THE CANCER LETTER INTERACTIVE

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# WHI Investigators Reiterate: Breast Cancer, CHD Risks Too Great For Routine HT Use

Lining up at the microphones at the NIH workshop on hormone therapy last week, gynecologists asked the one question of Women's Health Initiative investigators that every community-practice gynecologist in the U.S. wanted to ask: Is there a population of women who can take estrogen and progestin safely?

One after another, every questioner made a suggestion: Would it be possible to identify women at low risk of breast cancer? start them early in menopause? limit the medication to two years or five years? use a

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*In Brief:*

## University Of Oklahoma Wins Planning Grant; Wilding Is Acting Director, UW Cancer Center

**UNIVERSITY OF OKLAHOMA** has been awarded a P20 Cancer Center Planning Grant totaling $1.3 million for five years from NCI. **Howard Ozer**, Eason Chair of Oncology, director of the OU Cancer Center, is the principal investigator for the grant. The four OUCC programs include Breast Cancer, directed by **Ann Thor**, the Lloyd E. Rader Professor and chair of pathology; Gynecologic Cancer, co-directed by **Doris Benbrook**, associate professor of gynecology, and **Joan Walker**, the Brian and Sandra O'Brien Presidential Professor and Section Chief of Gynecologic Oncology; Community Cancer Prevention and Control, directed by **Morris Foster**, associate professor of anthropology and medicine; and Cell Cycle Control and Carcinogenesis, directed by **Marie Hanigan**, associate professor of cell biology and associate cancer center director for basic science. The center's core resources are co-directed by **Larry De Bault**, professor of pathology, and **Dan Brackett**, professor of surgery and director of surgical research. The planning grant received an excellent to outstanding priority score and was praised by peer reviewers for its focus on translational research and cancer research involving Native Americans. Oklahoma has the largest population of Native Americans in the U.S. totaling more than 263,000. There are no other NCI-designated cancer centers within a 450-mile radius of Oklahoma City. . . . **GEORGE WILDING** was named acting director of the University of Wisconsin Comprehensive Cancer Center, effective Nov. 1, said **Philip Farrell**, dean of the UW Medical School. Wilding will succeed **John Niederhuber**. Wilding will serve as acting director until a

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# NIH Workshop Reviews Estrogen-Progestin Results

(Continued from page 1)

different formulation than Prempro, the Wyeth Pharmaceuticals agent used in the recently concluded NIH study?

WHI investigators didn't waiver in the face of the onslaught, reiterating the findings first announced last July. The trial, designed to test whether estrogen and progestin reduced heart disease, was stopped because women taking Prempro had a 26-percent increased risk of developing breast cancer over those who took a placebo.

As National Heart, Lung and Blood Institute Director Claude Lenfant put it, that's "too high a price to pay even if there were a heart benefit" (**The Cancer Letter**, July 12).

**Not Just Another Hormone Study**

In fact, women taking Prempro had a 29-percent increased risk of coronary heart disease and a 41 percent increased risk of stroke, WHI investigators said at the NIH workshop Oct. 23-24. The youngest group of women in the study, ages 55-59, had the highest risk of CHD.

The coronary and vascular risks were not restricted to the first few years of use, but were displayed throughout the study, said Marian Limacher, professor of medicine at the University of Florida College of Medicine and a WHI principal investigator.

"I don't believe we should present this as just another hormone study," Limacher said. "This study removes estrogen and progestin from CHD prevention. We only tested one regimen, but we cannot assume other formulations will have different outcomes. We would have to do randomized controlled trials."

In other words, gynecologists, find other strategies to help patients with menopausal symptoms. The era of thinking that estrogen and progestin can be used long-term because it has other health benefits is over.

"The results [of the study] were somewhat unexpected, but this is a good example of the worth of clinical research," NIH Director Elias Zerhouni said.

Prempro was chosen because 80 percent of women in the U.S. who were taking hormone replacement therapy were prescribed Prempro, investigators said. The study was not designed to test Prempro's effectiveness in treating the symptoms of menopause.

**Eight More Breast Cancers Per 10,000**

Based on the WHI results, for women aged 50 to 79 years who have a uterus, 10,000 women taking estrogen and progestin for one year might experience eight more invasive breast cancers, seven more heart attacks, eight more strokes, and 18 more blood clots, including eight with blood clots in the lungs, than will a similar group not taking hormones.

While these are small annual increases in risk for individual women, they add up to tens of thousands of adverse events on a population-wide basis, the investigators said.

Some physicians tell women that the excess risk in the WHI of eight breast cancers per 10,000 women per year is small, Otis Brawley, professor of oncology and associate director for cancer control at the Winship Cancer Institute at Emory University, said at the workshop.

Brawley noted that mammographic screening only prevents one breast cancer death per year out of every 17,000 women over age 50 who are screened. For women in their 40s, the figure is even lower: one out of every 25,000, he said. Yet women are told that having mammograms is important in the fight against breast cancer.

Last week, NIH and FDA officials replaced the term "hormone replacement therapy" with

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"menopausal hormone therapy," arguing that hormone treatment wasn't a replacement.

"You can't reverse aging," said Susan Hendrix, a WHI investigator and associate professor of gynecology at Wayne State University. "We have to separate our aging from our going through menopause. We can't take a pill for the rest of our lives to make us young again."

Hendrix urged physicians to prescribe other therapies for vasomotor symptoms of menopause and topical treatments for vaginal dryness. "As gynecologists, we need to learn about other ways to help our patients, such as exercise and diet," she said.

To reduce the risk of CHD, Limacher advised women to reach and maintain ideal body weight, engage in regular physical activity, reduce blood pressure, maintain cholesterol levels with LDL less than 130 and HDL greater than 45, and triglyceride less than 150.

In the WHI, Prempro reduced the rate of hip fractures by one-third and all fractures by 24 percent, but other agents may confer the same benefit of reducing osteoporosis without increasing CHD and breast cancer, said Rebecca Jackson, WHI investigator and associate professor of internal medicine at Ohio State University.

The WHI is testing the effectiveness of calcium and vitamin D, and there are agents approved for osteoporosis, including raloxifene, she said.

FDA is evaluating how it regulates hormone therapy, and whether it should require long-term safety data from drug companies, said Janet Woodcock, director of the FDA Center for Drug Evaluation and Research. FDA requires one-year safety data for menopausal hormone therapies.

