

NEW YORK-PRESBYTERIAN ONCOLOGY

Affiliated with COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS and WEILL CORNELL MEDICAL COLLEGE

Fall 2007

New Research in Non-Hodgkins Lymphoma

At NewYork-Presbyterian Hospital, the exceptional collaboration between researchers and clinicians has moved the application of state-of-the-art therapies for non-Hodgkins lymphoma (NHL) from the bench to the bedside.

Investigators at the Herbert Irving Comprehensive Cancer Center (HICCC) of NewYork-Presbyterian Hospital/Columbia University Medical Center, for instance, are involved in everything from studying the genetics of cancer to conducting multimodality trials. The Lymphoid Malignancy Program at HICCC, which also includes Weill Cornell investigators at NewYork-Presbyterian Hospital, recently recruited Owen O'Connor, MD, PhD, from the Memorial Sloan-Kettering Cancer Center, where he was Head of the Laboratory of Experimental Therapeutics for Lymphoproliferative Malignancies.

Dr. O'Connor has a long history of innovations in the treatment of NHL, focusing on the biochemical and molecular activities that mediate gene transcription and tumor growth and generating new targets for treatment. Before coming to NewYork-Presbyterian/Columbia, Dr. O'Connor conducted studies of suberoylanilide hydroxamic acid (SAHA), which is one of several histone deacetylase inhibitors whose anticancer properties have attracted attention.

Since arriving at the Hospital, Dr. O'Connor has collaborated with Riccardo Dalla Favera, MD, on work to match gene targets with available or developing therapies, focusing on identifying the genes

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Prostate Studies Tout Gene, Anti-Angiogenesis Therapies

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital are setting the pace for innovations in the treatment of prostate cancer, focusing on targeted gene therapy and anti-angiogenesis therapy. "Today, treatment for prostate cancer is moving more toward targeted therapy," said David Nanus, MD. "Radioactive monoclonal antibody J591, for example, recognizes prostate-specific membrane antigen (PSMA), a highly restricted protein expressed on prostate cancer cells. PSMA expression increases in more advanced prostate cancer making it an ideal target for directed therapy."

At NewYork-Presbyterian/Weill Cornell Medical Center, patients are currently being enrolled in clinical trials using J591.

According to Dr. Nanus, promising results in Phase I and II studies have moved this agent forward. Current plans are to combine J591 with chemotherapy to boost response. The study is being conducted under a Department of Defense Congressionally Directed Medical Research Program.

"Adenovirus-delivered gene therapy has also demonstrated substantial promise in preclinical studies and could be a novel approach," said Dr. Nanus. Preclinical results published in *Cancer Gene Therapy* (2007;14:583-589) have shown its ability to "inhibit prostate cancer using gene transfer approaches in animal models," he added. "There is

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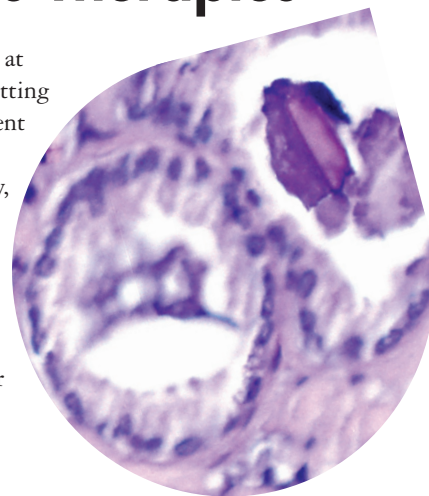


Photo courtesy of the National Cancer Institute

A histology of prostate cancer. Researchers at NewYork-Presbyterian Hospital are investigating promising new approaches to treatment, including gene therapy and anti-angiogenesis therapy.

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New Developments in Lymphoma Biology and Treatment

Web Cast
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Current Trends in Genitourinary
Malignancies: Third Annual Conference
October 27, 2007

Advances in Colorectal Cancer Therapies

Webcast
"Pure" laparoscopic versus "hand-assisted" laparoscopic surgery; new approaches to minimally invasive surgery.

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UPDATES

Lung Cancer: Do Early Screening, Treatment Yield Better Outcomes?

