upcoming events

UPMC
Cancer Centers

UPMC Cancer Centers and
University of Pittsburgh
Cancer Institute

Nancy E. Davidson, MD
Director

UPMC Cancer Pavilion
5150 Centre Ave.
Pittsburgh, PA 15232
412-647-2811

UPMC has consistently received national recognition from *U.S. News & World Report* magazine for offering one of America's top cancer programs. For more information about UPMC Cancer Centers' clinical services, or University of Pittsburgh Cancer Institute research, call **1-800-533-UPMC** or visit **www.UPMCCancerCenters.com**.

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

2009 ASTRO Conference

Physician-researchers from the University of Pittsburgh Cancer Institute (UPCI) and UPMC Cancer Centers will present findings from more than 15 studies at the 51st annual American Society for Radiation Oncology (ASTRO) meeting, November 1-5, in Chicago, including:

- Antioxidant gene therapy
- Small molecule GS-nitroxide ameliorates the ionizing irradiation-induced delay in bone wound healing measured in a novel murine model
- Analysis of the effect of edema on dosimetric and radiobiological parameters in 131Cs prostate brachytherapy
- Single versus multifraction radiosurgery for metastatic spine tumors
- Stereotactic body radiotherapy (SBRT) in the treatment of locally advanced, recurrent and unresectable pancreatic cancer

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UPMC Cancer Centers
cancerinsights

Hillman Cancer Center is the academic hub of the UPMC Cancer Centers network. The state-of-the-art facility offers cutting-edge cancer care and also is home to the research activities of the University of Pittsburgh Cancer Institute (UPCI). UPMC Cancer Centers and UPCI are the only center in western Pennsylvania with the elite Comprehensive Cancer Center designation from the National Cancer Institute.

Good Science Makes Good Medicine

Physicians understand that the latest cancer research doesn't make an impact until it touches a patient.

At UPMC Cancer Centers and the University of Pittsburgh Cancer Institute (UPCI), our unique structure gives us an unparalleled opportunity to translate what we are learning at the bench to clinical application through trials and changes in treatment standards.

As physicians and scientists we are committed to a personalized approach to cancer treatment — giving the right treatment to the right person at the right time — because this will ultimately reduce morbidity and mortality from the disease.

This edition of *Cancer Insights* focuses on initiatives that are helping us to refine treatments based on patient response — including the role of gene regulators and gene expression in predicting response to chemotherapeutic agents; new diagnostic approaches that will serve as an early marker in the success of radiotherapeutic techniques; and new generations of cancer vaccines that target cancer cell death more effectively, based on immune response.

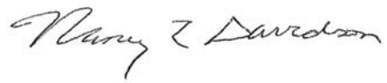
We are not just developing the next generation of cancer therapies, we also are developing the next generation of physician-researchers. Merill Egorin, MD, professor of medicine and pharmacology at UPCI, was honored with the 2009 American Society of Clinical Oncology Translational Research Professorship for his ongoing and passionate commitment to mentoring young researchers.

Ajay Bhatnagar, MD, who completed his residency with UPMC Cancer Centers' Department of Radiation Oncology and is now an assistant professor with the department, will present the results of a unique study investigating the impact of the physician-patient relationship on clinical outcomes at the 2009 annual meeting of the American Society of Radiation Oncology (ASTRO).

As the preeminent institution in western Pennsylvania for the delivery of cancer care, the conduct of basic and translational research, and the education of the next generation of cancer researchers and physicians, UPCI and UPMC Cancer Centers is exceptionally well positioned to make a significant impact on the burden of cancer.

To learn more about clinical research or patient care opportunities at the University of Pittsburgh Cancer Institute and UPMC Cancer Centers, please call 412-647-2811 or visit our website at www.UPMCCancerCenters.com.

