 18. The vaccine is administered to women between 9-26 years of age, intramuscularly in a three-dose regimen with succeeding doses at 2 and 6 months. Incidence of disease decreased by 90% in vaccinated subjects in a randomized double-blind placebo-controlled phase II study (Villa et al., 2005) and antibodies to the viral proteins were detected for five years following vaccination (Villa et al., 2006).

Several important molecular mechanisms are employed by viruses to inactivate or redirect cellular processes that regulate cell growth or anti-cancer defenses. For HPV several mechanisms have been described that lead to tumorigenesis. One of the best characterized examples is an action of the E6 oncoprotein encoded by HPV 16 and 18. The E6 protein can associate with the cellular tumor suppressor, p53, and a cellular ubiquitin ligase termed E6-associated protein (E6AP). The resulting protein complex targets p53 for ubiquitin-mediated proteasomal degradation, leaving the cells unable to protect their genomes from further damage (Scheffner et al., 1993). Many other viruses target p53 including Kaposi’s sarcoma-associated herpesvirus (KSHV, (Cai et al., 2006) and hepatitis C virus (HCV, (Deng et al., 2006). Several virus families contribute to cellular transformation by binding and inhibiting the Rb protein which controls entry into the S phase of the cell cycle. Binding of adenovirus E1A proteins (Whyte et al., 1988), SV40 large T (Batsche et al., 1994) or HPV E7 proteins (Munger et al., 1989) to Rb releases the transcriptional activator E2F. This results in the stimulation of E2F-mediated transcription of cellular gene products involved in cell cycle progression and DNA synthesis.

Other well studied examples of human viruses that cause cancer include a herpesvirus subfamily which consists of latent B lymphotrophic viruses. Epstein Barr Virus (EBV) causes Burkitt lymphoma which is characterized by chromosomal translocation, the most common being t(8;14) resulting in insertion of the c-myc oncogene in close proximity to the immunoglobulin heavy chain locus (Taub et al., 1982). In addition EBV is...
responsible for Hodgkin lymphoma, a subset of diffuse large B cell lymphomas, and immunodeficiency-associated lymphoproliferative disorders that contribute to both recurrent infectious mononucleosis and nasopharyngeal carcinoma. All EBV malignancies are characterized by the presence of virally encoded latent genes and multiple extra chromosomal copies of circular viral genome (Tao et al., 2006). Latent genes critical for transformation are EBNA2 (Hammerschmidt and Sugden, 1989) and LMP (Wang et al., 1985) which is capable of modulating the nuclear factor-kappa-B, c-Jun NH2-terminal kinase/AP-1 and mitogen-activated protein kinase pathways. The development of EBV-specific cytotoxic T lymphocyte therapy and vaccines to prevent primary infection are currently being researched.

Based on epidemiological studies, KSHV is proposed to be the etiological agent responsible for Kaposi’s Sarcoma (KS). This clinical manifestation was first described in 1872 as a pigmented sarcoma of the skin (Kaposi, 1872), and contemporarily is associated with the pathogenicity of a subgroup of acquired immune deficiency syndrome (AIDS) related B cell lymphoproliferative diseases; namely primary effusion lymphoma and multicentric Castleman’s disease. There are three epidemiological forms of KS which are associated with AIDS patients not receiving treatment, organ transplant recipients and patients receiving immunosuppressive therapy (Jarviluoma and Ojala, 2006). Like other herpesviruses, KSHV displays a lytic and latent phase explaining the activation of latent reservoirs of infection during immunosuppression. Although the molecular mechanisms describing how KSHV infection results in cellular transformation remain unknown, much research attention is being focused on the fact that KSHV encodes several proteins homologous to critical cellular regulatory proteins including a homolog of cyclin D (Cesarman et al., 1996), a virus-encoded interleukin-6 (Molden et al., 1997), and four viral homologs of interferon (IFN) regulatory factors (Li et al., 2000).

Viruses as Cancer Therapeutics: A New Hope

In contrast to the cancer-inducing effects of viruses, their ability to induce rapid cell death has been exploited in anti-cancer therapeutic agents based on the ability to replicate preferentially in tumor cells. It has been recognized that one element of cancer development involves elimination of cellular defense pathways that can also serve antiviral functions. Many cancer cells accumulate defects that influence their ability to make and respond to the primary antiviral cytokine, type I IFN. The use of IFNs to treat malignancy was intensely studied in the 1970’s, but despite high potential as an anti-cancer agent, IFN therapy has often proved unsuccessful (Kloke and Niederle, 1990) because of mutations acquired in essential genes involved in the IFN response pathways (Abril et al., 1996; Colamonici et al., 1992; Sun et al., 1998; Wong et al., 1997; Xu et al., 1994). Such mutations result in compromised anti-viral responses providing a selective proliferative advantage over wild-type cells. As a result, the cancer tissue is sensitive to virus infection while the healthy adjacent tissue is capable of mounting an IFN-inducible antiviral state that clears virus infections. Based on this observation, cytopathic infections have been used in the treatment of cancer as “oncolytic viruses”. The virus can replicate in the cancer cells, causing them to die, but their growth is restricted in the normal tissues nearby via our endogenous antiviral system. Many naturally occurring viruses including vaccinia, adenovirus, herpes simplex virus, reovirus, and Newcastle disease virus and laboratory-manipulated viruses show potential as oncolytic agents. Viral therapy is at an early stage and may need to be combined with other interventions such as surgery but has shown promise with metastatic cancers (Cross and Burnmester, 2006).

Currently two engineered viruses are in human clinical trials. ONYX-015, an adenovirus lacking the viral E1B protein, selectively lyses and replicates in p53-deficient cells (Bischoff et al., 1996). This virus has been used to treat p53-deficient tumors of the head and neck in a phase I study (Ganly et al., 2000). HSV-1 strains G207 and Nv1020 have a defect in the neurovirulent factor leading to attenuation and have been used to treat bladder cancer (Coszzi et al., 2001). Two promising examples of future therapeutic oncolytic viruses are the RNA virus, Vesicular stomatitis virus (VSV) and the DNA virus, myxoma virus (MV).

VSV is oncolytic and replicates efficiently in tumor cells lacking a functional IFN pathway while it is cleared by the anti-viral properties of IFN in normal cells (Stojdl et al., 2000).
However, the ability to clear VSV was found to be dependent on administration of exogenous IFN. To bypass this need, two naturally occurring VSV mutants with amino-acid substitutions in their M proteins were characterized as more potent IFN-inducers because the mutant viruses failed to block the export and translation of IFN mRNA in infected cells. These viruses are thereby attenuated for growth in normal cells, but in the IFN-incompetent tumor cells their lytic ability was retained (Stojdl et al., 2003). Thus the production of high levels of IFN and selective attenuation in IFN-responsive cells makes these VSV variants excellent candidates for virus therapy, and they have been used successfully in experimental models of multiple myeloma (Lichty et al., 2004), multifocal and invasive gliomas (Lun et al., 2006), and adult T cell leukemia (Cesaire et al., 2006).

