THE CANCER LETTER INTERACTIVE

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# Aranesp Approval Introduces Competition To $1.8 Billion U.S. Cancer Anemia Market

FDA last week approved the drug Aranesp for treatment of chemotherapy-related anemia, setting the stage for the drug's sponsor, Amgen Inc. of Thousand Oaks, Calif., to challenge Johnson & Johnson's dominance over the U.S. market for the indication.

Aranesp (darbepoetin alfa) will compete with the J&J agent Procrit for a share of the largest revenues produced by any agent administered by oncologists. Procrit (epoetin alfa) was first approved in 1990, and last year its U.S. oncology sales were $1.8 billion. Other uses, which include

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*In Brief:*

## Bush Appoints Niederhuber Chairman Of National Cancer Advisory Board

**JOHN NIEDERHUBER** was appointed chairman of the National Cancer Advisory Board by **President George W. Bush** last week.

The NCAB oversees the review of grant applications to the NCI and provides advice on all aspects of program and planning for cancer research, reporting to both the Secretary of Health and Human Services and the director of the National Cancer Institute.

Niederhuber is a nationally recognized cancer surgeon with a special clinic emphasis in gastrointestinal cancer, hepatobiliary cancer, and breast cancer. He is assistant dean for oncology and professor of surgery and oncology at the University of Wisconsin School of Medicine and director of the University of Wisconsin Comprehensive Cancer Center.

Niederhuber is the current president of the Association of American Cancer Institutes and the immediate past-president of the Society of Surgical Oncology. He was a member of the NCI Cancer Center Review Committee and the NCI Division of Cancer Treatment Board of Scientific Counselors. He also served on the Subcommittee to Evaluate the National Cancer Program.

"I have known John for many years and I believe that the President has chosen an outstanding leader whose expertise is invaluable to the National Cancer Program," NCI Director **Andrew von Eschenbach** said. "I look forward to what I know will be his exceptional counsel and advice."

Before joining the University of Wisconsin, Niederhuber was chairman of the Department of Surgery at Stanford University School of Medicine. Prior to that he was professor of surgery, oncology, and

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## New Choice, But Little Data: Procrit or Aranesp for Anemia?

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HIV, hepatitis, and critical care surgery, contributed another $500 million.

Last year, Aranesp was approved for chronic renal failure, and some physicians immediately began using it for chemotherapy-associated anemia. Now, with the oncology approval, physicians will have to decide which drug to use, and in the absence of authoritative head-to-head comparisons between Procrit and Aranesp, this will not be an easy choice.

According to the package insert, Procrit should be administered three times a week. However, nearly all physicians who work with the agent administer it once a week. Aranesp is labeled for once a week use, but it's routinely used every two to three weeks.

"If I have a patient coming in every week anyway for chemotherapy, I am not so sure there is an advantage to giving a drug like Aranesp every three weeks," said Corey Langer, an oncologist at Fox Chase Cancer Center. "It might cause confusion. One would wonder, 'Did I give it last week or the week before?' It's very easy and convenient to order chemotherapy and Procrit concurrently on the same sheet."

About half of Langer's patients receive weekly chemotherapy. Langer said he would prescribe Aranesp to patients who receive chemo every two or three weeks. "It would be very nice and convenient for my patients on cyclic chemo," he said. "The patient wouldn't have to drag in week after week."

Langer's approach is as good as any, because over the years, Ortho Biotech, a Raritan, N.J., unit of J&J which markets Procrit, was better at building the market for Procrit through direct-to-consumer advertising than at developing the agent's clinical potential. As a result, there is little data about using higher doses of Procrit or using loading doses followed by maintenance therapy.

In recent years, J&J put all of its oncology products into a single global operating company, Ortho, that may be better positioned to develop Procrit and other products, industry observers say.

The drug's potential has been hampered in part by its unusual history. Procrit was developed by Amgen and licensed to J&J. A 1985 agreement between the two companies gave J&J exclusive access to the U.S. chemotherapy market, while Amgen retained the dialysis market. Drugs used for dialysis are reimbursed in the same way as drugs administered in oncologists' offices.

Procrit sold in the U.S. is manufactured by Amgen. Outside the U.S., the two companies compete head-to-head. Now with Aranesp on the market, Amgen is waging war on Procrit, the product it developed and continues to manufacture.

The two agents differ on the molecular level. Aranesp has five N-linked oligosaccharide chains, two more than Procrit. This increase in molecular weight gives Aranesp a longer half-life than Procrit, Amgen said.

In the absence of clinical trial data, no one knows definitively whether this difference is clinically relevant. "In my mind, the ideal study compares two agents in the same disease, using the same basic chemo regimen," said Fox Chase oncologist Langer. "You would eliminate all the confounding variables. These polyglot studies, which incorporate multiple disease sites—breast, lung, etc.—the variables increase, and unintended selection biases may occur."

### U.S. Oncology Deal

In the absence of conclusive comparisons, Amgen is aggressively going after Ortho's territory, attempting to make sure that cancer patients who ask for anemia treatment get Aranesp rather than Procrit.

"What this entire story points out is the need for some objective-based medicine in which you can take the two drugs and actually compare them side

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by side, so that doctors would have accurate clinical information to know which one is better, or, if neither is better, knowing that they can make a determination based on other factors, for instance, price, or ease of use," said Merrill Goozner, professor of journalism at New York University and a Kaiser Family Foundation fellow who is writing a book about innovation in the pharmaceutical industry.

Last March, before approval of the cancer indication for Aranesp, Houston-based U.S. Oncology, a network of practices that purchases drugs, signed a long-term supply agreement with Amgen.

The network's practice guidelines now specify Aranesp as the treatment for chemotherapy-associated anemia.

Similarly, International Oncology Network, a Baltimore-based network of community oncology practices, designated Aranesp as the preferred treatment for anemia. The deals, which also gave preferred status to Neulasta and Neupogen, Amgen's treatments for chemotherapy-induced neutropenia, were a great coup for the company.

U.S. Oncology treats 15 percent of all newly diagnosed cancer patients in the U.S. That's 200,000 new patients per year, and overall, the network treats 500,000 patients a year.

"[U.S. Oncology] used to sell only Procrit," said Amgen spokesman Michael Beckerich. "And I know that they have replaced it with Aranesp. We normally don't announce deals, but that was pretty significant for us."

Physicians at U.S. Oncology are still able to prescribe Procrit, but the treatment guidelines give preference to Aranesp, said Steve Sievert, a U.S. Oncology spokesman. "Just because we are able to get preferred pricing on a pharmaceutical product doesn't translate into all patients getting this product," Sievert said. "It's up to our physicians to make those calls in the best interest of the patients."

**The Mystery of Cost**

Cost could be a factor in the decision, but, as is often the case with pharmaceuticals, cost comparisons can be elusive.

Though Aranesp is approved at the 2.25 mcg/kg per week dose, the company has made an unusual decision to market a dose lower than the maximum the FDA label allows, basing its cost comparison on the 1.5 mcg/kg per week dose.

"This is not a price war," said Amgen spokesman Beckerich. "Right now, the current standard of care is Procrit, 40,000 U once per week. The comparator with Aranesp is 200 mcg/kg every two weeks.

"With every two weeks, you are getting the same results with half the amount of shots, and the added bonus is when you look at those doses, Aranesp is less expensive," Beckerich said.