Sincerely,



Nancy E. Davidson, MD
Director, University of Pittsburgh Cancer Institute and UPMC Cancer Centers
Associate Vice Chancellor for Cancer Research and Hillman Professor of Oncology
Chief, Division of Hematology/Oncology and Professor of Medicine,
University of Pittsburgh School of Medicine

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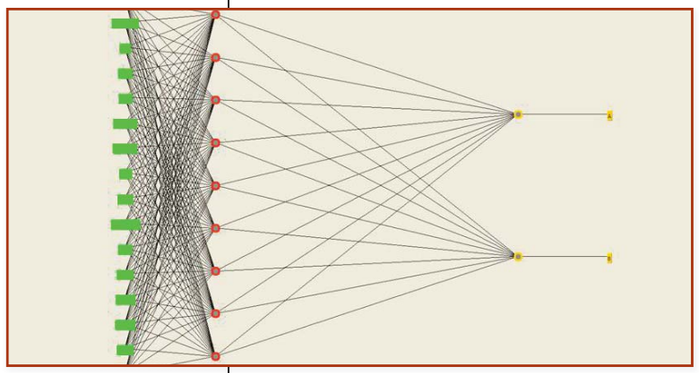
medical oncology

Epigenetics may hold the key to more effective cancer therapies

Defining the relationship between cancer, gene expression, and the cellular processes that control them has confounded researchers for decades, primarily because the genome is so complex that narrowing down what to analyze and how to use the information has been difficult. To date, most correlation studies have only focused on gene expression, not taking into account the other processes going on in and around these genes.



Refining our understanding of gene regulators and gene expression may help to predict a patient's response to treatment.

According to Hussein Tawbi, MD, MSc, principal investigator, refining our understanding of gene regulators and gene expression may help to predict a patient's response to treatment. In a recent retrospective analysis, Dr. Tawbi and colleagues used a more robust prediction model that not only considers gene expression, but also considers promoter methylation, a known gene regulator.

Promoter methylation is an epigenetic mechanism that can change throughout one's lifetime in contrast to genes which remain the same. Researchers once held the belief that changes in gene sequences (mutations) were responsible for a wide range of disease states including cancer.

As researchers gained a deeper understanding of processes that regulate gene expression, they identified epigenetic mechanisms at a higher order of regulation that can determine the level of expression of certain genes without affecting their sequence.

"We have learned that it is not just the sequence that determines the expression of oncogenes and tumor suppressor genes, but also the extent of promoter methylation," explains Dr. Tawbi. "Reversing promoter methylation may help patients with resistant cancer to respond to therapy."

The analysis examined the tumor tissues of 21 patients with metastatic melanoma, some of whom responded to chemotherapy and some who did not. Once the cases were divided, the researchers surveyed more than 25,000 genes and 14,000 promoter methylation regions, and used artificial intelligence algorithms, referred to as neural networks, to see if they could identify patterns that could distinguish responders from nonresponders.

"We are encouraged by the results of the analysis. Cancer cells contain massive amounts of information that, if analyzed appropriately, may inform us how to kill them," says Dr. Tawbi. "Neural network analysis, which uses pattern recognition algorithms, helped us to identify a signature of eight genes and their switches that predict a patient's likelihood of responding to treatment for metastatic melanoma."

The results from this study are being validated in a larger sample of 80 patients. Genetic (and epigenetic) testing could someday allow physicians to identify which patients will respond to standard chemotherapy and which patients won't, leading to improved treatments for both groups.

"While this analysis was done with a specific tumor type and a specific therapy, this model has wide applicability," says Dr. Tawbi. "We plan to expand our research to include other cancers and different therapies."

For more information on this study, contact Dr. Tawbi at tawbih@upmc.edu.

Sarah Cannon Research Institute partnership enhances availability of clinical trials in the community

Most advances in the diagnosis and treatment of cancer have occurred because of clinical trials that study the effect of cancer treatments. Yet, according to a recent article in *The New York Times* evaluating the state of cancer, only three percent of adult patients participate in this valuable research.

