THE CANCER LETTER INTERACTIVE

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News Analysis:

Reorganization, Money Will Cure Cancer In 21st Century, NCLAC Report Promises

With the thunder of an artillery barrage, the "white paper" of the National Cancer Legislation Advisory Committee brings back the combative rhetoric of the War on Cancer.

The word "war" figures three times on the first page and 20 times throughout the recently released 59-page document.

The word "conquer" figures in the title—"Conquering Cancer: A National Battle Plan to Eradicate Cancer in Our Lifetime"—and appears

(Continued to page 2)

In Brief:

Three Geneticists Of "Knockout" Mice Fame Win Lasker Award For Basic Research

MARIO CAPECCHI, of the University of Utah in Salt Lake City, **MARTIN EVANS,** of Cardiff University, UK, and **OLIVER SMITHIES,** of the University of North Carolina School of Medicine in Chapel Hill, were named the Albert and Mary Lasker Foundation award winners for basic medical research. The three geneticists were recognized for developing gene targeting technology that allows the breeding of "knockout" mice with specific genes disabled. The knockout technology can determine the function of newly discovered genes and create mouse models of genetically influenced human diseases such as cancer, cystic fibrosis and atherosclerosis. **ROBERT EDWARDS,** of the University of Cambridge, won in the clinical research category for the development of human in vitro fertilization. Edwards and his colleague **Patrick Steptoe**, who died in 1988, are credited with research that resulted in the birth of more than 1 million babies since the first test tube-baby was born in 1978. The Lasker award for public service in support of medical research and the health sciences was presented to **WILLIAM FOEGE**, of Emery University and former head of the Centers of Disease Control and Prevention. He is recognized for his work in toxic shock syndrome and Reye's syndrome. The awards, which came with a $50,000 per winner, were presented in New York City on Sept. 21. . . . **CARYN LERMAN**, professor of oncology, psychiatry, and pharmacology and associate director for cancer control and population science at the Lombardi Cancer Center at Georgetown University Medical Center, was named associate director for cancer control and population science at the University of Pennsylvania Cancer Center and director of the Tobacco Research Program at the Leonard & Madlyn

(Continued to page 8)

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NCLAC White Paper Revives Language Of "War On Cancer"

(Continued from page 1)

four times in the introduction. The word shows up 28 times throughout the document.

The report, which is part of a controversial effort by the American Cancer Society to develop a new version of the National Cancer Act, offers something for almost everyone.

NCI-funded investigators would like the recommendation to fund the Institute at above the Bypass Budget and increase the payline to 40 percent. Pharmaceutical companies may like the proposed incentives that include relaxing the requirement that clinical trials demonstrate patient benefit from cancer therapies. The Centers for Disease Control and Prevention would benefit from proposals to escalate a wide range of public health campaigns.

Conquering Cancer is a compendium of every laudable effort that can possibly be attempted in cancer research, cancer care, and cancer prevention and control. However, the document does not prioritize the multi-billion-dollar expenditures needed to make these changes. In contrast, the NCI Bypass Budget offers the President and Congress the opportunity to choose from a menu of "investments" in research programs.

The imagery of war and conquest in the white paper signals an attempt to return to rhetoric abandoned by the past two NCI directors, Samuel Broder and Richard Klausner. The document delivers an optimistic prognosis for the outcome of the war. "Now, we are poised to conquer cancer, but we must marshal the resolve and the resources," the document promises in the introduction. "We are convinced that if our nation takes the right steps, we can eradicate cancer in the 21st century; how early depends largely on how soon the recommendations in this report are transformed into public policy."

This argument—that research has reached critical mass and now the cancer program needs to proceed to application through public health campaigns—is not universally accepted. Cancer has not been reduced to an engineering problem. Though cancer therapies can be developed to attack molecular targets, only one therapy—the Novartis drug Gleevec, approved for acute myelogenous leukemia—does so.

Klausner, the departing NCI director, disagrees with the view that the time has come to speed the cures to the people. "I don't think we should give anyone, the public or the Congress, the sense that we did what we needed to do in basic research, and now it's just a question of application," Klausner said last fall in a debate with Vincent DeVita, former NCI director and co-chairman of the committee that produced Conquering Cancer (**The Cancer Letter**, Sept. 22, 2000).

Addressed to "Congress and the President," the white paper does not discuss the history of the committee and does not name the organization that paid for development of the document. In fact, the advisory committee that developed the paper is like no other in the U.S. government. It has no charter and it's advisory to only one member of the Senate, Dianne Feinstein (D-CA).

Funded by the American Cancer Society, the committee receives no government money and is therefore exempt from the Senate's open-door rules. It was Feinstein who chose DeVita and ACS chief executive John Seffrin to head the committee. The Senator planned to hold a hearing on the plan on Oct. 10, and has begun drafting legislation.

"With the news of recent scientific advances, I now believe that in my lifetime we can find a cure for cancer," Feinstein said in a statement that accompanied the release of Conquering Cancer. "This document provides a comprehensive blueprint for legislation I will introduce later this fall to form our nation's battle plan to win this war," she said.

Feinstein is also the vice chairman of the National

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World Wide Web: http://www.cancerletter.com

Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg
Editorial Assistant: Shelley Whitmore Wolfe

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016
E-mail: news@cancerletter.com

Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724
E-mail: info@cancerletter.com

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Dialogue on Cancer, an ACS initiative that had spun off the committee.

At a time when America is preparing for military action, which may affect the availability of funds for research and health programs, the Feinstein legislation is likely to face an uncertain future on Capitol Hill.

The Cancer Czar? Maybe…

The white paper does not recommend constructing any bureaucratic structure for overseeing what the report describes as the "cancer system." However, the report indicates that, under the proposed new system, the NCI director may no longer serve as head of the National Cancer Program.

The cancer program would need to include many entities, the report suggests:

"Planning should incorporate strategies for maximum communication, coordination and collaboration among involved agencies, organizations and experts to avoid unnecessary delay, discourage duplication, apply current knowledge to maximum advantage, and make optimum use of all resources."

The white paper does not explicitly recommend an earlier proposal by DeVita and Seffrin to create a White House office of the Cancer Czar (**The Cancer Letter**, June 1). However, the language does not contradict that proposal.

Under the Cancer Czar plan, presented to Feinstein earlier this year, behind closed doors and without approval of the committee, the oversight of the cancer program would be handled by a 20-member commission that would include representatives of advocacy groups, the private sector, and heads of government agencies that deal with cancer. The NCI director would be displaced as head of the cancer program and relegated to a smaller role on the council.

Considering that the government's cancer research is a meager $4 billion a year, while direct cancer care adds up to $100 billion, research could become a relatively minor voice, critics say. If you add in the voices of the pharmaceutical companies, advocates for the underserved, and federal agencies with a minor interest in cancer, science could end up drowned out in the noise.

