THE CANCER LETTER

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NCI's Oral Cancer Chemoprevention Trial On Hold After Fraud Allegations In Norway

By Paul Goldberg

Researchers at M.D. Anderson Cancer Center and collaborators in four Scandinavian countries were making final preparations to begin enrollment in what promised to be an important trial of chemoprevention in patients with high-risk oral pre-malignant lesions.

The trial was built in part on the work of the Norwegian investigator Jon Sudbo of the Radium Hospital of Oslo and funded through a $9 million grant awarded by NCI and led by M.D. Anderson.

An extensively published pioneer in the field of chemoprevention,

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In Brief:

Pitt Selects David Bartlett As Innaugural Bernard Fisher Professor Of Surgery

DAVID BARTLETT was appointed the inaugural Dr. Bernard Fisher Professor of Surgery at the University of Pittsburgh School of Medicine, where he serves as chief of the division of surgical oncology. Bartlett, director of the David C. Koch Regional Perfusion Cancer Therapy Center at the University of Pittsburgh Cancer Institute. specializes in the management of advanced, complex abdominal cancers. He helped develop a technique for delivering hyperthermia and chemotherapy directly to the peritoneal cavity as a recirculating perfusion. Bartlett also has worked with chemotherapy delivery to the arm or the leg, which can be a treatment strategy for melanoma that has spread throughout the limb. Bartlett was a senior investigator in the NCI Center for Cancer Research before moving to Pittsburgh in 2001. Bartlett will be installed in conjunction with the Bernard Fisher Lecture on Feb. 1. **Larry Norton**, of Memorial Sloan-Kettering Cancer Center, will deliver the lecture. Fisher is the Distinguished Service Professor of Surgery at the School of Medicine and past chairman and scientific director of the National Surgical Adjuvant Breast and Bowel Project which, in the late 1960s, found radical mastectomy to be no more effective than total mastectomy and, in turn, total mastectomy to be no more effective than lumpectomy in treating breast cancer. In 1990, NSABP showed the effectiveness of adjuvant chemotherapy and hormonal therapy (tamoxifen) in treating breast cancer. In subsequent studies, the group found that tamoxifen substantially reduces the incidence of breast cancer in high-risk women. . . . **SCOTT LIPPMAN** was named chairman of the Department of Thoracic, Head and Neck Medical Oncology at M. D. Anderson Cancer Center. He joined the department and M. D.

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Norway Officials Say Data Were "Complete Fabrication"

(Continued from page 1)

Sudbo was the principal investigator of the 300-patient trial that was to be conducted in Norway, Denmark, Sweden, and Finland.

However, on Jan. 13, a few weeks before the four-arm phase III trial of the COX-2 inhibitor Celebrex (celecoxib) and the epidermal growth factor receptor Tarceva (erlotinib) enrolled the first patient, scientists around the world received bad news from Norway: Sudbo had been caught—and reportedly acknowledged—fabricating data in a separate study.

Now, with the trial on hold, scientists are sifting through Sudbo's contributions in an effort to distinguish legitimate research from falsification—and to determine whether the NCI program project grant can go forward despite his role.

"It's painful to consider" what would have occurred had the trial actually begun, said Leonard Zwelling, vice president for research administration at M.D. Anderson. "Had we started the trial, it would have been a very painful episode."

It appears that Sudbo's alleged falsifications haven't affected patient care. One of the studies in question—published last year in The Lancet—was a retrospective analysis of data he claimed to have from Norway's cancer registries. Radium Hospital officials have since stated that the paper was based on "complete fabrication" of data.

The Lancet study appeared to demonstrate that chemoprevention could change the course of development of oral cancer. However, the agents used, non-steroidal anti-inflammatory drugs, differed from the treatments that would have been used in the NCI study. No federal funds were used in preparing the study published in The Lancet, officials say.

Norwegian officials said the problems with the data were obvious. According to news reports, an audit showed that 250 of the 908 patients in the retrospective study had the same birth date.

Further scrutiny of Sudbo's publication prompted the New England Journal of Medicine to post an "expression of concern" about mislabeling of a micrograph in a landmark 2001 paper and a follow-up paper from 2004. Scientists say they are alarmed by this development, because the 2001 paper defined the cohort of patients who would have been studied under the P01 grant from NCI.

The fabrication has spilled over to affect four M.D. Anderson researchers, who are listed as co-authors on Sudbo's publications now questioned by the journals.

These researchers had never seen Sudbo's patient files, Zwelling said. "There have been things in the press about the 250 birth dates being the same; that is not true of the data we got," he said. "I saw some of that data myself. The way this worked, they said they were extracting data from the registry, and the spreadsheets were sent to us. But we never saw the primary data."

Insiders said the Norwegian researcher's apparent falsifications are so damaging, because his conclusions seemed plausible.

"Basically, this guy took biological plausibility—things that others had reported in small numbers—and then made up the numbers that made it work," said a scientist familiar with the controversy. "He produced big numbers, and—boom—had a huge story, first for the New England Journal, and then for The Lancet."

The alleged fraud threatens a series of studies that were to be coordinated by Sudbo's M.D. Anderson collaborator Scott Lippman.

Lippman, former chairman of the M.D. Anderson's Department of Clinical Cancer Prevention who recently took the job as chairman of the Department of Thoracic, Head and Neck Medical Oncology, is the principal investigator on the P01 grant and a coauthor of The Lancet paper and the 2004 NEJM paper.

The list of authors on the papers in question also includes M.D. Anderson oncologist Li Mao and statisticians Jack Lee and Xian Zhor, who has left the center.

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NEJM Questions 2001 Paper Defining Cohort

Sudbo was the first author in the NEJM paper that defined the cohort of patients that was to be studied under the P01 grant.

That study, titled "DNA Content as a Prognostic Marker in Patients With Oral Leukoplakia," was published by NEJM on April 26, 2001.

The study claims to have followed 150 patients with verified epithelial displasia, and found that 25 of these patients—those found via biopsy to have aneuploid lesions—had an 84 percent chance of developing squamous-cell carcinoma. Finding a group of patients at such high risk of developing the disease would have made it possible to answer the prevention questions with relatively small trials.

This work laid the foundation for Sudbo's collaboration with M.D. Anderson, and was part of the scientific justification for the P01 grant, insiders said. To test the hypothesis in the population he defined, Sudbo was slated to run a trial that would have randomized 300 patients into four groups: Celebrex, Tarceva, Celebrex plus Tarceva, and placebo.

Other studies funded through the P01 included biostatistical and pathology analysis at M.D. Anderson. The role of COX-2 and EGFR and HER2 pathways was to be studied at Cornell University.

A summary of the study states that "the overall objectives of our program project are to help control the incidence of oral cancer, elucidate the biology of COX-2 and EGFR/HER2 signaling in and the impact of agents targeting these pathways in oral carcinogenesis, and elucidate the molecular biology and risk of oral cancer and the pharmacogenomic profiles of high-risk oral pre-malignant lesion patients with respect to preventive interventions directed at COX-2, EGFR and HER2."

After the P01 grant was funded in 2004, M.D. Anderson spent about $232,000 in preparation for the phase III trial. The funds were spent on regulatory approvals, development of case-report forms, and establishing the trial infrastructure in four countries.