The poxvirus MV causes a lethal disease that is restricted to certain rabbit species. Interestingly, this host restriction is related to the ability of the MV to induce an IFN response in infected cells of all species except the natural rabbit hosts (Johnston et al., 2005). These features suggested it may be suitable for use as an oncolytic virus, and this was tested in the case of gliomas that are difficult to surgically or chemotherapeutically resolve. Infection with MV was found to destroy glioma cells following intratumoral administration in orthotopic human malignant tumor models, thereby producing a long-lived infection (Lun et al., 2005). Importantly, MV preferentially eliminated glioma cells but not normal cells derived from surgical specimens (Lun et al., 2005). Analogous with VSV oncolytic therapy, the cancer selective properties of MV were originally hypothesized to be based on defects in the IFN pathway. However recent results implicate activated levels of the AKT protein in an NS3 sequence-dependent manner. J Gen Virol 87, 744-749.

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Aberrant activity of the epidermal growth factor receptor (EGFR) due to overexpression or activating mutations has been correlated with a poor prognosis and decreased survival in a variety of solid tumors (Hynes & Lane). The use of monoclonal antibodies or small molecules blocking ligand binding or intracytoplasmic domain phosphorylation, respectively, have shown prolonged survival times in advanced colorectal, head and neck, pancreatic, and non-small cell lung cancer (Imai & Tanaoka). The US Food and Drug Administration has approved erlotinib, cetuximab, and panitumumab for clinical use in various solid tumors, including head and neck, pancreatic, lung and colorectal carcinomas. The higher specificity of these drugs is associated with lower systemic and hematopoietic side effects, when compared to conventional chemotherapy (Dancey & Sausville).

In spite of these advantages, EGFR inhibitors (EGFRIs) frequently lead to dermatological (75-87%) and ocular (12%) toxicities (Robert C et al) (Figure 1). A papulopustular rash is the more frequent manifestation, affecting 45-100% of patients, and occurring in the face and upper trunk within the first few days-weeks of therapy. The rash is considered to be mechanistically related to EGFR inhibition in epidermal keratinocytes (Kari et al). Clinical and experimental data suggests that the papulopustular rash is a consequence of the blockade of EGFR mediated signaling pathway, which affects keratinocytes by inducing growth arrest and apoptosis, decreasing cell migration,
increasing cell attachment and differentiation, and stimulating inflammation, all of which result in the distinctive cutaneous manifestations (Lacouture M, 2006).

Periungual reactions develop in 12-16% of patients, and are notable for an exquisitely tender paronychia, which usually affects the thumbs and can be associated with onycholysis, onychodystrophy, and crusted lesions along nail folds. Although superinfection of the papulopustular rash and the paronychia may occur, the etiology of both disorders is not likely to be infectious as evidenced by negative cultures, lack of response to anti-staphylococcal antimicrobials, and improvement upon EGFR discontinuation. Hair abnormalities include a rapidly developing diffuse non-scarring alopecia, which is associated with scalp pruritus. Other hair alterations include trichomegaly of the eyebrows and eyelashes, the latter being the most clinically relevant, as these can potentially grow into the eye causing corneal erosions or ulcerations (Figure 2). These effects are also observed in mice with an inactivating EGFR mutation, in which alopecia and the development of curly whiskers are observed. Dry skin (xerosis) occurs in 7-35% of patients, and frequently appears at sites where the rash had developed. Moreover, it usually leads to pruritus which may be severe, necessitating oral antihistamines or pregabalin for control.

These undesired events result in decreased quality of life and the need for drug modification in 9-17% of treated patients, both of which may affect clinical outcome. Importantly, a correlation has been suggested between the severity of the papulopustular reaction and antitumor efficacy of the EGFR inhibitor (Perez Soler and Saltz, 2005). This finding supports the notion that skin toxicities should be managed effectively, as patients who could benefit the most are those likely to necessitate modifications in drug dose. The lack of management guidelines and poor understanding of these toxicities prompted the establishment of the SERIES (Skin and Eye Reactions to Inhibitors of the EGFR and kinaseS) clinic, an interdisciplinary effort between oncologists, dermatologists and ophthalmologists – a clinical program dedicated to the understanding and management of side effects to these novel anticancer therapies.

Since its inception in Q1 2006, the SERIES clinic has evaluated 98 patients for anti-EGFR induced ocular or cutaneous toxicities. A management algorithm has been developed for the management of the EGFR-induced rash, based on known pathophysiological mechanisms underlying toxicities. A combined approach using the semisynthetic tetracycline antibiotic doxycycline (100mg bid) and the topical immunomodulators pimecrolimus/tacrolimus or the corticosteroid alclomethasone 0.05% cr has been instituted for the management of the papulopustular rash. The use of doxycycline is based on its anti-inflammatory activity.

A retrospective analysis of patients receiving erlotinib (n=23) and cetuximab (n=15) treated...
with the SERIES algorithm for rash has shown that dose interruption / decrease is infrequent, needed in only 17% and 20% of patients treated with erlotinib and cetuximab, respectively (Figure 3). Drug interruption as a result of skin toxicity was needed in 0% erlotinib and 20% of cetuximab patients. Notably, the majority of these patients (85%) were experiencing moderate/severe toxicities. The higher dose modification/discontinuation with the monoclonal antibody cetuximab, when compared to the small molecule erlotinib may be due to its mechanism of action, in which the EGFR is internalized and degraded following binding, likely resulting in greater pathway inhibition.

The ocular toxicities that may occur with use of EGFR inhibitors can be broadly categorized as changes in the eyelids (eg, squamous blepharitis, trichomegaly, meibomitis), changes in the tear film (eg, dysfunctional tear syndrome), and miscellaneous changes (eg, iridocyclitis, corneal epithelial defect). Based on our experience in the SERIES clinic, such changes occur in approximately a third of the patients on these agents. The commonest symptoms correlate with a dysfunctional tear film secondary to eyelid margin inflammation. The latter changes are often seen in patients who develop the papulopustular rashes on the facial skin. Patients usually complain of a burning sensation and grittiness in their eyes as well as eyelid margin soreness. The eyelid margin inflammation is helped by use of systemic semisynthetic tetracyclines. A topical steroid eye cream (fluoromethalone 1%) is often necessary when the eyelid margin is intensely inflamed. Most patients also have some relief from tear supplementation. The other major eye change in patients on EGFR inhibitors is trichomegaly (elongated, curly thickened eyelashes – see figure) and this can occur silently. The eyelashes are almost always in their normal location but can be directed backwards and rub on the eyeball causing significant ocular discomfort as well as epithelial defect formation. The latter situation can potentially cause corneal ulceration and ocular morbidity if untreated. It is hence important to provide ophthalmological surveillance of patients on EGFR inhibitors at least quarterly. Prompt referral of symptomatic patients is also critical to avert such sequelae. We have seen patients who have discontinued their EGFR inhibitors at the onset of ophthalmologic symptoms and it is hence important to counsel patients regarding the possibility of ophthalmologic symptoms and

Figure 3. SERIES algorithm for the management of papulopustular rash to EGFR inhibitors. STCN = semisynthetic tetracycline antibiotics (i.e. doxycycline, minocycline); topicals = topical medium potency corticosteroids (i.e. alclometasone, triamcinolone).
to urge them to report these promptly. Fortunately, eye symptoms are treatable and are usually not vision threatening.

The introduction of targeted therapies has been very well received by patients and oncologists, based on the specific antitumor activity and a more relatively beneficial side effect profile. However, the use of these agents has been hampered by toxicities involving the eye and skin, which can interfere with evidence-based regimens and quality of life. Establishment of clinical programs such as the SERIES clinic, in which rapid access, and toxicity-driven specialists aid in mitigating these untoward events, may contribute to consistent therapy and optimal responses.