The Cancer Czar structure would threaten the NCI's "bypass" budget authority, which allows the Institute director to go over the heads of the NIH Director and HHS Secretary to inform the President about research opportunities in cancer.

Also under the plan, the National Cancer Advisory Board, which advises the NCI director on the implementation of the cancer program, would be downgraded to an ordinary institute council, and the President's Cancer Panel, a group that advises the President on obstacles to progress against cancer, would be abolished.

In an email to NCLAC leadership, a copy of which was obtained by **The Cancer Letter**, DeVita described the office of the Cancer Czar and the commission as "the one thing most needed, an effective mechanism for overview." The email also indicated that Feinstein favored the Cancer Czar plan.

After the plan was disclosed, ACS officials said on numerous occasions that the idea was advanced by DeVita personally, and was not advocated by the society. Be that as it may, the vague language of the final report allows Feinstein to craft almost any oversight structure she chooses—including that of the Cancer Czar.

The Cancer Czar schema would allow ACS to place its representatives on the policy-making commission. Also, the society would be represented through its common interests with CDC, its Atlanta neighbor and the beneficiary of the Society's Washington lobbying.

For the past two years, CDC has made $100,000-contributions to the ACS-led National Dialogue on Cancer (**The Cancer Letter**, Sept. 22, 2000). The money is added to a $750,000-a-year sole-source cooperative agreement between the federal agency and the society.

CDC Central to Cancer Control Plan

Conquering Cancer establishes CDC as the central agency in running the proposed cancer control campaign.

The white paper proposes development of a "cancer action plan" in every state, giving CDC the authority and sufficient funds to lead this effort. The action plans would include "prevention, early detection, treatment, support services, survivorship, palliative care and end-of-life needs," the document states.

The proposed program would be built on the foundation of the CDC National Comprehensive Cancer Control program, which helps local state departments formulate cancer control plans, the paper states. Only eleven states and one Native American tribe have such plans.

"The objective of the initiative is to establish a total coordinated approach in the war against cancer," the document states. "The CDC Comprehensive

Cancer Control Program is the right place to begin building this new cancer community network."

Other CDC-related initiatives include:

—Expansion of the CDC Racial and Ethnic Approaches to Community Health program.

—Expansion of the CDC National Program of Cancer Registries, the Youth Risk Behavioral Surveillance System, and the Behavioral Risk Factor Surveillance System. The report also recommends increasing funds for the NCI Surveillance, Epidemiology and End Results program.

The NCI SEER program monitors national trends in cancer. The CDC program would go a step further and collect data from all states and use registries in public health interventions. The data could "report on trends, assess program impact, identify cancer clusters and report on suspected increases in cancer occurrence," the document states.

Mainstream epidemiologists tend to be skeptical about "cancer clusters," since these apparent explosions in incidence rarely prove to be statistically significant.

The report also suggests an advertising campaign to increase public awareness of cancer detection. "Our nation needs a cancer public awareness campaign akin to the successful 'Smokey the Bear' campaign to educate providers and the public about cancer prevention, early detection, and the purpose and benefits of cancer clinical trials as a means of delivering quality cancer care," the report said.

FDA Reform?

The report's section on FDA is based on the premise that the agency invariably demands that new drugs demonstrate improvement in survival.

"The current approach for FDA approval of new cancer therapeutics requires that clinical trials uniformly demonstrate that the new treatment can prolong survival," the report states.

This is incorrect. The agency requires that new therapies demonstrate a *benefit to the patient*. That can include pain relief, tumor shrinkage, time to progression of the disease, and, potentially, quality of life.

For some solid tumors—advanced breast and colon cancers—survival is indeed the gold standard for full approval. However, hormonal agents, biologics and therapies for hematological tumors are routinely approved without a demonstration of a survival advantage.

According to FDA, of the 44 approvals of oncology New Drug Applications and supplemental NDAs between 1990 and 2001, 18 approvals were based on response rates and time to progression, and five were based on both response rates and subjective assessment of clinical benefit. This analysis excludes adjuvant indications, chemoprevention, and chemoprotection.

The report carries its fundamental error to the next logical step and recommends a solution:

"A more realistic, interactive and flexible approach using surrogate endpoints for all cancer drug approval decisions would be a meaningful incentive for cancer drug development in the private sector, particularly in the area of prevention and symptom management," the report states.

"Relevant endpoints for gauging clinical benefit, such as slowing disease progress, improving quality of life through management of fatigue and pain or other symptoms should be employed in the regulatory approval process of new cancer drugs."

Actually, the agency routinely uses "surrogate endpoints" for approval of cancer therapies. If FDA staff or the agency's outside clinical advisors agree that an endpoint such as tumor shrinkage may in fact be an indicator of benefit to a patient, a therapy can be given "accelerated approval."

Accelerated approvals are usually based on phase II data, and they usually require that the sponsor make an effort to continue studies to demonstrate a clinical benefit.

The report remains consistently adamant on this subject:

"The private sector can be enlisted to develop new cancer prevention and quality of life drugs and technologies, but negative incentives such as the rigid survival endpoint requirement currently used to assess all new cancer agents must be removed."

NCLAC Recommendations

Though ACS paid for development of the report, the document is not available on the society's Web site. Instead, the document is posted by CancerSource.com, a for-profit site owned by iKnowMed, a marketer of an electronic information management systems for oncologists.

DeVita heads the CancerSource medical advisory board.

The white paper is available at: http://www.cancersource.com/nclac/.

The unedited text of a summary of NCLAC recommendations follows:

1. Fund the NCI Bypass Budget in this and future years and provide additional supplemental funding for critical research that is not adequately covered in the Bypass Budget. Much of our current progress against cancer has been derived from the innovative research ideas of individual scientists. The NCI leads the frontline research effort in the war on cancer, however, currently the NCI is only able to fund about 25 to 30 percent of peer-reviewed and approved grants. As a result, most young investigators have a very difficult time getting their first grants, and every promising application that is unfunded is a missed opportunity. The cost of this loss is inestimable. We can substantially accelerate progress against cancer by funding a minimum of 40 percent of these approved cancer research grants. Fully funding NCI's bypass budget would immediately expedite finding cures, developing new methods for early detection, identifying why some populations have a higher propensity for some cancers, and would improve symptom management and quality of life for those living with cancer. To sustain proven, productive research programs, build our capacity for the future, and seize extraordinary opportunities in cancer research, Congress and the President should meet or exceed this goal.