A landmark study in *The New England Journal of Medicine* has shown that early detection of lung cancer can favorably change outcomes (2006;355:1763-1771). The study, a multinational collaboration published under the auspices of the International Early Lung Cancer Action Program (I-ELCAP), was initiated by Weill Cornell investigators at NewYork-Presbyterian Hospital under the direction of Claudia I. Henschke, MD, PhD, principal investigator. Dr. Henschke also chaired the Writing Committee of I-ELCAP; the other members were David Yankelevitz, MD,

substances as asbestos and radon, or exposure to secondhand smoke. Although these risk factors were the focus of I-ELCAP, they may not be the only ones used for screening now that there is evidence that screening can improve outcomes. New research protocols are being designed to look at a variety of other populations, such as a population of flight attendants who never smoked but who had previous occupational exposure to cigarette smoke.

"One of the important questions to address in future studies is how frequently to screen patients in the highest risk

groups, she said.

"This is clearly a critical avenue for research," said Dr. Austin. He noted that NewYork-Presbyterian Hospital/Columbia University Medical Center entered more than 500 patients into the I-ELCAP study, and results in this sub-population mirrored the overall results. He agreed that the new data very much weaken the arguments of the skeptics about the importance of early detection for improving outcomes. "We also have very sophisticated treatment protocols and are involved in trials of several different modalities in lung cancer, but the best results are going to be achieved in those who are diagnosed at the earliest possible stage," Dr. Austin said.

The evidence that screening can detect small lesions in the lung has opened up a range of research involving the collaboration of several innovators in radiology. Not least among these is Dr. Yankelevitz, who also served on the Writing Committee of I-ELCAP and has led

"One of the important questions to address in future studies is how frequently to screen patients in the highest risk groups in order to identify lung cancer at its earliest stages."

—Claudia I. Henschke, MD, PhD

Daniel Libby, MD, Mark Pasmantier, MD, James Smith, MD, and Olli Miettinen, MD, PhD. From the initiation of I-ELCAP, Columbia investigators led by John Austin, MD, have been key collaborators.

"We had previously demonstrated that screening is effective for early detection of lung cancer. The importance of this study is that it confirmed that early [lung cancer] detection, which can lead to early treatment, markedly increases the likelihood of survival," said Dr. Henschke.

The study, which employed low-dose, spiral computed tomography (CT) to identify noncalcified nodules for biopsy, opens the door for further efforts to expand lung cancer screening. In the study, 31,567 asymptomatic men and women were screened. Criteria included age older than 40 years and having a risk factor for lung cancer—most often a history of cigarette smoking, but also occupational exposure to such carcinogenic

groups in order to identify lung cancer at its earliest stages," Dr. Henschke said. Although cost-efficacy will have to be calculated according to risk status, current screening protocols have already been shown to be cost effective in high-risk

or contributed to a number of studies designed to identify prognostic factors at the time of detection, including early detection.

In current or former smokers aged 60 years or older, the baseline detection rate



A CT scan of the lung. NewYork-Presbyterian Hospital researchers are investigating the efficacy of low-dose CT in lung cancer screening.

Photo courtesy of Claudia Henschke, MD, PhD

in the original Early Lung Cancer Action Program study was 2.7%. In comparison, the baseline yield for breast cancer in women over the age of 40 who are screened with mammography has been 1% or less. Early detection is likely to be even more important in lung cancer than in breast cancer because mortality is higher, reaching approximately 85% currently.

Low-dose CT scan can be provided for less than \$300 per case. Because about 15% of lung cancer cases in the United States occur in never-smokers, periodic screening of all middle-aged or older adults would be an optimal step in lung cancer prevention. However, researchers must define populations in which screening is both practical and cost-effective.

"The economic analyses will be important in determining appropriate use of healthcare dollars for lung cancer screening. We are continuing to gather the data to recommend rational choices," Dr. Austin said.

Editor's Note: The utility of spiral CT screening for lung cancer is also the focus of a randomized clinical trial, the National Lung Screening Trial, being conducted under the auspices of the National Cancer Institute. For more information, please visit <http://www.cancer.gov/nlst>

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NewYork-Presbyterian Hospital's Cancer Prevention Newsletter and Web site offer information for professionals on the latest developments in the field of cancer prevention and screening. Visit www.nypcancerprevention.org.



Combination Procedures Improve Outcomes in Colorectal Cancer

NewYork-Presbyterian Hospital has taken a leadership role in clinical innovations that are improving outcomes and lessening the risks of therapy in colorectal cancer. Radical resections, for example, are being replaced with several different types of minimally invasive procedures. At the same time, some of the newer targeted medical therapies are dramatically building on the efficacy of conventional chemotherapy with very tolerable side effects.