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References
Chemotherapy-induced peripheral neuropathy is a painful and serious problem that occurs frequently in people undergoing treatment for cancer. The resultant pain and paresthesias can impair quality of life, and in some cases, result in the need to limit doses of potentially curative therapies. The agents known to produce sensor nerve dysfunction include bortezomib, platinum based chemotherapeutic agents, taxanes, thalidomide, and vinca alkaloids. While these drugs are recognized as neurotoxic, significant knowledge gaps exist when characterizing this adverse effect. The mechanisms of chemotherapy-induced peripheral neuropathy (CIPN) are poorly understood, hampering research regarding prevention and treatment options. The incidence of chemotherapy-induced peripheral neuropathy (CIPN) has not been well characterized and likely varies with the type of agent used, dose, duration of therapy, patient comorbidities, and other, as yet unidentified, risk factors.

Manifestations of CIPN
Patients with CIPN experience a constellation of symptoms over the course of treatment and beyond, ranging from mild to severe. The location of CIPN appears to be quite different from that experienced by those with diabetic or HIV-associated neuropathy, suggesting variances in the underlying mechanisms when compared with these syndromes. The initial symptoms of these neuropathies are similar to CIPN, including bilateral distal fingers and toes. While diabetic or HIV-associated neuropathy can
Although similarities in the etiology (chemotherapy) are known, the efficacy of a variety of agents in preventing CIPN, including vitamin E, glutamate, gingko biloba and others, has not been consistent. For example, several early trials suggested the usefulness of amifostine in prevention of CIPN, yet, later randomized controlled trials demonstrated no benefit. Despite its efficacy in ameliorating pain associated with other neuropathies, gabapentin does not seem to prevent or reduce CIPN associated with oxaliplatin. Calcium and magnesium infusions are currently under study in the prevention of oxaliplatin-induced CIPN. A randomized controlled trial of the neuroprotective drug xaliprodine, reduced the risk of grade 3 neuropathy associated with oxaliplatin, although the results of this trial are only available in abstract form. Thus, a wide array of agents have been implicated in the prevention of CIPN, but none have been adequately tested to include them in any evidenced-based clinical regimen.

Several agents are emerging from preclinical work in rodent models of CIPN and may one day be shown to be useful in the clinical setting. Daily administration of acetyl-L-carnitine while rats received paclitaxel prevented painful neuropathy. Acetyl ester of L-carnitine, is believed to work by transporting long-chain fatty acids across mitochondrial membranes. Its functions include cytoprotection, antioxidant and anti-apoptotic activity. Another agent under study is ethosuximide, which has been shown to reverse both paclitaxel and vincristine-induced peripheral neuropathy in rodent models.

Work underway at the Robert H. Lurie Comprehensive Cancer Center includes the study of D-cycloserine (Seromycin, Eli Lilly), an agent originally used to treat tuberculosis. Work conducted in the laboratory of Dr. Vania Apkarian has demonstrated the efficacy of this partial glycine agonist in treating a variety of neuropathies, including CIPN (Apkarian, personal communication). A randomized controlled trial of this compound is currently underway and successfully enrolling subjects (“D-cycloserine in treating cancer patient with peripheral neuropathy caused by chemotherapy”: Von Roenn J, Campbell T, and Paice J, Principal Investigators).

A Need for Standardization
There are numerous obstacles to our understanding of CIPN, including the absence of standardization in measurement, clinical evaluation, and grading. For example, when attempting to measure CIPN, there is no current “gold standard” self-report tool that captures the patient’s global experience. Many existing tools designed to measure painful peripheral neuropathy were validated in populations of patients with diabetic or post herpetic neuropathy. Although similarities exist, it is becoming clear that there are significant differences in the sensations and experiences reported by patients with neuropathies of non-malignant etiology when compared to those with CIPN.

Other tools have been developed to measure quality of life and CIPN associated with a specific type of drug or cancer. The most useful of these is the FACT-Taxane, developed by David Cella and colleagues at Northwestern. Although a few tools specific to CIPN attempt to address both sensations and impairment, most have not yet undergone rigorous validity testing. There is an urgent need for standardized tools to assess peripheral neuropathy that are multidimensional, addressing the nature, intensity, and time course of symptoms, as well as the effect of this toxicity on quality of life.
There is little agreement on the necessary components of sensory testing that should be performed during the clinical evaluation.\textsuperscript{14-20} CIPN is known to produce changes in vibration, temperature, touch, pain, proprioception and other sensorimotor changes. Diagnostic measures in the clinic must be sensitive and reliable, so that the results would be reproducible across practitioners and time points.\textsuperscript{7} This is not trivial, as treatment decisions regarding potentially curative therapy may be made based upon the results of these measures. Thus, the evaluation must be sufficiently specific to differentiate CIPN from other neurologic disorders. This absence of standardization extends into the research setting. Quantitative sensory testing (QST) may be employed, yet the methods vary widely, confounding the interpretation of these findings.\textsuperscript{21-23}

Finally, the use of grading scales is a longstanding method of characterizing toxicities in oncology clinical trials. The information derived from these scales can be used to make individual treatment decisions or compare data across clinical trials. Grading scales for CIPN have been developed by the World Health Organization, the Eastern Cooperative Oncology Group, and the National Cancer Institute (which includes a sensory scale and a separate scale for pain).\textsuperscript{24,25} These existing scales are inconsistent in their approach to measuring toxicity associated with CIPN, and their interpretation is highly subjective, precluding aggregation of data across studies to draw conclusions about the prevalence and impact of this toxicity.

**Future Directions**

A prospective clinical trial is underway to characterize CIPN associated with paclitaxel in women undergoing treatment for breast cancer ("Incidence and Risk Factors Associated with Paclitaxel-Induced Peripheral Neuropathy in Breast Cancer Patients"; Paice J, PI; funded by the Oncology Nursing Foundation). The results of this trial will describe the incidence as well as risk factors associated with paclitaxel-induced peripheral neuropathy. Women will be evaluated prior to receiving paclitaxel, after completing half of their 4 treatments, and 2 weeks after completing therapy using quantitative sensory testing, as well instruments evaluating sensation and quality of life. We also hope to correlate the subjects’ neurological and anatomic findings with those of rodents receiving paclitaxel to confirm the validity of existing animal models.

Many patients undergoing chemotherapy report that they are better able to cope with side effects when they have prior knowledge of what to expect. A better understanding of CIPN will allow clinicians to more effectively educate patients. Research regarding the evaluation of CIPN brings us closer to understanding this serious toxicity.

