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 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. Merrill Egorin, MD, professor of medicine and pharmacology at UPCI, is the inaugural holder of the Hillman 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,
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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 those genes.

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 21,000 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.

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 Institutes, 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 nab-paclitaxel versus taxol in an adjuvant therapy of triple negative breast cancer, compares the results of treatment with a standard adjuvant chemotherapy regimen with nab-paclitaxel added.

Refining our understanding of gene regulators and gene expression may help to predict a patient’s response to treatment.
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 three stages prior to therapy to determine a baseline, two to three days after treatment, and then again six to eight weeks after treatment. Patients will also 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 anatomical 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.

“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 heron2@upmc.edu.
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.

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 vaccine, 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 DC1 vaccine. By using polarized DC1, or mature DCs which secrete IL-12 to the T-helper-1 (TH1) cells and killer cells (CTLA and NK cells), researchers hope to facilitate a more efficient process of destroying the cancer cells. In preclinical studies, DC1s 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 DC1s 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.

“New vaccines teach the immune system to eliminate 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.

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