“In colorectal cancer, we are now moving to less radical surgical procedures with adjuvant chemotherapies that provide rates of cancer-free survival that are at least as good as those achieved previously but with less trauma,” noted Alfred I. Neugut, MD, PhD.

Within the goal of reducing the morbidity of radical resections, among the most exciting developments has been the use of a combination laparoscopy and colonoscopy procedure to reach lesions that would be difficult to treat with either alone. One of the key innovators of this approach, Jeffrey W. Milsom, MD, said that the combined approach became possible when he and his co-investigators introduced insufflation with carbon dioxide (CO₂) to largely eliminate the distension normally produced by colonoscopy using room air.

“We found that we had a very high success rate performing laparoscopy and colonoscopy together, and this was very well tolerated by the patients,” he noted. “This is an example of an important fusion of technologies that permits lesions to be treated from the inside of the bowel using backup support from the peritoneal cavity using minimally invasive or laparoscopic techniques. For example, in a patient with a difficult polyp in the right colon that is unresectable by colonoscopy, laparoscopy can be employed to position

the lesion so that it can be removed by the colonoscope. This provides the least amount of trauma without loss of surgical precision.”

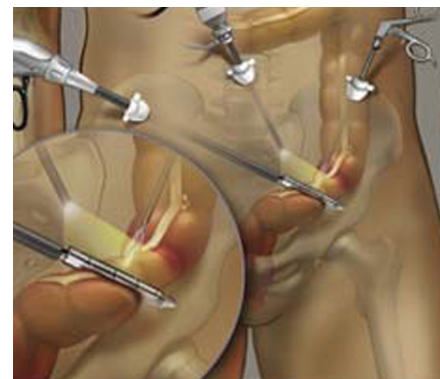
Initially, according to Dr. Milsom, there was concern that insufflation with CO₂ could dangerously alter the acid-base balance of the body. However, pre-clinical studies and clinical studies have demonstrated a very high level of safety using the combined technique. The only drawback is that it requires both an endoscopist and a laparoscopist.

“With this combined procedure, a bowel resection is avoided and no more than an overnight stay is required,” Dr. Milsom said. “Currently, this approach has a limited application for benign or very early malignant lesions, but this is only the beginning. I believe that in the future, more difficult lesions, including difficult malignant lesions, will be treated in this fashion.”

Laparoscopy has been widely incorporated into colon cancer resections at many centers, but the surgeons at NewYork-Presbyterian Hospital have sought to consider variations when appropriate. One such variation has been hand-assisted laparoscopy, which can have numerous advantages when employed in the right patient.

“The hand-assisted approach requires a longer incision than most pure laparoscopic operations,” explained Richard L. Whelan, MD. “However, we recognized that some patients undergoing laparoscopy already receive incisions large enough to insert a hand. In many cases, a hand can facilitate resection, including mobilization of tissue, without greatly detracting from the advantages of the minimally invasive approach.”

Some patients need large incisions because they have large tumors that require a significant abdominal wall incision in order to remove the specimen.



A diagram of laparoscopic colon resection.

Obesity is also an issue; obese patients often require longer fascial incisions to permit specimen extraction. In a review of obese patients from NewYork-Presbyterian/Columbia who underwent straight laparoscopic resection, a substantial percentage had a final incision between 7 cm and 11 cm long, which is large enough to permit hand-assisted laparoscopy. Very tall or muscular patients are also likely to require larger incisions during minimally invasive resection. Thus, in these 3 groups of patients, who together represent almost 40% of all surgical candidates, the advantages of hand-assisted laparoscopy can be obtained without substantially increasing the abdominal wall trauma when compared with straight laparoscopic methods.

“We look for patients in whom a large incision would likely be needed and then use the hand-assisted approach from the outset. We now have data to support this approach,” said Dr. Whelan, referring to a 5-center study that included investigators at NewYork-Presbyterian Hospital.

Presented at a recent meeting of the American Society of Colon and Rectal Surgeons, the study randomized 97 patients to laparoscopy alone or hand-assisted laparoscopy for left and total colectomy. For hand-assisted laparoscopy compared with laparoscopy alone, the average duration of the procedure was 33 minutes shorter for left colectomy and almost an hour less for total colectomy. There was no significant difference in recovery time, amount of pain medication required, or length of stay. The average incision length was 6.1 cm for laparoscopy alone but only 8.2 cm for the hand-assisted approach.