2. Increase the pool of talented and well-trained biomedical researchers. The number of health care professionals choosing careers in cancer research is critically low, and is fast approaching the crisis level. Our nation needs a new education initiative to summon the "best and brightest" minds to cancer's challenges and to take advantage of the advances already achieved against the disease. In the late 1950's, we faced a similar dilemma. With the launching of Sputnik, it became clear that the U.S. was suffering from a shortage of engineers, physicists and mathematicians. President Eisenhower and Congress responded with the National Defense Education Act which harnessed federal government resources to address the crisis in math and science education, and paved the way for advances in engineering, technology and space exploration. We must act against biomedical talent shortages with that same level of federal commitment by employing the power of the federal government to build a highly trained, culturally diverse cancer research workforce to set the stage for victory in the cancer war. Young investigators and their dreams and ideas are America's most valuable resources in the fight against cancer.

3. Increase National Institute for Environmental Health Science (NIEHS) and NCI funding for cancer research that examines the interaction of genes and the environment. Research has shown that environmental factorssuch as exposure to sun, pollution and certain chemicals-have a major influence on the development of a variety of types of cancer. Our understanding about this issue remains limited, and our investment in this area has been inadequate. We are only just beginning to understand how and why individuals who are exposed to the same environment do not necessarily develop the same health problems. Having sequenced the human genome, we are now in the position to ask new, more relevant research questions in gene-environmental studies, and to develop rational programs in the challenging areas of early detection and prevention of cancer. More attention needs to be focused on determining whether and when exposure to environmental chemicals can cause or exacerbate cancer risks.

4. Enhance our cancer research centers (and other cancer-focused efforts) to build a multidisciplinary network of "translational centers" to move new drugs and technologies forward into clinical trials, and ultimately develop new methods and products to prevent and cure cancer. Our nation's investments in basic research have yielded an explosion of new scientific discoveries. The value of much of this progress will go unrealized, however, unless we act to translate these basic science advances into the medicines to prevent, treat and ultimately cure cancer. The proposed new network of "translational centers" will bring together clinical and psychosocial investigators, biologists, chemists, physicists, mathematicians and computer scientists to accelerate the translation of laboratory advances into the highest practical benefit for those afflicted with cancer. To win the war on cancer, we must ensure that research travels out of the laboratory quickly, and into patients' lives.

5. Streamline and accelerate the Food and Drug Administration's approval system for cancer drugs, biologics, devices and technologies. Many forms of cancer still lack methods for treatment or early detection. New therapies offer those patients their only hope of survival and many cannot outlive the months (or years) it can take for the approval of a new drug or device. Currently, in the US, it takes an average of eight and a half years at a cost of approximately $500 million to develop and bring one new medicine from the laboratory to patients. The FDA review and approval of new cancer therapeutics,

preventives and devices must be accelerated, and differentiated from regulatory procedures for other diseases. Cancer patients need new therapies quickly and a streamlined FDA approval process is critical in order to make safe, efficacious new agents available in a much more timely fashion.

6. Empower federal agencies to build public-private partnerships across the entire continuum of cancer research to ultimately develop new cancer treatments, preventives and technologies. Optimizing the translation and application of scientific advances to defeat cancer will require active participation by the private sector specially the pharmaceutical, biotechnology and device industries. However, the development of new drugs and technologies for cancer is very expensive and few companies can assume all of this significant risk. In particular, the small size of the population with certain individual cancer types is a major barrier to private sector participation. To fully engage the private sector in drug development for all types of cancer, the government must help balance these risks. This will require regulatory changes, novel public-private partnerships and common sense incentives that recognize the difficulties associated with certain therapeutic markets, and the cost of developing new agents for cancer. Meeting this challenge will accelerate the development of new treatments and early detection tools for all cancers.

Recommendations that remove barriers and enhance access and quality. To remove the barriers to accessing quality care and treatment and to improve the delivery of timely, state-of-the-art cancer prevention and care, NCLAC challenges the President and Congress to:

7. Provide adequate health insurance coverage for all Americans concerned about or diagnosed with cancer. More than 40 million Americans lack health insurance, and an additiona120 million lack adequate coverage. A catastrophic illness like cancer means crippling expenditures and more limited access to quality care. Inadequate insurance coverage and unrealistic provider reimbursement rates not only impede access to quality cancer care, but also deter increased enrollment in clinical trials and the use of lifesaving cancer prevention and early detection programs. For example, compared to the insured, uninsured men are 40% less likely to have had a prostate exam and uninsured women are 60% less likely to have had a mammogram. All Americans must have assured access to a full-range of cancer-related services. Steps must be taken to strengthen public and private health care commitments so more Americans can benefit from proven cancer-fighting techniques.

8. Significantly increase the pool of health care professionals trained to conquer cancer. We must build a cancer workforce with the capacity to meet America's needs over the next ten to 30 years, yet the number of people in the United States trained to provide the highest quality cancer care continues its dangerous decline. There are current and impending shortages of oncology nurses, pharmacists, mammographers, and radiation oncologists. Ensuring that we have enough trained caregivers is vital, particularly as our nation grows older and the cancer burden increases. Our ability to deliver quality cancer care in the face of oncoming demographic changes will depend on the ability to recruit more physicians, nurses, social workers, genetic counselors and other healthcare and technical personnel who deliver services and care. We must also alleviate the inequitable and dangerous shortages of health care providers in underserved and poor communities.

9. Launch a National Cancer Screening Initiative to increase substantially the early detection of cancer. We have the tools to detect many of the more common cancers early, when they are more curable. For example, timely and regular screening mammography would prevent more than 30 percent of all deaths from breast cancer in women over the age of 40. Pap tests can prevent virtually all deaths from cervical cancer. Screenings can do the same for colorectal cancer. We urgently need a national initiative to ensure that people are aware of and have access to early detection tools—and to translate lessons learned from ongoing major early-detection initiatives to future screening programs for other types of cancer.

10. Implement comprehensive state-based cancer action plans, in collaboration with all relevant experts in the region. Enormous opportunities exist to prevent and control cancer through better organized efforts at the local, state, regional and national level. We must develop a national network of community-based cancer prevention and control plans in a11 50 states, and associated territories and tribal entities. This will help create the infrastructure our nation needs to reduce the cancer burden and provide better quality treatment at the community level. These plans should combine the

talents of Centers for Disease Control and Prevention (CDC) and experts and programs at the Health Resources Services Administration (HRSA), NCI and NIEHS research centers and other oncology leaders, community health providers and public health leaders.

Meeting this challenge will help establish a total, coordinated approach in the war against cancer. We also must improve the data tracking, surveillance and reporting systems that monitor emerging cancer trends.

11. Develop, communicate and use universal guidelines and practice standards to provide quality cancer care to all cancer patients, and monitor progress through improved quality care surveillance systems. Today no coordinated system exists for preventing, diagnosing, treating, paying for, and monitoring cancer care. Quality of cancer care standards vary by geographic location, socioeconomic status, and culture. We have the tools to deliver high quality cancer care across settings, but much work needs to be done to ensure that we do. Universally-available, high quality cancer care must be a national priority. We must also maintain efforts directed at end of life care and the growing needs and concerns of those living with cancer.

