NewYork-Presbyterian
Oncology

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Fall 2004

COX Inhibitors Reduce Breast Cancer Risk

Columbia and Weill Cornell researchers at NewYork-Presbyterian Hospital have found that aspirin use can lower the overall risk of developing breast cancer by 20%. More importantly, they also established that the protective benefit was limited to hormone receptor–positive tumors, which affect 60% to 70% of women with breast cancer.

The investigation, led by Mary Beth Terry, PhD, and Alfred I. Neugut, MD, PhD, linked data from a large, population-based case-control study, named the "Long Island Breast Cancer Study Project," to mechanistic studies carried out in the laboratory of Andrew J. Dannenberg, MD, and Kotha Subbaramaiah, PhD.

"This is among the largest empirical studies that have looked at this issue," said Dr. Neugut. "It's the first study to suggest that aspirin may be more effective at preventing certain types of breast cancer than others."

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit cyclooxygenase (COX)-1 and -2, enzymes that play a key role in synthesizing prostaglandins. In the past decade, studies have suggested that blocking prostaglandin production is a rational approach to preventing cancer. In cultured cells, prostaglandin E_2 (PGE_2) has been shown to increase aromatase gene expression and thus the production of estrogen.

Previously, Dr. Dannenberg had

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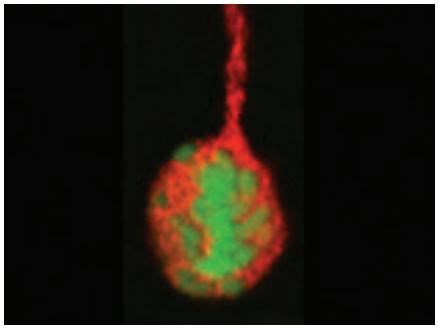
Maximizing the Use of Stem Cells In Research and Treatment

Seeking to unravel secrets of stem cells' pluripotent ability to repair defects, diseases, and injuries of the heart, blood, brain, skin, and other organ systems, interdisciplinary groups of leading scientists have joined together as part of 2 separate initiatives at NewYork-Presbyterian Hospital.

At Weill Medical College of Cornell University, a $15 million grant from Shahla and Hushang Ansary, prominent Houston philanthropists, helped establish the new Ansary Center for Stem Cell Therapeutics in May. Meanwhile, the Columbia University Stem Cell Consortium has likewise brought together previously disconnected researchers investigating the functioning of stem cells and seeking to use them to treat traumatic brain injury, strokes, mental illness, juvenile diabetes, melanoma, and a host of other ills.

"If we can find a way to stimulate these cells, either in the laboratory or in the body, we could deliver large amounts of a patient's own stem cells as a treatment," said Shahin Rafii, MD. "Such cells could be used to enhance brain recovery after stroke, accelerate wound healing in diabetics, and regenerate heart muscle after a heart attack."



Columbia University Stem Cell Consortium

Researchers are investigating the functioning of stem cells and seeking to use them to treat a host of ills.

Adult stem cells could also be genetically altered to carry therapeutic payloads to block tumor angiogenesis, said Ronald Crystal, MD. "Such genetically altered cells might also be used to reverse tissue injury in heart attack,

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Anti-angiogenic Therapy and Mantle Cell Lymphoma

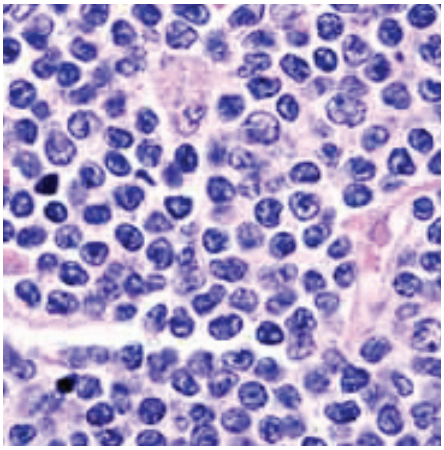
Researchers at NewYork-Presbyterian Hospital will be building upon their own findings as they investigate the novel combination of low-dose chemotherapy with daily prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) with thalidomide and rituximab in the treatment of mantle cell lymphoma.