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Oncologists Create Wellness Program For Young Cancer Survivors

Pediatric and medical oncologists at Morgan Stanley Children's Hospital of NewYork-Presbyterian/Columbia University Medical Center have established the Center for Survivor Wellness, a program that provides health education and support to pediatric, adolescent, and young adult cancer survivors—including women diagnosed with breast cancer before age 40.

Located in the Herbert Irving Child and Adolescent Oncology Center at Morgan Stanley Children's Hospital of NewYork-Presbyterian/Columbia, it is one of the few cancer survivorship pro-

grams in the country that treats people in this age range, said Michael Weiner, MD. "These individuals often have different psychological and social needs than do survivors in their 60s, 70s, and 80s," he said.

The program includes medical and pediatric oncologists, nutritionists, exercise physiologists, social workers, psychologists, clinical coordinators, and family nurse practitioners who treat patients across different age ranges.

One of the goals of the program is to summarize each patient's medical history and—based on past cancer treatments such as chemotherapy, radiation therapy, or surgery—develop a risk assessment of future complications, said Jennifer Levine, MD.

For example, some patients will have definable late effects such as trouble swallowing caused by radiation treatments, deformities in extremities due to surgery, or hypothyroidism resulting from radiation. Other patients who

receive these same therapies may not experience any side effects.

The psychological effects of being a survivor also vary, said Dr. Levine. Some children may feel the disease has made them stronger, whereas others may frequently worry about a cancer recurrence.

Patients may also have to contend with issues specific to the type of cancer with which they were diagnosed and the treatment they received. Young women who have survived treatments may be concerned about fertility and how the disease may impact their personal relationships.

Cancer survivors may also be dealing with neuropsychologic late effects of chemotherapy or radiation including learning disabilities, said Dr. Levine. Therapy is often needed to help patients compensate for these deficits.

Many of the health effects from chemotherapy that long-term cancer survivors face are issues that also affect young adult survivors of either pediatric or adult cancers, said Dawn Hershman, MD. "We have been studying the predictors of late effects and symptom management in adult survivors, and realize that pediatricians are dealing with the same problems, such as early osteoporosis, cognitive changes, weight gain, infertility, and chronic pain," she explained.

Increasing the patient's awareness about these potential long-term treatment risks is crucial to developing a tailored comprehensive wellness plan, said Dr. Levine. A key part of patient education is helping survivors understand how to stay physically healthy by eating well and exercising, as well as attending to any psychological issues that may arise from their diagnosis and treatment, said Dr. Levine. "We're looking at the whole person," she said.

Part of looking at the whole person is combining traditional treatment with homeopathic care, said Dr. Weiner. The NewYork-Presbyterian Hospital survivorship and wellness program follows the March 2006 Children's Oncology Group recommendations (available at www.survivorshipguidelines.org), but it also encompasses the Hospital's integra-

tive therapies initiative, which is using and evaluating complementary and alternative medicine in survivors.

Although attending to overall recovery issues is critical, so is navigating the often complex system of medical insurance, said Dr. Levine. Social workers are on staff to help patients learn about accessing medical insurance throughout the course of their care. If they were diagnosed with cancer as children, they eventually become ineligible for coverage under their parents' insurance because of their age or once they graduate from college, she said.

Another goal of the program is to help patients with job placement and education. For example, the survivorship initiative is launching an internship program this summer with CBS radio to give cancer survivors an opportunity in media. Physicians will also be assessing how patients can pursue exercise and increase their access to healthy foods in the program's area neighborhoods in northern Manhattan. "These services are not as accessible near the Hospital as in other areas of the city," said Dr. Levine.

Research is another important component of the program. "By combining efforts, we will be able to build a world-class clinical and survivorship research center," said Dr. Hershman.

Researchers have already begun using surveys to assess the needs of the program's diverse survivorship population. "We have found striking differences in the issues faced by members of our Hispanic community compared to other ethnic subgroups," said Dr. Hershman.

By understanding these differences, physicians can better intervene, she added. For example, the program is working with a multidisciplinary team to develop interventions to reduce short- and long-term side effects, to understand issues faced by survivors, and to evaluate programs that improve their understanding, health behavior, and quality of life.

In addition to the current initiatives, a future program goal is to specifically target the newly diagnosed teenage and young adult population, said Dr. Weiner. This population may be too old for pediatric oncology and may feel out of place seeing a physician who primarily treats

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Photo courtesy of the Herbert Irving Child and Adolescent Oncology Center



Cancer survivors tour Yankee Stadium as part of the Center for Survivor Wellness, a program that provides health education and support to pediatric, adolescent, and young adult cancer survivors.