**References**


Microenvironmental cues are increasingly being identified as complementary factors to the genetic mutations that lead to cancer progression. Cancer progression has been associated with a changing microenvironment, and normal cells placed in a microenvironment derived from malignant tissue can induce a tumor cell phenotype. Conversely, malignant cells placed into an extracellular matrix from normal tissue can revert to a normal phenotype. Cellular processes of normal cells, such as proliferation and migration, are highly regulated in order to avoid abnormal phenotypes. Typically, binding of cellular receptors with the target ligand initiates a cascade of intracellular reactions that lead to transcription factor (TF) activation and DNA binding. This network of signaling pathways integrates multiple signals from the extracellular environment. One signal consists of diffusible factors (e.g., growth factors), which can act in an autocrine or paracrine manner. Alternatively, the signal can consist of immobilized extracellular matrix proteins (e.g., laminin), whose organization combined with cell adhesion enables sensing of the mechanical environment. The combination of these cues can promote cancer development, and model systems are required to effectively link the specific cues with the cellular response.
Three-dimensional (3D) culture systems that provide appropriate microenvironments are powerful research tools for studying cellular processes, such as proliferation and apoptosis, and how these processes change throughout the progression from normal to cancerous tissue. Most research with cancer cells is performed by culturing the cells on tissue culture polystyrene, which does not provide the 3D architecture of a natural tissue and is far more rigid than most tissues. 3D culture systems that maintain an appropriate cell structure and support the formation of tissue structures can be used to investigate the interaction between cell genotype and signals present in the local microenvironment. The activity of many signaling pathways is context-dependent, and varies with the properties of the microenvironment. For example, autophosphorylation levels of focal adhesion kinase (FAK) are down-regulated in 3D cultures compared to 2D controls, even though phosphorylation levels of other adhesion-activated proteins remain similar, which suggests independence from the FAK-regulated pathway. Relative to culture on 2D substrates, cells cultured in 3D matrices exhibit a higher rate of cell adhesion, have a morphology that is consistent with in vivo histology, and adhere to the matrix through different sets of integrins. These differences in pathway activity can influence the crossregulation that is typically observed with growth factor signaling.

Relative to growth on 2D surfaces, cells of various types cultured in appropriate 3D environments form organized structures with polarity and function similar to those found in vivo. This report reviews the natural and synthetic hydrogels used for 3D culture of cancer cells, and provides examples of their application to link microenvironmental cues and cellular processes. While hydrogels have been used for a range of cancer cells, we will use examples from the culture of mammary epithelial cells. 3D systems for MEC culture have been a valuable tool for modeling cancer genes and pathways in a structurally appropriate context. MECs grown in 2D form monolayers, however, 3D cultures recapitulate numerous features of the glandular epithelium in vivo. Normal MECs form acinar structures with a hollow lumen, develop a structural apicobasal polarization, establish a basement membrane, and have tight control of proliferation. In contrast, MECs from early epithelial cancers form spheroids with filled lumens and exhibit invasive properties. 3D culture with hydrogels can be employed to elucidate mechanisms for tissue development and maintenance, and to study the roles of the microenvironment in disease states, especially cancer.

Hydrogels for 3D culture
3D cultures are often performed within hydrogels, which are gels composed of hydrophilic polymers that self-assemble (e.g., Matrigel) or are chemically crosslinked (e.g., alginate). Matrices composed of natural materials provide intrinsic functionality, though their composition can be complex and ill-defined, complicating the interpretation of results. In contrast, synthetic materials often lack the intrinsic cell interactions, yet can serve as controllable blank slates into which specific factors can be incorporated. Cells are incorporated into the hydrogel by suspending the cells in the solution of the hydrophilic polymers and subsequently allowing for gelation. Cells can be subsequently retrieved, using proteases or reversing the gelation process, for performing standard biochemical assays, such as real-time PCR and Western blots.

Natural hydrogels. Matrigel is a natural basement membrane that has been used for 3D culture of many cell types, including MECs. Matrigel is derived from Engelbreth-Holm-Swarm tumor cells, and is composed of many ECM molecules (e.g., laminin and collagen IV), proteases, and growth factors. The hydrogel is a liquid at 4°C, but its components, mostly collagen IV and laminin, self-assemble and form a weak gel when the temperature is elevated. The rigidity of this gel can be decreased by diluting Matrigel. MEC culture within Matrigel induces the formation of hollow spherical structures (acini), which are contrary to the flat monolayers that result from two-dimensional systems. These acini contain cells that senesce, form basal lamina, contain polarized organelles, and produce β-casein, a milk protein, all characteristics of the mammary gland in vivo. These differences in structural formation between 2D and 3D result, in part, from differences in signaling, including differential PI3K, glucocorticoid, and JNK signaling. Disparities between normal and cancerous MECs are also present in Matrigel, including structural differences (e.g., lost polarity) and differential responses to...
apoptotic inducing agents. Both normal and cancerous MECs grown in Matrigel replicate structures and processes found similar to those seen in vivo.

Hydrogels composed of individual proteins, such as collagen and fibrin, can provide more well-defined environments while retaining the intrinsic bioactivity of natural materials. Collagen fibers self-assemble and form a hydrogel upon a temperature increase, like Matrigel, but fibrin requires factor XIII as a chemical crosslinker for network formation. As the concentrations of the protein backbones can be varied to a greater extent than Matrigel, there is increased control over the rigidity of the resulting hydrogels. For collagen gels, MECs form spherical acini structures that look similar to those in Matrigel. However, the acinus lumen is filled and polarity is inverted, which contrasts with the behavior in Matrigel. Addition of laminin, or laminin-producing myoepithelial cells, to the matrix reverts these structures to the phenotype observed in vivo. The stability and rigidity of these hydrogels are dependent upon the protein concentration, and separating the mechanical and chemical cues within these materials can be difficult. Other materials are being developed which have increased plasticity for manipulation and they can be used to explore the variable roles the microenvironment plays in tissue development and cancer progression.

Synthetic hydrogels. Synthetic hydrogels can be customized to present well-defined microenvironments, and thus are ideal systems for investigating the responses of both normal and cancer cells. These hydrogels are often composed of a backbone that is responsible for creating the 3D structure, and can be decorated with biological stimuli that direct cellular processes, such as proliferation, migration, and apoptosis. Often, the specific stimuli can be varied independently from other design aspects, thereby enabling studies that focus on a specific factor.

Hydrophilic polymers form the basis of synthetic hydrogels, and they are crosslinked physically or chemically under mild conditions such that cell viability and function are maintained during the transition from liquid to hydrogel. Self-assembling synthetic gels are composed of self-assembling components, including peptide amphiphiles and Puramatrix. Self-assembly can be triggered by temperature, salt concentration, or simple mixing. Alternatively, hydrogels can be formed by crosslinking the hydrophilic chains to form a network, either covalently or ionically. Covalent crosslinking requires a chemical reaction to occur between subunits, such as the formation of diacylate or disulfide linkages. Alternatively, hydrogels can be crosslinked ionically, in which metallic ions bridge anionic moieties within the polymer. Examples of these hydrogels include alginate and other factors in situ for 3D culture.

3D stimuli and cancer progression
Besides providing the hydrophilic polymer backbone to provide a 3D architecture for cell culture, synthetic hydrogels can incorporate ECM proteins, growth factors, and cell-responsive moieties that influence tissue development and cancer progression. These hydrogels can directly control cell adhesion to the matrix, mobility of diffusible factors, migration of cells, and mechanics of the microenvironment. While other features such as cell-cell connectivity and ECM turnover can impact cellular processes, they are beyond the scope of this review.

Cell adhesion. The ECM mediates cellular adhesion through ligation of integrin receptors, which initiates intracellular signaling and confer the ability to sense mechanical stimuli. On tissue culture polystyrene, adhesion can induce the formation of focal contacts; however, cells cultured in 3D often do not form these adhesions.