Prescribing practices are likely to change, said Marcia Stefanick, of Stanford University, and chairman of the WHI Steering Committee. It's more likely that physicians will prescribe estrogen and progestin to younger women for short periods to counter menopausal symptoms, she said. However, physicians should discuss the results of the WHI with patients and assess each women's individual risks, she said. The WHI showed that "it's not appropriate to initiate hormone therapy with estrogen and progestin in older women," Stefanick said.

Other experts advised against trying to select women for hormone therapy on the basis of their breast cancer risk.

The increased risk of breast cancer in women taking Prempro appeared early in the trial and in all age groups, said WHI investigator Rowan Chlebowski, professor of medicine, University of California, Los Angeles, School of Medicine, and chief of medical oncology and hematology at Harbor-UCLA Medical Center.

Even women who took the drug only for a short time and then stopped had a greater risk of developing breast cancer than those who took placebo, he said.

Women on the trial began with a relatively low risk of breast cancer as measured by the Gail model, with two-thirds of the population having a risk of under 1.7 percent. By comparison, a 60-year-old woman with no additional risk factors besides age has a Gail risk factor of 1.7 percent.

About a quarter of the women had prior menopausal hormone therapy exposure. For the 75 percent of women who never had prior HT, their hazard ratio was modest, but after five years of exposure, their risk increased two-fold. At five to 10 years, it was a four-fold increase.

"One issue that comes up all the time is why not simply identify women at increased risk of breast cancer using risk assessment models and not give estrogen and progestin to those women?" Chlebowski said. "It's really very difficult at this time to select out the women who wouldn't be at increased breast cancer risk."

In an analysis of the Nurses Health Study, the Gail model predicted the number of breast cancer cases, but was only of modest sensitivity and specificity in determining the chance that any individual woman would develop breast cancer, Chlebowski said.

Further analyses of the WHI estrogen and progestin study are underway, including adjusting for possible correlates for breast cancer risk and looking at tumor characteristics (histology, ductal, lobular, grade, stage, and receptor status), relationship to body mass, prior hormone use including estrogen alone, and prior oral contraceptive use. These analyses should be available shortly, Chlebowski said.

A webcast of the NIH conference may be viewed at http://videocast.nih.gov/.

**Report Recommends Against Use**

On Oct. 15, the U.S. Preventive Services Task Force released a report recommending against the routine use of estrogen and progestin "for the prevention of chronic conditions in postmenopausal women." The text of the task force report is available at www.preventiveservices.ahrq.gov.

*Environmental Health:*

## Three Mile Island: No Increase In Cancer Deaths, Study Finds

In a 20-year follow-up study of mortality data on residents living within a five-mile radius of Three Mile Island, researchers at the University of Pittsburgh's Graduate School of Public Health found no significant increase overall in deaths from cancer.

The findings were published Nov. 1 on the Web site of Environmental Health Perspectives, http://ehis.niehs.nih.gov, a journal of the National Institute of Environmental Health Sciences.

"This survey of data, which covers the normal latency period for most cancers, confirms our earlier analysis that radioactivity released during the nuclear accident at TMI does not appear to have caused an overall increase in cancer deaths among residents of that area over the follow-up period, l979 to l998," said Evelyn Talbott, professor of epidemiology at GSPH and principal investigator on the study. Talbott's previous study, published in the June 2000 issue of Environmental Health Perspectives, analyzed 13 years of mortality data.

The TMI incident occurred near Harrisburg, Pa., on March 29, 1979, when a reactor leaked small amounts of radioactive gases. Scientists calculated that the average person in the area during the 10 days following the incident was exposed to considerably less radiation than the annual dose an individual receives from the everyday environment in the U.S.

The study examined causes of death that included heart disease and malignancies as well as specific cancers known to be sensitive to radioactivity: bronchus, trachea and lung; breast; lymphatic and hematopoietic tissue, excluding chronic lymphocytic leukemia and Hodgkin's disease; and the central nervous system. Thyroid cancer was considered, but only one death was reported during the study period.

Researchers used information collected by the Pennsylvania Department of Health in interviews conducted with 32,135 TMI residents within two months of the accident. The ratio of the number of observed deaths in the TMI "exposed" population was compared with the expected number of deaths in the general population. The overall number of cancer deaths among men and women in the TMI population was not significantly different from the general population, but there was a slight increase in the number of deaths from lymphatic and hematopoietic cancers in women in the TMI population.

*Guest Opinion:*

## Long Island Study's Repository An Opportunity For Research

**By John S. Kovach**

Public health advocates concerned about high rates of breast cancer on Long Island have been criticized recently in the regional and national press after two studies failed to show a link between environmental pollutants and breast cancer. The advocates, critics say, have long overstated the size of the breast cancer problem on Long Island in order to gain political leverage for support of research. Some critics went so far as to call for a halt to such research stating that there is no evidence for a significant environmental cause of breast cancer on Long Island, and even if there were, it could not be found (New York Times editorial, "Breast Cancer Mythology on Long Island," Aug. 31).

Nothing could be further from the truth. There is solid epidemiological data indicating that environment and lifestyle play major roles in breast cancer causation. North America leads the world in breast cancer. In the US, Suffolk County, Long Island is virtually tied for the third highest rate of breast cancer with Atlanta, San Francisco, and San Jose, ranking just behind Connecticut (Long Island's coastal neighbor), and the leader, Seattle-Puget Sound. Asia has four- to seven-fold less breast cancer than the West, but when Asians migrate to the US, their breast cancer incidence almost doubles within ten years and their daughters' and granddaughters' risk rises to the US level. Reproductive factors (primarily early menarche and late menopause, number of births, and duration of breast-feeding) account for some of this increase, but there is no doubt that environment and lifestyle contribute to the US breast cancer epidemic.

Rather than discount the community and political effort it took to fund and carry out challenging population-based case-control studies on Long Island, we should congratulate those who conducted rigorous investigations of a possible association of known pollutants with breast cancer. Experts in epidemiology and environmental toxicology designed the Long Island Breast Cancer Study Project (LIBCSP) in 1993 based on existing knowledge and technology. A reasonable decision was made to study polycyclic aromatic hydrocarbons (PAHs), chemicals in the smoke from fossil fuels and tobacco and in grilled and smoked meat known to cause breast cancer in

rodents; and organochlorines, pesticides that have estrogen-like characteristics and are widely distributed in the environment.

