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Institute for Cancer Prevention Closes As Audit Finds $5.7 Million "Overdraft"

By Paul Goldberg

The Institute for Cancer Prevention last week closed its doors and sought protection under bankruptcy laws after NCI alleged that the 35-year-old institution improperly withdrew $5.7 million in federal funds.

According to court papers dated Sept. 21, the Valhalla, N.Y., based NCI-designated cancer center that was formerly known as American Health Foundation had "overdrawn" its NCI accounts by about $5.3 million.

An Institute memorandum obtained by **The Cancer Letter** estimates the overdraft at $5.7 million. Citing the results of an audit, NCI officials said the

(Continued to page 2)

In Sudden Policy Change, NIH Proposes One-Year Consulting Ban For Scientists

By Paul Goldberg

NIH officials last week declared a one-year moratorium on outside consulting by intramural scientists.

Until this unexpected reversal of policy, NIH argued that outside activities are essential for attracting top-level scientists and encouraging them to maintain connections with colleagues in the private sector.

In Congressional testimony last June, NIH Director Elias Zerhouni said a complete ban should be avoided, and instead proposed that the scientists' interactions with the industry would have to be restricted, publicly disclosed and monitored (**The Cancer Letter**, June 25).

This sudden decision by NIH to declare the moratorium suggests flaws in the system of reporting the institutes used to track outside activities by intramural scientists.

In a memorandum to NIH staff, Deputy Director Raynard Kington said flaws in the reliability and accuracy of the system of disclosure became apparent in the course of a Congressional investigation that began earlier this year.

To test the reliability of the NIH system of disclosure, investigators at the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce asked 20 pharmaceutical and biotechnology companies to disclose lists of their consulting agreements and other arrangements with NIH employees. These lists provided evidence of over 100 arrangements that weren't previously reported to NIH.

"During the June 22 hearing, Congress informed us that they had

(Continued to page 8)

Cancer Center Shuts Down After NCI Freezes Accounts

(Continued from page 1)

overdrafts were made earlier this year and in 2003.

In a Chapter 11 filing, IFCP President Daniel Nixon said the center closed as a result of an "abrupt cessation of funds by NCI," which occurred despite his efforts to find financing or arrange a merger.

"Despite the IFCP's prompt and full compliance with NCI's several requests, the NCI informed IFCP on Aug. 31, 2004, that it would not provide short-term funding," Nixon said in an affidavit filed in the U.S. Bankruptcy Court for the Southern District of New York.

NCI officials said the center had ample warning.

"IFCP has known of its financial crisis for a long time," Leo Buscher, chief of the NCI Grants Administration Branch, wrote in a Sept. 9 email to IFCP investigators. "As far back as November 2003, or longer, IFCP was aware that it had overdrawn at least $2.9 million of federal grant funds. In the spring 2004, the HHS Office of Inspector General conducted an audit, which concluded that IFCP had, in fact, overdrawn $5.7 million. IFCP was advised of this finding in May 2004, and has not contested it."

Buscher wrote that NCI didn't immediately cut the center's access to money. "From the beginning, NCI has encouraged IFCP's management, both in conversations and in correspondence, to address its financial situation, and NCI chose not to terminate IFCP's grant awards in order to give IFCP an opportunity to do so," he wrote.

Over the years, scientists at the center published about 3,000 papers on cancer prevention, emphasizing the role of nutrition in cancer, and sometimes crossing over into alternative medicine.

Nixon was named president of the center five years ago, succeeding its founder Ernst Wynder, whose early work established the link between smoking and lung cancer. A cancer prevention expert, Nixon had worked at Emory University, NCI, American Cancer Society, and Medical University of South Carolina. Wynder died in 1999. Attempts to reach Nixon were unsuccessful.

Despite Wynder's enthusiastic promotion, AHF was vulnerable to financial instability. It had no endowment, and grew increasingly dependent on NCI grants and contracts. Altogether, NCI contributed over $14 million to the center's $18.9 million budget last year, court documents show.

This isn't the first time IFCP ran up an overdraft on its NCI accounts. In 1999, the center was forced to pay back about $4 million in misused funds. Despite these problems, the center retained its NCI designation and its Cancer Center Support Grant. Last year, that grant provided $3.3 million to IFCP.

ICFP, a New York non-profit corporation, is the second NCI-designated cancer center to go out of business since the Cancer Centers Program began in the 1970s. In 1992, the Illinois Cancer Council closed its doors after losing state funding.

Office on Fifth Avenue

Insiders describe the Nixon years at IFCP as a time of turmoil.

Chief financial officers came and went—there were three in four years—and many investigators took their grants elsewhere. As finances deteriorated, Nixon spoke of his plans to build a "preventive proteomics" program with as many as 15 principal investigators, insiders said.

In 2002, Nixon established a Manhattan office, leasing a 14,500-square-foot suite occupying the entire third floor of a landmark building on Fifth Avenue.

According to New York Landmarks Preservation Commission, the eight-story building, 390 Fifth Avenue, was designed by the architect Stanford White in the Florentine Renaissance style. The building's points of interest include bas-reliefs by the sculptor Andrew O'Connor, a massive copper cornice, and bronze friezes and balconies.

IFCP paid about $35,000 a month to rent the office,

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sources said. By contrast, the lease on the Valhalla campus, negotiated by Wynder, cost $1 a year, paid to New York Medical College. In about 20 years, at the end of the 50-year lease, the land and the building were to be turned over to the medical college.

Since the number of IFCP employees had dropped from over 200 to under 100 over the past decade, space in Valhalla was plentiful, which made the downtown office redundant, said Leonard Cohen, former head of the research animal facility and the nutrition and endocrinology section.

"When you walked into the Fifth Avenue office suite, it was anything but bustling," Cohen said. "There weren't enough people there. Offices stood empty, and space was allocated in mysterious ways. The chauffeur had a real office, with a door, and the data manager, who had the enormous job of archiving all our clinical and animal data, worked in a cubicle."

Common spaces were generously proportioned. "I have never seen such hallways in my life," said Veronica Fortunato, a nutritionist on the Women's Intervention Nutrition Study, who worked in the Fifth Avenue office. "More than once I had the inclination to rollerblade through the place. "

Nixon was the principal investigator on WINS, a randomized trial testing the hypothesis that dietary fat intake reduction as an adjuvant to standard breast cancer therapy can reduce disease recurrence and increase survival for women with localized breast cancer.

After the IFCP staff moved in, workmen continued to tear out acoustical tiles and move ducts and wiring to expose the graceful arches of the 20-foot vaulted ceilings. Nixon's corner office was furnished with antiques, and its windows faced Fifth Avenue and 35th Street.

"It was difficult to see all this work being done for one individual, when the rest of us hadn't had a pay increase for over two years," Fortunato said. "We were sacrificing for the participants in the breast cancer study. We believed in the study. We believed in the work. In that context, seeing all that money being spent on things that are trivial made it that much more difficult."

On Sept. 8, 2003, when management invited the Valhalla staff to the opening of the new office, researcher Thomas Spratt avoided the gathering. The expenditure seemed bizarre, considering that essential bills weren't being paid, he said.

More recently, in June, Nixon used the foyer to throw a party marking publication of his general-interest book on preventing prostate cancer. Nixon co-wrote the book with a New York television reporter.

Researchers knew that something had gone awry at their institution, but didn't understand the specifics or the full extent of the problems, said Spratt, who is preparing to join five other IFCP expatriates at Penn State Hershey Medical Center.