To increase participation, UPMC Cancer Centers and the University of Pittsburgh Cancer Institute are partnering with Sarah Cannon Research Institute, an industry leader in community-based clinical trials, to bring advanced oncology care to medical oncology practices across the country.

Sarah Cannon Research Institute, based in Nashville, Tenn., one of the largest research programs in the nation, is conducting clinical trials in 10 therapeutic areas through its affiliation with a network of hundreds of physicians in 24 states. The model is similar to UPMC Cancer Centers' hub-and-satellite network — making the partnership a natural fit for both institutions.

"Sarah Cannon has a great national reputation for successfully managing large-scale clinical trials in community locations," explains Stanley M. Marks, MD, director of Clinical Services and chief medical officer, UPMC Cancer Centers. "Their expertise in trial design and patient recruitment dovetails nicely with our academic mission to increase clinical trial participation across our network."

The TITAN trial is the first study being offered through this partnership. TITAN, a randomized trial of ixabepilone versus taxol in adjuvant therapy of triple negative breast cancer, compares the results of treatment with a standard adjuvant chemotherapy regimen with ixabepilone added. Additional trials for prostate and lung cancers are forthcoming.

"Moving forward we plan to work with Sarah Cannon to open UPCI trials within their network, which will ultimately result in patients accruing to trial faster," says Adam Brufsky, MD, PhD, director of Clinical Investigations, UPMC Cancer Centers. "This collaboration will result in more quickly translating research findings to clinical application."

To learn more about clinical trials currently available at UPMC Cancer Centers and UPCI, please call 412-647-2811 or visit our website at www.UPMCCancerCenters.com/clinicaltrials.

The partnership is a natural fit for both institutions.

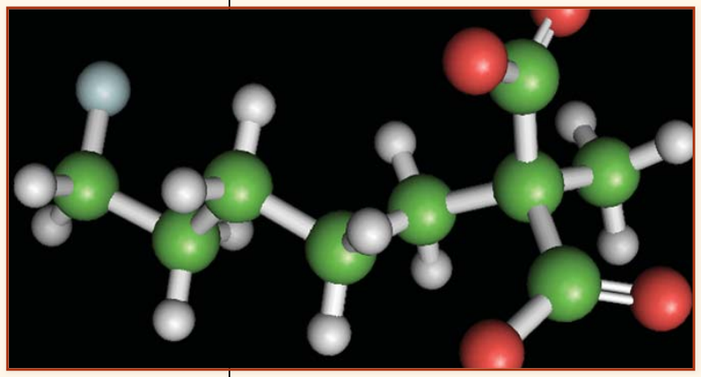
UPCI researcher awarded ASCO professorship

Merrill Egorin, MD, professor of medicine and pharmacology at the University of Pittsburgh Cancer Institute (UPCI), received the 2009 American Society of Clinical Oncology (ASCO) Translational Research Professorship during the 2009 Annual Meeting. Dr. Egorin received the award for his work in improving cancer treatments and supporting the next generation of researchers. Dr. Egorin will use the professorship, which provides $100,000 annually for five years, to continue his pre-clinical and clinical studies of the polymerase (PARP) family of enzymes and how they work as cancer therapies.

radiation oncology

Molecular radiotracer provides diagnostic information sooner

Stereotactic radiosurgery (SRS) plays an important role in the management of brain metastases. However, determining the effectiveness of treatment is complicated by the limitations of current diagnostic tools, such as CT or MRI, as they only assess anatomical response several weeks or even months after therapy has been completed. Additionally, radiation therapy may induce tumor changes and/or swelling of surrounding brain tissues, further complicating interpretation.



An early marker that is able to determine which patients are likely to respond to therapy and those who are likely to fail would be invaluable.

In many cases, patients who are not responding to therapy may be unnecessarily exposed to treatment-related side effects resulting in valuable time lost before starting a potentially more beneficial therapy. Thanks to the development of a novel, low-molecular weight probe, physicians may soon be able to predict treatment responses in days rather than weeks.