12. Implement a National Cancer Prevention Initiative that focuses on eliminating tobacco use, increasing physical activity and improving nutrition. Tobacco use and poor nutrition cause over 225,000 cancer deaths each year in America - more than one-third of all deaths from cancer. These deaths are entirely preventable. In fact, it is estimated that we could prevent up to two-thirds of all cancer cases if Americans followed existing guidelines for cancer screening, refrained from tobacco use, consumed a healthy diet, exercised, and limited their sun exposure. We need a unified national cancer prevention campaign to reduce the use of tobacco products and promote healthy lifestyles, including good nutrition and physical activity.

In Brief:

Caryn Lerman Recruited By Univ. Of Pennsylvania

(Continued from page 1)

Abramson Family Cancer Research Institute. Lerman, professor of psychiatry at the UP School of Medicine, will also have an appointment at Penn's Annenberg Public Policy Center. "Dr. Lerman's recruitment is such a vital component to realizing our overall mission," said **John Glick**, director of the UP Cancer Center and the Abramson Institute. "Caryn is a pre-eminent cancer control researcher with recognized expertise in tobacco control research. She's an exceptional scientific leader who will significantly elevate the level of research productivity and collaboration throughout the Cancer Center." Her research explores the relationships between genetics and cancer-related behaviors. At UP, Lerman investigates patient decision-making and outcomes of breast and colon cancer genetic testing for high-risk families. As part of a Transdisciplinary Tobacco Use Research Center Grant from NCI and the National Institute on Drug Abuse, her team studies the contribution of genetic factors to nicotine addiction through basic, clinical and population research. Lerman and her colleagues have linked genetic variants in the brain's dopamine and serotonin pathways with smoking behaviors. . . . **W. STRATFORD MAY JR**. has been appointed chairman of the NIH Hematology I Study Section that reviews grant applications and surveys the status of research in the field of hematology. May directs the University of Florida Shands Cancer Center and holds the Harry F. Innes professorship in cancer research at UF's College of Medicine. May's term began July 1 and will run through June 2003. May has been a member of the panel since 1998 and a special reviewer since 1996. He is recognized for his studies of cell signaling mechanisms responsible for growth and death in blood cells and leukemias. . . . **ELECTRA PASKETT** was named associate director of population sciences at the Ohio State University Comprehensive Cancer Center—Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, effective January 2002. She is program director of the Cancer Control Program at the Comprehensive Cancer Center of Wake Forest University School of Medicine and associate professor in the Department of Public Health Sciences. She is also director of the Cancer Prevention and Training Grant at WFUSM and director of the education program at the Women's Health Center of Excellence at the Wake Forest University Baptist Center. Paskett, whose research interests include breast, prostate and colon cancer prevention, is chairman of the Cancer Control and Health Outcomes Committee of the Cancer and Leukemia Group B and a member of the NCI Cancer Review Committee. "Her keen interest in women's health, and dedication to breaking down the barriers to health care among minority and rural populations will clearly enhance and strengthen our commitment to the citizens of Ohio and beyond," said

David Schuler, director of the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute and deputy director of the OSUCCC. Paskett plans to bring at least two researchers with her. . . . **MARCIA GRUBER**, clinical administrative director of the Gastrointestinal Multi-disciplinary Care Center at M.D. Anderson Cancer Center and a certified gastroenterology registered nurse, was named vice president of ambulatory care services at Roswell Park Cancer Institute. Her responsibilities will include all aspects of the ambulatory clinics, including clinical and business operations. . . . **JOAN MURRAY,** associate professor and clinical co-ordinator of pastoral and spiritual care, was named director of the Chaplaincy Service at Memorial Sloan-Kettering Cancer Center. Murray will direct a multifaith team of 50 chaplains. . . . **HHS** has appointed three regional representatives: **BRIAN CRESTA,** Massachusetts Republican Party chairman and state representative, was appointed regional representative for six states: Connecticut, Maine, New Hampshire, Rhode Island, Vermont and Massachusetts. **JOSH VALDEZ** was named regional representative for California, Arizona, Hawaii and Nevada, as well as Guam, the Trust Territory of the Pacific Islands and the American Samoa. Valdez was vice president of operations at AltaMed Health Services Corp. **DEBORAH KONOPKO,** former deputy secretary to New York Governor **George Pataki,** was appointed regional representative serving New York, New Jersey, Puerto Rico, and the U.S. Virgin Islands. Prior to joining the governor's office, Konopko was assistant director for the New York City Office of Management and Budget responsible for a $6.5 billion budget for the New York City Health and Hospitals Corp. Konopko will serve as a link between HHS and disaster relief efforts in the New York metropolitan area. . . . **AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY** Board of Directors decided to proceed with the organization's annual meeting scheduled for Nov. 4-8, in San Francisco. The ASTRO board agreed it was in the best interest of radiation oncologists throughout the world to continue on with the conference. "We plan to hold this meeting as scheduled," said **David Hussey**, ASTRO chairman. "This will be a demonstration of our commitment to the free expression and support of science, the maintaining of our scientific and clinical communities, and the continuation of a way of life and work that a tiny minority would seek to disrupt or end." Further information on ASTRO's 43rd annual meeting is available at http://www.astro.org.

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Business & Regulatory Report

Formerly "Cancer Economics"

Deals & Collaborations:

BMS, ImClone To Develop New Drug IMC-C225, Targets EGF Receptor

Bristol-Myers Squibb Co. (NYSE: BMY) said it has reached an agreement with **ImClone Systems** (Nasdaq: IMCL) to co-develop and co-promote IMC-C225 in the U.S., Canada and Japan.

IMC-C225 is an investigational drug designed to target and block the epidermal growth factor receptor, which is overexpressed on the surface of certain cancer cells, the company said.

The drug could treat several cancers, including colon, head and neck,

(Continued to page 2)

Product Approvals & Applications:

FDA Approves Xeloda For Breast Cancer After Failure Of Anthracycline Treatment

Hoffmann-La Roche Inc., of Nutley, NJ, said FDA has approved its oral cancer drug, Xeloda (capecitabine), in combination with Taxotere (docetaxel), given by infusion, for metastatic breast cancer where anthracycline treatment has failed.

Xeloda is an oral drug that is enzymatically converted into 5-FU. Taxotere, marketed in the U.S. by **Aventis Pharmaceuticals**, works independently to interrupt tumor cell division.

The combination of Xeloda and Taxotere is the first and only chemotherapy combination to extend survival compared to Taxotere alone, the company said. The median survival was extended by three months over Taxotere alone (median survival 14.5 months vs. 11.5 months).

Previously, Taxotere monotherapy (100 mg/m2 dose on day one of each 21 day cycle) has been the only regimen to show improved survival over a standard regimen of mitomycin and vinblastine combination, the company said. The recent findings indicate that treatment with the combination Xeloda+Taxotere had a superior survival with a 22.5 percent reduced risk of death (hazard ratio=0.775, p=0.013) compared to those treated with Taxotere alone, the company said.