"The budgets that we get from our grants and contracts only show what we spent," said Spratt. "They don't show what the institute took from the federal government. As far as we knew, everything was pretty good, until we started ordering supplies, and then supplies weren't being delivered to us, because bills weren't paid. That was our first clue that we were in pretty bad shape."

Drawing on HHS Payment Management System

Individual investigators are in no position to overdraw their grant funds, but an institution that holds multiple grants has the capacity to make improper withdrawals from the centralized HHS Payment Management System, experts say.

Though NCI requires grantees to file annual financial reports and reserves the right to conduct audits, the payment system relies on self-monitoring by institutions and functionality of their accounting practices.

After an investigator receives a grant, NCI sets the funds aside in the centralized system, and the investigator's institution acts as a middleman, drawing the funds and floating them through its checking account.

It's common for an entire cancer center or a department to have just one account, which is used to make electronic transfers on behalf of dozens of investigators. These transfers provide the money that goes directly to investigators, as well as indirect costs, a surplus of about 60 percent that supports the institution's overhead.

NCI documents warn that only funds needed by the investigators can be drawn in their name. However, investigators don't use up their funds at a constant rate, and many carry over unspent money from year to year.

In those cases, an administrator is able to withdraw additional funds, and, in effect, improperly use them as a short-term loan. Experts say that an administrator taking this risky step should be prepared to repay the "loan" by the time the investigator needs to make the final draw.

NCI requires grantee institutions to perform annual audits by public accountants or government organizations.

According to an NCI booklet, "this audit should include a review of internal controls that are maintained to provide reasonable assurance that financial operations are properly conducted; financial reports are presented fairly and accurately; applicable laws, regulations, and other grant terms have been complied with; resources are managed and used in an economical and efficient manner; and desired results and objectives are being achieved in an effective manner."

"This Place Was Really Like a Jewel"

In his Sept. 9 email, NCI official Boucher encouraged IFCP scientists to move their grants to other institutions.

"In the event IFCP ceases operations, we would like to facilitate, to the extent feasible, the orderly transfer of your grants and research resources," Buscher wrote. "To that end, NCI is exploring whether there is some means of preserving your research resources."

Buscher wrote that if researchers find new institutions, NCI would be prepared to "authorize the new institution to incur pre-award costs" covering the transfer of equipment, animals and research materials.

As he prepares to move to Hershey after 18 years at IFCP, scientist Spratt is uncertain about the status of his R01 grant. "I got one email from NCI, and they seemed to be supportive of moving the grants," he said. "I don't know if they will come back and say that money is used up."

Rowan Chlebowski, of Harbor-UCLA Research & Education Institute, is expected to replace Nixon as the principal investigator on the WINS study, sources said. Collection of data in the trial has been completed, but analysis continues.

As one of 10 former employees authorized to enter the building in Valhalla, Karam El-Bayoumy, former director for basic research, has been working with court-appointed trustees to keep animal experiments going.

Several technicians have been showing up to put in long days delivering carcinogens or experimental diets to about 3,000 animals, El-Bayoumy said. "All of them are loyal people," he said. "They actually continue to take care of the animals even though they don't have a guarantee that their salary will be paid."

The sense of loss has a way of reverberating in empty buildings. "This place was really like a jewel, really like a diamond," said El-Bayoumy as he sat in the office he would soon have to vacate. "And this is what we have now. So what can you do?

"You have to move on, and just feel bad about the number of people who don't have jobs."

Senate Committee Proposes $1.1 Billion Increase For NIH

By Kirsten Boyd Goldberg

The Senate Appropriations Committee approved a bill providing $28.9 billion to NIH for fiscal 2005, an increase of $1.1 billion over the current appropriation and $373 million more than the President's budget request.

The committee markup of the bill Sept. 15 included $4.894 billion for NCI, an increase of $155.7 million above the FY 2004 appropriation of $4.739 billion, and $25 million more than the President's budget request.

The House passed an appropriations bill for the Departments of Labor, HHS, and Education on Sept. 9, providing $4.87 billion for NCI, the same as the President's request.

It appears unlikely that Congress will be able to reconcile the Labor-HHS bills before the Oct. 8 target for adjournment. Earlier this week, Congress approved a continuing resolution to fund agencies at FY04 levels through Nov. 20.

Committee "Disappointed" With Bush Budget

In its annual report on NIH, the Senate committee said it was "disappointed" that the Bush Administration's budget request would require NIH to cut funding commitments to grantees.

"Forcing grantees to reduce the scope of research that is already underway would establish an unfortunate precedent and could erode confidence in NIH," the report said. "Therefore, the committee has included sufficient funding to enable NIH to fully pay the committed levels on its grants."

Also, the budget would permit the average cost of new and competing grants to rise by 2 percent instead of the 1 percent the President proposed.

The committee said it was "extremely disappointed" to learn about NIH scientists serving as consultants to pharmaceutical and biotechnology firms.

"These arrangements raise questions about potential conflicts of interest, the influence that these monetary compensations could have on the outcome of scientific research, and whether these employees are more interested in procuring lucrative consulting fees than in meeting the responsibilities of their full-time, taxpayer-funded jobs," the report said. "The Committee finds it difficult to understand how the most prestigious biomedical research institution in the world could allow these questions to be raised."

The report praised NIH Director Elias Zerhouni for

convening a panel to review policies, and directed him to "immediately put in place safeguards that will insure that no conflicts of interest exist between scientists and pharmaceutical and biotechnology companies, or any other entity."

The full text of the committee report is available at http://thomas.loc.gov/home/approp/app05.html.

Experts of the report's section on NCI follow:

Anticancer compounds: The Committee encourages NCI to increase research in the area of anticancer compounds. Sources of these compounds include marine invertebrates, terrestrial plants, and microorganisms that may be used to develop small molecule anticancer drugs. The Committee further understands that little research is conducted in this area and therefore urges the Institute to conduct appropriate research in this area.

Behavioral Research: The Committee recognizes the enormous progress NCI has made in the quality and breadth of cancer related behavioral science ranging from basic bio-behavioral research to health communication research and tobacco control research. Closing the gap between research and program delivery is both a challenge and a necessity if we are to ensure that all populations benefit from new scientific discoveries. Behavioral science can contribute to survival, reduced morbidity and increased quality of life, and the behavioral and cognitive sciences can be highly applicable in answering critical questions regarding patient care. The Committee sees NCI's behavioral science research program as a model for other institutes.

Bladder and Renal Cancer: The Committee is concerned about the poor implementation of the 2002 Progress Review Group Report on Bladder and Renal Cancers. The incidence and mortality of renal cancer has been steadily increasing over the past several decades. Renal cancers are silent killers; for many, renal cancers are not recognized until late in the disease, when cancer has already spread beyond the kidney. NCI is urged to expand studies to improve detection and diagnosis of renal cancer. For patients with metastatic renal cancer, survival is only 9 percent with a median survival time of 12 months. There are very few effective treatments. Metastatic bladder cancer also responds poorly to treatment. The Committee urges NCI to develop a novel treatment network to rapidly identify and test for new therapies for renal and bladder cancer in human patients and to expand studies on mechanisms of metastasis in these patients.