Numbers cited by Amgen indicate that a week of Aranesp on that schedule would cost $399, and a week of Procrit $445. This comparison is based on the list price charged by a manufacturer to a wholesaler.

The Average Wholesale Price may be one of the few real landmarks in pricing of cancer drugs. Though the price is derived by the industry and is in many ways artificial, it does determine Medicare reimbursement. For cancer patients, too, the number is very real. Their co-payment on medication is set at 20 percent of AWP discounted by 5 percent.

The majority of patients receiving Procrit receive the dose of 40,000 U per week.

The AWP of this amount of the drug is $534.24 for a patient who weighs 70 kg. Under Medicare, a patient's co-payment would be $101.51 for a week of treatment.

The lowest dose of Aranesp studied—1.5 mcg/kg per week—would cost $498.75. In this case, the Medicare co-payment would be $94.76 per week.

In the same patient, the dose on the Aranesp label—2.25 mcg/kg per week would have the AWP of $748.13, with the co-payment of $142.14.

Studies of Aranesp show that doses are escalated to as much as 4.5 mcg/kg per week, which would have the AWP of $1,496.25, and the Medicare co-payment of $284.29 per week.

According to clinical trials data included in the Aranesp label, 67 of the 156 patients enrolled in Amgen's clinical trial—43 percent—needed to have the dose escalated to 4.5 mcg/kg per week after receiving Aranesp for six weeks at the dose of 2.25 mcg/kg per week.

Patients receiving Procrit also require a dose escalation to 60,000 U if the 40,000 U dose fails to increase hemoglobin. The Medicare co-payment at that level is $152.26 per week. According to a non-randomized study by Janice Gabrilove, published in the June 2001 Journal of Clinical Oncology, about a third of patients receiving Procrit require this dose escalation.

"It all depends on how you cut the data up,"

said Amgen spokesman Beckerich. "Some of the confusion around pricing and dosing happened because we investigated so many doses. We wanted to figure out what's the best way to treat patients, and competitors have decided to cherry-pick data and use that data to put a negative spin on Aranesp."

According to J.P. Morgan analyst David Molowa, Amgen will market the 1.5 mcg/kg per week dose, which happens to be slightly less expensive than 40,000 U of Procrit, but oncologists would be likely to escalate that dose.

"While we think Amgen will start by marketing this dose, and that physicians will start their patients at this dose, we believe there will be a considerable amount of experimenting with the different doses and dosing regimens by the oncologists, since they are used to varying the drugs they give to their patients, and they can adjust the dosing in part depending on the patients' hemoglobin levels," Molowa wrote.

Physicians would be likely to increase the dose, "since Medicare and many other payers have reimbursement formats in which the more Aranesp physicians use, the more physicians will be reimbursed," he wrote.

**Big Market**

Observers say the market for anemia drugs is likely to expand.

"We will continue to see an increased use of erythropoietin products used to treat anemia associated with cancer and cancer treatment, given that this type of anemia has historically been under-treated," said Toby Herfindal, CEO of the National Oncology Alliance, a buying group that represents 2,000 cancer specialists. "There probably is an expanded role for both products."

Rodger Winn, chairman of the National Comprehensive Cancer Network guidelines steering committee, said the decision to treat anemia is heavily influenced by physicians' attitude.

"Some physicians are convinced that fatigue is a real symptom related to low hemoglobin that can be ameliorated by giving EPO," said Winn, who has consulted for Amgen. "There is another group of physicians who, for whatever reason, don't buy that fatigue is treatable. They say it's multifactorial.

"My gut reaction is that they are probably under-treating symptomatic people with hemoglobin of less than 10 g/dL," Winn said.

Experts say the potential of the two drugs is largely unexplored. "Not only are these agents not being used enough in the settings for which they are indicated, but Ortho and Amgen need to explore other indications in the context of properly conducted, phase III, disease-specific trials, where patients are receiving uniform cytotoxic therapy," said Langer.

"We can still look at all the collateral endpoints—quality of life, anemia, hematopoietic response, performance status," Langer said. "You can 'round up the usual suspects,' but we also need to go beyond the conventional goals."

## *Capitol Hill:*

## Senate Committee Provides $27B To NIH, $4.6B To NCI

The Senate Appropriations Committee sent a spending bill to the Senate that would provide $27.192 billion for NIH, including $4.642 billion for NCI for fiscal year 2003.

The amount for NIH represents a $3.7 billion increase over this year's budget and $25 million more than President Bush's budget proposal. The amount would complete the five-year effort to double the NIH budget.

In the report accompanying the bill, the committee urged NIH to reinstate the Nathan advisory committee on clinical research and "to consider creating an office of clinical research to oversee and coordinate activities across the NIH."

The committee opposed the HHS proposal to consolidate the department's public affairs and legislative affairs staffs. The bill does not include $24.79 million requested by HHS to transfer staff from operating divisions, including NIH, to the Office of the Secretary. "The committee has taken this action because of the concern that information necessary to make timely decisions by the Congress and requests for information by the public may be delayed by this consolidation," the report said.

For NCI, the committee mark of $4.642 billion matches the President's request and is $514 million more than this year's appropriation of $4.128 billion. This includes funds to be transferred from the Office of AIDS Research.

Following is the report language regarding NCI:

*Mission*- The NCI conducts and supports basic and applied cancer research in prevention, early detection, diagnosis, treatment, and rehabilitation. The Institute provides training support for research scientists, clinicians, and educators, and maintains a national network of cancer centers, clinical cooperative groups, community clinical oncology programs, cancer prevention and control

initiatives, and outreach programs to rapidly translate basic research findings into clinical practice.

The Committee continues to regard scientific investigation into the cause, cure, prevention, and treatment of cancer as one of the Nation's top priorities. Research offers the only hope for putting a stop to a disease that wastes precious human resources and contributes to spiraling health care costs.

*Anti-cancer drugs*- The Committee is aware that the NCI is collaborating on the development of synthetic small molecule drugs that target both novel and known targets in cell cycle regulation. The Committee understands that these compounds leave normal, non-cancer cells unharmed while inducing cell-suicide in cancer cells. The Committee encourages the NCI to continue to fund this unique research effort.

*Behavioral research*- The NCI is encouraged to continue its recent emphasis on the interactions of genetic, environmental, and lifestyle factors that affect cancer risk and the prevention, detection, and treatment of cancer. The Committee is particularly supportive of work on risk determination and better communication of that risk to the public and public health infrastructures. The NCI is uniquely positioned to develop and expand large collaborative human population studies that can help build the science base. The NCI is also encouraged to expand research efforts to define the biological, behavioral, and social bases of tobacco use and addiction, and to refine treatment options for specific groups (e.g. pregnant women or young smokers).

*Blood cancers*- The Committee urges the NCI to continue to implement the research priorities for leukemia, lymphoma, and multiple myeloma included in the May 2001 Progress Review Group Report.

*Bone metastases*- The Committee understands that bone metastases are common in a number of human cancers and contribute heavily to morbidity, most prominently in prostate cancer, breast cancer and multiple myeloma. Recognizing this, the NCI is encouraged to promote research to understand the underpinnings of tumor metastasis to the bone. The Institute is also encouraged to focus on understanding the interaction between tumor cells and a multitude of cells in the bone microenvironment, as well as the role of extra cellular matrix and a multitude of growth factors, cytokines and other proteins on tumor survival and growth in the bone microenvironment.