The combination of Xeloda+Taxotere also demonstrated a statistically significant superior tumor response of 32 percent compared to Taxotere monotherapy of 22 percent (p=0.009) in the phase III study of 511 patients, the company said. In addition, time to disease progression is significantly longer for patients treated with Xeloda+Taxotere: median 6.1 months vs. 4.2 months with Taxotere alone (p=0.001, hazard ratio=0.643).

"This represents a major advance in the management of women with metastatic breast cancer as improvements in survival are the bottom line,"

(Continued to page 8)

PO Box 9905
Washington DC 20016
Telephone 202-362-1809

BMS To Pay ImClone $1 Bill. At Three Milestones For Drug

(Continued from page 1)

pancreatic and non-small cell lung cancers, the company said. In February 2001, FDA granted ImClone Systems a Fast-Track designation for IMC-C225 for refractory colon cancer.

Under the agreement, BMS will pay ImClone Systems $1 billion in three cash payments for the following milestones: signing of the agreement, completion of the biologics license application submission with FDA, and marketing approval of IMC-C225 by FDA, the company said. In addition, ImClone will receive a share of product revenues.

The term of the commercial agreement runs through at least 2018.

In addition, BMS will acquire approximately 14.4 million shares of ImClone Systems stock though a tender offer made to ImClone shareholders at a price of $70 per share, the company said. Bristol-Myers Squibb estimates that the dilution from the transaction will be between $.05 and $.07 in 2002, and $.05 and $.07 in 2003. The strategic agreement that extends at least through 2018 will be accretive and incremental to the revenue and EPS growth of the company.

ImClone Systems is studying IMC-C225 in a series of phase II and phase III trials. The phase II studies evaluate IMC-C225 in combination with standard therapies for various stages of colorectal cancer, pancreatic cancer, head and neck cancer, and non-small cell lung cancer, the company said. A phase III trial is evaluating combining IMC-C225 with chemotherapy and another study is evaluating combining IMC-C225 with radiotherapy as first line treatments for head and neck cancer.

In another development, Bristol-Myers Squibb said it has entered into a biopharmaceutical collaboration with **Phytomedics Inc**, a private biotechnology company of Dayton,, NJ, to test the production of therapeutic proteins using the Phytomedics proprietary plant-based recombinant proteins secretion technology.

The REPOST technology uses genetically transformed live green plants to synthesize and continuously secrete large quantities of biopharmaceutical proteins from roots into a hydroponic solution comprised of water and low amounts of fertilizer, the company said. The technology, which is conceptually similar to natural rubber or maple syrup production, allows environmentally safe, continuous and efficient production of recombinant biopharmaceuticals. It was developed to provide a rapid and cost-effective solution to large-scale manufacturing of recombinant proteins, the company said.

"With the sheer numbers of biopharmaceutical product candidates under development as a result of the genomics revolution, there is a shortfall of manufacturing capacity for these important molecules," said Bertold Fridlender, CEO of Phytomedics Inc. "Multi-million dollar costs of constructing conventional bricks-and-mortar biopharmaceutical production facilities and years required for their construction creates a serious production bottleneck for the drug industry and a major opportunity for REPOST technology."

Phytomedics conducts its R&D under the leadership of Ilya Raskin, at the Biotech Center at Rutgers University. Raskin, a founder and chairman of the company, heads a research staff of twenty scientists, mostly Ph.Ds, from nine countries working in state-of-the-art facilities, the company said. Phytomedics has a broad research and licensing agreement with Rutgers University that allows it to exclusively license its core technologies and products.

* * *

Array BioPharma Inc. (Nasdaq: ARRY) of Boulder and **Vertex Pharmaceuticals Inc.** (Nasdaq: VRTX) of Cambridge, Ma, said they are developing small molecule drugs directed at two targets in the

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Editor: Paul Goldberg
Editorial Assistant: Shelley Whitmore Wolfe

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016
E-mail: paul@cancerletter.com

Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724

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phosphatase protein family.

Under the agreement, Vertex will provide Array with an upfront fee and research funding over three years, the companies said. Array will be responsible for initial drug discovery, including lead generation and lead optimization; the company may conduct its own research in the area and will be responsible for all aspects of clinical development and commercialization. For products it discovers, Array will be entitled to receive clinical milestone payments, which would be paid on an annual basis for a defined term and are tied to predetermined sales levels, the companies said.

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Boston Scientific Corp. (NYSE: BSX) of Natick, MA, said it has entered into an agreement with **Natural Pharmaceuticals Inc.**, a private company of Beverly, MA, under which NP would supply Boston Scientific with paclitaxel for medical devices.

Boston Scientific has also made an equity investment in Natural Pharmaceuticals, the company said. No terms were disclosed.

Natural Pharmaceuticals has a proprietary technology for producing paclitaxel from yew trees, the primary source for paclitaxel, the company said. The company has access to several million ornamental yew trees under cultivation in the U.S.

Boston Scientific said it plans to continue to coat its coronary stent products and other vascular and non-vascular products with paclitaxel under the worldwide, co-exclusive rights granted to it by **Angiotech Pharmaceuticals Inc.** (Nasdaq: ANPI; TSE: ANP), a Canadian pharmaceutical company that develops medical coatings and treatments for chronic inflammatory diseases through the reformulation of paclitaxel.

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Fast Track Systems Inc. of San Mateo, CA, said the **University of California** San Diego Cancer Center has received an NCI grant to setup the Fast Track TrialSpace technology with collaborating community oncologists participating in clinical trials.

The system distributes trial information through the Internet into handheld computers, enabling physicians and study coordinators to identify promising trials while in the exam room," the company said.

"With approximately 200 oncology trials ongoing in the UCSD system, it's almost impossible to keep up with requirements of every trial," said Georgia Robins Sadler, associate clinical professor of surgery at UCSD School of Medicine and associate director for community outreach at UCSD Cancer Center. "The system will make it easier for oncologists to know what trials are available, and to get current information on patient eligibility criteria."

Fast Track is an information technology company focused on improving and expediting the clinical trials process, the company said. The company applies advanced medical informatics to the labor-intensive, paper-based methods used in clinical trials.

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Gambro AB (Stockholmsborsen: GAMBaST, GAMBbST) of Stockholm, a medical technology and healthcare company, said its wholly owned subsidiary, **Gambro BCT**, has signed an exclusive distribution agreement with **BioTransplant Inc.** (Nasdaq:BTRN) for the distribution of the Eligix product line and with options on future products as stand-alone medical devices.

The Eligix products remove unwanted cells in cancer therapies thereby improving clinical outcomes, the company said.

The territory will be worldwide, exclusive of the US, Canada and Japan, the company said. BioTransplant will receive an upfront licensing fee of USD 4 M plus a milestone for CE marking and future milestones for other new products receiving CE marking, the company said. The two companies will share revenues, based upon a specific formula.