Blood Cancers: The Committee is pleased that important new therapies have been developed for the blood cancers--leukemia, lymphoma, and multiple myeloma. It has been brought to the Committee's attention that the Leukemia, Lymphoma, and Myeloma Progress Review Group, a blue ribbon advisory panel of NCI recommended in May 2001 the establishment of new multi-disciplinary and multi-institutional structures to shorten the timeline for new blood cancer drug development. The Committee encourages the NCI to develop new strategies to accelerate the development of new blood cancer therapies, which might include, among other options, public-private partnerships, multi-disciplinary collaborations, and multi-institutional initiatives. The Committee further urges the NCI to consider flexible uses of current funding mechanisms in order to respond to the key recommendation of the blood cancer Progress Review Group.

Bone Metastasis: The NCI is encouraged to develop an integrated approach to study bone metastasis, leveraging the expertise of cancer and bone biologists, clinical oncologists and metastasis experts and representatives of the pharmaceutical industry. Key issues to address include the generation of novel models which mimic tumor/bone interaction and which delineate mechanisms to determine why tumor cells prefer bone for metastasis. It is clinically relevant to learn how to use information to change the bone microenvironment so that it is hostile to the invading tumor cells. The Committee also urges NCI to expand research on osteosarcoma to improve survival and quality of life and to prevent metastatic osteosarcoma in children and teenagers who develop this cancer.

Brain Tumors: The Committee is concerned that insufficient attention is being given by NCI and NINDS to brain tumor research. The Committee encourages NCI to fund at least five Specialized Programs of Research Excellence in Brain Tumors grants in the upcoming fiscal year, with particular emphasis on those proposals which include both basic research and clinical treatment applications.

Cancer Centers and Minorities: The Committee commends NCI on the success of its cancer centers program. Given that minority populations suffer disproportionately from virtually every form of cancer, the Committee encourages NCI to support the establishment of a comprehensive center at a minority institution focused on research, treatment, and prevention of cancer in African American and other minority communities.

Cancer Genomics: The Committee is pleased that the NCI has focused considerable attention on building innovative public/private partnerships to accelerate the development and deployment of new technologies, which will facilitate the Institute's ambitious goal of dramatically altering the understanding and treatment of cancer by 2015. The Committee is also aware of the enormous potential for improved understanding and treatment of cancer presented by the use of microarray technology in both basic research and clinical setting. The Committee understands that the use of this technology can help accelerate the development of effective cancer drugs, the prediction of drug response, and ultimately the early detection and improved treatment of cancer. The Committee recommends that NCI continue to employ these enabling technologies to identify, characterize, and validate the gene pathways that cause cancer and that it continue to work cooperatively with public and private sector entities to do so.

Cancer and Native Hawaiians: The Committee remains concerned about the high incidence of breast, colon, and lung cancer among the native Hawaiian population. The Committee

anticipates an update on the Director's task force to explore the continuing unique needs of the people of Hawaii and the Pacific Basin region.

Chronic Lymphocytic Leukemia: This incurable disease is the most common form of adult leukemia in the United States. The Committee once again urges the NCI to increase research into CLL, including improved therapies and their rapid movement from the laboratory to the bedside. The Committee is pleased to learn that the unique multidisciplinary and multi-institutional research consortium funded by the NCI for the past 5 years is proceeding with a competing renewal of its initial grant to permit coordinated continued study of CLL at the cellular and clinical levels. The Committee strongly urges the NCI to give favorable consideration to continuing and expanding the scope of research activities funded through the the CLL Research Consortium as it works to defeat this devastating blood disorder.

Complementary and Alternative Cancer Therapies: The Committee expects 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.

Diethylstilbestrol: 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 NCI to continue its support of research in this area, and to continue to consult with organizations representing individuals impacted by DES as they carry out DES research and education efforts.

Gynecologic Cancers: The Committee commends the NCI for creating a cervical cancer and endometrial cancer SPORE, bringing the total number of gynecologic cancers SPORES to six, and expects that the NCI will expand the number of centers in the future. Unfortunately, 70 percent of ovarian cancer patients continue to be diagnosed in advanced stages when 5-year survival rates remain less then 25 percent. The Committee encourages continued research by the four ovarian SPORES that will lead to a better understanding of prevention and the development of a screening tool offering women earlier diagnosis when this cancer is more curable. The Committee also supports the expansion of NCI's collaboration with the NICHD for faculty development of gynecologic oncologists.

Health Care Decision-making: The Committee applauds NCI's investment in staff and resources to help build the science of health care decision-making. Such research will improve understanding of human decision-making processes so that individuals can make more informed choices about their health, and so more useful decision support systems can be constructed. Efforts to integrate basic behavioral and social research in judgment and decision-making, and applied cancer decision making will serve to harness the work of basic researchers, who may not have previously applied their work to health settings.

Imaging Systems Technologies: The Committee is encouraged by progress made by the NCI following its August 1999 conference on biomedical imaging, and urges 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 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 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.

Liver Cancer: The Committee notes that in contrast to many other cancers, the number of people who develop and die from liver cancer has increased 24 percent since the year 2000. As the symptoms of liver cancer often do not appear until the disease is advanced, only a small number of liver cancer cases are found in the early stages of the disease, when it can be easily treated. The Committee is aware that NCI, in collaboration with NIDDK, convened an Experts Conference that will help define the most urgent areas requiring additional research, professional education and public awareness initiatives. The Committee urges NCI to issue a Request for Applications based on the findings of this conference.

Lung Cancer: Lung cancer remains a major public health issue and is the leading cause of cancer death among women and minority populations. The death rate is expected to escalate as the population ages. Treatment and research now require an interdisciplinary approach and thoracic surgeons play an important role in both. The Committee encourages the Institute to work with the thoracic surgical community to identify priority areas for new clinical and translational studies and to ensure their participation in any interdisciplinary research efforts. Thoracic surgeons should be included in all relevant review and advisory committees and councils.

Molecular Cancer Diagnostics: The Committee understands that the NCI is aware of the potential for molecular cancer diagnostics using circulating nucleic acids, including in particular extracellular RNA in plasma. The Committee believes that this technology could have enormous potential for the early detection, monitoring, and selection of more effective treatment of a broad array of cancers and therefore encourages the NCI to explore the use and clinical application of this technology.

Multidisciplinary Research: NCI is commended for its innovative support of multidisciplinary training programs to enhance the scientific workforce. The Committee encourages NCI to explore new opportunities with the Office of Behavioral and Social Sciences Research to increase the

number of scientists who can bridge the realms of behavioral and social science research and public health or biomedical research.

Myelodysplasia and Myeloproliferative Disorders: The Committee recognizes NCI's support for a new research initiative in Myeloproliferative Disorders, which evolved from a recent conference involving the Institute and NHLBI. MPDs and Myelodysplasia are chronic diseases of bone marrow cells that can develop into acute leukemia. The Committee encourages NCI and NHLBI to bring together scientific and clinical experts in these fields to explore collaborative and crosscutting research mechanisms to further this research agenda. The Committee also urges NCI to utilize the Surveillance, Epidemiology, and End Results Program to collect data on the incidence and distribution of these diseases.

Nanosystems Biology: The Committee encourages NCI and the Office of the NIH Director to support a collaborative effort to bringing together nanotechnology, systems biology and molecular imaging to examine the molecular basis of cancer. Initial efforts have shown that cancers such as breast cancer are not a single disease, but may encompass many different diseases, when examined at the molecular level. Many clinical trials of new drugs are now considered a failure if only 10 percent of patients benefit, yet the 10 percent may represent a specific type of the disease, where the drug may be 100 percent effective. Bringing these three disciplines together may allow researchers to identify specific sub-types of cancer and to better target new interventions. Successful results of such an effort could lead to a molecular classification of many types of cancer and to targeted molecular treatments for molecular-specific diseases.