*Brain Tumor Progress Review Group*- The Committee is concerned that the NCI and NINDS have not proceeded with implementation of the Brain Tumor Progress Review Group's recommendations on advancing brain tumor research. The Committee strongly urges the NCI and NINDS to finalize their plan for implementing the recommendations and to provide additional funding for the NCI-NINDS Neuro-Oncology Program to ensure that the Federal research agency is a leader in brain tumor research. The two Institutes should also seek to expand their collaborative brain tumor research ventures, including interactive meetings involving scientists of different disciplines and interdisciplinary grant applications in brain tumor biology and etiology. The Committee requests that the NCI and NINDS report on their collaborative brain tumor research initiatives by December 31, 2003.

*Cancer and minorities*- The Committee remains concerned that cancer rates for Native Hawaiians and other Native American Pacific Islanders are disproportionately high. The Committee encourages the NCI to expand its research in this area.

*Cancer screening technologies*- The Committee recognizes the importance of novel technologies such as plasma K-RAS DNA in the NCI's efforts to develop non-invasive cancer screening technologies for clinical use.

*Cancer survivorship*- With the advances that have resulted from the ongoing commitment and investment in biomedical research, and the resultant advances in cancer treatment, cancer for many has become a chronic illness. Currently, there are over 9 million cancer survivors in the Nation, and this number is expected to grow dramatically. More must be done to improve the understanding of the growing cancer survivorship population, including determinations of physiological and psychological late effects, prevalence of secondary cancers, as well as further development of effective survivorship interventions. The Committee supports an aggressive expansion of the NCI Office of Cancer Survivorship activities, to include the convening of a consensus conference on cancer survivorship. The Committee requests the Director of NCI to submit a report, by April 1, 2003, outlining the activities the NCI is undertaking to enhance cancer survivorship research and to expand the Office on Cancer Survivorship.

*Chronic lymphocytic leukemia*- The Committee strongly encourages the NCI to increase the level of research aimed at determining the underlying cause and optimum therapies for CLL, the most common form of adult leukemia in the United States. The Committee is encouraged by the NCI's willingness to consider a supplementary application for research funding for the CLL Research Consortium. The Committee further urges the NCI to expand funding for the Consortium to speed up the progress in finding significant scientific breakthroughs.

*Chronic myeloproliferative disorders*- Polycythemia vera, idiopathic myelofibrosis and essential thrombocytosis are malignant diseases of the bone marrow that are underserved with respect to research funding, considering the number of people they strike. These disorders are chronic and can transform into acute leukemia. They offer great research promise with respect to insights into the behavior of blood cells, since the cells that they affect appear normal but behave abnormally. The major obstacle to research into the causes and the treatment of these disorders has been the lack of Federal funds designated for this purpose. The Committee strongly believes that the NCI should expand research into these

disorders, and it expects the NCI to report to Congress by April 1, 2003, about existing efforts, as well as planned future efforts, to better understand these disorders.

*Complementary and alternative cancer therapies*- The Committee expects the NCI to expand its work and its collaborative efforts with NCCAM to support research on promising complementary and alternative cancer therapies as well as on their integration with traditional therapies. Thousands of Americans are turning to these therapies, and consumers will benefit from a rigorous scientific review of them.

*DES*- The Committee continues to strongly support increased efforts to study and educate the public and health professionals about the impact of exposure to the synthetic hormone diethylstilbestrol. The Committee expects the NCI to continue its support of research in this area. In addition, the Committee urges the NCI to continue its agreement with the CDC to implement a national education program for consumers and health professionals. The Committee expects the NCI and these other agencies to continue to consult with organizations representing individuals impacted by DES as they carry out DES research and education efforts.

*Gynecologic cancers*- The Committee is concerned about the patterns of care for gynecological cancers, and it urges the NCI to expand CanCORS to gynecologic cancers. While the Committee commends the NCI for funding four ovarian cancer SPOREs and the one gynecologic cancer SPORE, it believes research into other gynecologic cancers needs to be enhanced. The Committee urges the NCI to continue funding ovarian cancer SPORES and to consider creating SPORES specifically for cervical and endometrial cancers.

*Imaging systems technologies*- The Committee is encouraged by progress made by the NCI following its August 1999 conference on biomedical imaging, and it urges the NCI to continue to take a leadership role with the Centers for Medicare and Medicaid Services and the Food and Drug Administration to avoid duplicative reviews of new imaging technologies which may prevent their benefits from reaching patients on a timely basis. The Committee is aware of the great potential for improved patient care and disease management represented by molecular imaging technologies, especially positron emission tomography through its ability to image the biology of many kinds of cancer and other diseases. The Committee continues to support the NCI's increased emphasis on examining the molecular basis of disease through imaging technologies such as PET and MicroPET. The Committee continues to encourage the large-scale testing of women for breast cancer and of men for prostate cancer to demonstrate and quantify the increased diagnostic and staging capabilities of PET relative to conventional diagnostic and staging technologies including mammography.

*Kidney and bladder cancers*- The Committee is concerned that funding for kidney and bladder cancer has not kept pace with that of other cancers. The Committee understands that the NCI has worked with the scientific community to develop an agenda for research into these cancers. The Committee encourages NCI to implement this agenda for other urologic cancers in the coming fiscal year.

*Liver cancer*- The Committee encourages NCI to work closely with the NIDDK to investigate prevention, diagnosis and therapy for hepatocellular carcinoma and other cancers of the liver.

*Neurofibromatosis*- Neurofibromatosis research has significant potential for cancer patients since NF genes have been implicated in the signaling process that determines cell growth and cell differentiation. The Committee commends NCI for recognizing NF's connection to many of the most common forms of human cancers and commencing phase II clinical trials of NF1 patients with plexiform neurofibromas. The Committee encourages the NCI to strengthen its NF research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation and clinical trials.

*Pancreatic cancer*- The Committee is very concerned that funding increases for pancreatic cancer research have not risen at a rate commensurate with the severity of this disease or the increases afforded the NCI for the past 5 years. Pancreatic cancer is the nation's fifth-leading cause of cancer death, and 99 percent of people diagnosed with pancreatic cancer die within 6 months. Therefore, the Committee strongly urges the NCI to: 1) fully implement the recommendations outlined in the Progress Review Group on pancreatic cancer during fiscal year 2003; 2) consider funding five pancreatic cancer SPOREs by fiscal year 2004; and 3) develop a plan to create a critical mass of pancreatic cancer researchers and grants over the next 3 years. The Committee asks the NIH to address these recommendations in a report to Congress by March 30, 2003.

The Committee also urges the NCI to explore new methods for identifying genetic and environmental factors and gene-environment interactions that contribute to pancreatic cancer, and to develop and implement methods for rapid case ascertainment, which may include immediate electronic reporting from pathology, radiology, and laboratory departments.

The Committee further notes the promise of utilizing proteomic analysis of blood samples to diagnose pancreatic cancer at its earliest stages. Proteomic analysis, which involves the identification of specific protein patterns in blood or other specimens that match known malignant patterns, is quicker than identifying separate proteins and the genes that create the proteins. This analysis was recently employed for the detection of ovarian neoplasms and is presently under study for the early detection of invasive prostate cancer. The Committee encourages the NCI to rapidly identify predictive proteomic patterns relevant to pancreatic cancer.