Under the agreement BioTransplant will develop, manufacture and obtain CE marking for its Eligix High Density Microparticles Cell Separation System, the company said. Gambro BCT will be responsible for continued clinical market development and all other aspects of marketing, sales and distribution. The initial applications are to remove tumor and immunoreactive cells for bone marrow and stem cell transplantations, the company said.

Unlike conventional systems which use positive selection of stem and progenitor cells, the HDM technology depletes the unwanted cells through use of specific antibodies targeted against the undesirable cells, thus preserving the spectrum of cells required for facilitating blood and immune system reconstitution, the company said. Enhanced recovery of desired cells plus ease of use factors make this system more suitable in stem cell transplantation and cell based immunotherapy marketplaces.

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Inex Pharmaceuticals Corp. (INEX; TSE: IEX) of Vancouver said it has signed a collaboration

agreement with **Elan Corp. plc** on the clinical development program for the Inex anticancer product Onco TCS, which has been expanded to include two pilot phase II trials evaluating the product in combination with the approved cancer drug Rituxan (rituximab) for non-Hodgkin's lymphoma.

Each trial will evaluate Onco TCS with Rituxan in 14 patients with relapsed B-cell aggressive NHL, the company said. The primary objectives will be to generate safety data of the combination of Rituxan and Onco TCS and to generate preliminary efficacy data.

One of the trials is being conducted at University of Leeds, England, under the direction of Gareth Morgan, the company said. The other is being conducted at University of California, San Francisco, CA, under the direction of Lawrence Kaplan.

Including the two Rituxan combination trials, Onco TCS is now being evaluated in six clinical trials, the company said. A pivotal phase II/III trial under way at medical centres in Canada and the U.S. is evaluating the product for second or later relapsed aggressive NHL. In addition, Onco TCS is being evaluated in three phase II clinical trials—as part of first-line treatment for aggressive NHL, for small cell lung cancer, and for relapsed pediatric malignancies.

Rituxan, developed and co-promoted by **Genentech Inc**. and **Idec Pharmaceuticals Corp.**, is the first monoclonal antibody found to be effective and safe for the treatment of cancer in the U.S and is indicated for relapsed or refractory, low grade or follicular, CD20-positive, B-cell NHL, the company said.

Onco TCS is a proprietary drug comprised of the widely used off-patent cancer drug vincristine encapsulated in the Inex patented drug delivery technology, Transmembrane Carrier Systems, the company said. The TCS technology provides prolonged blood circulation, tumor accumulation and extended drug release at the cancer site. These characteristics are designed to increase the effectiveness and reduce the side effects of the encapsulated drug., the company said.

Results from a phase II clinical trial of Onco TCS, at M. D. Anderson Cancer Center in 1998 and 1999, indicated the drug may reduce the size of tumors in relapsed aggressive and transformed non-Hodgkin's lymphoma, the company said.

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Maxygen Holdings Ltd. of Redwood City, CA, and a wholly owned subsidiary of **Maxygen Inc.** (Nasdaq: MAXY) and **InterMune Inc.** (Nasdaq: ITMN) of Brisbane, CA, said they have signed a license and collaboration agreement to develop and commercialize next-generation interferon gamma products.

Under the agreement, InterMune will take forward into clinical development product candidates created by Maxygen, the company said. InterMune will fund optimization and development of the next-generation interferon gamma products, and will retain exclusive worldwide commercialization rights for all human therapeutic indications. Maxygen will receive up-front license fees, full research funding, and development and commercialization milestone payments, the company said. Payments to Maxygen could exceed $60 million. In addition, Maxygen will receive royalties on product sales.

"We strongly believe in the broad therapeutic potential of interferon gamma and plan to capitalize on future market opportunities with a next-generation product," said W. Scott Harkonen, president and CEO of InterMune. "Our goal is to put a next-generation product into the clinic, with enhanced pharmacokinetics and a less-frequent dosing regimen, within the next two to three years."

Actimmune (Interferon gamma-1b), is marketed by **InterMune** in the U.S.chronic granulomatous disease and severe, malignant osteopetrosis, the company said. InterMune is continuing the development of Actimmune by conducting several advanced stage clinical trials, including a phase III trial for the treatment of idiopathic pulmonary fibrosis and is planning a phase III trial for ovarian cancer.

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MediChem Life Sciences (Nasdaq: MCLS) of Chicago and **Rigel Pharmaceuticals** (Nasdaq: RIGL) of South San Francisco, said they have entered into a two-year collaborative agreement in structural proteomics to develop drugs in ubiquitin ligases, an activity involved in cell division and the progression of certain cancers.

Under the agreement, the MediChem Emerald BioStructures structural proteomics division will express, purify and co- crystallize important protein complexes that are part of the Rigel anti-cancer program focusing on ubiquitin ligases, the company said. When the co-crystallizations are complete, MediChem will use the Argonne National Laboratory Advanced Photon Source to collect the data to determine the structures of the protein complexes at near-atomic resolution. Rigel researchers would then

have a detailed three-dimensional picture of their drug leads bound to the target protein complexes, the company said.

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PSMA Development Company LLC, a joint venture of **Progenics Pharmaceuticals Inc.** (Nasdaq: PGNX) of Tarrytown, NY, and **Cytogen Corp.** (Nasdaq: CYTO) of Lake Tahoe, said it has entered into a worldwide exclusive licensing agreement with **AlphaVax Human Vaccines Inc.** to use the AlphaVax Replicon Vector system to create a therapeutic prostate cancer vaccine incorporating the joint venture's proprietary PSMA antigen.

PSMA is a cell-surface protein that is abundantly expressed on prostate cancer cells at all stages of disease, including advanced or metastatic disease, the company said.

The ArV technology is a vaccine delivery and expression vehicle for prostate specific membrane antigen, a well-recognized marker that is expressed on prostate cancer cells, the company said. Mice inoculated with the vaccine developed robust and specific immune responses to PSMA that persisted for prolonged periods.

The terms of the agreement with AlphaVax were not disclosed.

The PSMA-based therapeutic vaccine, which employs the body's own defense mechanisms to identify and destroy prostate cancer cells, yielded both antibodies and killer T cells, the company said. A subcutaneous injection of a genetically engineered, non-replicating viral vector containing the human DNA sequence that encodes a form of PSMA protein, generated high levels of PSMA-specific cytotoxic CD8+ killer T cells, helper CD4+ T cells and antibodies in mice. The cellular and humoral responses were long lasting, and are essential mechanisms for targeting and eliminating prostate cancer cells, which typically express PSMA on their surfaces, the company said.