As part of a multi-institutional study, physician-researchers at UPMC Cancer Centers are evaluating the use of [18F] ML-10, a member of the ApoSense® family of compounds, which has been shown to detect cell death, a fundamental response for many cancer therapies.

According to Arlan Mintz, MD, co-investigator, this innovative radiotracer tool will provide the treatment team with diagnostic information much sooner. "From a patient management perspective, having an early marker that is able to determine which patients are likely to respond to therapy, and those who are likely to fail and may require additional intervention, would be invaluable."

The trial will examine [18F] ML-10 as a radiotracer for the PET-CT imaging of cell death in patients with brain metastases who are scheduled to undergo SRS. As part of the trial, each patient will receive intravenous administration of [18F] ML-10 followed by a PET-CT scan at these stages: prior to therapy to determine a baseline; two to three days after treatment; and then again six to eight days after treatment. Patients also will undergo an MRI 14 days prior to treatment and six to eight weeks post-treatment to evaluate anatomical response.

"We believe that the integration of anatomic imaging with molecular imaging in the management of patients with brain metastases with highly conformal radiotherapeutic techniques, such as radiosurgery, will give the treatment team the opportunity to refine patient selection and better predict outcomes in patients treated with radiosurgery," explains Dwight E. Heron, MD, FACRO, director of Radiation Oncology Services, UPMC Cancer Centers. "If proven effective, this tool will represent a new paradigm in the management of patients with brain metastases."

The trial is restricted to patients with one to four solid brain metastases, with a minimal diameter of 1.5 centimeters who are scheduled for SRS.

"For patients with brain cancer, time is of the essence. Our job is to try to control the brain disease to prevent neurological damage that can greatly affect the patient's quality of life," says Dr. Mintz. "We are not going to cure cancer with this tool, but knowing whether treatment is working early on could be vital in figuring out what the next step is for these patients."

For more information on eligibility criteria or for patient referrals, contact Dr. Heron, Dr. Mintz, or Steve Burton, MD, at 412-623-2061.

Study investigates physician-patient relationship

When receiving a cancer diagnosis, patients often turn to their health care provider for support. Yet many physicians are unsure as to what patients expect from the physician-patient relationship, making it difficult to meet their needs during this time of crisis.

Several studies have shown that patients are more likely to comply with their physician's recommendations if they have an established rapport with their physician. Yet, few studies have been conducted to determine patient expectations in developing that relationship.

Funded by a grant from the American Society of Radiation Oncology (ASTRO), UPMC Cancer Centers' Department of Radiation Oncology recently conducted a study of patient preferences to gain better insight into what is important to patients undergoing treatment.

"The physician-patient relationship is a crucial component of health care," explains Ajay Bhatnagar, MD, principal investigator, assistant professor, Department of Radiation Oncology. "In oncology, a strong physician-patient relationship is needed so that the patient's interactions with their doctor can help them to confidently make life or death decisions, including which cancer treatments are best for them."

The study evaluated 508 patients with a primary diagnosis of prostate, breast, or lung cancer referred to the Department of Radiation Oncology for consultation. Each patient completed a patient preference survey prior to meeting their radiation oncologist. Researchers hope that physicians will use the information gathered from the study to modify their physician-patient interactions to cater to the preferences of their patients in order to provide the best care possible.

For example, physicians generally address older patients more formally using their last name. However, the survey showed that a majority of patients, regardless of age, preferred to be addressed by their first name rather than their last name.

"By better understanding patient expectations, we can tailor office visits and approaches to therapy to meet the needs of our patients," says Dwight E. Heron, MD, FACRO, director of Radiation Oncology Services, UPMC Cancer Centers.

The benefits of a stronger physician-patient relationship extend beyond clinical outcomes. Studies have shown that patients who are more comfortable with their physician may be more willing to participate in a clinical trial.