The Weill Medical College of Cornell University has received a $950,000 grant from the Lymphoma Research Foundation (LRF) to evaluate this new treatment strategy involving 6 agents never before studied in combination. The grant is the largest of 18 grants, totaling $12.8 million, disbursed worldwide earlier this year by the LRF to study mantle cell lymphoma, an uncommon but aggressive illness (expected median survival, 3-4 years) diagnosed in up to 5,000 people in the United States each year. The combination of 4 of the drugs known as PEP-C was initially developed by Morton Coleman, MD.

"The PEP-C regimen was developed to deliver combination chemotherapy in a very convenient manner, particularly for those fragile, infirm patients who were unable to receive intravenous medications," explained Dr. Coleman. "This unique oral regimen proved not only very easy to use, but it was also well tolerated and extraordinarily effective."

At first, the researchers thought the efficacy of PEP-C was due to the combination of chemotherapies directly killing off the tumor that usually forms in the lymph nodes of mantle cell patients. "But more recently," Dr. Coleman said, "data suggest that the low doses of chemotherapy may be anti-angiogenic. In effect, these low doses may not impact the tumor directly, but may actually damage blood vessels that feed the tumor, thus preventing vital nutrients needed for cancer growth from ever reaching the malignant cells." The trial was then developed combining PEP-C with 2 other promising agents: thalidomide, also believed to be anti-angiogenic, and rituximab, a monoclonal antibody. The 2 had been used together with encouraging results in separate preliminary trials.

"The trial began this summer and will last 2 to 3 years," said John P. Leonard, MD, the principal investigator of the program. One of the benefits, he said, is that the treatment protocol primarily involves oral agents that will allow the approximately 50 participants to be treated as outpatients. Another benefit, he said, is that "because the chemotherapy is low-dose, it is expected to be better tolerated than more intensive regimens."



A photomicrograph of a mantle cell lymphoma specimen. Researchers are investigating a novel combination of low-dose chemotherapy with daily prednisone, etoposide, procarbazine, and cyclophosphamide (PEP-C) with thalidomide and rituximab to treat this challenging form of cancer.

Most importantly, he said, this approach may prove to be an effective and well-tolerated form of maintenance therapy that may help to provide long-term disease control.

The goal of managing incurable cancers over time as chronic disorders is one that is being explored in a variety of areas of oncology. Much of the laboratory analysis of the treatment effects will be conducted by Shahin Rafii, MD, and Jia Ruan, MD, PhD. "There's an intimate cellular and molecular interaction between blood cells and endothelial cells," Dr. Rafii explained. "What happens is really fascinating. Blood vessels and blood cells originate together in embryonic development. They come from 1 cell. They are like Siamese twins, born together, so they have common progenitors. The factors that support their survival are shared. If you are a leukemic cell, the only cells you come in contact with are vascular cells, so you take advantage of them to help you grow."

Blocking angiogenesis also blocks pro-survival signals in the lymphoma cells, said Richard Furman, MD, a co-investigator. "Some of the angiogenic factors involved in mantle cell lymphoma are important not only because they cause the growth of blood vessels, but because they can actually be pro-survival signals for the lymphoma cells," he said. "By blocking those signals with the anti-angiogenic agents in the trial, apoptosis may be encouraged in the lymphoma cells." The investigators anticipate that this work will not only apply to mantle cell lymphoma, but to other, more common forms of the disease. Lymphoma is among the most common cancers in the U.S. and has dramatically increased in incidence over the past several decades.

Morton Coleman, MD, is Director, Center for Lymphoma and Myeloma at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Clinical Professor of Medicine at Weill Medical College of Cornell University.
E-mail: mortoncolemanmd@aol.com.

Richard Furman, MD, is Assistant Attending Oncologist at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Assistant Professor of Medicine at Weill Medical College of Cornell University. E-mail: rrfurman@med.cornell.edu.

John P. Leonard, MD, is Assistant Attending Oncologist and Medical Director of Oncology Services at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Associate Professor of Medicine, Division of Hematology/Oncology, at Weill Medical College of Cornell University. E-mail: jpleonar@med.cornell.edu.