"Antigen-presenting cells are an important target for therapeutic cancer vaccines, because they alert the body to the presence of infectious agents and to cancers," said Howard Scher, chief, Genitourinary Oncology Service, Sloan-Kettering Cancer Center." PSMA is a human protein that escapes the immune system. Vaccine Replicon Particles help to break this tolerance, to r,etrain the immune system to recognize PSMA as a danger signal, and to eliminate PSMA-expressing cancer cells."

The core of the ArV system is an engineered, weakened form of Venezuelan Equine Encephalitis Virus, the company said. The re-engineering process produces vaccine replicon particles that encode PSMA but lack the viral genes required to make infectious virus. When VRPs infect a cell in the body, they direct the cell to churn out large amounts (as much as 20 percent of the total cellular protein) of the target antigen and thereby stimulate an immune response to the antigen. The VRPs are non-replicating. This is an important safety feature of the vaccine. The vaccine targets antigen-presenting cell populations in the body and elicits both killer T cell and antibody responses. The advantages of the ArV system over other vaccine technologies include: Natural targeting to the antigen-processing cells of the immune system, High antigen expression levels, Induction of strong humoral and cellular immune responses, sustained potency over multiple simultaneous or sequential inoculations, the company said.

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Zeltia Group (MSE: ZEL.MCM) of Madrid said it would collaborate with **Ortho Biotech Products, L.P.**, a subsidiary in the **Johnson & Johnson**, to co-develop and co-market ET-743, an oncology compound.

The compound, known was originally isolated from a marine invertebrate and is being developed by PharmaMar, a subsidiary of Zeltia, the company said. Phase II clinical trials have shown positive results in sarcoma, breast cancer and other tumors, and a comprehensive development program to further study ET-743 is in place.

Ortho Biotech said it would market ET-743 worldwide, with the exception of Europe, where PharmaMar will market the compound. PharmaMar will manufacture ET-743 drug substance for worldwide use.

Oncology Management:

Impath Buys Clinical Studies Support Services Network

Impath Inc. (Nasdaq: IMPH) of New York, NY said it had purchased the Oncology Clinical Studies network from **Innovative Clinical Solutions Ltd.** (OTC Bulletin Board: ICSN.OB) of Providence.

The national network of more than 20 sites offers clinical trial support services (phases I-IV) to the biotechnology and pharmaceutical industries including protocol design, protocol review, patient recruitment and data collection and analyses, the company said.

OCS has annualized revenues of approximately $2 million with a backlog of 47 contracted studies for 22 biotechnology and pharmaceutical sponsors, the company said.

"OCS's demonstrated ability in managing oncology clinical development within a number of different healthcare settings, including sites such as hospitals and physician practices, greatly enhances our efforts in this area," said Anu Saad, chairman and CEO of Impath. "With the acquisition of OCS, we will have more than 30 sites around the country, making us one of the largest oncology clinical trials networks in the U.S."

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Sanders Morris Harris Group Inc. (Nasdaq: SMHG), a financial services holding company of Houston, said it has entered into an agreement with **M. D. Anderson Cancer Center** and **The Styles Company,** a management and investment group for healthcare ventures, to secure financing for a $100 million advanced proton beam therapy center in Houston.

Sanders Morris Harris Group, M. D. Anderson, The Styles Company and other outside investors will form a limited partnership that will own and operate the project. M. D. Anderson will have full clinical and staffing authority for the center, the company said.

The project is expected to be completed in three years, the company said.

"The M. D. Anderson proton therapy center will be the third and largest facility of its kind in the nation," said Robert Garrison II, president and CEO of Sanders Morris Harris Group. "The 78,000 square foot, 4.0 acre center will have state-of-the-art equipment, including a particle accelerator-based system to provide proton radiation therapy, as well as a full range of related patient and research support services.

Compared to conventional radiation therapy, proton beam therapy has demonstrated significant advantages in the treatment of cancer and a few benign conditions, said James Cox, head, Division of Radiation Oncology at M. D. Anderson. Conventional radiation therapy, which uses photons and electrons, deposits most of its energy in and around tissue near the body's surface, as well as depositing undesirable energy beyond the cancer volume, which results in unnecessary and undesirable effects on healthy organs and normal tissue surrounding tumors and limits the dose of radiation that can be safely administered, which often leads to sub-optimal clinical outcomes. Conversely, proton beam therapy, with its millimeter precision, improves the ability of the physician to place radiation precisely within the tumor itself without destroying surrounding healthy tissue, said Cox.

Two proton beam therapy facilities are operating in the US: the Northeast Proton Therapy Center at Massachusetts General Hospital - Harvard University and the Proton Treatment Center at Loma Linda University Medical Center in southern California.

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Working Concepts Inc. of Columbia, MD, an eHR technology solutions provider, said it has implemented its PeopleSoft's 8 eBenefits Collaborative Application for **Memorial Sloan-Kettering Cancer Center.**

The application eliminates paperwork, makes benefits information more accessible, and improves employee satisfaction & ease of enrollment, the company said. Employees have direct access to personal benefits data and benefit provider Web sites.

Additional eBenefits project features include a flexible spending accounts link allowing employees to view claims processed, current contributions, and FSA balances, the company said. With Working Concepts assistance, eBenefits will enable us to reduce calls to the benefits department, eliminate unnecessary paperwork, and streamline our workflow," said Charnley Marsden, senior application analyst at Memorial.

Clinical Trials:

MGI Pharma, MethylGene Begin Phase II Trial Of MG98

MGI Pharma Inc. (Nasdaq: MOGN) of Minneapolis and **MethylGene Inc.** of Montreal said they have begun a phase II trial of MG98, a second-generation antisense inhibitor of DNA methyltransferase, for advanced and metastatic renal cell carcinoma.

MG98 is a second-generation antisense oligonucleotide that targets mRNA for the nuclear enzyme DNA methyltransferase, which is responsible for silencing tumor suppressor genes, the companies said.

MGI and MethylGene are developing the oligonucleotide to block production of DNA methyltransferase. Preventing DNA methyltransferase production may allow tumor suppressor genes that have been silenced by hypermethylation to be re-activated, the companies said.

The multicenter 30-patient trial will evaluate the efficacy of the inhibitor when given as a two-hour intravenous infusion, twice weekly, for three weeks out of every four-week cycle, the companies said. The primary endpoints are objective tumor response and to evaluate the time to disease progression, overall patient survival and to determine the toxicity and tolerability.

The trial is conducted by NCI of Canada Clinical Trials Group, the companies said. MGI Pharma is developing MG98 under an exclusive North American license, research and development agreement for MG98 and other inhibitors of DNA methyltransferase with MethylGene Inc., the companies said.

Another phase II clinical trial in head and neck cancer is ongoing.

MG98 is well tolerated and has already demonstrated anti-cancer activity in phase I trials, the companies said.