Neurofibromatosis: The Committee commends NCI for conducting phase II clinical trials of NF1 patients with plexiform neurofibromas. The Committee is concerned about recent large drops in funding for NF research, and recognizing NF's connection to many of the most common forms of human cancer, the Committee encourages NCI to substantially increase its NF research portfolio in such areas as further development of animal models, natural history studies, therapeutic experimentation, and clinical trials. The Committee is mindful of NF's rapid movement toward clinical research and encourages NCI to aggressively pursue clinical/translational research while still maintaining a solid basic research portfolio.

Pancreatic Cancer: The Committee remains concerned about the lack of scientists researching pancreatic cancer, the Nation's fourth-leading cause of cancer death. NCI's recent policy of offering a 50 percent extended payline for grants that are 100 percent related to pancreatic cancer was viewed as a critically important effort to encourage both young and experienced investigators to develop careers in this research field. Thus, the Committee is disappointed that NCI plans to weaken that policy and adopt a new strategy consisting of identifying grants that are 50 percent directed to pancreatic cancer and then bringing them to the attention of the NCI Executive Committee. The Committee notes that this special consideration will not necessarily result in actual funding. Therefore, the Committee urges NCI to maintain the 50 percent extended payline for 100 percent relevant pancreatic cancer research grants as the best way to attract a critical mass of scientists to this field.

Prostate Cancer: The Committee commends NCI for the considerable investment in prostate cancer, the leading cause of non-cutaneous cancer death among men, and encourages NCI to continue to support research to improve the accuracy of screening and early detection of prostate cancer.

Psychoneuroimmunology and Cancer: The Committee is interested in NCI's initiative to evaluate the complex interrelationships among emotional, behavioral, neural and immunological processes and how they may affect the etiology and progression of cancer. NCI's BiMPED initiative is a good example of leveraging the institute's resources to seed new research across NIH on fundamental mechanisms and processes that may affect multiple diseases and conditions.

Radio Waves: It has been brought to the Committee's attention that radio waves may prove promising in reducing cancerous tumors. While current radio frequency ablation requires placing electrodes directly into the tumor, this new non-invasive technique would target only the cancer cells while avoiding healthy tissue. The Committee urges NCI to support research using this non-invasive cancer-targeting technique.

Tuberous Sclerosis Complex: TSC is a genetic disorder that triggers uncontrollable tumor growth in multiple organs of the body, including the brain, heart, kidneys, lungs, liver, eyes or skin. In light of its similarities to the uncontrolled growth of cancer cells, many scientists believe that determining the cause of tumor growth in TSC could open the way for cures and treatments for cancer as well. To those ends, the Committee strongly encourages NCI to support programs examining the molecular and cellular basis of TSC, and the role of TSC in tumor development.

NIH Picks Pioneer Awardees

NIH selected the first recipients of the NIH Director's Pioneer Award to support scientists with innovative approaches to biomedical research. The award provides $500,000 in direct costs per year for five years to each recipient. The awardees are:

Larry Abbott, Brandeis University; George Daley, Children's Hospital Boston; Homme Hellinga, Duke University; Joseph McCune, J. David Gladstone Institutes, San Francisco; Steven McKnight, University of Texas Southwestern Medical Center; Chad Mirkin, Northwestern University; Rob Phillips, California Institute of Technology; Stephen Quake, California Institute of Technology, and Sunney Xie, Harvard University.

Funding Opportunities:

DoD Ovarian Cancer Research Program for Fiscal Year 2005

The fiscal 2005 Defense Appropriations Act provides $10 million to the Department of Defense Ovarian Cancer Research Program to support innovative research directed toward eliminating ovarian cancer. This program is administered by the U.S. Army Medical Research and Materiel Command through the Office of the Congressionally Directed Medical Research Programs.

The program seeks proposals for Pilot Awards, Historically Black Colleges and Universities/Minority Institutions Collaborative Research Awards, and Idea Development Awards.

The pre-proposal deadline is Oct. 26. A portion of those submitting pre-proposals will be invited to submit full proposals, due Feb. 15.

Information is available at http://cdmrp.army.mil and https://cdmrp.org/proposals.

Pilot Awards: These awards are intended to support initial work of innovative, potentially groundbreaking concepts in ovarian cancer. Preliminary data are not expected. Innovation will receive 50% of the score during peer review. Proposals must address at least one of the three research areas of emphasis: etiology/tumor biology; preclinical development of targeted therapeutics (excluding clinical trials); or early detection/diagnosis of ovarian cancer. Pilot Awards are targeted to junior faculty who are within five years of their last training experience, or established scientists or clinicians who have less than three years of experience in ovarian cancer research. Funding support is a maximum of $200,000 in direct costs over two years, plus indirect costs.

HBCU/MI Collaborative Research Awards: These awards are intended to establish a collaborative partnership at an investigator level between an HBCU/MI and another institution with faculty conducting ovarian cancer research. The partnering institution will provide research training and experience to the HBCU/MI doctoral-level faculty investigator. The collaboration will obtain the training and experience necessary for the HBCU/MI investigator to initiate and sustain an independent, competitive research program in ovarian cancer. Proposals must address at least one of the three research areas of emphasis: 1) etiology/tumor biology, 2) preclinical development of targeted therapeutics (excluding clinical trials), or 3) early detection/diagnosis of ovarian cancer. A maximum of $750,000 in direct costs for three years, plus indirect costs, can be requested.

Idea Development Awards: Letter of Intent Deadline: Jan. 15. The awards support research that represents a new paradigm, challenge existing paradigms, or investigate an existing problem from a new perspective. Independent investigators at all levels of experience are eligible. Proposals must address at least one of the three research areas of emphasis: 1) etiology/tumor biology, 2) preclinical development of targeted therapeutics (excluding clinical trials), or 3) early detection/diagnosis of ovarian cancer. Funding the awards is $600,000 in direct costs over three years, plus indirect costs.

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Consulting Vulnerabilities "Give Us Pause," NIH Says

(Continued from page 1)

identified a number of these outside activities with industry by NIH employees hat were not in the NIH data of approved activities previously provided to them," Kington wrote in a memorandum dated Sept. 24.

"Although NIH has not completed our review and analysis of individual consulting activities, we have identified vulnerabilities in our system that give us pause," Kington wrote. "It is clear to us that if these activities are to continue, we will need a substantially expanded system of oversight to assure Congress and the public that conflicts of interest are prevented."

The year-long moratorium will require approval from the Administration, sources said.

"During the period of the proposed moratorium, as appropriate, interactions with industry will continue as official duty activities," Kington wrote. "The moratorium will give us time to complete our review of specific cases, develop effective information systems to track outside activities, and develop more effective ethics training programs for staff before a final policy is put in place.

"This action is being taken to ensure that NIH retains full public confidence in its research. Although this has been a difficult decision, I, along with the leadership of NIH, believe that it is in the best interest of the NIH."

Earlier this year, NIH barred scientists from accepting stock as compensation and prohibited consulting by senior staff. Also NIH employees were prohibited from serving on the boards of directors of non-profit organizations, unless they do so in their official capacity.

The question of conflict of interest by NIH scientists emerged as a result of a series of stories that appeared in the Los Angeles Times last December. The stories prompted the Oversight and Investigations subcommittee to broaden its ongoing investigation, which initially focused exclusively on acceptance of lectureship awards, travel arrangements and other activities of former NCI Director Richard Klausner.