Shahin Rafii, MD, is Attending Physician at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Arthur B. Belfer Professor of Genetic Medicine at Weill Medical College of Cornell University. E-mail: srafii@med.cornell.edu.

CME Conference

The following CME conference will review current approaches to the diagnosis and treatment of brain tumors, with faculty from Columbia and Weill Cornell.

Brain Tumors: Advances in Diagnosis & Treatment—A Comprehensive Review

DATE: Friday, October 8, 2004
LOCATION: Grand Hyatt New York in New York City.
Full Day, maximum of 8 category 1 credits.

To register or for more information,
CALL toll-free 1-866-697-7755 or ONLINE at www.nypneuro.org.

Clarification

In the spring 2004 NewYork-Presbyterian *Oncology* Newsletter, an article entitled "Advancing Outpatient Laparoscopic Surgery in Colon Cancer" detailing the work of Richard L. Whelan, MD, contained an error. Study of the tumor suppressor protein known as insulin-like growth factor binding protein 3 (IGFBP-3) should have been described as follows: Columbia researchers have transformed a modified version of *Salmonella* with IGFBP-3 DNA. When injected into animal models, the transformed *Salmonella* reduces tumor size within 2 weeks. These same investigators are planning to study the agent in humans with colorectal cancer in the hope of avoiding surgery. Dr. Whelan is Associate Professor of Surgery, Columbia University College of Physicians and Surgeons.

NewYork-Presbyterian Oncology

is a publication of the Cancer Centers of NewYork-Presbyterian Hospital. The Cancer Centers are at the forefront of cancer screening and diagnosis, and basic science and clinical research. The Cancer Centers serve over 6,500 new cancer patients each year, who receive state-of-the-art multidisciplinary care. The Cancer Centers include the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/Columbia University Medical Center and the Weill Cornell Cancer Center at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, which are respectively comprised of faculty from the Columbia University College of Physicians and Surgeons and the Weill Medical College of Cornell University.

NewYork-Presbyterian Oncology Editorial Board

Promising Advances in the Treatment of Prostate Cancer

Historically, androgen-independent prostate cancer (AIPCa), also known as hormone refractory prostate cancer (HRPC), is uniformly fatal. However, a recent Phase III clinical trial led by senior author Daniel P. Petrylak, MD, and co-authored by Mitchell C. Benson, MD, at the Herbert Irving Comprehensive Cancer Center (HICCC) found that chemotherapy with docetaxel and estramustine can prolong the survival of patients with this difficult-to-treat cancer.

"In 1996, docetaxel was approved for breast cancer, but not for prostate cancer; estramustine had been approved for prostate cancer," said Dr. Petrylak in explaining the history behind the research. "We saw a synergy in the lab between these 2 drugs. Estramustine seemed to make the docetaxel more active. This is one of the first trials to show a survival advantage for chemotherapy in prostate cancer."

AIPCa does not require androgen to progress, making it resistant to current hormonal therapy. Roughly 10% of all prostate cancer patients suffer from AIPCa. The HICCC trial—part of the Southwest Oncology Group (SWOG)—was the first Phase III trial to study the use of combination therapy with docetaxel and estramustine and compare it to the efficacy of mitoxantrone–prednisone, a treatment combination that had been considered the standard of therapy since the late 1990s. When evaluated in separate trials, treatment with mitoxantrone–prednisone resulted in a median survival rate of 10 to 12 months for patients suffering from AIPCa, compared to 20 to 23 months for patients treated with docetaxel-estramustine. In his own practice, Dr. Petrylak noticed that there were some patients who were surviving 3 to 5 years; in fact, 1 patient from the original study in 1996 still is alive today.

The HICCC trial, called SWOG 99-16, consisted of 70 men with progressive AIPCa who were randomized into 1 of 2 treatment arms, both of which received treatment on the same schedule: 3 cycles of 3 weeks each. The first group received 60 mg/m^2 of docetaxel administered every cycle, plus 280 mg of estramustine administered 3 times daily for the first 5 days. The second group received 12 mg/m^2 of mitoxantrone plus 5 mg of prednisone twice daily. If no grade 3 or 4 toxicities were observed during the first cycle, doses were titrated to 70 mg/m^2 in the first group and 14 mg/m^2 in the second; patients were tested with bone scans and CT scans at the end of each cycle.