Colorectal

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"The hand-assisted approach is contraindicated for small or low BMI patients because the hand incision represents a much larger percentage of their abdominal wall and the larger incision is usually not required for specimen extraction," noted Dr. Whelan. "We believe hand-assisted methods are very useful when employed selectively."

"It's an exciting chapter on the surgical side... Now more than ever we have treatment options we can offer patients and with much, much safer outcomes."

—Jeffrey W. Milsom, MD

In adjuvant therapies, there have also been significant developments. While several combination chemotherapy regimens, such as FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) and FOLFIRI (5-FU), leucovorin, and irinotecan are now widely employed to extend survival in advanced colorectal cancer, recent

excitement has been generated by the monoclonal antibodies, such as bevacizumab, which inhibits vascular endothelial growth factor (VEGF) and is already a standard as first-line treatment for stage IV disease. This and other monoclonal antibodies, particularly cetuximab, an inhibitor of the epidermal growth factor receptor (EGFR), are now being tested in the adjuvant setting. Investigators recently tested bevacizumab and cetuximab in combination for stage IV colorectal cancer.

"We recently presented a Phase II paper that we conducted with the New York Cancer Consortium. We treated almost 70 patients with the FOLFOX regimen in combination with bevacizumab and cetuximab and observed an excellent response rate with acceptable toxicity," said Joseph T. Ruggiero, MD. "This double antibody approach in combination with chemotherapy is going into more advanced testing and may represent an important direction for future management."

"Evaluating FOLFOX with and without bevacizumab will answer one of the most pressing questions about optimal adjuvant therapy," added Dr. Neugut.

"It is an exciting chapter for patients from the surgical side as well," added Dr. Milsom. "Now more than ever we have treatment options we can offer patients and with much, much safer outcomes."

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Editor's Note: All of the physicians featured in the article participated in the "Advances in Colorectal Cancer Therapies" web cast on June 20, 2007. The web cast can be accessed at: www.nypcancer.org.

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older adults, he explained. This is why he hopes to add initiatives to the model of the wellness program that directly address this population's needs.

Addressing the specific needs of survivors is the program's overall goal.

Dawn Hershman, MD, is Co-Director of the Center for Survivor Wellness in the Herbert

involved in the development of human B cell lymphoma, a subtype of NHL. Ongoing studies are seeking to determine the role of chromosomal translocations involving the c-Myc proto-oncogene locus and immunoglobulin loci in the development of Burkitt's lymphoma as well as the identification of novel oncogenes and tumor suppressors involved in the pathogenesis of lymphoma. Finally, the colleagues are also studying the pathologic function of the BCL-6 gene, a recently identified proto-oncogene that codes for a transcription factor expressed in B cells and is altered in its regulatory region in a significant number of lymphoma patients.

"The goal is to treat the problem at the root rather than trying to trim the leaves, which is what we do with conventional chemotherapy," explained Dr. O'Connor, who also works closely with John Gregory Mears, MD, and Morton Coleman, MD (the latter is an investigator at Weill Cornell Cancer Center).

Studies at the Weill Cornell Cancer Center of NewYork-Presbyterian Hospital, meanwhile, have looked at the optimization of currently available monoclonal antibodies (the Hospital is a world-wide leader in this area) through the addition of cytokines and interleukin-2 as well as the study of new monoclonal antibodies such as epratuzumab, anti-CD74, and anti-CD80. Researchers at NewYork-Presbyterian/Weill Cornell, under the direction of John P. Leonard, MD, are leading trials with a number of monoclonal antibodies—including rituximab and tositumomab—that have since received FDA approval.

According to Dr. Leonard, much of the current research work is also focused on cancer growth and proliferation. A major translational project led by Jia Ruan, MD, PhD, which is evaluating strategies to

"Laboratory-based collaborations and clinical correlations allow us to better target treatments to patients who are most likely to benefit."

—John P. Leonard, MD

inhibit angiogenesis and starve lymphomas of their blood supply, has moved into the clinical arena. Dr. Leonard and his team have also studied the use of a customized vaccine developed from the lymphoma cells of individual patients.

"The studies of angiogenesis have led to an ongoing clinical trial of a novel combination of low-dose oral chemotherapy with new biologic therapy," Dr. Leonard explained. "Laboratory-based collaborations and clinical correlations performed with Amy Chadburn, MD, and other hematopathologists allow us to better target treatments to patients who are most likely to benefit. These efforts also may allow other patients to be spared unnecessary toxicity."