The composition of the extracellular matrix dictates which receptors are engaged for cell adhesion, and synthetic hydrogels can be designed to present specific receptor ligands within the matrix. The conditions for hydrogel formation are mild, and proteins will remain stable without aggregation. The simplest technique is to blend individual proteins into a synthetic polymer solution (e.g., PEG) that undergoes gelation. In this method, a uniform hydrogel with a range of protein concentrations and combinations can be created. Alternatively, proteins can be attached to the polymeric backbone of hydrogels, by chemically reacting thiols, carboxylic acids, amines or other functional groups present on the peptides or proteins. The incorporation of full length ECM proteins is complicated by the size of the...
molecule, which can produce low reaction yields and complicates purification. However, short peptide sequences (e.g., RGD sequence for collagen) within the larger protein are responsible for adhesion. These peptide sequences can easily be attached to hydrogels and are frequently used in place of the full length molecule. Nevertheless, these peptides do not necessarily recreate the entire function of the full length molecule.

Diffusible factors. Diffusible factors, such as growth factors and hormones, present in the microenvironment influence many cellular functions, and their ability to be transported through the matrix is critical to maintaining an appropriate concentration and to accessing the cell population. Growth factors, such as TGFβ, are added to culture media and bind extracellular receptors to initiate signaling, and must access cells within the matrix during media changes. Importantly, these diffusible factors may also be produced by cells within the microenvironment to initiate autocrine or paracrine signaling. The matrix may also be designed with groups capable of binding growth factors, and can thus serve as a reservoir of growth factors, or to initiate signaling by the immobilized growth factor. Transport of the diffusible factors through the hydrogel is affected by the pore size of the hydrogels, which can be manipulated by changing the polymer molecular weight and the extent of crosslinking. Thus, diffusible factors added to the culture media and secreted by the encapsulated cells can influence cell behavior, and the matrix can manipulate the availability of these factors by influencing transport within the gel. These systems allow the synergistic role of diffusible factors and ECM proteins to be investigated for their impact on tumor development and progression.

Migration. Cellular migration through microenvironments is essential for developing and maintaining a tissue and is a hallmark of metastasizing cancers. Cells can migrate along gradients of signals, communicated via molecules in the environment (e.g. morphogens) resulting in the making or breaking of direct cell-cell contacts. While cells can freely move along 2D surfaces, 3D environments present resistance in all directions. Within tissue, cells usually migrate via proteolytic, though sometimes nonproteolytic, mechanisms. For proteolytic migration, cells secrete and activate specific proteases (e.g., MMPs) that break down the matrix and provide a path for transport. Alternatively, cells can deform and squeeze their way through the ECM. 3D culture systems need to allow for his migration to mimic the native environment and to support cell-cell interactions post-seeding. While pore sizes are usually much smaller than cell diameters, synthetic hydrogels can be designed to facilitate both mechanisms of migration. For nonproteolytic migration, the migration rate can be controlled with the pore size of the matrix as cells can squeeze their way through hydrogels. Hydrogels can also incorporate degradable moieties, such as proteolytically degradable peptides or MMP degradable domains, to enhance cellular intrusion through the gel. The migration rate can thus be controlled by varying the number of degradable moieties. As such, synthetic hydrogels can provide the same mechanisms for cellular migration as natural tissues, yet can be modulated to study the role migration plays in natural tissue development and cancer.

Hydrogel mechanics. Mechanical forces within the microenvironment directly influence cellular processes and are sensed through the interaction of the cell with the ECM and the rigidity of the hydrogel. Within natural tissues, cells experience mechanical stresses from fibrous ECM proteins and neighboring cells, with increased tissue rigidity often being associated with cancer development. The mechanisms by which cells sense and respond to mechanical forces are not entirely understood, focal adhesion kinase (FAK) and Rho GTPase appear to be important players in mechanotransduction. Hydrogels with controllable mechanics and cell adhesion can enable the investigation of how physical forces influence cancer progression. Gel rigidity increases with increased molecular weight and concentration of polymeric units, as well as increased crosslinking density. While incorporation of ECM molecules can also alter rigidity of the gel, this effect can be compensated by altering the density of the polymeric backbone. Thus, synthetic hydrogels can be independently formulated to accommodate mechanical and chemical influences.

Conclusions
Hydrogels can provide a controllable scaffold for the investigation of tissue development and maintenance, and cancer progression, in a
cellular environment that phenocopies the in vivo environment. Environmental cues such as mechanics, ECM, and diffusible factors can be investigated in isolation for their role in promoting specific cellular processes involved in cancer progression. The improved understanding of the relationship between microenvironmental cues and the resulting cellular processes can lead to new insights about oncogenic progression that may ultimately facilitate novel clinical treatments.

References


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
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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
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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
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Managing Director: Chi-Hao Luan, PhD
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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
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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.
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.

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

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

Genomics Core Facility
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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 throughput DNA extraction by Autopure LS from Gentra.

Keck Biophysics Facility
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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.

Magnetic Resonance Research Facility
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This facility combines cutting-edge magnetic resonance techniques and an interdisciplinary approach to biomedical research to promote understanding of human diseases through MR research on animal models. The facility is a front-runner in developing novel MR imaging techniques and applications with potential to become clinical diagnostic tools. The facility includes supporting laboratories such as an animal surgery room, an image processing lab, and an electronics lab.
Monoclonal Antibody Facility
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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
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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
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The mission of this core facility is to provide consultation and support for research that involves collecting, analyzing or interpreting self-report data, and to promote the understanding of measurement fundamentals and the improvement of research practice. The facility provides consultative and analytic expertise on the best ways to measure outcomes derived by self-report, serve as a central resource for state-of-the-art instruments and measurement methods, and provides in-house research support services for the collection of outcomes data.

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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
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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.
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.
Chiu B, Gapstur SM, Greenland P, Wang R, Dyer A

**Body Mass Index, Abnormal Glucose Metabolism, and Mortality from Hematopoietic Cancer.** Cancer Epidemiol Biomarkers Prev 2006; 15(12):2348-54

Abstract: Background: High body mass index (BMI) and diabetes have been linked to risk of non-Hodgkin’s Lymphoma (NHL), but results are inconsistent and most studies use self-reported information. No study has evaluated the association of NHL with postload plasma glucose (PLG) levels, which are positively associated with BMI. We analyzed data from a cohort study to investigate associations of interviewer-measured BMI and PLG with risk of NHL mortality and to explore associations with leukemia and multiple myeloma.

Methods: Employees of 84 Chicago-area organizations, with an average age of 40 years at baseline, were screened from 1967 to 1973. Height and weight were measured by study nurses. A 50-g oral glucose load was administered to nondiabetic participants. Of the at-risk cohort of 35,420 men and women, 129 died of NHL, 151 died of leukemia, and 66 died of multiple myeloma during an average of 31 years of follow-up. Hazard Ratios (HR) and 95% confidence intervals (95% CI) were derived from Cox proportional hazards regression models.

Results: Among men, there were positive dose-response relations of BMI with mortality from NHL (HR, 2.57; 95% CI, 1.24-5.34 for the highest versus lowest quartile; $P_{\text{trend}} = 0.01$) and leukemia (HR, 1.98; 1.07-3.69; $P_{\text{trend}} = 0.02$). PLG also was positively related to NHL mortality (HR, 2.86; 95% CI, 1.35-6.06 for the highest versus lowest category; $P_{\text{trend}} = 0.004$).

For women, a higher BMI was positively associated with leukemia mortality (HR, 2.47; 95% CI, 0.96-6.36; $P_{\text{trend}} = 0.02$) and the highest level of PLG was associated with risk of mortality from multiple myeloma (HR, 3.06; 95% CI, 1.05-8.93). The risk estimated for BMI and PLG remained unchanged after adjustment for each factor.