The results of SWOG 99-16, presented at the 2004 annual meeting of the American Society of Clinical Oncology in June and scheduled for publication in *New England Journal of Medicine* later this fall, demonstrated a 20% improvement in median survival in men treated with docetaxel–estramustine over mitoxantrone–prednisone (see Figure for overall survival data). That, along with a relatively favorable side-effect and toxicity profile, supports the use of the combination as first-line therapy for AIPCa.

According to Dr. Benson, the implications of these results parallel findings in breast cancer in the 1990s. "When the effects of chemotherapy on breast cancer were identified, it was in advanced breast cancer, just like we're identifying highly effective chemotherapy in highly advanced prostate

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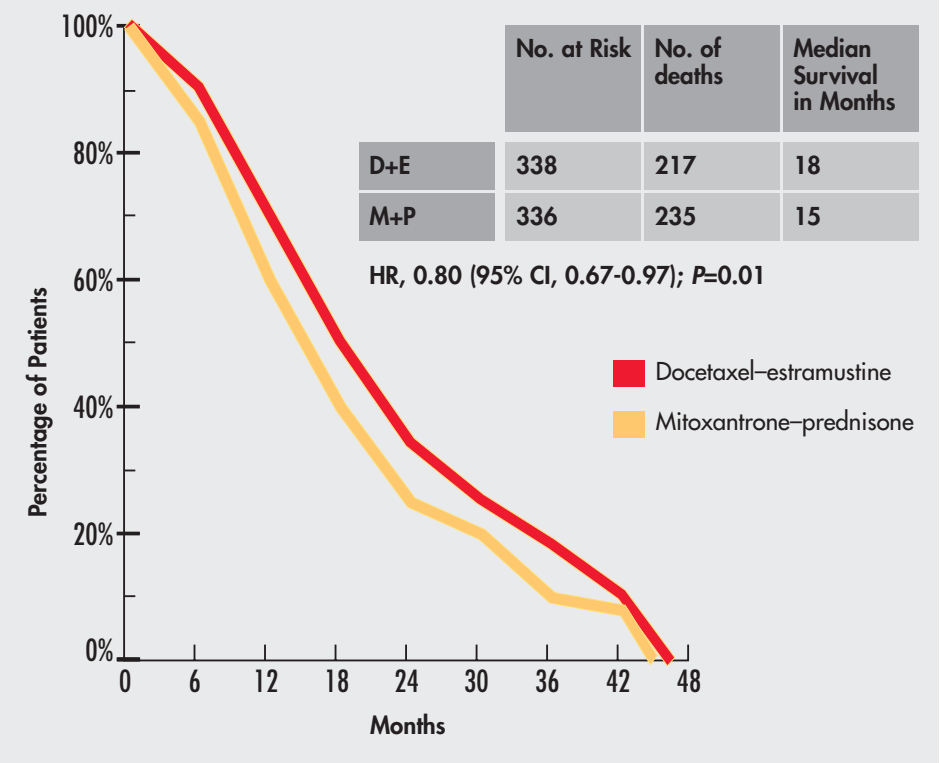


Figure. Overall Survival.

D+E, docetaxel–estramustine; **M+P,** mitoxantrone–prednisone
Source: Petrylak DP, Tangen C, Hussain M, et al. SWOG 99-16: Randomized phase III trial of docetaxel (D)/estramustine (E) versus mitoxantrone(M)/prednisone(p) in men with androgen-independent prostate cancer (AIPCA) [abstract]. Presented at: American Society of Clinical Oncologists Annual Meeting; June 3-8, 2004; New Orleans, La. Abstract 3.

Coordinating the Use of Complementary And Alternative Medicine in Pediatric Patients

When Columbia physicians at Morgan Stanley Children's Hospital of NewYork-Presbyterian first began investigating complementary and alternative medicine (CAM) in pediatric cancer patients 8 years ago, they found the interest in the use of these therapies was much higher than expected.