Results from the study will be presented in an oral discussion at the annual ASTRO meeting. For more information, contact Dr. Heron at herond2@upmc.edu.

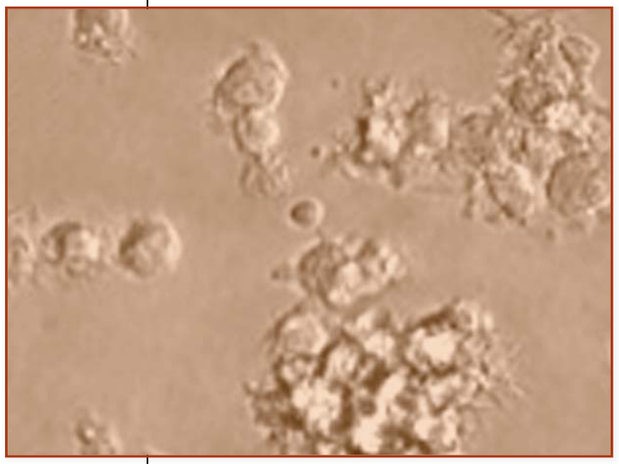
Grant funds development of drug to mitigate effects of radiation

Radiation oncologists at the University of Pittsburgh Cancer Institute (UPCI) are using their experience with radiation therapies to develop a drug that could counter the effects of radiation in the event of a large-scale radiologic or nuclear emergency. UPCI researchers have received a $2.7 million grant, with the option of further funding up to $9.8 million over the next three years, from the Biomedical Advanced Research and Development Authority (BARDA) of the Department of Health and Human Services (HHS) to develop an easily administered drug that the Centers for Disease Control (CDC) and HHS can store and fly to hospitals and care facilities if an emergency occurs. In 2004, the research team, led by Joel Greenberger, MD, professor and chairman of the Department of Radiation Oncology at the University of Pittsburgh School of Medicine, identified GS-nitroxide drug JP4-039 as a radioprotector. Results from preliminary studies have shown cells treated immediately after irradiation with JP4-039 demonstrated significant radioprotection, suggesting a potential role for the drug as a mitigator of radiation damage. The research team is evaluating the safety and toxicity of JP4-039, with the goal of taking the drug through a phase I clinical trial.

surgical oncology

New vaccines teach the immune system to eliminate cancer cells

Recent advances in the understanding of the cellular processes of cancer and the biology of the immune system are paving the way for the next generation of therapies. At the University of Pittsburgh Cancer Institute (UPCI), researchers are working to develop cancer therapies that target cancer cells with greater specificity to decrease side effects and improve quality of life for patients by instructing the patient's own immune system to find and kill cancer cells.



Researchers hope to facilitate a more efficient process for destroying cancer cells.

UPCI has played a major role in the development of therapeutic vaccines. Most recently, researchers in the Division of Surgical Oncology at UPMC Cancer Centers received an $8.5 million grant from the National Cancer Institute to test the applicability of polarized dendritic cells (DC) combined with the modulators of tumor-associated inflammation to treat different types of cancer, including melanoma, malignant glioma, and colorectal cancer.

According to Pawel Kalinski, MD, PhD, director of Research, Division of Surgical Oncology, there are many questions about our immune system that need to be answered so that these types of therapies can be used more effectively.

"The grant is providing the opportunity to address many of these questions," says Dr. Kalinski. "Dendritic cell-based vaccines have unique advantages over other therapies, such as the ability to target multiple variants of tumor cells and low toxicity. We need to find the optimal application of such vaccines, including route and dose of administration, optimal frequency of vaccination, and application in different stages of the disease."

In earlier versions of DC-based vaccines, researchers used two signals to target the cancer. The first signal was to provide the DC with antigens to identify the cancer cell, and the second was to activate the dendritic cells to induce high levels of expansion in tumor-specific effector cells. Although the results of these trials were modest, it enabled researchers to observe immune responses to the vaccines, which has been instrumental in making the next generation of vaccines more effective.