Conclusions: High BMI and/or abnormal PLG is associated with higher risk of mortality from NHL and possibly leukemia and from myeloma in women. These findings might have public health significance because BMI and glucose levels are amenable to modification.

Donahue CP, Muratore C, Wu JY, Kosik KS, and Wolfe MS

**Stabilization of the Tau Exon 10 Stem Loop Alters pre-mRNA Splicing.** Journal of Biological Chemistry, 281(33): 23302-6, 2006 Aug 18

Neurofibrillary tangles containing filaments of the microtubule-associated protein tau are found in a variety of neurodegenerative diseases. Mutations in the tau gene itself cause
frontotemporal dementia with parkinsonism, demonstrating the critical role of tau in pathogenesis. Many of these mutations in tau are silent, are found at the 5' splice site of exon 10, and lead to increased inclusion of exon 10. These silent mutations are predicted to destabilize a stem loop structure at the exon 10 5'-splice site; however, the existence of this stem loop under physiological conditions and its role in splice regulation are controversial.

Here we show that base changes that stabilize this stem loop in vitro substantially decrease exon 10 inclusion in a wild type tau minigene and rescue the increase in exon 10 splicing caused by a dementia-causing point mutation. Moreover, we probed the intracellular structure of the tau stem loop with antisense RNA and demonstrate that the stability of the stem loop dictates antisense effectiveness. Together these results validate the stem loop as a bona fide structure regulating tau exon 10 splicing.

Giafis N, Katsoulidis E, Sassano A, Tallman MS, Higgins LS, Nebreda AR, Davis RJ, Platanias LC


Arsenic trioxide (As(2)O(3)) induces differentiation and apoptosis of leukemic cells in vitro and invivo, but the precise mechanisms that mediate such effects are not known. In the present study, we provide evidence that the kinases MAPK, kinase 3 (Mkk3) and Mkk6 are activated during treatment of leukemic cell lines with As(2)O(3) to regulate downstream engagement of the p38 mitogen-activated protein kinase. Using cells with targeted disruption of both the Mkk3 and Mkk6 genes, we show that As(2)O(3)-dependent activation of p38 is defective in the absence of Mkk3 and Mkk6, establishing that these kinases are essential for As(2)O(3)-dependent engagement of the p38 pathway. Pharmacologic inhibition of p38 enhances As(2)O(3)-dependent activation of the c-jun NH(2)-terminal kinase (JNK) and subsequent induction of apoptosis of chronic myelogenous leukemia (CML)- or acute promyelocytic leukemia (APL)-derived cell lines. In addition, in APL blasts, inhibition of p38 enhances myeloid cell differentiation in response to As(2)O(3), as well as suppression of Bcl-2 expression and loss of mitochondrial membrane potential. Similarly, induction of As(2)O(3)-dependent apoptosis is enhanced in mouse embryonic fibroblasts (MFF) with targeted disruption of both the Mkk3 and Mkk6 genes, establishing a key role for this pathway in the regulation of As(2)O(3)-induced apoptosis. In other studies, we show that small-molecule p38 inhibitors SD-282 and SCIO-469 potentiate As(2)O(3)-mediated suppression of myeloid leukemic progenitor growth from CML patients, indicating a critical regulatory role of p38 in the induction of antileukemic responses. Altogether, our data indicate that the Mkk3/6-p38 signaling cascade is activated in a negative regulatory feedback manner to control induction of As(2)O(3)-mediated antileukemic effects.

Hebner CM, Wilson R, Rader J, Bidder M, Laimins LA


Abstract: The Double-stranded RNA protein kinase (PKR) pathway plays a vital role in the innate immune response to viral infection. Activation of PKR following virus entry can lead to a shutdown in translation, thereby inhibiting viral protein synthesis and replication. Little is currently known about whether human papillomaviruses (HPVs) modulate PKR expression and activity. In this study, normal human foreskin keratinocytes (NHKs) transfected stably with the HPV 31 or 16 genomes and cell lines expressing the HPV 16 E6 and E7 oncoproteins were used to examine effects on the PKR pathway. HPV gene products were found to modulate PKR phosphorylation, activity and localization. The levels of total PKR protein were reduced modestly in cells that maintained HPV 16 or 31 episomes through a reduction in PKR transcription. However, levels of phosphorylated PKR were decreased 4-fold through a post-transcriptional mechanism mediated by E6 and E7 that was independent of the transcriptional downregulation mediated by HPV. In response to infection by vesicular stomatitis virus, phosphorylation of eIF2alpha was blocked in cells expressing HPV.
oncoproteins, but not in NHKs. Finally, it was observed that the cellular localization of PKR was altered by HPV gene products in HPV raft cultures, as well as HPV-positive patient biopsies. This effect was mediated by the HPV E6 oncoprotein and leads to the co-localization of PKR with P-bodies. These studies demonstrate that high-risk HPVs target the PKR pathway by multiple mechanisms.

Lynne-Marie Postovit, Elisabeth A Seftor, Richard E.B. Seftor and Mary J.C. Hendrix


Tumor cells communicate bi-directionally with the surrounding microenvironment, sending and receiving topographical and molecular cues that direct diverse cellular phenomena including differentiation, growth and invasion. The microenvironment has long been acknowledged as a facilitator of melanoma progression, and recent studies have illuminated tumor-associated factors, including hypoxia and the extracellular matrix, as important mediators of melanocyte transformation and transdifferentiation. Although these findings portray the microenvironment as a perilous obstacle to the successful treatment of advanced melanomas, it is important to note that certain molecular milieus may be capitalized on as potential treatment modalities. Indeed, our group and others have elucidated the unique ability of embryonic microenvironments to normalize aggressive melanoma cells toward a more benign melanocytic phenotype. The microenvironment therefore presents a novel target for the treatment and ultimately the prevention of melanoma progression and metastasis.

Huang W, Horvath E, Eklund EA

PU.1 Interferon Regulatory Factor (IRF) 2, and the Interferon Consensus Sequence-binding Protein (ICSBP/IRF8) Cooperate to Activate NFI Transcription in Differentiating Myeloid Cells. Journal of Biol Chemistry 2007 Mar 2; 282(9):6629-43

Nfi (neurofibromin 1) is a Ras-GAP protein that regulates cytokine-induced proliferation of myeloid cells. In previous studies, we found that the interferon consensus sequence-binding protein (ICSBP; also referred to as interferon regulatory factor 9) activates transcription of the gene encoding Nf1 (the NFI gene) in differentiating myeloid cells. We also found that NFI activation requires cytokine-stimulated phosphorylation of a conserved tyrosine residue in the interferon regulatory factor (IRF) domain of ICSBP/IRF8. In this study, we found that ICSBP/IRF8 cooperates with PU.1 and interferon regulatory factor 2 to activate a composite ets/IRF-cis element in the NFI prompter. We found that PU.1 binds directly to the NFI-cis element, and DNA-bound PU.1 interacts with IRF2, recruiting IRF2 to the cis element. This interaction requires cytokine-induced phosphorylation of specific serine residues in the PU.1 PEST domain and of a conserved tyrosine residue in the IFR domain of IRF2. We found that ICSBP/IRF8 interaction with the NFI1-cis element requires pre-binding of PU.1 and IRF2. The conserved IRF domain tyrosine in ICSBP/IRF8 is required for interaction with the DNA-bound PU.1-IRF2 heterodimer. NFI deficiency in myeloid progenitor cells results in cytokine hypersensitivity and myeloproliferation. Therefore, these studies identify a target gene for the previously observed tumor-suppressor effect of PU.1. Additionally, these studies identify a tumor-suppressor function for the “oncogenic” transcription factor, IRF2.