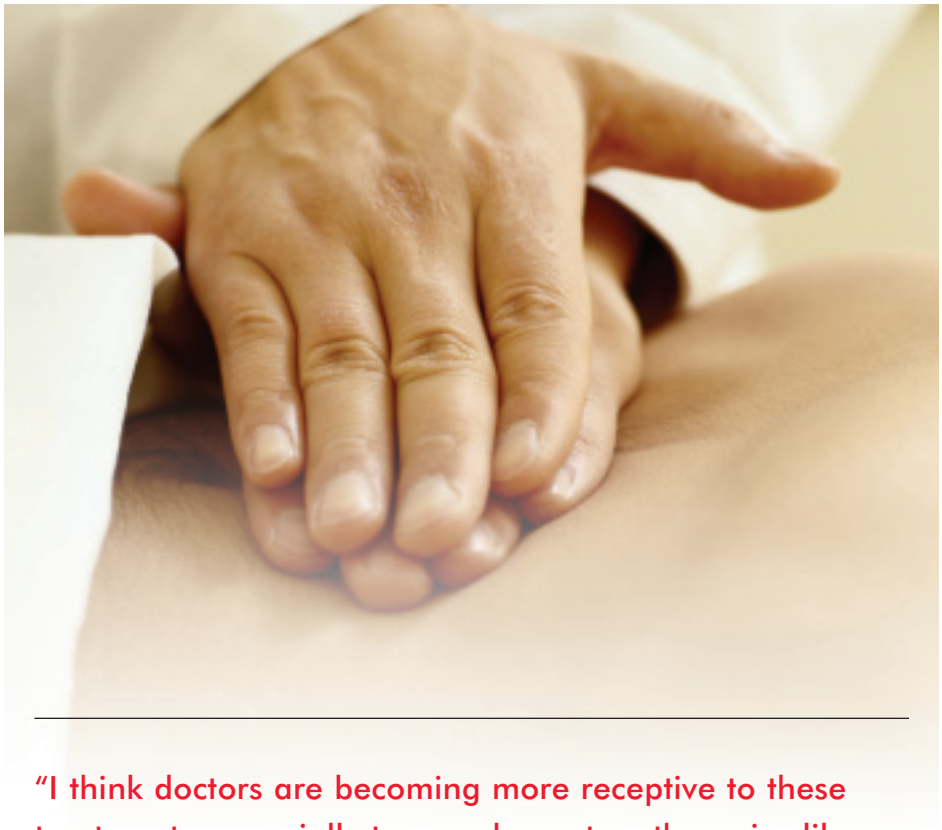
"At the time, there was a dearth of information on CAM in cancer, especially in pediatric cancer," recalled Kara Kelly, MD. "I interviewed the parents of 75 of our patients. Much to my surprise, we found that 84% were using some form of CAM therapy."

In addition, she found that families weren't using these therapies in lieu of traditional therapy (the true definition of "alternative" treatment), but rather for additional support. Specifically, they were hoping to fight the side effects of other cancer treatments (e.g., nausea, infection, stress), while reassuring themselves that they were doing everything possible.

"We recognized that patients and their families wanted to know more about them," noted Michael Weiner, MD.

Today, the Herbert Irving Child and Adolescent Oncology Center (HICAOC) at Morgan Stanley Children's Hospital of NewYork-Presbyterian is leading the way in the use of CAM, particularly in the treatment of children with cancer. The HICAOC established the Integrative Therapies Program for Children with Cancer in 1998. The program has been an important impetus for initiating research in these therapies nationally. This spring, under Dr. Kelly's leadership, the Children's Oncology Group, the nationally funded research consortium of centers for the treatment of childhood cancer, opened its first clinical trial.

"It's an investigation into the homeopathic preparations for preventing stomatitis during stem cell transplant," she explained. "I think doctors are becoming more receptive to these treatments, especially to complementary therapies like massage, acupressure, and so forth. There's no real risk of interaction with such treatments, and they seem to play a role in symptom management."



"I think doctors are becoming more receptive to these treatments, especially to complementary therapies like massage, acupressure, and so forth. There's no real risk of interaction with such treatments, and they seem to play a role in symptom management."