Study of over 3000 women with and without breast cancer did not show a link between the amount of these toxins in the blood and the disease. However, the analysis failed to show a correlation between intensity of exposure and the amount of PAHs in blood, raising the possibility that women (at least) differ in their ability to eliminate these toxins from the body. The recent report by Pierre Band and colleagues (*Lancet*, October 5, 2002) that early smoking by premenopausal women who had been pregnant and heavy smoking by premenopausal nulliparous women significantly increases breast cancer risk demonstrates that PAHs are important to breast cancer causation in some women after all. However, as was shown for radiation in studies of breast cancer in Hiroshima and Nagasaki, the time of exposure to PAHs in the life of a woman is a critical determinant of risk. Carefully constructed databases like the LIBCSB repository provide opportunities to address such questions and other hypotheses rapidly and efficiently in the future. Rather than despair about the difficulties in tracking down environmental contributors to the cause of complex diseases like breast cancer, we should seize the opportunity provided by modern biotechnology to discover the basis of inborn and acquired susceptibility to serious chronic illnesses.

For most cancers and other complex diseases, no single toxin is clearly linked to high risk. Unlike infectious diseases for which a sole cause can be identified, cancer occurs only after several genes are damaged in the same cell. Many factors contribute to the body burden of altered genes including normal metabolism, intrinsic ability to repair gene damage, and a host of environmental agents such as PAHs and other chemicals, radon, and cosmic radiation.

Everyone accumulates genetic damage with aging. Most of us are lucky and either do not sustain the several gene "hits" in the same cell that must occur for cancer to develop, or our bodies promptly reject such altered cells. In a kind of macabre biological bingo, some of us are not so lucky and do sustain the multiple hits needed to let a single cell run wild. For those who inherit one or more altered genes that contribute to the cancer process (present in 5 to 10% breast cancer cases), fewer hits are needed to fill their cancer bingo card. These individuals are more likely to develop cancer and to do so at an earlier age than those who begin life without a genetic predisposition. Of course, those who intentionally or unintentionally are exposed to high concentrations of gene toxins day in and day out, such as cigarette smokers and farmers working in the sun, have greatly increased risks of lung and skin cancer, respectively, as compared to those not exposed to tobacco smoke and ultraviolet radiation.

The explosion in knowledge about the human genome and advances in environmental research, biotechnology and computer science offer unprecedented opportunities to discover the origins of cancer and other chronic diseases. The resources needed for this research are databases of two or more generations of families that can be followed for years. Such databases will pay dividends in understanding the basis of inherited disease risk and, in time, the role of environment-gene interactions in disease causation. A ***proprietary*** database in Iceland has already demonstrated the power of genomics, merged with epidemiology, in discovering genetic determinants of susceptibility to a variety of chronic diseases *(A Genomic Treasure Hunt*, *New York Times*, June 18, 2002).

Establishing equally robust databases in the ***public domain*** that can be readily shared among qualified investigators is a daunting challenge for academic centers and requires government support. It is an even greater challenge for the public, who must be willing to give their time, personal information, blood and tissue samples, and permission to investigate potentially their entire genome in normal and diseased tissue without expectation of direct benefit. Without large public securely coded databases, time and expense are wasted by the need to create a new database each time an investigator wants to test a new hypothesis. Small databases abound but in general are not shared for competitive reasons or because their content or consent procedures do not permit evaluation of a new concept. The inability to test multiple hypotheses and compare results in the same well-defined populations makes it difficult, if not impossible, to detect gene/environment interactions within individual patients, the very processes which lie at the heart of the problem.

An informed community, knowledgeable about the potential benefits, risks (both personal and societal), and costs is an essential partner in modern medical research. Long Island was and is an excellent region to develop ***public*** databases for the study of breast cancer and other chronic diseases. This is not

because Long Island is number one in breast cancer but because the people of the Island have demonstrated the political will, community support, and scientific expertise to actually do it.

Regardless of the locale, a carefully constructed repository of medical and personal data associated with properly stored DNA, RNA, serum and diseased tissue from a few hundred thousand individuals, supplemented by smaller databases of underrepresented ethnic groups, could provide an invaluable national resource. With such a resource we can realize the potential of the post-genomic era for the benefit of public health.

*The writer is director of the Long Island Cancer Center, Stony Brook University, Stony Brook, New York.*

## *Funding Opportunities:*

# RFA Available

**RFA-TW-03-004: International Cooperative Biodiversity Groups**

NIH, the National Science Foundation, and the U.S. Department of Agriculture invite applications that address the interdependent issues of biodiversity conservation, economic capacity, and human health through discovery and development of therapeutic agents. The agents would be for diseases of importance in developing countries as well as those important to developed countries. Particularly relevant disease areas and health needs include cancer, HIV-AIDS and its opportunistic infections, tuberculosis, malaria, and other emerging diseases, mental disorders of adults and children, drug abuse and cardiovascular and pulmonary diseases. The RFA calls for the development of interdisciplinary programs through the establishment or continuation of international cooperative biodiversity groups, with active and substantial participation by U.S. and developing country scientists and institutions. The overall goals of the ICBG program are drug discovery, biodiversity conservation, and economic development. The RFA is available at http://grants1.nih.gov/grants/guide/rfa-files/RFA-TW-03-004.html.

Inquiries: Joshua Rosenthal, deputy director, Division of International Training and Research, Fogarty International Center, NIH, 31 Center Dr., MSC 2220, Bethesda, MD 20892-2220, phone 301-496-1653; fax 301-402-0779; e-mail joshua_rosenthal@nih.gov.

# Program Announcements

**PA-03-013: Small Business Grants for Identifying Molecular Signatures of Cancer**

NCI Cancer Diagnosis Program invites small business innovation research or small business technology transfer grant applications proposing the application of existing comprehensive molecular technologies to the discovery of DNA, RNA, or protein signatures in human specimens. The molecular signatures should correlate with clinical parameters in cancer or address questions or needs in clinical cancer research. The PA encourages interdisciplinary teams of investigators to refine and/or translate molecular analysis technologies to uncover molecular profiles of cancer. Support for the PA is through the SBIR and STTR mechanisms. Applications can be submitted for phase I STTR R41 or phase I SBIR R43 grants; phase II STTR R42 or phase II SBIR R44 grants; or the SBIR/STTR Fast-Track option. The PA is available at http://grants1.nih.gov/grants/guide/pa-files/PA-03-013.html.