Authors: Kim YL, Turzhitsky VM, Liu Y, Roy HK, Wali RK, Subramanian H, Pradhan P, Backman V


The phenomenon of enhanced backscattering (EBS) of light, also known as coherent backscattering (CBS) of light, has been the object of intensive investigation in nonbiological media over the last two decades. However, there have been only a few attempts to explore EBS for tissue characterization and diagnosis. We have recently made progress in the EBS measurements in tissue by taking advantage of low spatial coherence illumination, which has led us to the development of low-coherence enhanced backscattering (LEBS)

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spectroscopy. In this work, we review the current state of research on LEBS. After a brief discussion of the basic principle of EBS and LEBS, we present an overview of the unique features of LEBS for tissue characterization, and show that LEBS enables depth-selective spectroscopic assessment of mucosal tissue. Then, we demonstrate the potential of LEBS spectroscopy for predicting the risk of colon carcinogenesis and colonoscopy-free screening for colorectal cancer (CRC).


The p53 tumor suppressor protein functions as a critical component of genotoxic stress response by regulating the expression of effector gene products that control the fate of a cell following DNA damage. Unstressed cells maintain p53 at low levels through regulated degradation, and p53 levels and activity are rapidly elevated upon genotoxic stress. Biochemical mechanism that control the levels and activity of p53 are therefore of great interest. We and others have recently identified hAda3 (human homologue of yeast alteration/deficiency in activation 3) as a p53-interacting protein and enhancer of p53 activity. Here, we show that endogenous levels of p53 and Ada3 interact with each other, and by using inducible overexpression and short hairpin RNA-mediated knockdown strategies we demonstrate that hAda3 stabilizes p53 protein by promoting its acetylation. Use of a p53 mutant with mutations of known p300/CREB-binding protein acetylation sites demonstrated that hAda3-dependent acetylation is required for increase in p53 stability and target gene induction. Importantly, we demonstrate that endogenous hAda3 is essential for DNA damage-induced acetylation and stabilization of p53 as well as p53 target gene induction. Overall, our results establish hAda3, a component of coactivator complexes that include histone acetyltransferase p300/CREB-binding protein, as a critical mediator of acetylation-dependent stabilization and activation of p53 upon genotoxic stress in mammalian cells.


Enzastaurin (LY317615), A Protein Kinase C, Inhibitors, Inhibits the AKT Pathway and Induces Apoptosis in Multiple Myeloma Cell Lines. Molecular Cancer Therapy July 2006 5(7):1783:1789

Enzastaurin (LY317615), an acyclic bisinodolymaleimide, is an oral inhibitor of the protein kinase Cß, isozyme. The objective of this study was to assess the efficacy of enzastaurin in inducing apoptosis in multiple myeloma (MM) cell lines and to investigate possible mechanism of apoptosis. Cell proliferation assays were done on a variety of MM cell lines with unique characteristics (dexamethasone sensitive, dexamethasone resistant, chemotheraphy sensitive, and melphalan resistant). The dexamethasone sensitive MM.1S cell line was used to further assess the effect of enzastaurin in the presence of dexamethasone, insulin-like growth factor-1 (IGF-I), interleukin-6, and the pan-specific caspase inhibitor ZVAD-fmk. Enzastaurin increased cell death in all cell lines at clinically significant low micromolar concentrations (1-3 µmol/L) after 72 hours of treatment. Dexamethasone and enzastaurin were shown to have an additive effect on MM.1S cell death. Although IGF-I blocked the effect of 1 µmol/L enzastaurin, IGF-I did not abrogate cell death induced with 3 µmol/L enzastaurin. Moreover, enzastaurin-induced cell death was not affected by interleukin-6 or ZVAD-fmk.

GSK3ß, phosphorylation, a reliable pharmacodynamic marker for enzastaurin activity, and AKT phosphorylation were both decreased with enzastaurin treatment. These data indicate that enzastaurin induces apoptosis in MM cell lines in a caspase-independent manner and that enzastaurin exerts its antmyeloma effect by inhibiting signaling through the AKT pathway.


Chemoprevention of Colon Carcinogenesis by Polyethylene Glycol: Suppression of Epithelial Proliferation via Modulation of

Polyethylene glycol (PEG) is one of the most potent chemopreventive agents against colorectal cancer; however, the mechanisms remain largely unexplored. In this study, we assessed the ability of PEG to target cyclin D1-beta-catenin-mediated hyperproliferation in the azoxymethane-treated rat model and the human colorectal cancer cell line, HT-29. Azoxymethane-treated rats were randomized to AIN-76A diet alone or supplemented with 5% PEG-8000. After 30 weeks, animals were euthanized and biopsies of aberrant crypt foci were subjected to immunohistochemical and immunoblot analyses. PEG markedly suppressed both early and late markers of azoxymethane-induced colon carcinogenesis (fractal dimension by 80%, aberrant crypt foci by 64%, and tumors by 74%). In both azoxymethane-treated rats and HT-29 cells treated with 5% PEG 3350 for 24 hours, PEG decreased proliferation (45% and 52%, respectively) and cyclin D1 (78% and 56%, respectively). Because beta-catenin is the major regulator of cyclin D1 in colorectal cancer, we used the T-cell factor (Tcf)-TOPFLASH reporter assay to show that PEG markedly inhibited beta-catenin transcriptional activity. PEG did not alter total beta-catenin expression but rather its nuclear localization, leading us to assess E-cadherin expression (a major determinant of beta-catenin subcellular localization), which was increased by 73% and 71% in the azoxymethane-rat and HT-29 cells, respectively. We therefore investigated the effect of PEG treatment on levels of the negative regulator of E-cadherin, SNAIL, and observed a 50% and 75% decrease, respectively. In conclusion, we show, for the first time, a molecular mechanism through which PEG imparts its antiproliferative and hence profound chemopreventive effect.


Arsenic trioxide (As(2)O(3)) exhibits important antitumor activities in vitro and in vivo, but the precise mechanisms by which it induces its effects are not known. We provide evidence that during treatment of BCR-ABL-expressing cells with As(2)O(3), there is activation of a cellular pathway involving the p70 S6 kinase (p70S6K). Our data show that p70S6K is rapidly phosphorylated on Thr(421) and Ser(424) and is activated in an As(2)O(3)-inducible manner. The mammalian target of rapamycin (mTOR) is also phosphorylated/activated in an As(2)O(3)-inducible manner, and its activity is required for downstream engagement of p70S6K. p70S6k subsequently phosphorylates the S6 ribosomal protein on Ser(235)/Ser(236) and Ser(240)/Ser(244) to promote initiation of mRNA translation. Treatment of chronic myelogenous leukemia-derived cell lines with As(2)O(3) also results in phosphorylation of the 4E-BP1 repressor of mRNA translation on Thr(37)/Thr(46) and Thr(70), sites required for its deactivation and its dissociation from the eukaryotic initiation factor 4E complex to allow apoptosis. Here we establish that Akt is required for normal cell proliferation and susceptibility to oncogenesis independently of its antiapoptotic activity. Partial ablation of Akt activity by deleting Akt1 inhibits cell proliferation and oncogenesis. These effects are compounded by deleting both Akt1 and Akt2. In vivo, Akt1 null mice are resistant to MMTV-v-H-Ras-induced tumors and to skin carcinogenesis. Thus, partial ablation of Akt activity is sufficient to suppress tumorigenesis in vitro and in vivo. The effect of Akt deficiency on cell proliferation and oncogenesis is p53 independent but mTORC1 dependent. Surprisingly, upon mTORC1 hyperactivation, the reduction in Akt activity does not impair cell proliferation and susceptibility to oncogenic transformation; thus, Akt may mediate these processes exclusively via mTORC1.