— *Kara Kelly, MD*

The HICAOC established the Integrative Therapies Program to provide both parents and primary care physicians with accurate and up-to-date information on complementary therapies; develop integrative therapies that help to lessen the side effects of chemotherapy, radiation, and surgery; evaluate the safety and potential interactions of complementary therapies with conventional treatments; and lead future research efforts. Its staff includes a full-time director, full-time program coordinator, and part-time massage therapist, aromatherapist, yoga instructor, exercise physiologist, Reiki practitioner, and natural foods chef.

Perhaps the biggest role the Integrative Therapies Program plays in the treatment of patients involves governing the implementation of CAM for individual patients. According to Dr. Kelly, one major concern with CAM is the use of supplements, which can offer a real risk of interactions with chemotherapy. There's also concern that supplements may contain lead, mercury, and other hazardous elements, due to the lack of quality control in

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their manufacture.

"The physician has to find out as much as possible about what the patient is taking," said Dr. Kelly. "Start with the assumption that they are taking something. At least half of the time they're using [a complementary therapy] and not telling us." Unless there's real evidence against using that treatment—in which case she's found that families will listen to the doctor—she advises colleagues to respect the patient's decision, monitoring carefully for toxicity.

According to Dr. Weiner, the Integrative Therapies Program is also "trying to separate fact from fiction" by conducting trials on various supplements. One such trial is currently seeking patients with acute lymphoblastic leukemia who are receiving chemotherapy in order to measure the effects of silymarin (milk thistle extract) in preventing liver toxicity. Another aims to evaluate the efficacy of glutamine as a protectant against the neurotoxicity of some chemotherapy drugs.

Kara Kelly, MD, is Medical Director of the Integrative Therapies Program at the Herbert Irving Child and Adolescent Oncology Center at Morgan Stanley Childrens Hospital of NewYork-Presbyterian/Columbia University Medical Center, and is Associate Professor of Clinical Pediatrics at Columbia University College of Physicians and Surgeons. She is also Chair of the Complementary Therapies Subcommittee of the Children's Oncology Group. E-mail: kk291@columbia.edu.

Michael Weiner, MD, is Chief of Pediatric Oncology at the Herbert Irving Child and Adolescent Oncology Center at Morgan Stanley Childrens Hospital of NewYork-Presbyterian/Columbia University Medical Center, and is Professor of Clinical Pediatrics at Columbia University College of Physicians and Surgeons. E-mail: mw216@columbia.edu.

For more information on current issues and trends in CAM before recommending these therapies to patients with cancer, visit: www.integrativetherapiesprogram.org. For information on clinical research studies within the program, please call Drs. Weiner or Kelly at (212) 305-5808.

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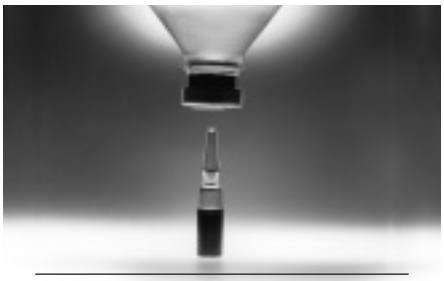
cancer," he explained. "The next step in breast cancer was to take these same drugs into an earlier stage of the disease. Our next step is to try this regimen in a patient who's had a radical prostatectomy and in whom the pathology is unfavorable. Hopefully, we'll be treating smaller volumes of cancer and thus have a much better chance of establishing a cure with an adjunct therapy."

The docetaxel-estramustine group in SWOG 99-16 did have a significantly higher rate of nausea and vascular events than the mitoxantrone-prednisone group. As a result, docetaxel-estramustine is currently contraindicated for patients with myocardial infarction, blood clots, and cerebral vascular accident. However, the SWOG 99-16 investigators "did not see a higher rate of toxic deaths nor study discontinuation due to toxicity in patients treated with docetaxel and estramustine," noted Dr. Petrylak.

"This is the first study of a head-to-head comparison of the new combination therapy versus established prior 'best practice,' " noted Carl A. Olsson, MD. "The results show a statistically significant overall increase in survival in androgen-independent prostate cancer. Since this is the form of prostate cancer that eventually kills, having a new, more effective standard of care will not only help patients at the Hospital, but patients throughout the world."

National Cancer Institute



"This is one of the first trials to show a survival advantage for chemotherapy in prostate cancer."