The trial's estimated cost was $2.5 million, and the remainder of the $9 million grant would have been spent on analysis of data and biospecimens.

On Jan. 20, a week after allegations of irregularities surfaced in The Lancet, NEJM editors wrote that two figures in Sudbo's 2001 paper, "which purport to represent two different patients and stages of oral epithelial displasia, are in fact different magnifications of the same photomicrograph."

NEJM editors said they were similarly concerned about a 2004 article by Sudbo and M.D Anderson collaborators, which was based on follow-up of the same patients.

"It shows how science is built on other science," Zwelling said. "You are always building on a knowledge base. And if there is a brick in that wall that's really not there, the whole thing can collapse. That's what would have happened. Fortunately, this was found out prior to anybody being put on the trial.

"Now the trial is on hold, and the next step will be to sit down and think about what we know and what we don't know, which is why that investigation in Norway is so important."

Several experts in chemoprevention said the rationale for the treatment in the planned trial is still compelling. What's uncertain is the existence of the patient population described in Sudbo's 2001 paper.

"We need to be certain that this enriched population of patients in fact exists in Scandinavia or in the U.S., so they can be accrued to the trial to answer the question posed," said a scientist familiar with the situation. "It's a question that can be answered, but it's going to take some time."

Lippman Supports Going Forward

In a statement issued through the M.D. Anderson press office, Lippman said that, despite Sudbo's former role, he supports going forward with the P01.

"We do have a rationale to go ahead with the study, and we are extremely hopeful that we can proceed," Lippman wrote. "For example, the clinical rationale supporting oral cancer prevention in high-risk patients remains compelling because of the tremendous burden of this disease, not least of which is disease and treatment morbidity.

"The biologic and mechanistic rationale for the two proposed inhibitors in this population has, if anything, grown stronger with new data in the past year. This rationale has not been changed by the recent disclosures concerning The Lancet NSAID/oral cancer epidemiology study, which was published long after, and did not play a part in, the trial design."

Lippman cited the following data in support of going forward:

—"Based on new clinical data, erlotinib has been U.S. FDA-approved recently for treating the two tobacco-related cancers non-small cell lung cancer (late 2004) and pancreatic cancer (2005).

—"Single-agent erlotinib was approved for treating non-small cell lung cancer based on a definitive randomized controlled trial (Shepherd et al, NEJM 2005; accompanied by a related translational paper by Tsao et

al, NEJM 2005).

—"The approval of erlotinib for pancreatic cancer was based on clinical trial data presented at ASCO in 2005.

—"The combination of a related oral EGFR inhibitor (gefitinib) and celecoxib was well tolerated and produced encouraging responses in a recently reported clinical trial in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (Wirth et al, J Clin Oncol 2005).

—"The following new laboratory data also support inhibitors of EGFR and/or COX-2:

—"A recent report by DM Shin's group (Zhang et al, Clinical Cancer Research 2005) accompanied by an editorial (Lippman et al, Clinical Cancer Research 2005) showed that targeting EGFR and COX-2 is very active in a head and neck xenograft model.

—"[Andrew] Dannenberg's group produced recent laboratory data showing that oral mucosa of human smokers had significantly higher levels of EGFR ligands and COX-2 (versus non-smokers) and that an EGFR inhibitor can block tobacco-smoke-induced COX-2 expression in vitro in oral leukoplakia cells (Moraitis et al, Cancer Research 2005). [Danneberg is the director of cancer prevention at New York Presbyterian Hospital-Cornell and an investigator on the P01 grant.]

"Therefore, clinical results with an EGFR inhibitor alone or combined with celecoxib and preclinical results with inhibitors of EGFR and COX-2 strengthen the rationale for our trial," Lippman's statement said. "Finally, Jon Sudbo had no involvement in any of the new supportive data cited above."

NCI officials said they are working with M.D. Anderson to determine how the project can be redesigned. One plan, floated by the cancer center, is to conduct a trial in the U.S., sources at the Institute said.

Any plan NCI would consider acceptable would hinge on defining the target population, sources said.

Information Seemed Suspicious

Sudbo's alleged falsifications were discovered when another Norwegian researcher sat down to read The Lancet paper.

Sometime over the Christmas vacation, Camilla Stoltenberg, director of the Division of Epidemiology at the Norwegian Public Health Institute, was looking over a paper The Lancet had published in October.

The study claimed to show that NSAIDs taken regularly appeared to be associated with lower risk of mouth cancer but a higher risk of heart disease. The study claimed to have traced the cases of 454 heavy smokers with oral cancer and another 454 smokers without the disease. The data came from the Cohort of Norway, the paper said.

"That was entirely wrong," Stoltenberg, who works on that registry, later said in an interview with the National Public Radio. "First of all, Cohort of Norway didn't exist at the time when the data collection allegedly took place, namely between 1975 and 1995." Also, the paper claimed that it drew on data from another registry, which didn't exist until 2004, she said.

Stoltenberg notified the Radium Hospital, and on Jan. 13, the institution informed The Lancet that the paper was based on "manipulated data." A day later, Norwegian officials reported that the data were, in fact, fabricated.

Cancer Research Advocacy:

U.S. Failing To Address Lung Cancer, Group Says

The U.S. in failing in addressing research, treatment, early detection, and prevention of lung cancer, according to a "Report Card on Lung Cancer" issued by The Lung Cancer Alliance, a non-profit organization.

"Lung cancer is the leading cause of cancer death in men and women," said Paul Bunn Jr., director of the University of the Colorado Cancer Center and a board member of the Lung Cancer Alliance. "We have made insufficient progress in this dreaded disease in part due to a lack of resources. Hopefully, it will encourage our public health leaders to come together to develop an overall plan with a sense of urgency to increase lung cancer's survivorship."

The report graded seven categories:

—Number of Deaths: Lung cancer is the No. 1 cancer killer. An estimated 172,570 people were diagnosed in 2005 and about 163,510 died. Grade: F.

—Five-Year-Survival-Rate is 15 percent, virtually no improvement since President Nixon and Congress declared "War on Cancer" in 1971. By comparison, the five-year survival rate for breast cancer is 88 percent and for prostate cancer, 99 percent. Grade: F.

—Number of Late-Stage Diagnoses is 70 percent. Grade: F.

—Youth Smokers: About 2,000 new "daily" smokers under the age of 18 become addicted each day, more than 700,000 a year. Grade: F.

—Number of New Treatment and Diagnostic Options in the last 30 Years: Slight progress has been made only within the last few years. Grade: D.

—Federally-Supported Early Detection Program: The federal government does not support early screening for lung cancer, while it does for other major cancer with comparable public health service ratings. Grade: F.

—Overall Federal Commitment: Lacks overall plan and sense of urgency. Lung cancer is under-funded and under-researched. Only $1,829 spent per lung cancer death, compared to $23,474 per estimated breast cancer death and $14,369 per estimated prostate cancer death. Grade: F.

"Lung cancer is the most lethal of all major cancers," said Laurie Fenton, president of The Lung Cancer Alliance. "This Report Card on Lung Cancer will put public health leaders and the American public on notice that it is time to change this."