*Primary immunodeficiencies*- Research has shown that patients suffering from primary immunodeficiencies have a 100-200 times greater risk of developing cancer than persons not suffering from PI. This has been a particular problem in minority communities, where PI is often underdiagnosed. The Committee urges the NCI to fund an aggressive research agenda that will target methods of identifying undiagnosed patients and appropriate treatments as a means of preventing cancer. In addition, the Committee continues to urge NCI to play a meaningful role in the national physician education and public awareness campaign of the Jeffrey Modell Foundation.

*Prostate cancer*- Incidences of prostate cancer have been on the rise in recent decades. Evidence is growing that in addition to genetic disposition, numerous other factors—including lifestyle, nutritional imbalances, chronic infections, and hormonal, psychological and environmental components—play a role in the development of prostate cancer. The Committee strongly urges the NIH to renew its commitment to prostate cancer research, with a special emphasis on accelerating new avenues for basic research, drug development, and clinical research.

Text of the full Senate report on S. 2766 is available at ftp://ftp.loc.gov/pub/thomas/cp107/sr216.txt.

*In Brief:*

## Bush Appoints Six To NCAB; Murphy To Direct New Center

(Continued from page 1)

molecular biology and genetics at Johns Hopkins University School of Medicine. Niederhuber is a graduate of Bethany College, Bethany, W.Va., and the Ohio State University School of Medicine. He completed his internship in surgery at University Hospital, Columbus, and his residency in surgery at University Hospital, Ann Arbor, Mich. He served as a captain in the U.S. Army Medical Corps.

**PRESIDENT BUSH** also appointed the following individuals to the NCAB for six-year terms: **Marlys Popma**, executive director of the Republican Party of Iowa; **Franklyn Pendergast**, director of the Mayo Clinic Comprehensive Cancer Center; **Moon Shao-Chuang Chen Jr**., professor of epidemiology and preventive medicine at University of California, Davis, School of Medicine; **Lydia Gonzalez-Ryan**, clinical director, AFLAC Cancer Center, Children's Healthcare of Atlanta; **Kenneth Cowan**, director of the Eppley Institute at University of Nebraska Medical Center; and **Jean deKernion**, the Fran and Ray Stark Professor of Urology, chairman of the Department of Urology, and director of the Prostate Disease Research Program, University of California, Los Angeles.

* * *

**SHARON MURPHY** was named the first director of a new Children's Cancer Research Center at the University of Texas Health Science Center at San Antonio, effective Oct. 1. Murphy has been chief of the Division of Hematology/Oncology at Children's Memorial Hospital, Chicago, and professor of pediatrics at Northwestern University Medical School since 1988. The new center in San Antonio will be housed in a $50 million research facility currently under construction and scheduled for completion next year. The center is supported by a $200 endowment—the largest single oncology endowment in the U.S.—set aside by the Texas legislature from the tobacco settlement. "Unlike other states that use the tobacco settlement money to balance their budgets, Texas in its wisdom decided to set up a Children's Cancer Research Center," Murphy said to **The Cancer Letter**. "I'm excited by the challenge and the opportunity to start something big from scratch." Murphy is recognized as an international authority on the diagnosis and treatment of non-Hodgkin's lymphomas and developed a staging classification, known as the Murphy System, to define stages of the disease. She was chairman of the Pediatric Oncology Group until its merger in 2001 with three other cooperative groups to form the Children's Oncology Group. Murphy served on the staff of St. Jude Children's Research Hospital in Memphis from 1974-1988, and was appointed professor of pediatrics at the University of Tennessee for the Health Sciences in 1985. Earlier this year, Murphy was named as a candidate for dean of the University of Minnesota Medical School. . . . **JOHN RUCKDESCHEL** was named director, president and chief executive officer of the Barbara Ann Karmanos Cancer Institute in Detroit. Ruckdeschel was formerly the director and chief executive officer of the H. Lee Moffitt Cancer Center and Research Institute at the University of South Florida in Tampa. Ruckdeschel will oversee 1,200 faculty members and staff and all research, treatment and education programs. He succeeds **Vainutis Vaitkevicius**, who served as interim president since January 2001. Ruckdeschel also will serve as president of the Barbara Ann Karmanos Cancer Foundation, director of the Meyer L. Prentis Comprehensive Cancer Center of Metropolitan Detroit and principal investigator of its NCI core grant, associate dean for

cancer affairs at Wayne State University School of Medicine and director of WSU's Cancer Institute; and president of the cancer hospital and senior vice president at the Detroit Medical Center. Ruckdeschel's appointment was unanimously recommended by a committee of the Institute's board following a one-year national search. His selection was made by the Institute's executive committee, composed of representatives of the Institute, Wayne State University, and Detroit Medical Center. "Jack Ruckdeschel is an extraordinary oncologist and cancer center administrator who is deeply committed to the welfare of cancer patients," NCI Director **Andrew von Eschenbach** said. "He will no doubt continue the great work conducted by the Karmanos Cancer Institute and help move us further toward our shared goal of eradicating this disease." Ruckdeschel completed his medical degree at Albany Medical College in 1971. He served an internship at Johns Hopkins in 1972, a fellowship at NCI from 1972 to 1975 and residency at Beth Israel Hospital in Boston in 1976. . . . **RICHARD CARMONA,** an Arizona trauma surgeon, was confirmed as Surgeon General by the Senate on July 24. He succeeds **David Satcher**. Carmona said he plans to emphasize antismoking efforts, obesity, diabetes, and the spread of infectious diseases, including HIV/AIDS. He will be commissioned as a three-star admiral in the Public Health Service Commissioned Corps. . . . **LANCE ARMSTRONG**, recently appointed to the President's Cancer Panel, won his fourth consecutive victory in the Tour de France on July 28, crossing the finish line in Paris with a lead of 7 minutes 17 seconds over his closest competitor. Armstrong, 30, is a survivor of metastatic testicular cancer. He completed the 2,036-mile course in 82 hours 5 minutes 12 seconds. . . . **NATIONAL COMPREHENSIVE Cancer Network** Clinical Trials Network awarded $1.3 million to NCCN investigators to evaluate the therapeutic potential of pharmaceuticals through translational and clinical research. The funding was made possible by a research collaboration between the NCCN and Pharmacia Corp. The awardees are: **J. Creaven** and **Y. Rustum**, Roswell Park Cancer Institute; **P. Ramirez**, University of Texas M.D. Anderson Cancer Center; **A. Badawi** and **N. Lewis**, Fox Chase Cancer Center; **M. Hidalgo**, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; **R. Komaki**, University of Texas M. D. Anderson Cancer Center; **B. Rini**, UCSF Comprehensive Cancer Center; **Y. Rustum** and **M. Javle**, Roswell Park Cancer Center Institute; **M. Shah**, Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University; **C. Shapiro**, Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University and **P. Twardowski**, City of Hope Cancer Center. . . . **V CRAIG JORDAN,** breast cancer surgeon at the Northwestern University Feinberg School of Medicine, was named Officer of the Most Excellent Order of the British Empire by Queen Elizabeth II for the development of tamoxifen. He is the Diana, Princess of Wales Professor of Cancer Research, and director of the Lynn Sage Breast Cancer Research Program of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. . . . **DANIEL VON HOFF**, director of the Arizona Cancer Center in Tucson and professor of medicine at the University of Arizona, was selected to receive the Clinical Research Award from the Association of Community Cancer Centers. The award will be presented at the ACCC National Oncology Economics Conference in Albuquerque on Sept. 20. . . . **MICHAEL BOOKMAN** was promoted to director of ambulatory care and clinical information systems at Fox Chase Cancer Center. He is responsible for overseeing clinical services in the department of ambulatory care and for implementing medically related information systems. Bookman will continue as director of the protocol management facility, a position he has held since 1996. . . . **REBECCA PENTZ**, professor of hematology and oncology research ethics at The Winship Cancer Institute at Emory University, has been appointed to the American Society of Clinical Oncology Ethics Committee.