Studies of molecular profiling are under way so that therapies can be more appropriately selected based on the molecular and metabolic aspects of the tumor cell biology in individual patients. According to Drs. Leonard and O'Connor, work by Dr. Coleman, Dr. Stanley Goldsmith, and other colleagues has been presented in a variety of international forums. In addition, the Hospital has hosted a key conference on NHL, other lymphomas, and multiple myeloma. "The Lymphoma and Myeloma 2006 meeting was held in the fall and drew nearly 800 international participants, including most of the key leaders in this area," noted Dr. Leonard, who was one of the co-chairs.

As important contributors to some of the most groundbreaking collaborative groups working in NHL, such as the Cancer and Leukemia Group B and the New York Cancer Consortium, Dr. Leonard and his colleagues, among them

Richard Furman, MD, have received funding from a broad spectrum of public and private organizations, including the National Cancer Institute, the Leukemia and Lymphoma Society, the Lymphoma Research Foundation, and the Lymphoma Foundation. "We have focused on the unmet needs of these patients, largely through the development of more effective and less toxic therapies, but other efforts have been directed toward better isolating prognostic variables in order to identify which patients are likely to have more or less favorable outcomes and to target treatment accordingly," said Dr. Leonard.

"We are looking at new paradigms of treatment," added Dr. O'Connor. "There may be no program anywhere that can offer more options for treatment, and we expect these advances to be reflected in better outcomes."

Editor's Note: Drs. Leonard and O'Connor will be hosting a web cast entitled, "New Developments in Lymphoma Biology and Treatment," on October 17, 2007. For more information, visit www.nypcancer.org.

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"There may be no program anywhere that can offer more options for treatment, and we expect these advances to be reflected in better outcomes."

—Owen O'Connor, MD, PhD

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an urgent need for better treatments in advanced disease, and we have been very encouraged by the progress in understanding molecular and genetic targets.”

Edward Gelmann, MD, who recently joined NewYork-Presbyterian/Columbia University Medical Center, also has a strong interest in prostate cancer research. In a recent publication, he reported on the prostate-specific homeodomain protein NKX3.1, a tumor suppressor that is commonly downregulated in prostate cancer in humans.

Study results revealed that NKX3.1 can modify the activity of the DNA-resolving enzyme topoisomerase I, which may have implications for organ-specific DNA replication, transcription, or repair (*Cancer Res* 2007;67:455-467).

In addition, in a study published in the *Journal of Biological Chemistry* (2005;280:37853-37867), Dr. Gelmann and Liang-Nian Song, MD, proposed that the multifunctional oncoprotein β -catenin “may play an integral role in formation of the androgen-receptor transcriptional complex.”

At NewYork-Presbyterian/Columbia, Dr. Gelmann will be able to work with other leaders in the field, such as Daniel Petrylak, MD, who has conducted several studies directed at improving outcomes in hormone-refractory prostate cancer. “We have been looking at first- and

second-line treatments for hormone-refractory prostate cancer,” said Dr. Petrylak.

Dr. Petrylak led 1 of the 2 pivotal trials supporting the FDA approval of docetaxel in hormone-refractory prostate cancer and was a principal investigator in a study evaluating the efficacy of treatment with satraplatin, a novel oral platinum compound, in patients whose cancer has progressed after docetaxel treatment. The open-ended Phase I study is actively recruiting patients, and Dr. Petrylak hopes to have results at the end of 2008.

“An NDA for this drug has been filed with the FDA,” Dr. Petrylak reported. If the FDA approves satraplatin, he will be directly involved in the approval of 2 drugs for this disease.

Columbia researchers at NewYork-Presbyterian Hospital are also looking at other ways to block the angiogenesis pathways by combining different anti-angiogenesis agents. Dr. Petrylak and colleagues are currently investigating the use of lenalidomide and the combined use of bevacizumab and erlotinib; preliminary results look promising. Currently, he is collaborating with Carlos Cardon-Cardo, MD, who was recently recruited to NewYork-Presbyterian/Columbia. “We need to find the markers of resistance and progression, and why particular patients respond the way they do to certain medications,” said Dr. Petrylak.

Editor's Note: Drs. Nanus and Petrylak will be co-chairs of the “Current Trends in Genitourinary Malignancies” symposium to be held on October 27, 2007. For more information, please visit www.nycancer.org.

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