The report is available at www.lungcanceralliance.org.

In Brief:

S. Lippman Named Chairman Of MDA Thoracic, Head & Neck

(Continued from page 1)

Anderson in 1988 as assistant professor of medicine, and was appointed chairman of the Department of Clinical Cancer Prevention, with a joint appointment in Thoracic, Head and Neck Medical Oncology, in 1995. He is professor of medicine and cancer prevention and holds the Ellen F. Knisely Distinguished Chair in Colon Cancer Research. . . . **PAUL FLINT** was named the first Charles W. Cummings, M.D., Professor in the Department of Otolaryngology-Head and Neck Surgery at Johns Hopkins University. Flint, co-director of the Minimally Invasive Surgical Training Center at Hopkins, is known for his robotic-surgery techniques for removing tumors in the airway and for use of botulinum toxin to restore voice strength. More than 330 donors contributed $2.2 million over five years to fund the professorship. . . . **DANIEL LIEBLER** was named director of the Jim Ayers Institute for Pre-Cancer Detection and Diagnosis at Vanderbilt-Ingram Cancer Center. He is director of the Proteomics Laboratory at Vanderbilt University Medical Center. The institute, established in 2005 with a $10 million gift, will work to identify molecular markers for colorectal cancer. . . . **CHARLES SMITH** was named the Charles and Carol Cooper Chair in Pharmacy at the Medical University of South Carolina. Smith, who was director of the Drug Discovery Core Facility at Pennsylvania State University College of Medicine, is known for his work in high-throughput screening and quantitative structure activity relationships At MUSC, Smith will direct the new Drug Discovery Core, Department of Pharmaceutical Sciences. He is founder, president, and CEO of Apogee Biotechnology Corp. . . . **KENNETH TEW** of the Hollings Cancer Center at Medical University of South Carolina, was named the John C. West Endowed Chair in Cancer Research. He is professor and chairman of the Department of Cell and Molecular Pharmacology and Experimental Therapeutics. . . . **WILLIAM SLIKKER JR.**, was appointed acting director of the FDA National Center for Toxicological Research. Slikker replaces **Dan Casciano**, the NCTR director for more than six years, who will work in the private sector on molecular, cellular, and general toxicology issues. Slikker has held a variety of research and management positions within FDA, most recently serving as the NCTR deputy center director for research. . . . **JOAN BAILEY-WILSON and ALEXANDER WILSON**, husband-and-wife team of senior investigators at National Human Genome Research Institute, were appointed co-chiefs of the Inherited Disease Research Branch, said **Eric Green**, scientific director at NHGRI. Bailey-Wilson is head of the Statistical Genetics Section, and Wilson is head of the Genometrics Section. The IDRB identifies the genetic contributions to disease, particularly in genetically complex disorders, such as cancer and diabetes. The branch also serves as the NHGRI link to the Center for Inherited Disease Research at Johns Hopkins University. . . . **MARVIN ROMSDAHL**, cancer surgeon and educator for more than 30 years at University of Texas M. D. Anderson Cancer Center, died Jan. 10. He was 75. Romsdahl established the first surgical research laboratory at M. D. Anderson and developed combination therapies that included limb-salvage for bone cancer and breast conservation for breast cancer. He also began an academic surgical fellowship program to provide laboratory research experiences as well as training in oncology surgery. After earning his medical degree at the University of Illinois College of Medicine in 1956, Romsdahl spent two years as a clinical associate in the NCI Surgery Branch before completing his general surgery residency at the University of Illinois Research and Educational Hospitals in Chicago. He joined M.D. Anderson in 1967. He served as chief of the Section of Surgical Soft Tissue and Skeletal Sarcomas, deputy chairman of the Department of General Surgery, and chairman of the Division of Surgery Research Committee. He retired in 1997, but continued a part-time private surgical practice at St. Luke's Episcopal Hospital. Romsdahl is survived by his wife, Virginia, a former nursing

administrator at M. D. Anderson; four children; a sister; and three brothers. . . . **WILLIAM SORRELL**, Vermont attorney general, was selected chairman of the board of the American Legacy Foundation. Also, current board member **Ellen Gritz**, of M. D. Anderson Cancer Center, was named vice chairman, and Idaho Attorney General **Lawrence Wasden** was named treasurer. The foundation is facing a decrease in funding, having received its last major payment resulting from the Master Settlement Agreement with tobacco companies. Sorrell served as chairman of the Tobacco Committee of the National Association of Attorneys General for three years. He is the past -president of NAAG.

In the Cancer Centers:

FOX CHASE CANCER CENTER received a $500,000 gift to name and endow the John A. Ridge Surgical Oncology Fellowship from philanthropists Carol and Louis E. Della Penna Sr. This is the second gift from the couple, who gave $1 million in 2003 to urologic oncology research. The fellowship, which recognizes John Ridge, chief of head and neck surgery at FCCC, is a two-year training program of a physician in surgical oncology. **Kimberly Brown** is the first fellowship recipient. . . . **EMORY WINSHIP CANCER INSTITUTE** announces three appointments. **Mitchell Berger** was named director of medical oncology at the Georgia Cancer Center of Excellence at Grady, said **Jonathan Simons**, director of the Emory Winship Cancer Institute, and **Otis Brawley**, medical director of the Georgia Cancer Center of Excellence at Grady. Berger was national director for regional scientific directors at Novartis Oncology. Berger, who is board certified in medical oncology and internal medicine, also will see patients at Grady and Emory Crawford Long Hospitals. **Sheryl Gabram** was named professor of surgery in the Emory University School of Medicine and Winship Breast Cancer Clinical Program. She also will serve as director of the Avon Breast Cancer Center and director of Oncologic Services at the Georgia Cancer Center of Excellence at Grady. Gabram was professor of surgery and director of the Breast Clinical Program at the Cardinal Bernardin Cancer Center, Loyola University Medical Center. **Doug Shin**, professor of hematology, oncology, and otolaryngology, director of the Cancer Chemoprevention Program and co-director of the Translational Lung Cancer and Aerodigestive Tract Malignancies Program at Emory Winship Cancer Institute, was appointed associate director of academic development. Shin will develop a formal system of mentorship for hematology and oncology faculty.

Professional Societies:

AMERICAN SOCIETY FOR Therapeutic Radiology and Oncology announced three additions to its healthcare policy and research staff. **Debra Lansey,** a former HMO supervisor, was appointed assistant director of healthcare policy. **Alan Gay** was named program manager for research. Gay was program analyst for a radiation therapy and dosimetry consulting organization and worked as a dosimetry technician. **Omari Keeles**, who was a public health analyst with a similar association and was a research associate teacher at the Walter Reed Institute of Research, was named research and health policy analyst.

NCI Programs:

Signatures Grants Awarded

NCI awarded six grants to collaborative research groups as part of its Strategic Partnering to Evaluate Cancer Signatures program.

The projects are designed to confirm and evaluate molecular signatures that previously have been demonstrated to be clinically useful. These projects will also focus on developing robust, reproducible assays for specific molecular signatures that will then be tested in clinical trials.

The grants, which total $10 million for the first year of funding, were awarded to six teams:

—Children's Hospital, Los Angeles, Timothy Triche.