— *Daniel P. Petrylak, MD*

Mitchell C. Benson, MD, is Interim Director, Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is George F. Cahill Professor of Urology and Director, Urologic Oncology, Columbia University College of Physicians and Surgeons. E-mail: mcb2@columbia.edu.

Carl A. Olsson, MD, is Director, Department of Urology at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Chairman, Department of Urology, and J.K. Lattimer Professor of Urology at Columbia University College of Physicians and Surgeons. E-mail: cao2@columbia.edu.

Daniel P. Petrylak, MD, is Associate Attending Physician in Oncology, Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Associate Professor of Medicine at Columbia University College of Physicians and Surgeons. E-mail: dpp5@columbia.edu.

Breast Cancer

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postulated that if the same mechanism applied in humans, the suppression of PGE_2 would provide more protection against breast tumors that rely on estrogen production for growth than those that do not. "That is what we found," he said. "The ability to translate a preclinical finding to the clinic is very exciting."

The NewYork-Presbyterian Hospital findings, published in the May 26 issue of the *Journal of the American Medical Association*, were based on a study led by Marilie Gammon, PhD, of 1,442 Long Island women diagnosed with breast cancer between August 1996 and July 1997; 1,420 women without breast cancer were included as controls.

Both groups were questioned about their use of aspirin and ibuprofen as well as acetaminophen. Aspirin or NSAID use at least once per week was reported by 301 women (21%) with breast cancer and 345 (24%) controls. While the findings suggested an overall 20% breast cancer risk reduction associated with aspirin and ibuprofen use, the protective effect was most pronounced among frequent users—women who used aspirin 7 times or more per week. The number of ibuprofen users was not large enough to reach any definitive conclusions about its preventive benefits. As expected, no benefit was noted for acetaminophen, an analgesic that lacks the anti-inflammatory properties of aspirin and NSAIDs.

> "This is among the largest empirical studies that have looked at this issue. It's the first study to suggest that aspirin may be more effective at preventing certain types of breast cancer than others."
>
> — *Alfred I. Neugut, MD, PhD*

Although the results suggested a possible role for aspirin in breast cancer prevention, the researchers were cautious about recommending it for that purpose because of aspirin's serious potential side effects, including gastrointestinal bleeding. According to Dr. Terry, it is too early to advise women to use aspirin as chemoprevention for breast cancer, adding that the risk reduction associated with aspirin use is "still fairly modest."

"We'd like to see a replication of our results," Dr. Terry added. "We'd like to see another large study suggesting that only the hormone receptor–positive" breast cancers are affected by aspirin use.

Andrew J. Dannenberg, MD, is Co-Director of Cancer Prevention at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Henry Erle, MD–Roberts Family Professor of Medicine at Weill Medical College of Cornell University. E-mail: ajdannen@med.cornell.edu.

Alfred I. Neugut, MD, PhD, is Co-Director of Cancer Prevention, Herbert Irving Comprehensive Cancer Center, and Acting Chief of the Division of Medical Oncology at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Professor of Medicine and Epidemiology at Columbia University College of Physicians and Surgeons and the Mailman School of Public Health. E-mail: ain1@columbia.edu.

Kotha Subbaramaiah, PhD, is Associate Professor of Medicine at Weill Medical College of Cornell University. E-mail: ksubba@med.cornell.edu.

Mary Beth Terry, PhD, is Assistant Professor of Epidemiology at Columbia University Mailman School of Public Health. E-mail: mt146@columbia.edu.

Stem Cells

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stroke, liver damage, or heart disease–damaged arteries," he said.

Dr. Rafii's own research discovered vascular stem cells present in the adult bone marrow that contribute both to wound healing and tumor angiogenesis. Other researchers at the new Ansary Center include Neeta Roy, MD, who recently isolated neural progenitor cells from fetal spinal cord tissue that could one day be used to treat damaged nerves and brain tissue, and Jay Edelberg, MD, who studies the use of bone-marrow precursor cells to mend damaged and aging hearts.