Akt Deficiency Impairs Normal Cell Proliferation and Suppresses Oncogenesis in a p53-independent and mTORC1-dependent Manner. Cancer Cell 10(4):269-80, 2006 Oct

Akt contributes to tumorigenesis by inhibiting apoptosis. Here we establish that Akt is required for normal cell proliferation and susceptibility to oncogenesis independently of its antiapoptotic activity. Partial ablation of Akt activity by deleting Akt1 inhibits cell proliferation and oncogenesis. These effects are compounded by deleting both Akt1 and Akt2. In vivo, Akt1 null mice are resistant to MMTV-v-H-Ras-induced tumors and to skin carcinogenesis. Thus, partial ablation of Akt activity is sufficient to suppress tumorigenesis in vitro and in vivo. The effect of Akt deficiency on cell proliferation and oncogenesis is p53 independent but mTORC1 dependent. Surprisingly, upon mTORC1 hyperactivation, the reduction in Akt activity does not impair cell proliferation and susceptibility to oncogenic transformation; thus, Akt may mediate these processes exclusively via mTORC1.
cap-dependent mRNA translation. In studies to determine the functional relevance of this pathway, we found that inhibition of mTOR and downstream cascades enhances induction of apoptosis by As(2)O(3). Consistent with this, the mTOR inhibitor rapamycin strongly potentiated As(2)O(3)-mediated suppression of primitive leukemic progenitors from the bone marrow of chronic myelogenous leukemia patients. Altogether, our data show that the mTOR/p70S6K pathway is activated in a negative feedback regulatory manner in response to As(2)O(3) in BCR-ABL-transformed cells and plays a key regulatory role in the induction of anti-leukemic responses.

Qiăng Zhang¹, Shilajit D. Kundu¹, Ximing Yang², Michael Pins², Borko Javonovic³, Robert Meryer², Seong-Jin Kim², Luk Van Parijs³, Norman M. Greenberg⁴, Timothy Kuzel⁵, Richard Meagher⁶, Yinglu Guo⁷, and Chung Lec¹,⁸,*

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Blockade of TGF-β, signaling in tumor-reactive CD8+ T cells activates the anti-tumor immune response cycle.

Transforming growth factor-β (TGF-β) is a potent immunosuppressant. Over-production of TGF-β by tumor cells leads to evasion of host immune surveillance and tumor progression. Results of our early studies demonstrated that adoptive transfer of tumor-reactive TGF-β-insensitive CD8+ T cells into immunocompetent mice was able to eradicate lung metastasis of mouse prostate cancer. The present study was conducted with three objectives. First, we tested if this technology could be applied to the treatment of solid xenograft tumors in allogeneic immunodeficient hosts. Next, we determined relevant parameters in the tumor microenvironment with the treatment. Finally, we tested if immune cells other than CD8+ T cells were required for the anti-tumor effect. Mouse prostate cancer cells, TRAMP-C2 of the C57BL/6 strain, grown in immunodeficient allogeneic hosts of Balb/c strain, were used as a xenograft model. Tumor-reactive CD8+ T cells from C57BL/6 mice were isolated, expanded ex vivo, and rendered insensitive to TGF-β by introducing a dominant negative TGF-β type II receptor vector. Seven days following subcutaneous injection of TRAMP-C2 cells (5 x 105 cells) into the flank of male BALB/c−Rag1−/− mice, tumor-reactive TGF-β-insensitive CD8+ T cells (1.5 x 107 cells) were transferred, with and without the co-transfer of an equal number of CD8-depleted-splenocytes from C57BL/6 donors. Naïve CD8+ T cells or GFP-empty vector transfected tumor-reactive CD8+ T cells were transferred as controls. Forty days following the transfer, the average tumor weight in animals that received co-transfer of tumor reactive TGF-β-insensitive CD8+ T cells and CD8-depleted splenocytes was at least 50% less than that in animals of all other groups (p<0.05). Tumors in animals of the former group showed a massive infiltration of CD8+ T cells. This was associated with secretion of relevant cytokines, decreased tumor proliferation, reduced angiogenesis, and increased tumor apoptosis. Based on these results, we postulated a concept of anti-tumor immune response cycle in tumor immunology.


Biochemical mechanisms that control the levels and function of key tumor suppressor proteins are of great interest as their alterations can lead to oncogenic transformation. Here, we identify the human orthologue of Drosophila melanogaster ecdysoneless (hEcd) as a novel p53-interacting protein. Overexpression of hEcd increases the levels of p53 and enhances p53 target gene transcription whereas hEcd knockdown has the opposite effects on p53 levels and target gene expression. Furthermore, hEcd interacts with murine double minute-2 and stabilizes p53 by inhibiting murine double minute-2-mediated degradation of p53. Thus, hEcd protein represents a novel regulator of p53 stability and function. Our studies also represent the first demonstration of a biochemical function of hEcd protein and raise the possibility that altered hEcd levels and/or function may contribute to oncogenesis.
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### Internal Advisory Board

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The Robert H Lurie Comprehensive Cancer Center of Northwestern University

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Director, University of Michigan Comprehensive Cancer Center
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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 the programs for the remainder of 2006. For specific dates or more information about these programs, visit www.cancer.northwestern.edu or call the Cancer Center at 312.695.1304.

9th Annual Lynn Sage Breast Cancer Symposium
The Fairmont Chicago
September 27-September 30, 2007
Chair: William Gradishar, MD

Berlin Lecture
October 23, 2007
Lewis Cantley, PhD

Head and Neck NCCN Guidelines
October 11, 2007

Oncology Nursing Conference
December 7, 2007
Chairs: Kara Catsaros, RN, Vicki Maurer, RN and Connie Augustynaik, RN
COMMUNITY EVENTS / PATIENT PROGRAMS
The 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 Cancer Center at 312.695.1304.

Cancer Prevention Programs at the Green City Market
August 1 and 8, 2007
Katie Marquardt, MS, RD, LD

What You Should Know About Cancer
Wednesday, August 15, 2007
Mark Agulnik, MD and Lynne Wagner, PhD

Lynn Sage Breast Cancer Town Hall Meeting
September 30, 2007
Chair: William Gradishar, MD
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Affiliated Research Facilities and Teaching Hospitals

The Robert H. Lurie Comprehensive Cancer Center of Northwestern University is the focus of cancer research, treatment and education at Northwestern University. The 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 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, Evanston Northwestern Healthcare, the Rehabilitation Institute of Chicago and Veterans Administration Chicago Healthcare System.
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 nation’s leaders as the only cancer center in Illinois and one of only 40 in the nation to hold this NCI distinction. In addition, the Cancer Center is a founding member of the National Comprehensive Cancer Network, an exclusive alliance of 21 of the nation’s leading cancer centers.

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.
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

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