—University of California, Irvine, Dan Mercola.

—University of Nebraska Medical Center, Wing Chan.

—University of New Mexico, Cheryl Willman.

—Vanderbilt-Ingram Cancer Center, David Carbone.

—Washington University, Matthew Ellis.

Funding Opportunities:

RFPs Available

RFP No. N01-CO-57034-48: Notice of Request For Proposals for NCI Best Case Series Program: Developmental Support and Prospective Research Projects

The NCI Office of Cancer Complementary and Alternative Medicine is seeking contract proposals that will enhance the state of science on cancer treatment. The NCI Best Case Series Program is designed to seek out alternative approaches to cancer treatment. This Broad Agency Announcement will support developmental support and prospective research projects as part of the BSC as well as additional research when warranted. This BAA is intended

to provide funding opportunities that will support compilation of the documentation on patient cases to be submitted to NCI OCCAM and reviewed as part of the NCI BCS Program. It seeks to encourage researchers with expertise and experience in cancer treatment who might otherwise not be aware of the opportunity to apply their expertise to alternative cancer treatments. It is also intended to foster collaborative activities between Complementary & Alternative Medicine practitioners and experienced cancer researchers. Specifically, topics eligible under this BAA are alternative cancer therapies for which documentation on patient cases is available and for which the intervention is available for prospective investigation. This BAA requests proposals for collaborative projects that involve pairing cancer investigators with CAM practitioners for conduct of the proposed efforts. Proposals submitted in response to this solicitation should be two-part contracts consisting of two distinct phases. The first phase (Phase I) of the contract provides support to document a series of patients that meet the NCI BCS Program criteria and to develop a prospective research project (pre-clinical, clinical, or both). At the completion of Phase I, the findings of the submitted case series and the final report detailing the developed research project will be used by the NCI to determine eligibility for Phase II support. It is anticipated that Phase II funding will result in a completed research project within 2 years. Phase II support of a project is not guaranteed and will be an option exercised on the basis of the success achieved in the Phase I portion. The BAA is available at http://rcb.cancer.gov/rcb-internet/appl/rfp/published_rfps.jsp.

Inquiries: John Manouelian, phone: 301-435-3813, email: manouelj@mail.nih.gov.

RFP S06-143 Biospecimen and Biorepository Facility

SAIC-Frederick, the Operations and Maintenance Contractor for the NCI Frederick Cancer Research Facility will be soliciting for biorepository and biospecimen services to The Cancer Genome Atlas, the three-year pilot that would establish a centralized Biospecimen Resource Center. The facility would provide ongoing services for importing materials from biospecimen repositories, processing the materials into molecular derivatives, and distributing the derivatives to the analytical sites. The BRC would also develop, implement and publish standard operating procedures for all processes of cancer tissue sample acquisition, preparation, storage, and distribution, including operating and QA/QC procedures that can be validated. Biospecimen types will include tumor tissue, and normal cell sources such as blood and/or buccal cells. The BRC will also establish SOPs for prospective collections of other tumor types, and develop new protocols for extracting molecular isolates from tissues in synchrony with new analytical procedures being developed within the Cancer Genome Atlas framework. The RFP is available at http://www.fbodaily.com/archive/2006/01-January/08-Jan-2006/FBO-00962270.htm.

Inquiries: Jeanne Lewis, jlewis@ncifcrf.gov.

SS-N02-PC-65008-58: Development and Technical Services for the NCI Applied Research Program

NCI is interested in identifying small business organizations that can continue following activities for the NCI Risk Factor Monitoring and Methods Branch: development, modification, and updates of general health-related and, specifically, dietary questionnaires that include nutrient databases; provide logistic support for collection and management of biological specimens; development and management of new projects, including surveys and methods in the areas of cancer risk factors--such as diet, physical activity, screening, smoking, family history--health services research, and cancer outcomes research; development and implementation of quality control procedures for data collection and field operations; and, the design and maintenance of computer databases and associated reporting software. Only capability statements are being requested from small businesses at this time. The RFP is available at http://www.fbodaily.com/archive/2006/01-January/12-Jan-2006/FBO-00963781.htm

Inquiries: Virginia DeSeau, 301-435-3798; vd9t@nih.gov.

Program Announcements

PA 06-120: PHS 2006-02 Omnibus Solicitation of the NIH, CDC, and FDA for Small Business Innovation Research Grant Applications

NIH, CDC, and FDA encourage U.S. small business concerns to submit Small Business Innovation Research phase I, phase II, Fast-Track, and phase II Competing Renewal grant applications through www.grants.gov. The research topics described in the PHS 2006-2 Omnibus Solicitation for these agencies represent scientific program areas of interest to applicant SBCs in the development of projects for commercialization. The PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-06-120.html.

Inquiries: For NCI--Michael Weingarten, 301- 496-1550; mw498z@nih.gov.

PA-06-119: **Structural Biology of Membrane Proteins**

The PA solicits applications of methods for expression, oligomerization, solubilization, stabilization, purification, characterization, crystallization, isotopic labeling, and structure determination of unique and biologically significant membrane proteins by x-ray diffraction, nuclear magnetic resonance, electron microscopic, mass spectrometry, and other biophysical techniques are encouraged. Projects that will lead in the near term to determining the structures of biologically important membrane proteins are also encouraged. PA will use the NIH individual research project grant R01 award mechanism. The PA is available at http://grants.nih.gov/grants/guide/pa-files/PA-06-119.html.

Inquiries: John Knowlton, 301-435-5226; jk339o@nih.gov.

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THE CANCER LETTER

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Business & Regulatory Report

Product Approvals & Applications:

Drug Cleared For GIST And Kidney Cancer, FDA's First Two-Indication Cancer Approval

Pfizer Inc. agent Sutent (sunitinib) received FDA approvals for gastrointestinal stromal tumors and advanced kidney cancer.

The action marks the first time FDA has approved a new oncology product for two indications simultaneously, the agency said. The tyrosine kinase inhibitor was approved in less than six months.

"Today's approval is a major step forward in making breakthrough treatments available for patients with rare and difficult to treat forms of cancer," said Steven Galson, director of FDA's Center for Drug Evaluation and Research. "New targeted therapies such as Sutent are helping FDA expand options for patients for whom there are limited alternatives."

The drug received full approval for GIST patients whose disease has progressed on Gleevec, and those unable to tolerate Gleevec.

The drug was approved for the indication based on an interim that showed

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Clinical Trials:

Avalon Begins Phase I Trial Of AVN944 For Advanced Hematological Cancers

Avalon Pharmaceuticals Inc. (Nasdaq and ArcaEx: AVRX) of Germantown, Md., said it has begun a phase I trial of AVN944 for advanced hematological malignancies.

The trial, taking place at the University of Arkansas for Medical Sciences, also will begin enrollment at University of Texas M.D. Anderson Cancer Center, Stanford University, and The Ohio State University Comprehensive Cancer Center-Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, the company said.

The 36-patient study is an open-label, repeat dose-escalation trial to evaluate safety and tolerability of the agent for leukemia, lymphoma or myeloma, the company said. The optimal dosage also would be determined.

Information on the trial, including other site locations when they initiate treatment, will be available at the NIH clinical trial database at www.ClinicalTrials.gov.