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THE CANCER LETTER

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Business & Regulatory Report

Clinical Trials:

Celsion To Begin Phase I Trial at NIH Of ThermoDox With RFA For Liver Cancer

Celsion Corp. (AMEX: CLN) of Columbia, Md., said FDA will allow a phase I trial for its investigational proprietary therapy, ThermoDox, in combination with radiofrequency ablation for liver cancer.

The trial will be conducted at the NIH Clinical Center and funded under a CRADA between Celsion and NIH, the company said. Under the agreement, Celsion will supply ThermoDox and provide regulatory and clinical support and NIH will enroll and treat the patients.

The trial would determine the maximum safely tolerated dose and

(Continued to page 2)

Product Approvals & Applications:

FDA Approves Palladone Pain Medication, Develops Risk Management Program

FDA earlier this month approved Palladone (hydromorphone hydrochloride, by **Purdue Pharma L.P.**, of Stamford, Conn.) capsules for the management of persistent moderate to severe pain in patients requiring continuous around-the-clock opioid pain relief for an extended period of time.

Palladone is an extended-release formulation that comes in 12, 16, 24, and 32 milligram (mg.) capsules. This drug should only be used in patients who are already receiving opioid therapy and who require a total daily dose of at least 12 mg. of oral hydromorphone or its equivalent, FDA said. Palladone offers a therapeutic choice for opioid-tolerant patients who might otherwise be candidates for other opioids and who do not achieve satisfactory therapeutic results with these other products.

The active ingredient in Palladone, hydromorphone, is currently a Scheduled II controlled substance, which is the highest level of control for drugs with a recognized medical use. Based on the risks associated with the drug, including the potential for abuse of Palladone, FDA has worked with the sponsor to develop a comprehensive risk management program (RMP), the agency said.

The RMP was designed with three potential risk situations identified. These are the risks posed by improper dosing, indication, or patient selection; the risk posed by accidental pediatric exposure to the drug; and the risk posed by abuse or diversion of Palladone Capsules.

As a controlled substance in Schedule II of the Controlled Substances

(Continued to page 6)

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NIH CRADA To Fund Celsion ThermoDox Phase I Trial

(Continued from page 1)

pharmacokinetic profile of the therapy when used in combination with radiofrequency ablation for liver cancer, the company said. The study approach will utilize RFA (80 degrees Celsius or above) to ablate the center of the tumor and the lower temperature zone (greater than 40 degrees Celsius) in the tumor margins to activate and release the doxorubicin to kill any remaining viable cancer cells.

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Cyclacel Group plc of Dundee, Scotland, said it has begun enrollment in a third phase I trial of CYC682, an anticancer drug acting on the cell cycle.

CYC682 is an orally available small molecule nucleoside analog drug. The trial is an open-label, phase Ib study testing CYC682 for solid tumors or lymphoma, the company said. The primary objective is to evaluate the safety profile of escalating doses of CYC682.

Treatment will be given in cycles of 14 days every three weeks until evidence of disease progression. Secondary objectives are to analyze the pharmacokinetics of CYC682 and its metabolite together with investigating the use of biomarkers to predict tumor sensitivity. Assessment of CYC682 objective tumor response will also be reported. The study is taking place at two clinical centers in the U.S., the company said.

CYC682 has been in two phase I studies in the U.S. to explore safety and pharmacokinetics, the company said. The trials involved 87 patients with a variety of cancers, who were dosed by mouth either three or five days per week for four weeks of each six week cycle.

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Genentech Inc. (NYSE:DNA) of South San Francisco and **OSI Pharmaceuticals Inc.** (NASDAQ: OSIP) of Melville, N.Y., said they have initiated a phase IIIB study of the investigational therapy Tarceva (erlotinib HCl) for second- and third-line non-small cell lung cancer after failure of at least one chemotherapy regimen.

The trial is a multi-center, open-label study of once-daily oral Tarceva, with endpoints of survival and response rate, the company said.

Tarceva is an investigational product designed to block tumor cell growth by inhibiting the tyrosine kinase activity of the epidermal growth factor receptor (HER1/EGFR), thereby blocking the HER1/EGFR signaling pathway inside the cell, the company said.

IGFBP-3 is a naturally occurring protein whose normal role is to regulate the activity of Insulin-Like Growth Factor-I (IGF-I), the company said. Although the IGF-I is critical for normal growth and metabolism, aberrant signalling through this pathway is closely linked to the abnormal and unregulated growth of a variety of tumors. Blocking tumor-associated IGF signaling has been proven to prevent tumor growth in a variety of preclinical models, the company said. In preclinical models, rhIGFBP-3 has demonstrated efficacy in preventing tumor formation and progression. Based on these findings, Insmed is developing rhIGFBP-3 as a novel anti-IGF-I treatment for cancer.

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Insmed Inc. (NASDAQ: INSM) of Richmond, Va., said it has begun a phase I study of its anti-tumor agent, recombinant human Insulin-Like Growth Factor Binding Protein-3.

The study is an open-label, dose-escalation trial designed to evaluate the safety, tolerability and pharmacokinetics of a single intravenous dose of rhIGFBP-3, the company said. The primary goal of the 30-patient study is to identify the appropriate dose of rhIGFBP-3 for a planned phase II trial in 2005.

"The FDA approval of growth factor inhibitors to treat cancer not only validates this approach but also encourages the development of other growth factor inhibiting agents, such as rhIGFBP-3," said Laura Shiry, head oncology scientist at Insmed. "Our research shows that rhIGFBP-3 is an essential regulator of the IGF signaling pathway, which is known to be permissive to

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tumor growth while facilitating other tumor-promoting pathways, including EGF and VEGF. We have what we believe to be solid preclinical evidence demonstrating that rhIGFBP-3 could provide substantial benefit in treating a number of human cancers, including those of the breast, prostate, colon and lung."

* * *

OXiGENE Inc. (NASDAQ:OXGN, XSSE: OXGN) of Waltham, Mass., said its compound, Combretastatin A4 Prodrug, would enter a phase I trial in combination with cisplatin for cervical cancer.

CA4P, a vascular targeting agent will be involved in six concurrent clinical oncology trials in seven tumor types in the U.S. and Europe, the company said.

"Strong pre-clinical data showed that CA4P in combination with cisplatin enhances tumor cell death in mice by 10-500 fold, the company said," said Fred Driscoll, president and CEO of OXiGENE

CA4P will be studied in combination with cisplatin in a dose-escalating open label trial for advanced or recurrent cervical cancers incurable by standard treatments, the company said. Jacob Lindegaard, of Aarhus University Hospital in Denmark and member of the Nordic Society of Gynecological Oncology, will head up three clinical sites in Denmark, Norway, and the U.K. Among the objectives trial: assessment of the safety profile of the combination of cisplatin and CA4P, preliminary evidence of efficacy and to determine the recommended phase II dose, the company said.

The phase I trial has been approved by the Danish Medicines Agency and approval is being sought from the regulatory authorities governing the additional sites, the company said.

CA4P, a vascular targeting agents, attacks the vasculature structure of solid tumors and other diseases characterized by the formation of aberrant blood vessels, the company said. The compound triggers a change in the shape of the endothelial cells lining the tumor's blood vessels in turn, blocking the flow of blood to the tumor and depriving it of oxygen and nutrients essential to its survival

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Threshold Pharmaceuticals Inc. of South San Francisco said it has received a special protocol assessment from FDA for a phase III trial for Glufosfamide in metastatic pancreatic cancer refractory to first-line treatment.