Inquiries: Min Song, Division of Cancer Treatment and Diagnosis, NCI, Executive Plaza North, Rm 6035, Bethesda, MD 20892, phone 301-402-4185; fax 301-402-7819; e-mail ms425z@nih.gov.

**PAR-03-010: Small Grants Program for Cancer Epidemiology**

Application Receipt Dates: April 21, Aug. 20, Dec. 22, 2003; April 20, Aug. 20, Dec. 20, 2004; April 20, Aug. 22, 2005

NCI Division of Cancer Control and Population Sciences invites Small Grant R03 applications for short-term awards with a primary focus on etiologic cancer research. The awards would support pilot projects, testing of techniques, or development of projects that could provide a basis for more extended research. High priority areas in cancer epidemiology research include multiple myeloma and cancers of the breast, colon/rectum, prostate, lung, pancreas, and brain. Reports are available at http://www.nci.nih.gov/research_programs/priorities/. Applicants are encouraged to review the reports and consider research in these areas.

Examples of research proposals that would apply to this PA include, but are not limited to: validating measurements in body fluids and tissues of exogenous exposures associated with the development of cancer; planning an epidemiologic study to apply validated relevant carcinogenesis markers to better understand the natural history of neoplasms and identify individuals at high risk; determining applicability of biomarkers of tumor initiation and progression for epidemiologic studies; developing and validating methods, including statistical applications, to measure dietary components and metabolites in foods and body fluids; developing a novel way to explore the relationship of obesity to cancer risk; or developing methodology to collect epidemiological data via the internet, maintaining integrity and confidentiality. The PA is available at http://grants1.nih.gov/grants/guide/pa-files/PAR-03-010.html.

Inquiries: Virginia Hartmuller, Division of Cancer Control and Population Sciences, NCI, 6130 Executive Blvd., Rm 5102, Bethesda, MD 20892-7324, phone 301-594-3402; fax 301-402-4279; e-mail hartmulv@mail.nih.gov

*In Brief:*

## Childhood Cancer Foundation Changes Back To Its Old Name

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permanent director is selected through a national search. Wilding, the Donald and Marilyn Anderson Professor of Medicine, is head of the Medical Oncology section in the Department of Medicine at the UW Medical School and is director for clinical programs at UWCCC. He directs the UWCCC Experimental Therapeutics Program and is chairman of the Genitourinary Cancer Committee of the Eastern Cooperative Oncology Group. . . . . **NATIONAL CHILDHOOD CANCER FOUNDATION**, which changed its name to the Foundation for the Children's Oncology Group, has decided to be known once again as NCCF due to popular demand. Information about the group, whose mission is to support the Children's Oncology Group, is available at www.nccf.org. . . . **CATHERINE LYONS** was named associate director for Strong Health cancer services of the James P. Wilmot Cancer Center at the University of Rochester Medical Center. Lyons was chief of clinical trials support and research nursing at NCI. . . . **PETER DEMANT** has been appointed distinguished member of the Department of Molecular & Cellular Biology at Roswell Park Cancer Institute. He was head of the Division of Molecular Genetics at the Netherlands Cancer Institute in Amsterdam. . . . **SOCIETY OF GYNECOLOGIC ONCOLOGISTS** has established its first endowed lectureship in honor of **Hugh Barber**, a founding member. **Lawrence DeLucas**, astronaut, space scientist, and optometrist at the University of Alabama at Birmingham, was selected as the first Barber lecturer. . . . **LEONARD GOMELLA** has been named chairman of the Department of Urology at Jefferson Medical College of Thomas Jefferson University. Gomella, the Bernard W. Godwin Jr. Professor of Prostate Cancer and director of Urologic Oncology, Jefferson Kimmel Cancer Center, will serve as chairman of urology at TJU Hospital. . . . **NEW MEXICO** is the most recent state to take advantage of the federal Breast and Cervical Cancer Prevention and Treatment Act of 2000, which allows states to expand Medicaid coverage to women were screened through the National Breast and Cervical Cancer Early Detection Program.

THE CANCER LETTER

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# Business & Regulatory Report

*Clinical Trials:*

## BMS, ImClone Submit New Protocols For Large Phase III Trials Of Erbitux

**Bristol-Myers Squibb Co.** (NYSE:BMY) and **ImClone Systems Inc.** (Nasdaq: IMCL) said they submitted to the FDA two protocols for large phase III trials of Erbitux in colorectal cancer.

The plan includes a proposed phase III trial evaluating the monoclonal antibody and irinotecan vs. irinotecan as a single agent in patients with EGFR-positive second-line metastatic colorectal cancer.

Another proposed phase III trial would evaluate Erbitux and

(Continued to page 2)

*Oncology Management:*

## NCCN Expands Web Site, Guidelines; Firm Offers Management System

**National Comprehensive Cancer Network** of Rockledge, PA, said it has improved its Web site (www.nccn.org) to make clinical trials information more accessible through its Treatment Guidelines for Patients.

"NCCN is committed to providing patients with convenient access to clinical trials information as a means of seeking out new oncology treatments," said William McGivney, CEO of NCCN. "It is our hope that through the use of our newly-expanded Web site, more patients will be encouraged to enroll in these trials."

Patients looking for clinical trials will find direct links to current trial information from NCCN member institutions, the organization said.

The guidelines were produced by NCCN and the American Cancer Society by translating the NCCN Clinical Practice Guidelines, originally designed for oncologists, into reliable, specific, easy-to-understand educational materials for patients with cancer, their family, and caregivers.

The series covers supportive care topics such as nausea and vomiting and cancer pain, and provides information on cancer of the prostate, lung, breast, ovaries, colon and rectum. In addition to information about specific types of cancer, patients are provided with the same decision trees used by their doctors.

NCCN, an alliance of 19 cancer centers, develops, updates, and disseminates a library of clinical practice guidelines.

* * *

**DoctorQuality Inc.**, an Internet-based healthcare management company, said it will provide its Web-based Risk Prevention and

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## Bristol-Myers, ImClone Plan Two Phase III Erbitux Studies

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oxaliplatin/5FU vs. oxaliplatin/5-FU in patients with EGFR-positive second-line metastatic colorectal cancer.