AVN944 is an oral, small molecule inhibitor of the enzyme inosine monophosphate dehydrogenase, an enzyme for the de novo synthesis of the nucleotide guanosine triphosphate, the company said. The agent inhibits cell proliferation by denying dividing cells of the GTP necessary for synthesis of DNA and RNA. IMPDH is highly upregulated in hematologic cancers and other types of cancer cells are also sensitive to IMPDH inhibition.

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FDA Approves Pfizer's Sutent For GIST And Kidney Cancer

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that the median time-to-tumor progression for patients treated with Sutent was 27 weeks compared to 6 weeks for patients who were not treated.

The agency granted an accelerated approval for Sutent in the treatment of patients with advanced renal cell carcinoma. Approval was based on Sutent's ability to reduce the size of the tumors in patients. An overall response rate ranging from 26-37 percent was found in patients with metastatic kidney cancer whose tumors had progressed following cytokine-based therapy, the agency said.

"Today's approval of this drug for these indications provides compelling evidence that the use of alternative data endpoints allows us to see the benefits of novel therapies earlier in patients," Richard Pazdur, director of FDA's Office of Oncology Drug Products, said in a statement.

In the GIST trial, significant clinical benefit was determined through an early interim analysis of data, thereby allowing researchers to convert all patients in the trial to treatment. For the RCC indication, the FDA used its accelerated approval process, a regulatory mechanism that expedites drug approvals for serious and life-threatening diseases.

Also, FDA said it worked with the product sponsor to offer an expanded access program prior to approval, making the product available to patients not enrolled in a clinical trial. Currently, more than 1700 patients are being treated with Sutent through the expanded access program.

"Expanded access programs have proven to be an effective way to get treatment to patients who need it most, especially in cancer," said Ellen Stovall, president of the National Coalition of Cancer Survivorship. "There needs to be a greater awareness among patients and doctors about both the option to participate in clinical research as well as in these expanded access programs in order to make promising new therapies available to as many patients as possible."

The most commonly reported Sutent-related side effects included diarrhea, skin discoloration, mouth irritation, weakness, and altered taste. Patients treated with Sutent also experienced, fatigue, high blood pressure, bleeding, swelling, and taste disturbance. Hypothyroidism was also observed.

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Bayer Pharmaceuticals Corp. (NYSE: BAY) of West Haven, Conn., and **Onyx Pharmaceuticals Inc.** (Nasdaq: ONXX) of Emeryville, Calif., said FDA has approved Nexavar (sorafenib) tablets for advanced renal cell carcinoma.

Nexavar, which has been shown to double progression-free survival in advanced RCC, is the first FDA-approved treatment for advanced renal cell carcinoma in more than a decade, the companies said.

The approval was based on phase III data from the largest randomized, placebo-controlled trial ever conducted for the disease, the companies said. In the study, the product doubled progression-free survival when compared to placebo. PFS was doubled to a median value of six months in patients receiving Nexavar as compared to three months for those receiving placebo (p-value < 0.000001). All subgroups examined, including those who had not received conventional treatment with biologics, such as interleukin-2 or interferon-alpha, appeared to benefit as well, the companies said.

At the time of a planned interim survival analysis, based on 220 deaths, overall survival was longer for Nexavar than placebo with a hazard ratio—Nexavar over placebo–of 0.72, the companies said. The analysis did not meet the prespecified criteria for statistical significance.

The most common reported treatment-emergent adverse events of any severity were diarrhea, rash/desquamation, fatigue, hand-foot skin reaction, alopecia, nausea, pruritus, hypertension, vomiting, and anorexia, the companies said. Grade 3 and 4 treatment-emergent

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adverse events were reported in 31 percent (vs. 22 percent for placebo-treated patients) and 7 percent (vs. 6 percent for placebo-treated patients) of Nexavar treated patients, respectively.

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Bristol-Myers Squibb Co., (NYSE: BMY) of Princeton said it has completed the rolling submission of its NDA for dasatinib for chronic myelogenous leukemia in chronic, accelerated or blast phases, as well as Philadelphia chromosome-positive acute lymphoblastic leukemia.

The NDA seeks approval of dasatinib, an investigational multi-targeted kinase inhibitor, for adult CML and Ph+ ALL with resistance or intolerance to therapy, the company said.

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Celgene Corp. (Nasdaq: CELG) of Summit, N.J., said FDA has approved Revlimid (lenalidomide) for transfusion-dependent anemia due to low or intermediate1 risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.

"The clinical data from a phase II trial of 148 patients demonstrated that Revlimid can reduce or even eliminate the need for transfusions in many patients with del 5q MDS," said Alan List, lead investigator, professor of oncology and medicine, and chief, Division of Hematologic Malignancies Hematologic Malignancies at H. Lee Moffitt Cancer Center.

The safety profile for the agent has shown that neutropenia and/or thrombocytopenia were the most common adverse event and that a dose adjustment may be required, the company said. Other observed and common AE's include diarrhea, pruritis, rash, fatigue, constipation, nausea, nasopharyngitis, arthralgia, pyrexia, back pain, peripheral edema, cough, dizziness, headache, muscle cramp, dyspnea, and pharyngitis.

Revlimid will be available through a Revlimid Education and Prescribing Safety Program, called RevAssist via contracted pharmacies.

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Genentech Inc. (NYSE: DNA) of South San Francisco said it has submitted a supplemental BLA for Avastin (bevacizumab) in combination with 5-fluorouracil-based chemotherapy for relapsed, metastatic colorectal cancer.

Avastin is approved as a first-line treatment of metastatic colorectal cancer in combination with intravenous 5-FU-based chemotherapy.

The submission is based on a randomized, controlled, multicenter phase III trial, known as E3200, of 829 patients with advanced or metastatic colorectal cancer whose disease progressed following previous treatment with 5-FU and irinotecan-based chemotherapy.

The study showed that Avastin plus the 5-FU-based chemotherapy regimen FOLFOX4 (oxaliplatin/5-FU/leucovorin) had a 25 percent reduction in the risk of death (hazard ratio of 0.75), the primary endpoint, which is equivalent to a 33 percent improvement in overall survival, compared to FOLFOX4 alone, the company said.

In the E3200 study, adverse events were similar to those seen in previous trials of Avastin plus FOLFOX4; however, increases in the incidence of Grade 3 and 4 sensory neuropathy and Grade 3 and 4 nausea and vomiting were observed, the company said. Adverse events that were consistent with those observed in previous Avastin studies included Grade 3 and 4 hypertension, bleeding, diarrhea, gastrointestinal perforation, and arterial thromboembolic events. There was no significant increase in the incidence of Grade 3 and 4 venous thromboembolic events or proteinuria events with the addition of Avastin to FOLFOX4 in the study.

The trial was sponsored by NCI and led by the Eastern Cooperative Oncology Group. Genentech provided Avastin for the trial under the CRADA with the NCI for the clinical development of the drug, as well as financial support for data management.

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GW Pharmaceuticals (AiM: GWP) of London said U.S. FDA has accepted its IND application for Sativex, a cannabis-derived, oro-mucosal spray for advanced cancer that is not relieved by opioid medications.