The UPCI trials are investigating a third generation of DC-based vaccines, called polarized αDC1 vaccine. By using polarized αDC1, or mature DCs which secrete IL-12 to the T-helper-1(TH1) cells and killer cells (CTLs and NK cells), researchers hope to facilitate a more efficient process of destroying the cancer cells. In preclinical studies, αDC1s have been shown to provide two additional signals which promote the induction of enhanced tumor-killing properties in CTLs and NK cells and their ability to find tumors. They will examine the combination of αDC1s with treatments by enhancing the production of T cell-attracting chemokines within tumor lesions. By directing the vaccination-induced immune effector cells to tumors, researchers hope to enhance tumor regression.

"What is unique in our approach is the induction of the immune cells that are able to respond to tumor-produced guiding factors (chemokines), combined with tumor selective enhancement of the production of such chemokines, in order to direct the vaccination-induced immune cells to tumors," explains Dr. Kalinski.

The grant also will investigate whether DC-based vaccines can stand as a single-line therapy for patients who have exhausted conventional treatment options and for patients with less advanced disease in combination with standard therapies.

For more information about these trials, contact Dr. Kalinski at kalinskip@upmc.edu.

Robotic technology enhances a suite of surgical procedures

The Division of Surgical Oncology at UPMC Cancer Centers is expanding the scope of the Surgical Robotics Program to include the pylorus preserving pancreatico-duodenectomy (Whipple), a highly technical procedure used to treat a number of tumors of the pancreas, duodenum, and bile duct.

For patients with pancreatic cancer, surgery is often the best option for treatment. But because of location and tumor involvement, nearby structures have made it difficult for surgeons to perfect a minimally invasive version of this technically demanding procedure. During the Whipple, surgeons must reattach vital organs, requiring flexibility and precision that conventional minimally invasive surgery (MIS), performed using two-demensional, long-shafted instruments, does not provide.

"The enhanced visualization and dexterity that the robot offers, allows us to perform this complex procedure that would otherwise have to be performed with conventional open incisions," says A. James Moser, MD, co-director, Pancreatic Cancer Specialty Care Center.

Dr. Moser and fellow co-director Herbert J. Zeh, MD, are two of only a handful of surgeons worldwide who perform the Whipple using robotic surgical technology. While it is too early to assess patient outcomes, the surgeons say that advancements in robotic technology have made it feasible to do these types of complex operations.

"Our hope is that this will result in better outcomes for our patients in terms of length of hospital stay and being able to start chemotherapy sooner," says Dr. Zeh.

Very few centers worldwide offer the range of surgical robotic procedures available at UPMC Cancer Centers. To date, the Department of Surgery at UPMC has performed more than 500 cases, 150 within the Division of Surgical Oncology, ranging from liver and pancreatic resections to colon, rectal, adrenal, spleen, and many non-oncologic abdominal procedures with great success.

For the more established procedures, robotic surgery outcomes are consistent with standard MIS. With recovery times reduced, patients with malignant cancer can start follow-up chemotherapy or radiation therapy almost immediately, giving the drugs a chance to work before the tumor potentially returns.

"Robotic surgery is changing the landscape of surgical oncology," says David L. Bartlett, MD, chief, Division of Surgical Oncology. "As the technology continues to get better and surgeons gain more experience, it is only a matter of time until robotic surgery becomes the standard of care for many traditionally open procedures."

Urologic surgeon reaches milestone

The Department of Urology at UPMC and UPMC Cancer Centers is one of the leading centers in the country for the treatment of prostate cancer. Joel B. Nelson, MD, chairman, Department of Urology, recently performed his 2,000th radical prostatectomy — a milestone achieved by only a handful of surgeons worldwide. Studies show that recovery from prostate cancer is significantly associated with a surgeon's lifetime experience performing the operation.