"We have compelling reasons to conduct this phase II trial of MG98 because hypermethylation of tumor suppressor genes is common in many cancers, and a long-lasting objective partial response (75 percent shrinkage of pulmonary metastases) was observed in a metastatic renal cell cancer patient in a phase I trial of MG98 using this dose schedule," said Michael Cullen, vice president of medical affairs and chief medical officer of MGI Pharma. "Preclinical research has demonstrated that targeted inhibition of DNA methyltransferase may result in tumor growth inhibition or tumor regression. This work is considered to be one of the most exciting new approaches for cancer therapeutics in areas such as renal cell carcinoma."

Patents:

Vasopermeation Technology Awarded Patent For CA Firm

Peregrine Pharmaceuticals (Nasdaq:PPHM) of Tustin, CA said it has received a patent for its vasopermeation enhancing agent platform technology, which expands on the claims issued under the patent covering vasopermeability enhancing immuno-conjugates.

The technology has application across solid tumor cancer types and can be used in conjunction with chemotherapeutic agents, monoclonal antibodies, cytokines and other anti-cancer therapeutic agents, the company said.

The VEA technology works by targeting vasoactive compounds to tissues on or in close proximity to tumor endothelial cells, where the compound increases the space between the tumor endothelial cells and permits more of the therapeutic agent to localize at the tumor cells themselves, the company said.

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Board of Regents of The University of Texas System and **Introgen Therapeutics Inc.** (Nasdaq: INGN) said the U.S. Patent and Trademark has granted a patent to UT that covers administration of chemotherapeutic drugs, radiation therapies, or other agents that have a damaging effect on the DNA of cancer cells, followed by administration of gene therapy, regardless of the gene used in the therapy.

Approvals & Applications:

FDA Approves Xeloda For Breast Cancer Treatment

(Continued from page 1)

said Joyce O'Shaughnessy, co-director of breast cancer research at Baylor-Sammons Cancer Center and US Oncology.

The FDA decision was based on the results of a phase III study comparing Xeloda in combination with Taxotere to women treated with Taxotere alone and looked at survival, time to disease progression and tumor response rate, the company said. Women were randomized into either combination (oral Xeloda - 1250mg/m2, twice daily, days 1-14 with one week of rest - plus i.v. Taxotere - 75mg/m2, day 1 of each 21 day treatment cycle) or monotherapy (i.v. Taxotere 100mg/m2, day 1 of each 21-day treatment cycle) groups.

Xeloda+Taxotere combination was better than Taxotere alone in all major outcome measures, the company said. Median survival among women treated with the Xeloda+Taxotere combination compared to Taxotere alone was 14.5 months vs. 11.5 months, (p=0.013). Median time to disease progression was 6.1 months vs. 4.2 months (p=0.001). Tumor response rate was 32 percent vs. 22 percent (p=0.009). The Xeloda+Taxotere study was conducted in the U.S., Canada, Australia and countries in Europe, Asia and Latin America.

The combination of Xeloda and Taxotere caused more adverse events than Taxotere alone including more diarrhea, stomatitis, hand-foot syndrome and nausea and vomiting, the company said.These were

manageable with appropriate medical intervention and by dose interruptions.

Dose reductions decreased the overall incidence of adverse events in subsequent cycles, the company said.

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Genta Inc. (Nasdaq: GNTA) of Berkeley Heights, CA, said it has received notice from FDA that Genasense, its anticancer compound, has been granted orphan drug designation for three cancer indications: multiple myeloma, acute myelocytic leukemia, and chronic lymphocytic leukemia.

Genasense already was granted orphan drug status for malignant melanoma, the company said.

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EntreMed Inc. (Nasdaq: ENMD) of Rockville, MD, said that its aniangiogenesis agents Endostatin in neuroendocrine tumors and Panzem for multiple myeloma, received FDA orphan drug status.

Endostatin is a protein drug candidate and Panzem is an orally available small molecule drug candidate, the company said.

FDA accepted the application for Endostatin after reviewing data that demonstrated an absence of dose-limiting toxicities and some clinical benefit in phase I trials, the company said. Although the on-going studies were designed to investigate safety, some patients with neuroendocrine tumors of the pancreas at the Dana-Farber Partner's Cancer Consortium demonstrated tumor stabilization or tumor regression during treatment with Endostatin.

EntreMed also received orphan drug status Panzem, the company said. The drug is in phase II studies for multiple myeloma at the Mayo Clinic and at the Dana Farber Partner's Cancer Consortium.

Panzem also is under clinical investigation for breast cancer, and hormone refractory prostate cancer at University of Indiana Cancer Center and the University of Wisconsin, the company said.

The studies are investigating the effects of the drug candidate as a single agent, as well as in combination with Taxotere, in collaboration with Aventis.

Endostatin is under clinical investigation for solid tumors, including melanoma and sarcoma, where it is being administered by continuous infusion or by subcutaneous injections at M.D. Anderson Cancer Center, Dana-Farber Partners Cancer Consortium, and at the Free University Academic Hospital in Amsterdam, the company said.

Phase I trials are underway at Thomas Jefferson University Hospital in Philadelphia for Angiostatin as a single agent and in combination with radiation therapy, the company said.

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Novartis (NYSE: NVS) of East Hanover, NJ, said it has submitted an application to FDA, seeking marketing authorization for Zometa (zoledronic acid for injection) of bone complications associated with tumors, including prostate and lung cancer, breast cancer and multiple myeloma for which no bisphosphonate therapy is approved..

Zometa is a new generation intravenous bisphosphonate recently approved by FDA for hypercalcemia of malignancy the most common life-threatening metabolic complication of cancer, the company said.

Novartis said it has received marketing clearances for HCM in more than 30 countries, including the EU, Switzerland, Brazil, Canada, and Australia and has filed a supplemental application in the EU for the treatment of bone metastases.

The FDA submission is based on data from three trials evaluating more than 3,000 patients and is the largest set of clinical trials ever conducted to evaluate the efficacy and tolerability of bisphosphonates in treating bone metastases, the company said.

The trials evaluated 4 mg of Zometa given as a 15-minute infusion every three or four weeks.

In the prostate cancer trial, the drug demonstrated efficacy when compared to placebo in the reatment of bone metastases. Over the 15-month evaluation period of the trial, a lower proportion of patients receiving the drug experienced an SRE compared to those receiving placebo, the company said. Patients on the biophosnate had a delay in the onset of the first SRE when compared to placebo.

In the trial in lung cancer and other solid tumors (excluding breast and prostate cancer), Zometa had a positive impact on median time to the first SRE when compared to placebo.

The results of these two well-controlled clinical trials mark the first time any bisphosphonate has demonstrated efficacy in treating SREs associated with prostate cancer, lung cancer and other solid tumors, the company said.

In the third trial, in breast cancer and multiple myeloma, the drug was as effective and well tolerated as Aredia (pamidronate disodium for injection)—the current standard of treatment—with the added convenience of a 15-minute infusion time versus two-to-24 hours for Aredia, the company said.

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