As part of the IND, FDA has agreed to a phase III in the U.S., the company said. The planned 250 patient, double-blind, randomized placebo controlled study will evaluate the effect of Sativex in relieving average daily pain, reducing the use of breakthrough opioid medications, improving the quality of sleep, and relevant aspects of quality of life among other outcome measures, the company said.

GW said it has completed a multi-center double-blind, randomized, placebo-controlled parallel group phase III 177-patient study in Europe for cancer pain. In addition to study medication, patients remained on their existing opioid and other analgesic medication. Sativex achieved a statistically significant improvement in comparison with placebo in pain as measured on a numerical rating scale (p=0.014), a primary endpoint of

the study. A responder analysis showed that about 40 percent of patients on the treatment showed a greater than 30 percent improvement in their pain (p=0.024), the company said.

Sativex is composed of tetrahydrocannabinol and cannabidiol, a non-psychoactive cannabinoid. GW said it would begin two phase III trials in cancer pain in the U.S. prior to filing a U.S. regulatory submission.

* * *

Idenix Pharmaceuticals Inc. (Nasdaq: IDIX) of Cambridge, Mass., and **Novartis Pharmaceuticals Corp**. (NYSE: NVS) of East Hanover, N.J., said they submitted an NDA seeking marketing approval of the 600 mg dose of telbivudine for chronic hepatitis B.

The NDA is based on one-year data from the GLOBE study, an ongoing two-year phase III trial comparing telbivudine with a standard therapy, lamivudine, in 1,367 adults with chronic hepatitis B. The study was conducted at 112 clinical centers in 20 countries.

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Morphotek Inc. of Exton, Penn., said it has submitted an IND application to FDA for MORAb-009, a monoclonal antibody.

Preclinical data indicate that mesothelin is highly over-expressed in pancreatic adenocarcinoma tumors, non-small lung carcinoma, ovarian carcinoma and mesothelioma and may be associated with disease activity, the company said. MORAb-009 inhibits tumor growth by inhibiting mesothelin binding to extracellular substrate and also through antibody dependent cellular cytotoxicity.

Morphotek obtained exclusive rights to develop and commercialize the antibody worldwide from NCI.

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Novartis of East Hanover, NJ, said it has been given U.S. regulatory approval of Femara (letrozole) in a new indication for use after surgery in postmenopausal women with hormone-sensitive early breast cancer.

The approval was based on results of the ongoing Breast International Group, BIG 1-98, a randomized, double-blind study, which compared the effectiveness and tolerability of the agent versus tamoxifen when used as initial therapy after surgery, the company said.

Femara reduced the risk of breast cancer returning by an additional 21 percent (p=0.002) over the reduction offered by tamoxifen. Treatment with the agent demonstrated a 27 percent (p=0.0012) reduction in the risk of metastasis.

The drug demonstrated its greatest benefit in two groups at increased risk of recurrence, the company said. Risk was reduced by 29 percent in women whose breast cancer had already spread to the lymph nodes at the time of diagnosis and by 30 percent in women who had undergone chemotherapy. The data also showed that in these high-risk subgroups, the agent reduced the risk of metastasis by 33 percent and 31 percent, respectively, the company said.

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Pharmion Corp. (Nasdaq: PHRM) of Boulder said it would submit a Marketing Autorization Application for thalidomide in first-line multiple myeloma in Europe.

An external Independent Data Monitoring Committee analysis of a multi-centered, randomized, placebo-controlled phase III study of combination thalidomide plus dexamethasone versus dexamethasone alone as induction therapy for previously untreated multiple myeloma met the pre-specified p<0.0015 value for stopping the trial, the company said.

The IDMC found time to disease progression—the primary endpoint—of 75.7 weeks versus 27.9 weeks (p=0.000065), plus progression-free survival of 55.7 weeks versus 24.3 weeks (p=0.0003) with Thalomid plus dexamethasone compared to dexamethasone alone.

Treatment assignments for ongoing trials will be unblinded, and patients not on the treatment would be able to add the agent to the dexamethasone regimen.

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SuperGen Inc. (Nasdaq: SUPG) of Dublin, Calif., said it has withdrawn its Marketing Authorization Application for Orathecin (rubitecan) capsules from the European Medicines Agency.

Orathecin is being developed for the treatment of pancreatic cancer in patients who have failed at least one prior chemotherapy regimen. SuperGen said the withdrawal followed "extensive discussions with the EMEA."

The company is conducting a phase II trial ongoing in the U.S., studying Orathecin and gemcitabine as a first-line combination therapy for advanced pancreatic cancer patients who have not undergone chemotherapy. SuperGen said it intends to make a decision on future development or the alternative disposition of Orathecin based on a review of the interim results of that trial.

* * *

Tanox Inc. (Nasdaq: TNOX) of Houston said it has filed an IND application with FDA for TNX-650 for Hodgkin's lymphoma that is refractory to chemotherapy or radiation treatment.

The clinical development of the agent will be as monotherapy where patients have relapsed or are

refractory to standard chemotherapy with or without radiation therapy and who have not responded to or are unable to undergo autologous bone marrow transplantation, the company said.

Enrollment in a phase I trial of TNX-650, a monoclonal antibody targeting Interleukin 13, a growth factor for malignant lymphoma cells, would begin in the first half of 2006, the company said.

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Xoft Inc. of Fremont, Calif., said it has received clearance from FDA for the Axxent Electronic Brachytherapy System for breast cancer.

Electronic Brachytherapy is a proprietary technology platform that delivers localized, non-radioactive, isotope-free radiation treatment in a minimally-shielded clinical setting, the company said.

Clinical Trials:

BioCryst Begins Phase I/II Trial Of Fodosine For Leukemia

(Continued from page 1)

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BioCryst Pharmaceuticals Inc. (Nasdaq: BCRX) of Birmingham, Ala., said it has begun a phase I/II trial of Fodosine (forodesine hydrochloride) for cell acute lymphoblastic leukemia.

Fodosine is a purine nucleoside phosphorylase inhibitor, which blocks the DNA synthesis machinery of the T-cells, the company said. The small molecule drug is being developed for of T-cell malignancies, and has been designated an Orphan Drug for indications, including cutaneous T-cell lymphoma, chronic lymphocytic leukemia and acute lymphoblastic leukemia.

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Chemokine Therapeutics Corp. (OTCBB: CHKT; TSX: CTI) of Vancouver said it began a second clinical study of CTCE-0214.

The phase Ib study will evaluate the safety, pharmacodynamics, and pharmacokinetic profile of CTCE-0214 as a single injection, multi-dose, and in combination with granulocyte colony stimulating factor, the company said. CTCE-0214 is a stable peptide agonist of stromal cell-derived factor-1, a signaling molecule in the homing and engraftment of stem cells.

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EntreMed Inc. (Nasdaq: ENMD) of Rockville, Md., said it has begun phase II clinical trials of two of its agents, MKC-1 and Panzem NCD.