"These protocols have been submitted to the FDA for a formal FDA review process called a special protocol assessment, and the companies are awaiting feedback from the agency," the companies said.

The update by Bristol and ImClone followed a report by TheStreet.com that a randomized phase II study of Erbibux conducted by Merck KGaA study in Europe appears to be negative. ImClone and Merck denied this report.

Merck has a license to develop and market the agent in Europe. Bristol and ImClone are partners in U.S. development.

The Merck KGaA phase II study completed enrollment of 330 patients last May. "When the results are available, ImClone Systems, Bristol-Myers Squibb and Merck KGaA intend to review these European data with the FDA," the companies said.

Bristol and ImClone are also conducting a phase II single-agent trial in 250 patients with colorectal cancer who are refractory or intolerant to chemotherapy. That trial was initiated in August, the companies said.

"The companies have met with and are engaged in ongoing discussions with FDA regarding the implementation and execution of the clinical development program and registration strategy in colorectal cancer," Bristol and ImClone said in the joint statement. "Pending analysis of the data, the clinical trials could provide multiple opportunities for the companies to seek accelerated approval.

* * *

**Aton Pharma Inc.** of Tarrytown, NY, a privately-held company, said it has initiated a single-agent phase II trial of its lead product candidate, SAHA, in cutaneous T cell lymphoma and peripheral T-cell lymphoma.

An additional single-agent phase II study in recurrent or metastatic squamous cell cancer of the head and neck has also been initiated, the company said. SAHA is an inhibitor of histone deacetylase. The trials will be conducted at M. D. Anderson Cancer Center.

Aton Pharma, Inc. has an exclusive license to SAHA, which was discovered by researchers at Memorial Sloan-Kettering Cancer Center and Columbia University. Defects in histone acetylation may occur in several cancer types, the company said. Aton has shown that administration of SAHA increases histone acetylation in cancer patients. Increased levels of histone acetylation lead to changes in gene expression that are believed to inhibit tumor growth, the company said.

* * *

**Dendreon** (Nasdaq: DNDN) of Seattle said it has resumed enrollment in the second phase III trial of Provenge, a vaccine for hormone-resistant prostate cancer.

Following a partial clinical hold FDA placed on the trial in April, Dendreon submitted additional information on the manufacture and characterization of the vaccine, the company said. The phase III study in men with hormone-sensitive prostate cancer, which was not subject to the partial hold, has continued, the company said.

"We view the successful review of our manufacturing and characterization information as a major step forward," said Christopher Henney, chairman and CEO of Dendreon. "We believe this action, combined with the positive results received this summer from our first phase III trial of Provenge place Dendreon in a strong position and will work with FDA to move Provenge toward registration."

Results from the first phase III trial

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demonstrated that men with hormone resistant prostate cancer who have a Gleason score of 7 or less, which represents over 75 percent of this patient population, significantly benefited from the treatment, the company said.

The trial involved 127 men with metastatic, hormone-resistant prostate cancer, 82 of whom received Provenge. All patients enrolled in the trial had advanced prostate cancer and most had failed all conventional medical and surgical therapy options at the time they were enrolled. The primary endpoint for the study was time to objective disease progression, the company said.

In patients with a Gleason score less than or equal to 7, the placebo group had a median time to disease progression of 9.0 weeks compared to 16.0 weeks in the Provenge treated group, with a highly significant p-value of 0.002 and a treatment effect of 78 percent, the company said.

The patients receiving Provenge whose disease had not progressed six months after randomization, had a greater than eight-fold advantage in progression-free survival compared to the patients who received placebo (34.7 percent of Provenge patients versus 4 percent of placebo patients).

In addition to the Provenge trial D9902 for patients with hormone-resistant prostate cancer, a Provenge trial, P-11, continues enrollment for hormone sensitive prostate cancer, the company said.

* * *

**Direct Therapeutics Inc.** of Redwood City, CA., said it has received approval of the United Kingdom Medicines Control Agency to begin the first European trial of DTI-015, a chemotherapy designed for direct injection to brain tumors.

The single-center study will be conducted at the Walton Centre for Neurology and Neurosurgery under the direction of physicians from the University of Liverpool, the company said.

The study will examine the clinical safety and efficacy of DTI-015 administered at time of tumor biopsy for newly diagnosed primary anaplastic astrocytoma (grade III brain tumor) or glioblastoma multiforme (grade IV brain tumor) and will also examine the effects of DTI-015 on tumor vasculature.

The trial also paves the way for DTI-015 to be considered for marketing approval throughout the European Union, where it has already received orphan drug designation for the treatment of gliomas, the company said.

"The European study provides an important opportunity to extend treatment to patients with newly diagnosed disease, where our drug's impact on overall survival time may be greatest," said Edward Luck, president and CEO of Direct Therapeutics.

After DTI-015, patients will go on to receive standard therapies for the treatment of their brain tumors as directed by their physician, the company said. In the U.K., the treatments include radiation therapy and intravenous chemotherapies, and surgery.

Two earlier phase I/II studies, both conducted in the U.S., established the maximum tolerated dose of DTI-015 and demonstrated its safety and activity for recurrent inoperable high-grade gliomas, the company said.

A single-center, physician-sponsored phase I/II trial, conducted at the University of Texas M.D. Anderson Cancer Center for recurrent inoperable high-grade gliomas, demonstrated a doubling of median overall survival time—from the expected 25 weeks to 55 weeks—for patients with recurrent inoperable glioblastoma multiforme who were treated at or below maximum tolerated dose, the company said.

Direct Therapeutics said it had concluded the treatment portion of its multi-center, company-sponsored, phase I/II study of DTI-015 for recurrent inoperable glioblastoma multiforme.

Patients in both the Direct Therapeutics and M.D. Anderson studies had recurrent tumors that were deemed inoperable, the company said. All had been heavily treated for their disease before entering the study. Many had undergone two or more surgical procedures, all received radiation therapy, and most received intravenous chemotherapy with nitrosoureas.

DTI-015 contains carmustine (1-3 bis [2-chloroethyl]-1-nitrosourea) in an ethanol solvent base, the company said. Carmustine is used to treat brain tumors by intravenous injection, a method that limits the dose because it exposes the whole body to the serious toxicities of the drug. DTI-015, in contrast, is injected directly to brain tumors using standard image-guided stereotactic injection, a minimally invasive surgical procedure similar to that used for obtaining brain tumor biopsies, the company said.