## The Cancer Letter Takes Summer Publication Break: No Issues For Four Weeks

This issue of **The Cancer Letter**, Vol. 28 No. 31, Aug. 2, 2002, is the final issue prior to a four-week summer publication break.

The next issue, Vol. 28, No. 32, is scheduled for publication on Sept. 6, 2002. The deadline for advertising and "In Brief" news items for that issue is Sept. 4.

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THE CANCER LETTER

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# Business & Regulatory Report

*Product Approvals & Applications:*

## Novartis Seeks Gleevec Approval In US, Europe For First-Line Treatment Of CML

**Novartis Oncology** of East Hanover, NJ, a unit in **Novartis AG** (NYSE: NVS) said it has simultaneously submitted marketing applications with health authorities in the U.S. and the European Union seeking marketing authorization for Gleevec (imatinib mesylate) for the first-line treatment of newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia.

The filings are based on data from the International Randomized Study of Interferon vs. STI571, which demonstrate that in the first-line

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*Clinical Trials:*

## Phase II Trial Of Irofulven Plus Camptosar For Advanced GI Solid Tumors Begins

**MGI PHARMA Inc**. (Nasdaq:MOGN) of Minneapolis said it has initiated a phase II trial of irofulven in combination with Camptosar (irinotecan or CPT-11) for advanced gastrointestinal solid tumors.

The multicenter, international trial will evaluate the anti-tumor activity of irofulven when used in combination with irinotecan. The primary endpoint is objective tumor response rate. Secondary endpoints are time to progression, duration of response, overall survival, and safety, the company said.

Up to 125 patients for whom there is no standard chemotherapeutic treatment or whose disease progressed after standard treatment, will be enrolled. Gastrointestinal cancers to be studied include colorectal, gastric, liver and pancreatic. Both drugs will be administered intravenously on an every-other-week dosing schedule.

"There is an excellent basis for evaluating this drug combination in a phase II setting for gastrointestinal cancers," said Eric Van Cutsem, head of the gastrointestinal tumors department at the University Hospital Gasthuisberg in Leuven, Belgium, and lead investigator for the MGI trial. "Based on the activity noted with both of these agents individually in the tumor targets, further exploration is warranted. In particular, the clinical anti-tumor effect of combining irofulven with irinotecan has the potential to be synergistic in treating colon cancer."

"In preclinical studies, the combination of irofulven and irinotecan resulted in synergistic or greater than additive tumor reduction of human colon tumors growing in mice," said John MacDonald, senior vice president

(Continued to page 6)





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# Novartis Seeks Approval For Earlier Gleevec Treatment

(Continued from page 1)

treatment of newly diagnosed CML patients, Gleevec achieved an 83 percent major cytogenetic response rate, compared to 20 percent for the combination of interferon-alpha and cytarabine arabinoside, a form of chemotherapy, the company said. The study also found that Gleevec delayed the time to progression to the more advanced stages of CML compared with IFN/Ara-C.

Gleevec was approved by FDA one year ago for Philadelphia chromosome-positive (Ph+) CML in the blast crisis, accelerated phase or in chronic phase after failure of interferon-alpha therapy.

The effectiveness of Gleevec is based on overall hematologic and cytogenetic response rates, the company said. There are no controlled trials demonstrating a clinical benefit, such as improvement in disease-related symptoms or increased survival.

"The first-line data show that earlier treatment with Gleevec significantly increases the likelihood of achieving a major cytogenetic response—a major goal of CML treatment—and delays the time to progression to the more advanced stages of CML," said David Epstein, president, Novartis Oncology.

IRIS is an open-label phase III trial that enrolled 1,106 patients in 177 centers across 16 countries, the company said. In the two arm study, one group received Gleevec at 400 mg/day by mouth, those in the other arm received IFN by subcutaneous injection at a target dose of 5 MIU/$M^2$/day with Ara-C 20 mg/$M^2$/day by subcutaneous injection for 10 days each month. At time of analysis, median follow-up was approximately 14 months.

The results showed that patients taking Gleevec had a probability of achieving major (Ph<35 percent) and complete (Ph=0 percent) cytogenetic responses of 83 percent and 68 percent at 12 months, respectively, compared with patients in the IFN/Ara-C arm, for whom the estimated rates of experiencing major and complete cytogenetic responses were 20 percent and 7 percent, respectively, the company said. The complete hematologic response rates were 94 percent for the Gleevec arm and 55 percent for the IFN/Ara-C arm.

In the study, patients taking Gleevec had an improved overall progression-free survival compared to those taking IFN/Ara-C, the company said. The estimated rate of progression-free survival at 12 months was 97.2 percent in the Gleevec arm as compared with 80.3 percent in the patients randomized to IFN/Ara-C (P<0.001). Progression was defined as progression to accelerated phase or blast crisis, rapid increase in white blood cell count, loss of either complete hematologic response or major cytogenetic response, or death during treatment. The estimated probability of being free of progression to accelerated phase or blast crisis at 12 months was also significantly higher in the Gleevec arm (98.5 percent) as compared to the IFN/chemotherapy combination (or control) arm (93.1 percent), regardless of crossover, the company said.

* * *

**Andrx Corp.** (Nasdaq:ADRX) of Fort Lauderdale said FDA has tentatively approved the marketing of its abbreviated new drug application for 10 mg and 20 mg tamoxifen citrate tablets USP for breast cancer.

The generic drugs, which are bioequivalent to Nolvadex, are marketed by Astrazeneca Pharmaceuticals LP, the company said.

"This is the second of our generic products to receive FDA tentative approval in the past two weeks," said Richard Lane, CEO of Andrx.

A tentative approval indicates that FDA has made an initial determination that the application for a generic drug satisfies the substantive requirements for approval, subject to the expiration of all statutorily imposed periods during which approval cannot be

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granted, the company said. Final marketing approval is required for the applicant to market the generic drug.

The earliest the generic version of Nolvadex could receive FDA final marketing approval is February 2003, which covers Nolvadex and which includes a pediatric extension scheduled to expire then, the company said.

* * *

**Antigenics Inc**. said FDA has given the company's investigational cancer vaccine Oncophage an orphan drug for metastatic melanoma.

The FDA orphan drug designation was designed to encourage the development of therapies for conditions affecting fewer than 200,000 people in the US. The designation entitles the sponsor to aid with the development program, tax breaks, waivers from certain regulatory fees and seven years of additional marketing exclusivity if the product eventually is approved.

To prepare Oncophage, physicians remove a tumor from the patient and isolate the "antigenic fingerprint" of the particular cancer. Antigenics then develops a vaccine from heat-shock proteins, which are bound to other proteins specific to each patient's tumor.

The protein complex, when purified from tumor cells and reintroduced to the patient, appears to stimulate cellular immunity, the company said.