The open-label study of MKC-1 will be conducted at about 15 centers in the U.S. in patients with advanced or metastatic breast cancer who have failed conventional therapies are expected to be enrolled. MKC-1, an orally-active, small molecule cell cycle inhibitor, has been shown to inhibit mitotic spindle formation, prevent chromosome segregation in the M-phase (mitosis) of the cell cycle, and induce apoptosis in multiple cell lines, consistent with a mechanism in which MKC-1 blocks the nuclear uptake of proteins essential to cell replication, the company said.

Panzem NCD(2-methoxyestradiol or 2ME2) will be studied in patients with recurring glioblastoma multiforme, the company said.

The study will be conducted at the Brain Tumor Center at Duke University Medical Center. David Reardon, medical director, clinical research at the center, will serve as principal investigator.

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Exelixis Inc. (Nasdaq: EXEL) of South San Francisco said it has begun a multi-trial phase II development program for XL999 in six trials for cancer indications.

Four solid tumor trials for renal cell carcinoma, colon, ovarian, and non-small cell lung cancer are open for enrollment at centers in the U.S. Two more trials, in acute myelogenous leukemia and multiple myeloma, are scheduled.

XL999, a spectrum selective kinase inhibitor, is a small molecule inhibitor of receptor tyrosine kinases implicated in the development and maintenance of tumor vasculature and in the proliferation of tumor cells.

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Favrille Inc. (Nasdaq: FVRL) of San Diego said FDA has granted Fast-Track designation of FavId for B-cell follicular non-Hodgkin's lymphoma.

In the phase II trial, the drug showed positive long-term follow-up data following Rituxan administration over Rituxan alone, the company said.

FavId is in a randomized, double-blind, placebo-controlled phase III registration trial as a treatment following Rituxan therapy for follicular B-cell NHL.

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Infinity Pharmaceuticals Inc. of Cambridge, Mass., said it has begun a second phase I trial of IPI-504 for gastrointestinal stromal tumors resistant to Gleevec (imatinib mesylate).

The open-label, dose-escalation phase I is being conducted at Dana-Farber Cancer Institute under the direction of George Demetri, director of the Center for Sarcoma and Bone Oncology.

* * *

Keryx Biopharmaceuticals Inc. (Nasdaq:

KERX) of New York said it has begun a clinical program to evaluate KRX-0401 (perifosine) for multiple myeloma.

Paul Richardson, clinical director of the Jerome Lipper Myeloma Center at Dana-Farber Cancer Institute, will lead the multi-center study, the company said.

* * *

Oncolytics Biotech Inc. (TSX:ONC, Nasdaq: ONCY) of Calgary, AB, said the Cancer Therapy Evaluation Program of the U.S. NCI has issued a solicitation for Letters of Intent for two clinical trials using Reolysin proprietary formulation of the human reovirus as a cancer therapeutic.

CTEP is soliciting proposals for a phase II study of Reolysin administered systemically for melanoma. The dosage and dosing regimen will be determined on data from ongoing U.K. and U.S. phase I systemic administration studies being conducted by Oncolytics.

CTEP is also soliciting proposals for a phase I/II study of the drug co-administered both systemically and intraperitoneally for ovarian cancer, the company said. The purpose of the phase I portion of the trial is to determine the maximum tolerated dose of Reolysin given by IP administration in combination with a constant systemic dose and dosing regimen.

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Pharmacyclics Inc. (Nasdaq: PCYC) of Sunnyvale, Calif., said it has results for its phase III study of Xcytrin (motexafin gadolinium) Injection for of non-small cell lung cancer with brain metastases.

Although patients receiving Xcytrin had a longer time to neurologic progression, the study's primary endpoint, the difference compared to patients in the control arm did not reach statistical significance, the company said.

The randomized, controlled phase III 554-patient trial, known as the Study of Neurologic Progression with Motexafin Gadolinium And Radiation Therapy or SMART, compared the safety and efficacy of whole brain radiation therapy alone to WBRT plus Xcytrin, the company said. The trial took place at 94 centers in North America, Europe and Australia, the company said.

In the intent-to-treat analysis, the median TNP was 15.4 months for WBRT plus Xcytrin compared to 10.0 months for WBRT alone (P=0.122, hazard ratio=0.78). Substantial differences in patient characteristics were observed for the 348 patients enrolled in North America (63 percent of all patients enrolled in the study) compared to the other regions. In North America, there were more females, there was a shorter time from primary cancer diagnosis to development of brain metastases, and there was less use of post-randomization chemotherapy compared to the other regions. In North America, the median TNP for WBRT plus Xcytrin treatment was 24.2 months compared to 8.8 months for WBRT alone (P=0.004, hazard ratio=0.53), the company said.

There was no significant difference in survival, a secondary endpoint of the trial.

The most common drug related grade 3 and 4 adverse events were hypertension (4 percent), elevated liver enzymes (3 percent) and fatigue (3 percent), all of which were reversible, the company said.

Three trials with Xcytrin for the systemic therapy of relapsed lung cancer are in progress evaluating its use as a single agent and in combination with other agents. Additional trials in hematologic malignancies and other advanced cancers are also underway.

* * *

Sunesis Pharmaceuticals Inc. (Nasdaq: SNSS) of South San Francisco said it has begun a phase II trial of SNS-595 for non-small cell lung cancer following failure of first-line platinum-based therapy.

SNS-595 is a cell-cycle modulator that induces apoptosis as cells progress through the S phase of the cell cycle, the company said.

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Tapestry Pharmaceuticals Inc. (Nasdaq: TPPH) of Boulder said it has begun a second phase I trial of TPI 287, a proprietary third generation taxane.

The study will be conducted at the Rocky Mountain Cancer Center in Denver, under the direction of Allen Cohn, chairman of the GI Research Committee, and at the Sheba Medical Center in Tel Aviv, Israel, under the direction of Yaacov Baram.

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ViaCell Inc. (Nasdaq: VIAC) of Cambridge, Mass., said FDA has lifted its clinical hold on the phase I study evaluating CB001, an investigational cord blood stem cell product for hematopoietic stem cell transplantation for cancer.

ViaCell said it would submit information to the Investigational Review Boards at each study site to request immediate resumption of enrollment in the trial. To date, CB001 has been administered to eight of 10 patients in the study.

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Xanthus Life Sciences Inc. of Cambridge, Mass., said it has begun a phase II trial with Symadex for metastatic breast cancer following anthracycline and taxane failure.

The objective of the European 49-patient study is overall response rate.

Deals & Collaborations:

ImClone Board Hires Lazard To Consider Possible Sale

ImClone Systems Inc. (Nasdaq: IMCL) said its board of directors has engaged **Lazard** to "review of the company's strategic alternatives," which could include a merger, sale or strategic alliance.

At the same time, the company replaced its CEO, Philip Frost, who will remain as executive vice president and chief scientific officer. Joseph Fischer, a board member since 2003, was named interim CEO.

"Following a review of the company's business, products, assets and current strategic position, the board of directors has determined that it is now appropriate to initiate an external process to explore ways of enhancing shareholder value," Fischer said in a statement. "During this process, the company will continue to move forward in the ordinary course, with the goal of maximizing the potential of Erbitux and developing novel oncology therapeutics to benefit patients with cancer."

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Avigen Inc. (Nasdaq: AVGN) of Alameda, Calif., said it has agreed to sell its AAV gene therapy assets to **Genzyme Corp**.