The ethanol solvent vehicle in DTI-015 transports the carmustine selectively throughout the tumor mass and into both the aqueous and lipid compartments of tumor cells. As a result, DTI-015 saturates tumor tissue with high doses of carmustine, the company said.

*Oncology Management:*

## Children's Hospital Of Omaha Uses DoctorQuality System

(Continued from page 1)

Management System to Children's Hospital of Omaha.

The system allows employees to report and track patient safety incidents online at its facilities. Authorized employees at the facilities can either anonymously report an error or near error or complete an actual incident report online—and the data is entered into a secure data base that each institution exclusively owns, the company said.

"We are eager to embrace the DoctorQuality Risk Prevention and Management System and become a leader in early adoption of Internet tools that can impact on medical outcomes," said Gary Perkins, CEO of Children's Hospital. "We have an aggressive commitment to putting into place a surveillance and reporting system that can keep our environment as safe as possible for our patients."

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**Nextphase International Corp**. of Austin, TX, has developed clinical trial data management solutions with built-in mobility.

The new solutions, which are based on the company's ctSeries clinical trial data management product, enable medical professionals to capture patient data through a variety of wireless devices.

The company also announced the formation of Nextphase Clinical Mobility Group, a wholly-owned division that will continue to develop and implement new mobile clinical trial solutions for the future.

"From our experience and research at clinical trial sites around the country, we have learned that patient examination rooms are not always equipped with Web-enabled PCs, and that traditional desktop data entry points are not always available when data needs to be entered," said Ed Risinger, chief operating officer of Nextphase. "Now, our mobile solutions give sites the added option of equipping medical professionals with wireless computing devices such as the new Tablet PC. As a result, patient data can be captured from anywhere within the office, so that it is immediately available for management purposes."

The company said it plans to introduce supporting technologies, including turnkey network solutions for clinical trial sites, wireless patient event management systems, and wireless/wireline patient diary reporting systems.

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**Ohio State University Medical Center** of Columbus, OH, said it has entered into an agreement with **McKesson Automation Inc**. to use its MedCarousel, a medication delivery process.

MedCarousel is a vertical medication storage and retrieval system for hospital pharmacies, that automates the dispensing of medications through the use of bar code scanning and pick-to-light technologies, comprehensive workflow software and rotating shelves, the company said.

"MedCarousel improves the efficiency of the dispensing process, consolidates shelving and brings the shelves to the person doing the restocking," said Jerry Siegel, senior director of pharmaceutical services at OSUMC. "I was most attracted to the system's efficiency and accuracy, achieved as a result of MedCarousel dispensing after receiving a real-time order from the pharmacy system."

Built on the foundation of McKesson's ROBOT-Rx automated dispensing technology, the MedCarousel system uses barcode verification to reduce errors during the dispensing process, the company said.

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**Royal Philips Electronics** (NYSE:PHG, AEX: PHI) of Cleveland is marketing AcQSim MR, a software package that uses magnetic resonance imaging to plan radiation treatments and the Panorama 0.23T R/T, an MR system for radiation therapy planning.

MRI for treatment planning can be used in cancers of the prostate, brain, head/neck, spine, and soft tissue sarcomas of the extremities, the company said.

Fox Chase Cancer Center has been conducting a study using AcQSim simulation software with MR in conjunction with CT images to evaluate the differences in targeting accuracy, the company said. Since Fox Chase acquired a Philips MRI scanner for its radiation oncology department in May 2000, their studies have included more than 400 patients with prostate, brain and other cancers.

"Can you routinely plan treatment with MR simulation and not require the CT?" said Gary Freedman, radiation oncologist, Department of Radiation Oncology, Fox Chase Cancer Center. "This is what we hoped to determine when we began using the MR for simulation. Our studies have shown that the addition of MR images has improved our targeting



accuracy particularly for tumors in soft tissue like prostate cancer. Using MRI for simulation, we are able to design a more precise treatment plan to target the disease and spare more normal tissue. We have been using MRI technology for all of our prostate cancer treatments for the last year. Philips' AcQSim MR is an important new breakthrough that brings together the MRI imaging and AcQSim technologies into one system. This could simplify the simulation and treatment planning process and will improve the overall accuracy and efficiency of the department, and the simulation process for the patients."

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**Johns Hopkins University** has licensed the **Spotfire Inc.** DecisionSite software to analyze genetic data across a wide spectrum of its medical research, Spotfire announced today.

Spotfire, based in Somerville, MA, is a provider of Guided Analytic applications for interpreting, capturing and sharing analyses of large amounts of data from multiple sources.

The license extends to any researchers involved in gene expression data analysis, including scientists in its biomolecular and microarray core facilities. Scientists analyze gene expression data to study how cellular structures, often in a disease state, carry out specific genetic instructions. Spotfire's software provides a visual data query and analysis environment that can replace spreadsheets and other painstaking data analysis tools.

*Deals & Collaborations:*

## Cell Pathways Selects CP461 As Lead Oncology Agent

**Cell Pathways Inc.** (Nasdaq: CLPA) of Horsham, PA, said that it has selected investigational drug CP461 as the lead oncology indication as a single agent in hormone-refractory prostate cancer.

The decision was based on three ongoing pilot phase IIa studies investigating the safety and efficacy of CP461 as a single agent in hormone-refractory prostate cancer, renal cell carcinoma, and chronic lymphocytic leukemia, the companies said.

"All three pilot studies have generated encouraging early results," said Robert Towarnicki, chairman and CEO of Cell Pathways. "Moreover, the activity seen even at low doses of CP461 in prostate cancer, coupled with our past prostate cancer results with Aptosyn, a drug that attacks the same molecular target as CP461, suggest moving forward with hormone-refractory prostate cancer as a lead oncology indication for CP461."

**In another development,** Cell Pathways and **Celgene Corp.** (Nasdaq:CELG) signed a three-year agreement aimed at broadening physician awareness and sales of Gelclair Concentrated Oral Gel within the U.S. oncology market.

Under the agreement, Celgene will promote Gelclair using its oncology sales force of approximately 90-95 representatives. Cell Pathways will be responsible for product marketing. Celgene's compensation will be performance-based as determined by a percentage of product sales, the companies said.

Gelclair, launched by Cell Pathways to the U.S. oncology market in June 2002, is a prescription product cleared by FDA for the management and relief of pain due to various causes, including oral mucositis, a side effect of cancer therapy.