In May, Antigenics reported that it had begun enrolling patients in the US and Europe in a pivotal phase III trial of Oncophage for stage IV metastatic melanoma. Having already received FDA fast-track status for Oncophage for this indication, Antigenics anticipates finishing patient accrual in the first quarter next year and fully analyzing the trial data by mid-year.

Oncophage also has already received FDA orphan drug and fast-track status for renal cell carcinoma.

* * *

**BioTransplant Inc.** (Nasdaq: BTRN) of Charlestown, MA, said it has received marketing approval from the European Union for its ex-vivo Eligix CD8+ T cell separation system for allogeneic bone marrow and peripheral stem cell transplantation for hematological disorders.

Two other HDM cell separation products have previously received CE Mark approval; these are the CD8-DLI and BCell-SC systems, the company said.

"With the help of Gambro, our sales and marketing partner, we intend to make this product widely available in Europe," said Donald Hawthorne, CEO of BioTransplant.

The CD8-SC cell separation system is an ex-vivo system for the removal of CD8+ T cells from donor stem cell transplants, and is the only commercially available product in Europe, the company said.

Allogeneic transplantation for hematological disorders can encounter immunological incompatibilities between the donor and the recipient and graft-versus-host disease can occur, the company said. The rate of treatment related mortality 100 days post transplant ranges as high as 40 percent in advanced leukemias.

In preclinical studies, the majority of CD8+ T cells were selectively removed from the allograft, while the immune cells and stem cells that are necessary to repopulate the bone marrow and develop into the different blood cells were preserved, the company said. In addition, results presented by Robert Soiffer, clinical director of the Hematologic Oncology Center and the co-director of the Adult Hematopoietic Stem Cell Transplantation Program at the Dana Farber Cancer Institute, suggested that CD8 depletion of allogeneic stem cells may be performed without impairing engraftment. The treatment related mortality 100 days post transplant has been approximately 8 percent in the first cohort of 25 HLA matched patients, the company said.

* * *

**Hoffmann-La Roche Inc**. of Nutley, N.J., the prescription drug unit of the **Roche Group**, said FDA has granted a six-month priority review status to the biologics license application and new drug application for the combination therapy of Pegasys (peginterferon alfa-2a) and ribavirin tablets for chronic hepatitis C without cirrhosis and with cirrhosis with compensated liver disease.

Roche submitted the file with FDA in June, 2002 and approval action is expected by the end of the year, the company said.

"With the expected approval, Pegysys will be an important new therapy for patients," said Georges Gemayel, vice president, national specialty care business operation, at Roche. "Roche has invested in clinical trials to answer key questions about hepatitis C treatment and we will continue to do so."

The Pegasys combination filing is based on two studies conducted with more than 2,400 patients, the company said. Data filed with the FDA include

findings from a study evaluating the treatment duration and dose of ribavirin for patients with genotype 1 and non-1 hepatitis C.

Pegasys is a ready-to-use solution for once weekly injection, the company said. The pharmacokinetic data show that weekly subcutaneous injections maintain therapeutic concentrations throughout the week. The treatment is composed of a high molecular weight (40 kilodalton) branched polyethylene glycol molecule linked to interferon alpha-2a. Evaluated high and low weight branched and linear PEGs in the development of Pegasys. The PEG used in the treatment was licensed by Roche from Shearwater Corp., a subsidiary of Inhale Therapeutic Systems, Inc. (Nasdaq: INHL) in San Carlos, CA, the company said.

* * *

**NeoPharm Inc.** (NASDAQ: NEOL) of Lake Forest, IL, said it has submitted an investigational new drug application to FDA for liposome encapsulated SN38 (LE-SN38).

SN38 is the active metabolite of CPT- 11 (irinotecan), a chemotherapeutic pro-drug marketed as Camptosar in the U.S. by Pharmacia, which has been approved in the U.S. for metastatic colorectal cancer, the company said.

CPT -11 is marketed by Aventis in Europe, and Yakult as well as Daiichi in Japan, the company said. With reported 2001 sales of $613 million in the U.S. and over $800 million world-wide, CPT- 11 is an established first and second-line colorectal cancer treatment standard.

By employing the NeoPharm proprietary NeoLipid technology to deliver SN38, the active drug can be delivered to the tumor cells without the need for high doses of the pro-drug, the company said.

"LE-SN38 is evidence of the utility of the NeoLipid system to formulate an insoluble drug such as SN38 in a way that can be delivered to cancer targets where it previously was impossible," said James Hussey, president and CEO of NeoPharm. "We hope to commence phase I/II trials by the end of this year."

The NeoLipid technology combines electrically charged drugs or other compounds with proprietary oppositely charged lipids, the company said. The drug and the lipids thus become strongly attracted to each other, resulting in an exceptionally stable liposome. This physical property is especially important during drug storage and after the product has been reconstituted and administered intravenously to the patient. NeoPharm uses a proprietary synthetic form of cardiolipin, which in its natural form, occurs as a negatively charged lipid found in cardiac tissue. When combined with proven anti-cancer agents such as paclitaxel or mitoxantrone, liposome based drugs appear to improve patient safety and comfort during administration and may liposomes may also help to overcome cancer chemotherapy drug resistance, the company said.

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**Sanofi-Synthelabo** of Paris said it has submitted the last component of the rolling new drug application for oxaliplatin in the U.S. for the second-line treatment of advanced colorectal cancer.

The NDA is based on a study of advanced colorectal cancer patients who have progressed while on/or within six months following treatment with irinotecan in combination with 5-fluorouracil/ leucovorin (ISL regimen), the company said.

Based on the data obtained with oxaliplatin in combination with 5-fluorouracil/leucovorin from the study, FDA had granted oxaliplatin a Fast-Track review in April.

* * *

**TransMolecular Inc**. of Birmingham, AL, said it has received FDA orphan drug designation for its investigational new drug, 131I-TM-601for glioma and will begin phase I/II trials in January.

The drug, 131I-TM-601 is a radiopharmaceutical anti-cancer drug containing a synthetic version of a substance derived from scorpions called chlorotoxin, the company said.

A multi-center clinical study to evaluate the safety and tolerability of a single dose of 131I-TM-601, as well as overall tumor response rate in an initial study group of 18 patients has already begun, the company said.

In pre-clinical studies, 131I-TM-601 was able to extend survival in a mouse model that mimicked human brain tumors, the company said.

"We are extremely pleased by the FDA's action in granting orphan drug designation for 131I-TM-601, an important step in bringing this drug to market," says

"Therapeutic options for glioma patients are rather limited," said Matthew Gonda, president and CEO of TransMolecular. "Orphan drug designation could greatly assist us in the clinical development and marketing of our new drug candidate for patients suffering from this devastating and deadly disease."

TM-601 is based on chlorotoxin sequences that

have evolved to precisely locate and bind to their receptor, which is abnormally expressed on tumor cells, but is not expressed on normal cells, the company said. The chlorotoxin sequences in 131I-TM-601 are the guidance system that delivers 131I, the radioactive therapeutic payload, to its target, precisely killing the tumor cells.

No toxicities have been observed with TM-601 administration in pre-clinical animal studies, the company said.

*Oncology Management:*

## Allegheny Opens Center, Partners With Seven Hospitals

**Allegheny General Hospital** of Pittsburgh said it has opened a state-of-the-art multi-disciplinary cancer center with diagnosis and treatment, clinical trials and support services.