At Columbia's Stem Cell Consortium, Charles Hesdorffer, MD, is working with colleagues in cardiology to prepare a paper on their results in treating amyloidosis patients with a one-two combination of a heart transplantation followed by a stem cell transplant. "This is the only center in the United States where amyloidosis patients can undergo a heart transplant and then come back 6 months later for a stem cell transplant," he said. Without the promise of a stem cell transplant aimed at halting the deposit of amyloid proteins on vital organs, cardiologists see little point in performing a heart transplant.

Dr. Hesdorffer is planning to collaborate with Betty Diamond, MD, on stem cell transplants for people with severe lupus and rheumatoid arthritis, as part of a large NIH trial. On the research front, he is investigating ways to identify and stimulate stem cells that target tumors when used in allogeneic transplants, while tamping down those stem cells that lead to graft-versus-host disease.

The research of Arnold R. Kriegstein, MD, has recently begun to focus on reptiles. "Everyone knows a lizard can regenerate a tail," he said. "In fact, the lizard can also regenerate parts of its brain. We'd very much like to know how that happens."

Using turtles as a model, his group has found that after a physical lesion occurs in the adult brain, lizards somehow manage to generate new neurons, which move into the area of injury, make appropriate connections, and permit the animal to recover functioning.

Fiona Doetsch, MD, has shown that the adult mammalian brain also has a continued capacity to generate neurons. But understanding how to harness neural stem cells to treat patients devastated

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by Alzheimer's, stroke, or traumatic injury may prove one of the daunting challenges of stem cell research.

"The neural stem cells would have to form hundreds of thousands of connections with other neural cells to recover lost function," Dr. Kriegstein said. "It's a big challenge, and nobody understands how that can happen. But the fact that something like that already does happen in the brains of lower reptiles and in certain parts of the mammalian brain suggests this is not impossible."

Mitchell S. Cairo, MD, uses stem cells derived from umbilical cords to conduct fundamental research and offer clinical treatments to patients suffering from cancers and genetic defects. Rebecca Morris, MD, has devoted the past 18 years to identifying stem cells that give rise to hair follicles. A byproduct of the research in the next decade could lead to a treatment for baldness—not the leading cause of human suffering, no doubt, but then no one knows where today's research into stem cells at the medical centers of NewYork-Presbyterian will ultimately lead.

Mitchell S. Cairo, MD, is Chief, Division of Pediatric Hematology and Blood and Marrow Transplantation at the Herbert Irving Child and Adolescent Oncology Center at Morgan Stanley Childrens Hospital of NewYork-Presbyterian/Columbia University Medical Center, and is Professor of Pediatrics, Medicine and Pathology at Columbia University College of Physicians and Surgeons. E-mail: c1310@columbia.edu.

Ronald G. Crystal, MD, is Director, Institute of Genetic Medicine and Attending Physician at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Bruce Webster Professor of Medicine at Weill Medical College of Cornell University. E-mail: rgcryst@med.cornell.edu.

Charles Hesdorffer, MD, is Director, Adult Marrow and Stem Cell Transplant Program at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Professor of Clinical Medicine at Columbia University College of Physicians and Surgeons. E-mail: hesdorffer@cuccfa.ccc.columbia.edu.

Arnold R. Kriegstein, MD, is Scientific Director, Neural Stem Cell Program at NewYork-Presbyterian Hospital/Columbia University Medical Center, and is Professor of Neurology at Columbia University College of Physicians and Surgeons. E-mail: ark17@columbia.edu.

Rebecca Morris, MD, is Associate Professor of Epithelial Biology in the Divisions of Dermatology and Pathology at Columbia University College of Physicians and Surgeons. E-mail: rm2046@columbia.edu.

Shahin Rafii, MD, is Director, Ansary Center for Stem Cell Therapeutics and Attending Physician at NewYork-Presbyterian Hospital/Weill Cornell Medical Center, and is Professor of Genetic Medicine and Professor of Medicine in the Division of Hematology-Oncology at Weill Medical College of Cornell University. E-mail: srafii@med.cornell.edu.

SERVICE LINE ADMINISTRATOR: **Susan Silverman, 627 West 165th Street, New York, NY 10032, 212.305.1340** E-mail: **sus9005@nyp.org**

NEW YORK-PRESBYTERIAN Oncology

Fall 2004

NewYork-Presbyterian Hospital
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