Gelclair, a bioadherent oral gel, adheres to the mucosal surface of the mouth where it creates a protective film barrier, the company said. This barrier is designed to protect irritated tissue and exposed or sensitized underlying nerve endings from over-stimulation, thus relieving pain.

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**Correlogic Systems Inc**. of Bethesda, MD, **FDA**, and **NCI** said their collaborative study confirms the success of using proteomics and bioinformatics technology to test for prostate cancer.

Pattern discovery technology was applied to detect patterns of proteins rather than individual biomarkers for prostate cancer, researchers said.

In the study, researchers used the approach and technology employed in an ovarian cancer test to detect 95 percent of prostate cancer cases from a single drop of blood from each patient, the groups said.

Researchers were able to rule out prostate cancer for 71 percent of men with intermediate PSA scores (4-10), which would have allowed them to avoid an unnecessary, invasive biopsy procedure. Most men with PSA scores between 4 and 10 are recommended for a biopsy, even though 75 to 80 percent of them do not have prostate cancer, the groups said.

Using Proteome Quest, the Correlogis proprietary technology for identifying hidden patterns, researchers first examined blood samples of 31 men with known prostate cancer and 25 men without disease, the company said.

From more than 15,000 data points per patient, the technology identified a proteomic pattern that discriminated the cancer from non-cancer samples. Researchers then used the pattern—a computational disease model-to classify an independent set of 266 blinded patient blood samples. The model correctly identified 36 out of 38 cases as prostate cancer. Of the controls, it correctly identified 95 percent as non-cancer, the groups said.

"This new technology has the potential to revolutionize how men are diagnosed with prostate cancer," said David Ornstein, a co-author of the study and assistant professor of Urology at the University of North Carolina, Chapel Hill. "It is likely that it will be possible to use a simple blood test, to accurately identify men who are affected with a harmful prostate cancer but spare healthy men from undergoing unnecessary biopsies."

The study was conducted by researchers from FDA, NCI, Clinical Proteomics Program, the University of North Carolina Lineberger Comprehensive Cancer Center, and Correlogic Systems.

Correlogic Systems is both the co-inventor of the concept of uncovering hidden patterns of proteins and the sole developer of the proprietary algorithms and processes that identified the protein patterns in the study, the company said.

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**Cytyc Corp.** (Nasdaq:CYTC) of Boxborough, MA, said it has a sole source contract with the **U.S. Navy** to provide the ThinPrep Pap Test as the standard of care at its cervical cancer screening centers worldwide.

U.S. Navy screening facilities process 263,000 Pap tests annually, the company said.

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**Dyax Corp.** (Nasdaq:DYAX) of Cambridge, MA, and **Thios Pharmaceuticals Inc.** of Emeryville, CA, announced a collaboration and licensing agreement for the development of therapeutic antibodies against Thios' sulfated glycoprotein target.

The Thios target may play a key role as a mediator of inflammation, the company said. Under the agreement, Dyax will utilize its antibody phage display technology to identify and characterize antibodies that bind specifically to the Thios target, with the goal of blocking the sulfated target and inhibiting inflammation in vitro and in vivo.

Thios will have a specified time period to evaluate the antibodies identified by Dyax' technology, and to obtain an exclusive license from Dyax to further develop and commercialize those antibodies as therapeutic and/or in vitro diagnostic product candidates.

Thios will provide research funding to Dyax for the development of the antibodies, and has also agreed to pay research-based milestone payments should the antibodies identified meet established criteria. If Thios proceeds with clinical development of any of the antibodies identified, Dyax would also receive contingency-based milestone payments, as well as royalties upon successful product commercialization, the companies said.

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**Inhale Therapeutic Systems Inc**. (Nasdaq:INHL) of San Carlos, CA, and **Celltech Group plc** (LSE:CCH)(NYSE:CLL) of Slough, England, said they have entered into a licensing, manufacturing and supply agreement for a multi-product agreement.

Celltech will use the Inhale PEG technology and services for three of its proprietary pipeline products including CDP 860, a PEGylated antibody fragment drug in phase II trials for cancer, a PEGylated antibody fragment products CDP 791 and CDP 484 in pre-clinical development for cancer and rheumatoid arthritis respectively, the companies said.

PEGylation is a technology that prolongs or improves the effectiveness of pharmaceutical products, the company said.

Under the agreement, Inhale will provide exclusive development and manufacturing for each activated PEG, the companies said. In exchange, Inhale will receive milestone and manufacturing payments and royalties on sales of commercialized products.

CDP 860 (PEGylated Anti-PDGF beta-receptor antibody fragment) is a PEGylated humanized antibody fragment that binds to and blocks the beta receptor for platelet derived growth factor (PDGF), the company said. Research suggests that inhibition of the PDGF beta-receptor may enhance the uptake of chemotherapeutic agents selectively into tumors, enhancing the efficacy of the agents. Blockage of the receptor may also have a direct anti-proliferative effect in some tumor types. CDP 860 is being assessed in a phase II study to determine whether it is able to increase the blood flow into a solid tumor, the companies said.

CDP 791 (PEGylated Anti-GFR antibody fragment) is a PEGylated humanized antibody

fragment directed against a growth factor receptor, the companies said. Research suggests that antibodies blocking receptors for certain growth factors will be potent inhibitors of angiogenesis, for treatment of solid tumors when used in conjunction with existing chemotherapeutic regimes. CDP 791 is expected to enter clinical development during 2003.

CDP 484 (PEGylated Anti-IL-1 beta antibody fragment) blocks the effects of the pro-inflammatory cytokine IL-1 beta, the companies said. Research suggests the molecule as a treatment for rheumatoid arthritis and other immunity-related and inflammatory disorders. CDP 484 is in pre-clinical development.

The Inhale proprietary advanced PEG technology was developed by its subsidiary, Shearwater Corp., the company said. PEGylation increases drug circulation time in the bloodstream and improves its solubility and stability. The advantages of PEGylation are to decrease dosing frequency, improve drug efficacy and safety, improve stability, reduce immunogenicity and simplify drug formulation, the companies said.

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**Myriad Genetics Inc.** (Nasdaq:MYGN) of Salt Lake City and **Genetic Technologies Ltd** (ASX: GTG; Nasdaq: GNTLF) of Melbourne, Australia, signed a strategic alliance to cross-license technologies related to the identification of non-coding DNA alterations and the assessment of inherited human diseases.