Designed to promote comprehensive care and convenience for cancer patients and their families, the center offers one-stop access to disease specific medical clinics directed by top medical, radiation and surgical oncologists and equipped with the latest diagnostic and therapeutic technology; therapies being explored through clinical trials; genetic counselling; and vital social and spiritual support services, the center said.

"Our resources consist not only of leading edge technology, top medical expertise and scientific innovation, but also a philosophy that the most ideal approach to cancer treatment transcends the battle at the cellular level to embrace a patient's complete needs," said Michael O'Connell, director of the Allegheny Cancer Center and the AGH Division of Medical Oncology.

O'Connell was deputy director of clinical affairs at the Mayo Clinic Cancer Center chairman of the Mayo Clinic-based North Central Cancer Treatment Group.

The Allegheny Cancer Center is emblematic of the hospital's longstanding tradition of excellence in the field of cancer care and symbolic of both the AGH and the WPAH commitment to providing high level tertiary healthcare services in the region, said Norman Wolmark, chairman of the Department of Human Oncology at AGH and director of oncology for the West Penn Allegheny Health System.

In addition to the cancer center, WPAHS said it has formed a cancer care partnership that will combine the resources of its six member hospitals with seven community-based hospitals in western Pennsylvania, including those affiliated with Conemaugh Health System in Johnstown, Somerset Hospital and the Westmoreland Health System.

"The opening of this cancer center sends a very definitive message that AGH, the West Penn Allegheny Health System and the West Penn Allegheny Cancer Institute are deeply committed to making substantial investments in program development that will elevate the quality of healthcare in this region," said Wolmark.

The facility offers breast care center with four state-of-the-art digital mammography units that will enable pinpointing the tiniest of breast abnormalities in real time, allowing many women to receive a diagnosis and treatment plan options, if necessary, in just one visit., the center said. Additional technology include two digital, stereotactic breast biopsy systems, two breast ultrasound units and a digital bone densitometry unit.

The Cancer Center also offers an expansive medical oncology center for patients requiring the full range of chemotherapeutic and biologic-response treatment regimens, the center said. The clinic houses 18 infusion stations, three fully equipped private infusion rooms and 2 pheresis beds for specialized treatment of certain blood disorders. Other advanced specialty clinics within the center include programs for the treatment of lung, prostate, brain, gynecologic, colorectal and head and neck cancer, clinics devoted entirely to the treatment.

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Pharmaceutical and biotechnology companies have more than 800 medicines in the pipeline to better treat diseases of a graying population such as Alzheimer's, arthritis, Parkinson's and osteoporosis, as well as heart disease, cancer and stroke.

The survey by the **Pharmaceutical Research and Manufacturers of America**, "New Medicines in Development for Older Americans," found that 135 companies are developing 294 medicines targeted at diseases that disproportionately affect seniors, along with 402 medicines in the pipeline for cancer and 122 in testing for heart disease and stroke.

"With an elderly population that is growing daily, millions of people will be counting on the fruits of the pharmaceutical industry's research into diseases of aging," said Alan Holmer, president of PhRMA . "Our survey makes a compelling case for the need for a prescription drug benefit under Medicare. We want seniors and the disabled—now and in the future—to

have access to these remarkable drugs that will push the limit on what we consider old age."

The new medicines in development for older Americans include: 17 medicines for Alzheimer's disease; 14 medicines for chronic obstructive pulmonary disease; 19 medicines for depression; 30 medicines for diabetes; 20 medicines for osteoporosis; 14 for Parkinson's disease. Other medicines in the pipeline target bladder and kidney disorders, critical limb ischemia, eye disorders, gastrointestinal disorders, osteoarthritis, pain, prostate disease, rheumatoid arthritis, sexual dysfunction, skin conditions, sleep disorder and other diseases.

*Clinical Trials:*

## Phase II Trial Of Irofulven Begins For GI Solid Tumors

(Continued from page 1)

of research and development at MGI. "In addition, a large body of preclinical evidence shows a synergistic cytotoxic interaction between topoisomerase I inhibitors similar to irinotecan, and irofulven."

Irofulven (also known as MGI 114, hydroxymethylacylfulvene, or HMAF) is being tested in a series of clinical trials for solid tumors, across a variety of cancers, the company said. Irofulven has demonstrated anti-tumor activity as a single agent in clinical testing against pancreatic, ovarian, prostate and liver cancers. The treatment is also being studied for use in combination with Camptosar (irinotecan or CPT-11), Gemzar (gemcitabine hydrochloride), Taxotere (docetaxel), cisplatin, and Xeloda (capecitabine).

Side effects from irofulven are similar to marketed chemotherapies and include bone marrow suppression (decreases in platelets or white blood cell counts), nausea, vomiting, fatigue, and visual disturbances, the company said.

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**EntreMed Inc**. said it had selected non-small cell lung cancer as the first indication to test its angiogenesis inhibitor Angiostatin in a phase II trial.

"The results of the phase I trials, including stable disease reported in some NSCLC patients and Angiostatin's safety profile, led us to initiate a phase II combination trial with standard chemotherapy agents for treating NSCLC patients," said EntreMed President and COO Ed Gubish, in a statement.

Angiostatin demonstrated last year that it was safe when combined with radiation therapy in advanced head, neck, prostate, lung and breast cancers, the company said.

Additional, undisclosed cancers will be tested with Angiostatin as part of the phase II program, the company said.

EntreMed said Angiostatin would be used in combination with paclitaxel and carboplatin to treat advanced NSCLC patients in a randomized trial at the Indiana University School of Medicine.

Patients will self-inject one of two doses (one high and one low) the drug subcutaneously twice daily. At the same time, investigators will administer paclitaxel and carboplatin, the standard chemotherapy regimen for NSCLC, every three weeks via intravenous bolus administration for a maximum of 18 weeks.

Investigators will evaluate tumor response, safety and the pharmacokinetic profile of the two different Angiostatin doses, the company said.

In the 15-patient, phase I trial, Angiostatin was given five times a week before radiotherapy in a regimen lasting 5 to 7 weeks.

Researchers did not observe any additional toxicity other than what is normally experienced with radiotherapy.

Some tumor responses in the radiation combination trial were reported in May at the American Society of Clinical Oncology meeting, as well as evidence of long-term stable disease in the single agent component of the phase I trial.

*Deals & Collaborations:*

## Pfizer To Buy Pharmacia In $60-Billion Transaction

**Pfizer Inc.** (NYSE:PFE) and **Pharmacia Corp**. (NYSE: PHA) said they have signed a definitive agreement providing for Pfizer to acquire Pharmacia in a stock-for-stock transaction valued at $60 billion.

Pharmacia also said its Board of Directors intends to proceed with its previously announced spin-off of its remaining 84% ownership of Monsanto (NYSE: MON) to its current shareholders.

After the Monsanto spin-off, Pfizer will exchange 1.4 shares of Pfizer common stock for each outstanding share of Pharmacia stock in a tax-free transaction valued at $45.08 per Pharmacia share, based on Pfizer's July 12 closing stock price of $32.20.

"This is an extraordinary opportunity to combine two of the fastest-growing and most innovative

pharmaceutical companies and to position Pfizer for sustained long-term leadership of the global pharmaceutical industry," said Hank McKinnell, chairman and chief executive officer of Pfizer. "By combining with Pharmacia, we are ensuring that our core capabilities in the discovery, development and commercialization of new medicines are strong around the world."