The primary endpoint will compare the median survival of treatment with Glufosfamide and best supportive care to BSC alone, the company said. Because there are no approved therapies for metastatic pancreatic cancer refractory to first- line treatment, expected survival has been approximately three months.

The randomized, multi-center, multinational 306-patient trial would evaluate the safety and effectiveness of Glufosfamide, the company said. Eligible patients will be randomized to receive the treatment every three weeks in addition to BSC or BSC alone. BSC includes all medical or surgical interventions that a pancreatic cancer patient should receive to palliate the cancer but excludes treatment with systemic therapies intended to kill the cancer cells.

Previous studies have demonstrated that Glufosfamide kills cancer cells and can shrink pancreatic cancers, the company said. Data from an initial phase 1 trial of Glufosfamide determined the maximum tolerated dose of Glufosfamide in patients with a variety of solid tumors. The only pancreatic cancer patient enrolled in the phase I trial achieved a complete remission of disease and remained in remission over five years later after receiving Glufosfamide treatment alone, the company said.

Data from a phase II trial of the drug for pancreatic cancer of 35 chemotherapy-naive patients with locally advanced or metastatic pancreatic cancer documented objective tumor shrinkage, which was verified by an independent review of radiographs, the company said. An updated analysis of the survival shows an estimated 9 percent two-year survival, which compares to 1 percent or less in historical studies with other first-line therapies. Careful monitoring of renal function was required, the company said. Hematological toxicity was mild, and the most common adverse effects were grade I nausea and vomiting.

Deals & Collaborations:

Agencourt Contract With NIH For Sequencing Renewed

Agencourt Bioscience Corp. of Beverly, Mass., said NIH renewed its contract for genomic sequencing services.

Under the two-year contract, Agencourt said it would continue to provide expressed sequence tags and serial analysis of gene expression sequencing for two NIH initiatives, the Mammalian Gene Collection Project and the Cancer Genome Anatomy Project.

The goal of the MGC project, a trans-NIH initiative co-managed by the National Human Genome Research Institute and NCI, is to identify and sequence representative full open reading frame cDNA clones for all human and mouse genes, as well as a subset

of rat genes, the company said. Agencourt said it has sequenced over 1.3 million cDNA ESTs, which are being used to identify candidate full-ORF cDNAs.

The primary goals of CGAP, a program supported by NCI, are mapping, evaluating and sequencing the genes of cells at various stages of cancer growth, the company said. The research program provides scientists with sequence data of the molecular anatomy of cancer cells, thus improving the detection, diagnosis and treatment of cancer patients. Agencourt said it is responsible for sequencing the CGAP SAGE libraries; an experimental technique to quantify all expressed genes within cells.

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Artemis Pharmaceuticals GmbH of Cologne, Germany, and **Acceleron Pharma Inc**., of Cambridge, Mass., said they have signed a cooperation agreement in mouse genetics.

Under the agreement, Artemis will apply its ArteMice technology platforms to generate a genetically engineered mouse model system for Acceleron, the company said.

ArteMice Conditional gene targeting and ArteMice speed technologies allow the generation of genetically modified mouse lines, the companies said. The lines are used as model systems in drug discovery research and functional target validation to identify genes that play a central role in disease processes and disease therapy. Acceleron said it would use the mouse model to develop drugs for musculoskeletal and metabolic disorders.

* * *

Callisto Pharmaceuticals Inc. (OTCBB:CLSP: Frankfurt:CA4;WKN:479303) of New York, NY, said it has signed a licensing agreement with **M. D. Anderson Cancer Center** for Annamycin, an anthracycline drug for leukemia.

Callisto would initiate a phase IIb trial for relapsed acute lymphocytic leukemia and relapsed acute myeloid leukemia in the first half of 2005, the company said. Co-principal investigators Hagop Kantarjian and Michael Andreeff, of M. D. Anderson Cancer Center, will lead the trial.

Annamycin completed a phase I/IIa trial for AML and ALL with Andreeff as principal investigator, the company said.

Annamycin was discovered and developed by Waldemar Priebe and Roman Perez-Soler, scientists at M.D. Anderson Cancer Center, the company said. In animal studies, the treatment was demonstrated to circumvent multiple drug resistance, displaying increased antitumor activity and decreased cardiotoxicity. The drug also demonstrated the ability to achieve greater than 98 percent incorporation into liposomes. The subsequent phase I/IIa trial for leukemia showed that responses were observed in patients with high levels of multi-drug resistance, a condition that typically predicts for lack of anthracycline activity, the company said.

Annamycin is the only anthracycline in clinical development that circumvents MDR resistance, the company said. Annamycin also exhibited no cardiotoxicity at the drug levels used in the phase I/IIa trial.

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IC-MedTech, of San Diego, said it has exclusively licensed Apatone, an anti-cancer therapeutic, from **Summa Health System** for cancer.

The treatment exploits a dual small molecule strategy that induces oxidative stress within cancer cells, causing those cells to die without damaging adjacent healthy cells, the company said.

In combination with established chemotherapeutic and radiological protocols, Apatone demonstrated enhanced tumor-specific antitumor and antimetastatic activity against human breast, oral epidermoid and endometrial tumor cell lines as well as human prostate cancer cell lines (DU145 and PC3) and a battery of seven other urologic tumor cell lines, the company said.

Cell lines representing prostate, ovarian, breast, liver, colon, stomach, cervical, kidney, bladder, testicular, cervix, nasopharynx, leukemia and lymphoma respond well to the treatment, the company said.

* * *

MedAptus Inc., of Boston, said its mobile charge capture and dictation applications would be installed at M. D. Anderson Cancer Center.

M. D. Anderson will be providing the majority of its physicians with MedAptus Charges In Hand and Notes In Hand applications to both streamline workflow and improve operational efficiencies, the company said.

"We decided to anchor our mobile computing initiative with charge capture due to its ability to improve revenue cycle management efforts," said Lori English, associate director of patient business services. "Ultimately it was left to our physicians to choose the application that they found best suited to their daily workflow." participation in selecting the product would be critical to our long-term success."

* * *

MGI Pharma Inc. (Nasdaq:MOGN of Minneapolis, Minn., and **Zycos Inc**., said they have signed a definitive merger agreement under which MGI

Pharma will acquire Zycos for $50 million in cash.

The Zycos pipeline of products includes ZYC101a, an immune response therapeutic that has completed a randomized phase II study for high-grade cervical dysplasia, the companies said. Administration of ZYC101a stimulates an immune response that targets cells containing human papillomavirus. Patients received an intramuscular injection of ZYC101a every three weeks for a total of three doses. ZYC101a was shown to be safe and well tolerated. In a prospectively defined cohort of patients under 25 years of age, the drug promoted resolution of high-grade dysplasia in 70 percent of patients, versus 23 percent in the placebo arm. In all patients, resolution was 43 percent for patients on drug and 27 percent for patients on placebo, the companies said.

In other open label trials, the drug was found to be safe and well tolerated and disease resolution was observed in a high percentage of young patients, the companies said.

The second Zycos compound in clinical development is ZYC300, the companies said. ZYC300, an encapsulated plasmid encoding a novel tumor antigen, has completed a phase I/IIa study in 17 patients with late stage metastatic hematological and solid tumors.

In another development, MGI Pharma Inc. and **Aesgen Inc** said they have signed a definitive merger agreement under which MGI Pharma will acquire all outstanding equity of Aesgen for $32 million in cash.