Under the agreement, Genzyme will acquire the Avigen non-pain related AAV assets, the company said. The assets include rights to a patent estate and the Avigen Parkinson's disease clinical trial program, which is in a phase I /II study at University of California, San Francisco. Genzyme said it would make an upfront cash payment of $12 million to Avigen, with additional milestone payments and royalty payments.

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454 Life Sciences Corp., a majority-owned subsidiary of **CuraGen Corp.** (Nasdaq: CRGN) of Branford, Conn., said it has entered into a collaborative research agreement with the Broad Institute of **MIT** and **Harvard**.

Under the collaboration, researchers at the Broad Institute will use the 454 Life Sciences system to study the genetic basis for complex diseases, such as cancer, diabetes and heart disease, the company said.

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Elan Corp. plc (NYSE: ELN) of Dublin and **EntreMed Inc.** (Nasdaq: ENMD) of Rockville, Md., said they have entered into a License Agreement in which EntreMed has been granted rights to the Elan proprietary NanoCrystal Technology to develop the oncology product candidate, Panzem NCD (2-methoxyestradiol).

Under the license agreement and corresponding services agreement, Elan said it would manufacture the EntreMed Panzem NCD.

In 2004, the parties signed a Clinical Supply Agreement covering the supply of Panzem NCD for phase I trials; the agreements extend the Panzem NCD supply arrangement to phase II and later trials. Panzem NCD is in phase Ib studies for advanced cancer.

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Eli Lilly and Co. (NYSE: LLY) said it has reached a settlement with Department of Justice Office of Consumer Litigation and the U.S. Attorney's Office for the Southern District of Indiana in the investigation into marketing and promotional practices for Evista.

As part of the settlement, Lilly said it has agreed to plead guilty to one misdemeanor violation of the Food, Drug, and Cosmetic Act for the off-label promotion of Evista during 1998. The government has not, however, charged the company with any unlawful intent, nor does Lilly acknowledge any such intent. The settlement is subject to approval by the federal court in Indianapolis; the company anticipates a hearing on the settlement will occur within the next few weeks, the company said.

The investigation began in 2002 with the government alleging that, during 1998, Lilly employees promoted Evista for the prevention and reduction in the risk of breast cancer and cardiovascular risk reduction, the company said. The product is not approved by FDA for either of the uses, although both uses are the subject of large, multi-year registration clinical trials that began in the late 1990s. Evista is approved in the U.S. for both the prevention and treatment of osteoporosis in post-menopausal women.

The government also filed a civil complaint alleging similar Evista-related conduct continued into 2000, the company said. The company said it disagrees and has not admitted to the allegations. However, Lilly said it has agreed to settle the dispute over the allegations in order to reach a final resolution of the investigation.

In the overall settlement, Lilly said it has agreed to pay $36 million. The company also will be required to continue its compliance program and to undertake a set of defined corporate integrity obligations related to Evista for five years, a requirement of a civil consequence decree, the company said.

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EntreMed Inc. (Nasdaq: ENMD) of Rockville, Md., said it has entered into a definitive merger agreement in which it will acquire the outstanding capital stock of **Miikana Therapeutics Inc.** in exchange for 9.96 million shares of EntreMed common stock

valued at $21.2 million.

Under the transaction, EntreMed Inc. said it would issue up to 9,964,000 shares of its common stock in exchange for all of the Miikana outstanding Series A & B preferred and common stock. EntreMed said it would not assume outstanding Miikana options or warrants and each option or warrant would be exercised or terminated.

EntreMed said it might pay up to $18 million upon the achievement of certain clinical and regulatory milestones. The acquisition does not require regulatory approvals.

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GPC Biotech AG (Frankfurt Stock Exchange**:** GPC**;** TecDAX index; Nasdaq: GPCB) of Martinsried and Munich and **Pharmion Corp.** (Nasdaq: PHRM) of Waltham, Mass., said they have entered into a co-development and license agreement for satraplatin.

Satraplatin is in a phase III registrational trial as second-line chemotherapy treatment for hormone-refractory prostate cancer.

Under the agreement, Pharmion would gain exclusive commercialization rights for Europe, Turkey, the Middle East, Australia and New Zealand, while GPC Biotech would retain rights to the North American market and all other territories.

Pharmion would provide an upfront payment of $37.1 million, including an $18 million reimbursement for past satraplatin clinical development costs and $19.1 million for funding of ongoing and future clinical development to be conducted by the companies.

The companies said they would share global development costs, for which Pharmion has made an additional commitment of $22.2 million, in addition to the $37.1 million in initial payments. Pharmion also would pay GPC Biotech $30.5 million based on the achievement of regulatory filing and approval milestones, and up to an additional $75 million for up to five subsequent EMEA approvals for additional indications.

GPC Biotech also would receive royalties on sales of satraplatin in the Pharmion territories at rates of 26 to 30 percent on annual sales up to $500 million, and 34 percent on annual sales over $500 million. Pharmion would pay GPC Biotech sales milestones totaling up to $105 million, based on the achievement of annual sales levels in the Pharmion territories, the companies said.

GPC Biotech will also receive royalties on sales of the drug in the Pharmion territories. Also, Pharmion will pay GPC Biotech sales milestones totaling up to $105 million.

In another development, **Spectrum Pharmaceuticals Inc.** (Nasdaq: SPPI) of Irvine, Calif., said **GPC Biotech AG** (Frankfurt Stock Exchange: GPC; Nasdaq: GPCB), its co-development partner, has begun the rolling submission of an NDA for satraplatin in combination with prednisone as a second-line chemotherapy treatment for hormone-refractory prostate cancer.

The chemistry, manufacturing and controls section of the NDA has been filed with FDA.

Target enrollment was achieved in a phase III registrational trial, known as the SPARC trial, as a second-line chemotherapy treatment for HRPC, the company said.

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Human Genome Sciences Inc. (Nasdaq: HGSI) of Rockville, Md., said it has entered into a license agreement with **Amgen** under which Amgen has acquired exclusive worldwide rights to develop and commercialize therapeutic biological products for autoimmune diseases, immune deficiencies or suppression, and cancer.

Under the agreement, Human Genome Sciences said it will receive an upfront payment and annual fees, as well as development milestone payments and royalties on annual net sales for therapeutic and diagnostic products developed and commercialized using such rights.

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Lexicon Genetics Inc. (Nasdaq: LEXG) of The Woodlands, TX, said it has completed two performance milestones related to a collaboration with **Genentech Inc**. (NYSE: DNA) which entitles Lexicon to payments of up to $20 million.

The payments are based on the completion of the fourth and final performance milestone in the analysis of the physiological and behavioral functions of targets selected from the Genentech Secreted Protein Discovery Initiative program, the company said.

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YM BioSciences Inc. of Mississauga, Ontario, said it has entered into a collaborative agreement with **Sanofi-Aventis** to investigate the combination of tesmilifene and docetaxel for rapidly progressing metastatic breast cancer.

The initial study will be conducted in Europe and at US Oncology Inc. sites in the U.S., the company said.

Data from a phase III trial using the combination of tesmilifene and chemotherapy demonstrated an increase survival in metastatic and recurrent breast cancer, the company said.