"Combining Pfizer with Pharmacia is a strategic opportunity that immediately creates a global pharmaceutical company with unsurpassed resources and capabilities," said Fred Hassan, chairman and chief executive officer of Pharmacia. "Our companies are already highly effective partners as shown by the extraordinary success of the COX-2 products. A strategic combination with the industry leader, Pfizer, will now give us the opportunity to maximize the potential of both our current products and our pipeline."

Upon closing of the transaction, Hassan will become vice chairman of Pfizer, assisting with integration and corporate strategy, and a member of the Pfizer Board of Directors.

The combined company will have an R&D pipeline containing nearly 120 new chemical entities in development and over 80 additional projects for product enhancements.The companies' combined R&D budget for 2002 exceeds $7 billion, making it by far the largest privately funded biomedical research organization in the world.

With Pharmacia, Pfizer plans to file 20 new drug applications with global regulatory authorities over the next five years.

Pfizer and Pharmacia will have combined annual revenues for 2002 of approximately $48 billion, including $39 billion in prescription sales.

Already the leading pharmaceutical company in the United States and Canada, Pfizer with Pharmacia will move from fourth to first in Europe; from third to first in Japan; and from fifth to first in Latin America in pharmaceutical sales.

Pharmacia's oncology products include Camptosar for treatment of metastatic colorectal cancer as well as therapies for breast cancer.

Pfizer's shareholders will own about 77% of the combined company, and Pharmacia's shareholders will own about 23%. The transaction is expected to close by the end of the year, subject to the approval by shareholders of both companies, governmental and regulatory approvals.

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**Amersham Biosciences**, of Piscataway, NJ, said it has begun a two-year collaboration with the **Sloan-Kettering Institute**, the research arm of Memorial Sloan-Kettering Cancer Center.

The Functional Proteomics Project was established to develop the first technology to scan the entire expressed human genome in a day to test each gene for its function in a cellular process. Researchers will screen tens of thousands of genes in real time, enabling rapid identification of the genes and related proteins involved in key biological pathways or disease states. Initial areas of focus will include cancer and the immune system.

Technology generated from the collaboration will be used by Amersham Biosciences to create new tests for pharmaceutical and other researchers to use in automated high throughput cellular screening to discover and validate therapeutic and diagnostic targets, and to facilitate lead development. Memorial Sloan-Kettering will gain a deeper knowledge of critical pathways, such as cell cycle, cell death, and angiogenesis. Both parties will also benefit from the generation of significant intellectual property rights related to the methods and technologies developed for the research, and to the new tests and targets identified.

The project has been made possible by the use of Amersham Biosciences' IN Cell Analyzer, a high throughput cellular screening system capable of scanning 30,000 chemical compounds or genes in cell-based assays in less than 24 hours. The IN Cell Analyzer was developed to enable pharmaceutical companies to test potential new drugs directly in living cells more quickly and cost-effectively.

The Functional Proteomics Project will be initially staffed by a team of 20 scientists at SKI, under the leadership of James Rothman and Urs Rutishauser. The project will be funded jointly by Amersham and the Sloan-Kettering Institute. Commercial terms of the agreement were not disclosed.

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**DAKO A/S** of Copenhagen and **Cytomation Inc.** of Colorado said they will merge July 1, strengthening their position in the vitro diagnostic industry.

DAKO develops reagents for diagnostic use and Cytomation produces in flow cytometry instruments used for advanced cellular analysis, the companies said.

In the last fiscal year, DAKO saw a 20 percent increase in sales, while Cytomation reported 35

percent growth, the companies said. The combination results in a global, market-leading company with 1,400 employees, activities in more than 70 countries, and $175 million in total sales.

"The merger is an important step towards an IPO," said Jes Ostergaard, who will serve as president and CEO of DakoCytomation A/S. "Time and place depend on the integration and how the market develops. However, an IPO during 2003 continues to be a major element in our overall strategy."

Nigel Ferrey, president and CEO of Cytomation, Inc., will serve as president of the DakoCytomation U.S. subsidiary and join the DakoCytomation Corporate Management Group.

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**Fujirebio Diagnostics Inc**. of Malvern, Pa., said it has acquired the rights from **Pacific Northwest Research Institute** of Seattle to develop two newly discovered ovarian tumor markers, mesothelin and HE4.

Pre-clinical research has shown that mesothelin and HE4 augment the diagnostic potential of FDI's serum-based assay, CA125II. Based on research findings, combining the three ovarian cancer tumor markers may result in improved diagnostic performance, particularly for the detection of early stage disease.

"The development of a complementary assay for use with CA125II for improved use in early detection of ovarian cancer represents another step forward in the standard of care," said Aris Petropoulos, president and COO of FDI. "Successfully developing these tumor markers will create a useful tool for physicians to use in the early detection of ovarian cancer and will have a tremendous impact in saving women's lives."

"We are happy that work from the Tumor Immunology Laboratory at PNRI has been licensed to Fujirebio Diagnostics for further clinical development," said Ingegerd Hellstrom, who developed the HE4 and mesothelin assays and is the lead scientist on the project.

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**OXiGENE Inc.** (Nasdaq: OXGN, SSE: OXGN) of Watertown, MA, said its anti-tumor compound, Oxi-6197, has been selected by NCI for preclinical efficacy and pharmacology studies.

Oxi-6197 is a member of a new family of vascular targeting agents that were discovered through the collaboration with Baylor University, the company said. The family of compounds is structurally distinct from the Oxigene Combretastatin platform of VTAs.

Under its stage IB level of approval, NCI will conduct in vitro anti-tumor activity and selectivity studies with various tumor types, the company said. Additionally, in vivo xenograft studies will be performed to evaluate the biological activity of the compound.

When administered intravenously, Oxi-6197 is designed to reduce blood flow in newly formed tumor vasculature, triggering the death of downstream tumor cells, the company said.

"The agreement with the NCI builds on our platform of VTAs that includes Combretastatin A4 Prodrug and the pre-clinical compound Oxi-4503," said Dai Chaplin, chief scientific officer and the head of research and development of Oxigene. "This compound represents the culmination of several years of drug discovery efforts with our research collaborators and demonstrates our ability to expand our pipeline of new chemical entities with significant biological activity."

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**InKine Pharmaceutical Co. Inc**. (Nasdaq:INKP) of Blue Bell, PA, said it will collaborate with **ZaBeCor Pharmaceutical Co.** of Philadelphia to develop antisense and FcReceptor technologies.

The technologies are related to the discoveries of Alan Schreiber, professor of medicine and assistant dean of research at the University of Pennsylvania School of Medicine, the company said.

Under the agreement, InKine has granted ZaBeCor the exclusive right to develop, manufacture, market and sell products and technologies covered by its own patents relating to inflammatory disease, the company said. As compensation for the license granted to ZaBeCor, InKine received a 47.5 percent ownership in ZaBeCor.

ZaBeCor will pay InKine an undisclosed royalty based on net sales of all products discovered or developed by ZaBeCor or its partners. ZaBeCor will be responsible for all development costs. InKine, however, will retain all rights to Colirest and Hematrol, the company said.

"Our arrangement with ZaBeCor provides InKine with immediate expense reductions and further reduced cash outlays, while retaining a share of the upside potential of these technologies," said Leonard Jacob, chairman and CEO of InKine.

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