MGI Pharma may also be obligated to make performance milestone payments of $33 million upon regulatory approval and $25 million if sales exceed $50 million in the second year following product launch, the company said. In addition, MGI Pharma will pay a 5 percent royalty on product sales, including sales of Saforis a product candidate for oral mucositis.

Saforis is an oral formulation of L-glutamine in a proprietary delivery vehicle designed to increase uptake of glutamine by the oral mucosa, the company said. Glutamine is an amino acid essential in the healing and regeneration of mucosal cells.

Also, **MGI Pharma Inc**. and **SuperGen Inc.** (Nasdaq:SUPG) of Dublin, Calif., said they have signed a definitive agreement granting MGI Pharma exclusive worldwide rights to the development, manufacture, commercialization and distribution of Dacogen (decitabine), the SuperGen investigational anti-cancer therapeutic for myelodysplastic syndromes.

Under the agreement, MGI Pharma will make a $40 million equity investment in SuperGen at $10.00 per share and will pay SuperGen up to $45 million based upon achievement of specified regulatory and commercialization milestones, the company said. SuperGen will receive a royalty on worldwide net sales starting at 20 percent and escalating to a maximum of 30 percent. MGI Pharma has also committed to fund further development costs associated with Dacogen, at a minimum of $15 million, the company said.

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PerkinElmer Inc. (NYSE:PKI) of Boston and **Predictive Diagnostics Inc,** a wholly owned subsidiary of **Large Scale Biology Corp.** (NASDAQ:LSBC) said they have entered into a collaborative partnership for advanced biomarker discovery technology for drug development and diagnostic testing.

Under the agreement, PerkinElmer will provide access to its proprietary Biomarker Amplification Filter Technology customized for its prOTOF 2000 MALDI O-TOF mass spectrometer for biomarker discovery and analysis, the company said.

The PDI BAMF Technology is a suite of in silico machine learning technologies and informatics tools that use a blood test for biomarker fingerprints to diagnose diseases with high-resolution mass spectrometry data, the company said. The technology was for serum-based tests for early diagnosis of cancer.

"Predictive Diagnostics proprietary set of algorithms and informatics capabilities will complement our mass spectrometry and proprietary consumables offerings and complete our total solution for biomarker discovery and screening." said Peter Coggins, president of PerkinElmer Life and Analytical Sciences. "We believe this solution will be enabling technology for our pharmaceutical, biotech, and academic customers in the proteomic biomarker field."

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University of Massachusetts Medical School of Boxborough, Mass., and **Cytyc Corp.** (Nasdaq:CYTC) of Worcester, Mass., said they have signed licensing and sponsored research agreements for cancer detection technology developed at UMMS to predict the onset and severity of certain cancers before tumor formation.

The technology, which focuses on centrosomes in cancerous and pre-cancerous cells, was developed by Stephen Doxsey, associate professor of molecular medicine, biochemistry & molecular pharmacology, and cell biology at UMMS.

The agreement gives Cytyc a worldwide exclusive license to use the Doxsey technology to develop products of cancer diagnostics and prognostics, the company said. Cytyc will also sponsor research in the lab belonging to Doxsey for breast and cervical

cancers.

Doxsey is known for his work on the centrosome, a small part of a cell that helps chromosomes line up properly during cell division, the medical school said. His team has demonstrated that in nearly all carcinomas, including breast, prostate, lung, brain and cervical cancers, the centrosomes are defective either in number, or structure, or both. He also demonstrated that the centrosome defects are present early in pre-cancerous lesions, including HPV-induced cervical abnormalities. In addition, the degree of centrosomal defects in certain lesions is correlated to the aggressiveness of the cancer that may eventually develop, the medical school said.

* * *

TransTech Pharma Inc. of High Point, N.C., and **Merck & Co. Inc**. of Whitehouse Station, N.J., said they have entered into a research collaboration using the TransTech proprietary TTP Translational Technology to discover and develop small molecules for a therapeutic target of interest to Merck.

Under the agreement, Merck has the exclusive right to develop and commercialize all compounds directed at the target covered by the collaboration, the companies said. TransTech could receive payments of more than $26 million for the discovery, development and marketing approval of a small molecule for the top priority indication. The agreement also provides for milestone payments for the discovery and development of additional small molecules and lower priority indications. TransTech would receive an upfront payment, research support and payments upon the achievement of specified research, clinical and commercialization milestones. In addition, TransTech would receive royalties on future product sales.

The TransTech Translational Technology is an automated and integrated drug discovery process including proprietary software modules, the companies said.

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Ziopharm Inc. of New Haven, Conn., said it completed a worldwide licensing agreement with **M. D. Anderson Cancer Center** and **Texas A&M University** for a class of organic arsenicals for cancer, such as ZIO-101.

Ralph Zingaro, professor of chemistry, Texas A&M University, conducted the original synthesis of this class of organic arsenicals, the company said.

Phase I studies in adults with blood cancers and lymphomas would begin in the first half of 2005, the company said. Parallel phase I studies in solid cancers are planned for late 2005. Once the maximum tolerated dose is determined, phase-II studies are planned in both hematologic and solid cancers.

An arsenic atom is complexed to organic molecules, the company said. As a result, ZIO-101 is safer than inorganic arsenics like arsenic trioxide (As2O3, or Trisenox). Animal studies show the ability to give 5- to 10-fold more ZIO-101 than arsenic trioxide without damaging the heart, the company said. Other dose-limiting toxicities of inorganic arsenics, including damage to the liver, bone marrow and skin, are much less prominent with ZIO-101, the company said.

A large dose increase, possible with ZIO-101, would allow arsenic to cause cell cycle arrest and cell death rather than cell differentiation, as is the case with inorganic arsenic, the company said.

"The key obstacle to using arsenic to treat solid cancers is the inability to give enough to kill cancer cells without causing serious side effects," said Srdan Verstovsek, of M. D. Anderson Cancer Center. "Preclinical data on ZIO-101 suggests an ability to increase the dose 5- to 10-fold over traditional arsenic while increasing efficacy with minimal toxicity. Prospects for clinical trials in solid cancers are very promising."

Product Approvals & Applications:

FDA Develops Program For Managing Opioid Risk

(Continued from page 1)

Act, Palladone also comes under the jurisdiction of the Drug Enforcement Administration, which administers the CSA. Schedule II drugs are subject to manufacturing quotas set by DEA with input on medical need from FDA, distribution tracking, import and export controls, registration of prescribers and dispensers, and written prescriptions without refills.

In addition to the protection afforded patients through the status of Palladone as a controlled substance, the RMP includes provisions for clear and appropriate labeling, and appropriate education of healthcare professionals, patients, and caregivers. In addition, the sponsor has committed to offer appropriate training to sales representatives. To guard against the inappropriate use of the drug, the RMP also establishes a multifaceted program for monitoring and surveillance of abuse. If abuse, misuse, and diversion occur the program includes an array of interventions.

As part of the RMP, a Medication Guide (FDA-approved patient information which is required to be dispensed with each prescription) has been written

for patients prescribed Palladone. FDA requires a Medication Guide only when one or more of the following circumstances exists: (1) the drug is one for which patient labeling could help prevent serious adverse effects; (2) the drug is one that has serious risks of which patients should be made aware because information concerning the risks could affect patients' decision to use, or continue to use the drug; and (3) the drug is important to health and patient adherence to directions for use is crucial to the drug's effectiveness. In addition, the physician labeling for Palladone contains a "black box" warning.