Under the agreement, Myriad will receive a broad, non-exclusive license to Genetic Technologies' non-coding DNA analysis and mapping patents for all applications in human therapeutics and diagnostics. Genetic Technologies will become Myriad's exclusive marketing agent in Australia and New Zealand for its predictive medicine products for diseases, including breast cancer, ovarian cancer, colon cancer, melanoma and hypertension.

Myriad will pay Genetic Technologies an upfront licensing fee of $1 million, plus annual license fees, the companies said. Genetic Technologies will pay Myriad various option fees and annual product royalties.

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**NuGEN Technologies Inc** of San Carlos, CA, said it has entered into a research collaboration with **Genome Institute of Singapore** to advance the NuGEN amplification and labeling technology for gene expression profiling on the GIS custom-made oligonucleotide microarrays.

"The Single Primer Isothermal Amplification technology is extremely versatile and can be easily integrated with a wide range of detection platforms including microarrays, biochips, beads, and microfluidics technologies," said Jan D'Alvise, CEO of NuGEN Technologies. "GIS is known for its expertise in adapting and integrating cutting-edge technologies to answer biological questions. Our SPIA application for gene expression profiling, called Ribo-SPIA enables gene expression profiling from very small RNA samples."

Lance Miller, formerly of NCI, heads the Microarray and Expression Genomics Laboratory at GIS.

Gene expression profiling provides a snapshot of the genes expressed in specific tissues at specific points in time, the company said. By comparing gene expression profiles, information about the function of certain genes as well as the effect of certain compounds on a gene's function can be gathered.

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**PenRad Technologies Inc.** of Plymouth, MN, and **R2 Technology Inc.** of Sunnyvale, CA, said they have entered into a non-exclusive business alliance to display computer aided detection results for breast cancer on PenRad mammography workstations.

"This integration of CAD and mammography reporting provides physicians a total solution, enabling them to track patient histories accurately and efficiently while identifying more women with breast cancer earlier," said Greg Gustafson, president of PenRad Technologies. "It should help the imaging centers save time and money."

The PenRad Mammography System is a Windows-based software package that improves workflow and increases productivity, the companies said. The system eliminates the need for a keyboard with its touch screen monitors, and through this interface, the radiologist is able to capture patient information and generate interpretive reports. By using a client/server architecture, the system allows for multiple workstations and remote centers, as well as networking with other hospital information systems, the companies said.

Date from clinical trials demonstrated that the system could result in earlier detection of up to 23.4 percent of the cancers detected with screening mammography in women who had a prior screening mammogram nine to 24 months earlier, the companies said.

FDA approved data that shows that the

ImageChecker system on screening mammograms led to a clinically significant reduction in missed cancers, or false negatives, of at least 33.6 percent, the companies said.

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**Paladin Labs Inc.** (TSX:PLB) of Montreal and **Hydro Med Sciences Inc.** of Canbury, N.J., said they have entered into a licensing agreement for a once-yearly implant, Histrelin Hydrogel Implant, for the palliative treatment of advanced prostate cancer.

Under the agreement, Paladin receives exclusive rights for the sale and marketing of the product in Canada while Hydro Med assumes responsibility for manufacturing and development, the companies said.

The implant is a drug-filled, miniature hydrogel implant that utilizes the Hydro Med patented and proprietary Hydron Implant technology, the companies said. It is surgically placed under the skin in the inner aspect of the upper arm during an in-office procedure and provides 12 months of continuous, steady-state drug delivery with a single treatment. The implant is an alternative to leuprolide, goserelin and buserelin injections, which are administered once every one, three or four months.

The implant is in a multi-center, phase III trial in Canada and the U.S., the companies said. Based on interim data, a regulatory submission could be filed in the U.S. by Q3 2003 and in Canada by Q1 2004, the companies said.

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**ZeptoMetrix Corp.** of Buffalo said it is collaborating with **Roswell Park Cancer Institute** on a $500,000 grant from NCI to develop assays for measuring DNA damage caused by reactive oxygen species.

Harold Box, Department of Molecular & Cellular Biophysics, RPCI, and James Hengst, president and CEO, ZeptoMetix Corp., will oversee the operation, the company said.

## *Product Approvals & Applications:*

# FDA Accepts Submission From DOBI For Scan System

**DOBI Medical Systems, LLC** of Mahwah, NJ, said FDA has accepted the fourth module of the pre-market approval application for ComfortScan, its dynamic optical breast imaging system.

The fourth module, submitted earlier this year, is part of the DOBI five-module submission plan accepted by FDA, the company said.

The ComfortScan System identifies angiogenesis and differentiates malignant from benign tumors, the company said.

DOBI is using the FDA modular-submission approach, which divides the traditional PMA application into modules, the company said. Module 4 contains information on manufacturing processes.

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**FeRx Inc.** of San Diego said it has been awarded a $300,000 first-year grant by the FDA Office of Orphan Products Development to conduct an international, multi-center phase II/III trial of MTC-DOX (doxorubicin) for hepatocellular carcinoma.

The company said it may apply for continued funding of up to $300,000 annually for two more years. FeRx received orphan medicinal product designation from the European Agency for the Evaluation of Medicinal Products in August, the company said.

The MTC technology uses a small, externally positioned magnet to create a localized magnetic field within the body, the company said. MTCs enable pharmaceutical agents to be magnetically targeted to specific sites.

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**Mentor Corp.** (Nasdaq:MNTR) of Santa Barbara, CA, said its isoloader prostate brachytherapy workstation has received FDA marketing approval.

"The system provides greater planning flexibility, improved radiation safety, improved control and better documentation, all while saving hours of time for each procedure," said Christopher Conway, president and CEO of Mentor.

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**Nucletron Corp.** of New Orleans said FDA has cleared its Kuske Breast Template, which allows greater precision guidance during interstitial accelerated partial breast irradiation.

Interstitial APBI used with the Kuske Breast Template will standardize the procedure and improve the accuracy of high dose rate breast brachytherapy procedures, allowing treatment in four to five days rather than five to seven weeks with external beam radiation, the company said.

The template was developed by Robert Kuske Jr., professor of oncology at the University of Wisconsin in conjunction with Nucletron Corp., the company said.

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