In addition to the potential for abuse and addiction, respiratory depression is the chief potential risk associated with Palladone, if not properly dosed. Respiratory depression is manifested by a reduced urge to breathe and a decreased rate of respiration, often referred to as "shallow" breathing, and can result in severe effects or fatalities. The risk of respiratory depression is greater in patients not used to taking opiates, and in elderly or debilitated patients.

Palladone must be swallowed whole because chewing, dissolving, or crushing the contents of the capsules leads to the rapid absorption of a potentially fatal dose. Other common side effects include nausea, vomiting, dry mouth, dizziness, urinary retention, and constipation.

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Aventis (NYSE:AVE) of Bridgewater, N.J., said that FDA has approved Taxotere (docetaxel) Injection Concentrate in combination with doxorubicin and cyclophosphamide for the adjuvant treatment of operable, node-positive breast cancer.

The supplemental new drug application received a priority review designation by FDA, the company said. The additional indication also is under review by the European regulatory authorities.

The FDA decision was based on a second interim analysis from the Breast Cancer International Research Group 001/TAX 316 study, which demonstrated that women with node-positive, early stage breast cancer who received a Taxotere-based chemotherapy regimen after surgery experienced a significant 25.7 percent reduction in their risk of relapse as compared to women treated with another adjuvant combination regimen of 5-fluorouracil, doxorubicin, and cyclophosphamide, the company said. With five-years of follow-up, the significant reduction in the risk of relapse of the regimen was observed regardless of a woman's hormone receptor status, the company said.

Additionally, at the time of the interim analysis, based on a total of 219 deaths, overall survival was longer for TAC than FAC (hazard ratio=0.69, 2-sided 95 percent CI=0.53, 0.90), the company said.

"The nearly five-year follow-up data suggest that by substituting Taxotere for 5-fluorouracil in a standard chemotherapy regimen in the adjuvant setting, we now have a treatment that may be able to benefit more women with early stage breast cancer," said Dennis Slamon, chairman of the BCIRG Scientific Committee and director of Clinical and Translational Research at the Jonsson Comprehensive Cancer Center, UCLA. "With this approval, Taxotere takes a leading role in the treatment of women with node-positive, early stage breast cancer."

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Aphton Corp. (Nasdaq:APHT) of Miami said it has submitted the regulatory documentation to Health Canada for the registration of Insegia as a monotherapy for advanced pancreatic cancer where chemotherapy is not indicated.

Aphton said it was authorized to file a submission by Health Canada under the Notice of Compliance with conditions policy.

Insegia targets the hormone gastrin 17 to treat gastrointestinal cancers, including pancreatic, gastric, esophageal and colorectal cancer, the company said. The anti-gastrin targeted immunotherapy induces antibody production that bind and neutralize the gastrin hormones involved in tumor progression in gastrointestinal cancers.

Gastrin is a key hormone in the embryological development of the gastrointestinal system, the company said. In post embryological development, most of the gastrin and gastrin receptor genes throughout the GI system are shut down, the company said. Gastrin genes are reactivated in precancerous cells and polyps and in cancer cells early in the development of cancer. Gastrin secretion and the expression of gastrin receptors increase as the cancer progresses. Gastrin works by signaling through its receptor, the gastrin receptor (CCK-2/Gastrin-R), the company said.

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Aptamera Inc.of Louisville, Ky., said FDA has granted orphan drug designation to AGRO100 for pancreatic cancer.

AGRO100 is an anti-nucleolin aptamer, the company said.

"AGRO100 could contribute to the effective treatment of many types of cancer," said Kerry Barnhart, chief scientific officer of Aptamera.

* * *

ILEX Oncology Inc. (Nasdaq:ILXO) of San Antonio said it would provide FDA with new patient data to support the new drug application it submitted for clofarabine for refractory or relapsed acute leukemia in children.

The decision to update the filing was based on encouraging efficacy results from a cohort of additional patients, the company said. Based on the data added to the original filing, the FDA has reset the Prescription Drug User Fee Act response date to December 2004.

The NDA filing was based on data from 70 pediatric patients enrolled in two phase II acute lymphoblastic leukemia and acute myeloid leukemia trials, the company said.. The update is data from 14 additional patients, bringing the total number to 84. Of the new cohort, four of nine ALL patients and two of five AML patients responded to clofarabine.

The total ALL group (n=49) achieved a 31 percent overall response rate, with six complete remissions, four complete marrow remissions in the absence of platelet recovery (CRp) and five partial remissions (PR), the company said. The total AML group (n=35) achieved a 26 percent response rate, with one CRp and eight PRs. An interim monitoring of the AML patients showed that seven of the nine responders went on to receive transplants following their responses to clofarabine, which provides an opportunity to prolong life for the patients.

Clofarabine was granted orphan drug designation for adult and pediatric ALL and AML, the company said.

Clofarabine is a next generation of the drug class purine nucleoside analogs which all inhibit DNA production necessary for cancer cell growth, the company said. Bioenvision Inc. (NASDAQ:BIVN) sub-licensed ILEX the right to develop and market clofarabine for cancer indications in the U.S. and Canada. Bioenvision is entitled to milestone payments tied to the development of the compound and is entitled to royalties on North American sales.

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OSI Pharmaceuticals Inc. (NASDAQ:OSIP) of Melville, N.Y., said that its international partner, **Roche**, submitted a marketing authorization application to the European Health Authorities for Tarceva (erlotinib HCl) as a monotherapy for advanced non-small cell lung cancer where chemotherapy has failed.

Tarceva is being evaluated in a clinical development program by a global alliance among OSI, Genentech, and Roche, the company said.

The BR.21 phase III trial was a double-blind, placebo-controlled study which included 731 patients and compared Tarceva to placebo for relapsed NSCLC where chemotherapy had failed, the company said. The drug demonstrated a 42 percent improvement in median survival and improved one-year survival by 45 percent. The trial also demonstrated statistically significant improvement in all secondary endpoints of the trial including time to symptom deterioration, progression-free survival and response rate, the company said.

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Millennium Pharmaceuticals Inc. (Nasdaq: MLNM) said it has submitted a supplemental New Drug Application to FDA for Velcade (bortezomib) for the treatment of patients with multiple myeloma who have received at least one prior therapy.

The submission is based on data from the phase III APEX study that compared Velcade to high-dose dexamethasone.

The submission of this supplementary filing comes after the approval of Velcade for the treatment of relapsed and refractory multiple myeloma in the U.S. by the FDA 16 months ago, and in the European Union states by the EMEA five months ago.

The sNDA submission was based primarily upon the results of the phase III APEX confirmatory study, halted a year early after an independent data monitoring committee concluded the findings of a pre-specified interim analysis showed a statistically significant improvement in time-to-disease progression in favor of Velcade.

The APEX trial enrolled 669 patients with relapsed or refractory multiple myeloma at 94 centers in North America, Europe, and Israel. Preliminary results presented at ASCO 2004 included:

—A statistically significant survival advantage ($p<.01$) in patients treated in the Velcade alone arm. Statistical significance was maintained even though approximately 50 percent of patients crossed over to receive Velcade after experiencing progressive disease on the dexamethasone arm.

—During the first year, there was an estimated 30 percent reduction in risk of death in patients receiving Velcade compared to those receiving dexamethasone.

—Data from the interim analysis showed a 58 percent improvement in time to progression ($p<.0001$) in patients receiving Velcade (5.7 months) compared to high-dose dexamethasone (3.6 months).

—The incidence of adverse events was similar between the two groups. Millennium anticipates the final APEX data will be presented at the December American Society of Hematology annual meeting in San Diego.