THE CANCER LETTER

Vol. 30 No. 44
Nov. 19, 2004

Price $335 Per Year

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

NCI Advisors Approve Recompetition Of $62 Million Phase II Contracts Program

By Kirsten Boyd Goldberg

NCI advisors last week approved the Institute's plan to commit $62 million over five years to support eight contracts for phase II clinical trials of NCI-sponsored therapies.

The NCI Board of Scientific Advisors voted unanimously Nov. 8 in favor of the program, begun in 2001, which conducts phase II trials only with agents for which NCI holds the Investigational New Drug license.

The current contracts, which expire in December 2005, are held by University of Texas M.D. Anderson Cancer Center, University of Chicago,

(Continued to page 2)

In the Cancer Centers:

DuBois To Direct Vanderbilt-Ingram Center, Succeeding Founding Director Harold Moses

RAYMOND DUBOIS will become director of the Vanderbilt-Ingram Cancer Center on Jan. 1, succeeding the center's founding director, **Harold Moses**, the Benjamin F. Byrd Professor of Oncology, who will refocus his attention on his research, activities on the national cancer scene, and service to Vanderbilt-Ingram as an advisor and fundraiser. DuBois, associate director for cancer prevention and control and the Hortense B. Ingram Chair in Molecular Oncology, has been a member of the center's faculty since 1991. He is known for his work on understanding the molecular causes of colon cancer and in devising better ways to prevent the disease. Under Moses' leadership, the center became an NCI-designated comprehensive cancer center, increased its NCI research funding base six-fold to more than $50 million a year, and carried out a fundraising campaign that brought in more than $180 million. "Hal Moses is the architect of the Vanderbilt-Ingram Cancer Center," said **Harry Jacobson**, vice chancellor of health affairs. "When **Ike Robinson** asked him to become center director, it was with the explicit goal of building a world-class cancer center worthy of comprehensive designation from the National Cancer Institute. Hal has achieved that and so much more. The cancer center he has built is a model for conducting stellar team science that will make a huge difference to our patients and families." NCI Director **Andrew von Eschenbach** said, "Hal Moses is one of those rare, gifted leaders whose vision can see beyond the horizon and whose dedication can motivate others to create a future that exceeds all expectations. The Vanderbilt Cancer Center is a shining tribute to this special man's contribution to creating a future where people no longer will suffer and die from cancer." **Orrin Ingram**, chairman

(Continued to page 7)

BSA Says NCI Program's Strength Is In Combinations

(Continued from page 1)

Montefiore Medical Center, Mayo Clinic, Memorial Sloan-Kettering Cancer Center, Princess Margaret Hospital, and University of California, Davis.

NCI approves about 40 letters of intent a year for new phase II trials through this program, and expects to enroll 1,600 patients in 2005, said project officer James Zwiebel, of the Cancer Therapy Evaluation Program.

The phase II contracts program is the only place where investigators can do combination studies with drugs from different pharmaceutical companies, BSA members said.

"There is a role for NCI in the combination of new agents," said BSA member Neil Clendeninn, of Clinical Pharmaceutical Consulting, of Hanalei, Hawaii. "It's very difficult for pharmaceutical companies to work together to put two experimental drugs together, and one of the advantages of this program is that it can do that. That is a very strong feature of this program."

"It's very difficult for an academic laboratory to do combination drugs from two different companies," said BSA member Susan Horwitz, the Falkenstein Professor of Cancer Research at Albert Einstein College of Medicine. "It's almost impossible."

The subcommittee that reviewed the proposed recompetition recommended approval, but had a question about the cost, said BSA member Richard Schilsky, one of the reviewers. "We were struck by what seemed to be a broad range of reimbursement rates for clinical trials across NCI programs, with some programs getting $1,500 or $2,000 a case, this program getting $6,000 a case, and the AIDS Malignancy Consortium, which is getting around $10,000 a case," said Schilsky, associate dean for clinical research in the Biological Sciences Division at University of Chicago. "What process was used to decide the level of funding?"

"The determination is based on the amount of resources necessary to carry out the activity," Zwiebel said. "During the negotiation process, the actual costs are negotiated between the NCI and the contractor. It's based on FTEs and whatever is required to carry out the phase II trials."

Horwitz said the pharmaceutical companies should pay for some of the expensive correlative studies involved. "Many of these drugs are not the very best drugs that the pharmaceutical company has," she said. "They go and do those drugs themselves. So the things that we are doing with this amount of money is an enormous favor for the pharmaceutical companies, and I would like to see them participate financially in getting some of these tests worked up.

"There should be something written into this that if one of these drugs that comes from pharmaceutical companies makes it big, which is very possible, after all the work that has been put into it, that the NCI should get something back from it," Horwitz said.

"We actually try to engage the pharmaceutical companies when we can," Zwiebel replied. Merck is conducting some genetic studies through the program and will share the data with investigators, he said.

Three professional societies recently met with NCI and industry representatives to discuss early clinical trials, said BSA member William Hait, director of the Cancer Institute of New Jersey. The American Society of Clinical Oncology, the American Association for Cancer Research, and the Association of American Cancer Institutes took part. He asked whether NCI officials could discuss the meeting.

"It was a very interesting approach about putting multiple institutions together, disease-focused, to do heavily correlative science driven, early phase clinical investigation," replied Division of Cancer Treatment and Diagnosis Director James Doroshow, who attended the meeting. "There was a lot of discussion about where pharma would interface with those kinds of studies, who would own the intellectual property, etc. I think the initial discussions at that meeting really evolve around how you set up a non-governmental enterprise

THE CANCER LETTER

Member, Newsletter and Electronic Publishers Association

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

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016
Letters to the Editor may be sent to the above address.

Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724
Customer service FAQ: www.cancerletter.com

Subscription $335 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc.
Founded Dec. 21, 1973, by Jerry D. Boyd.

to attract pharmaceutical resources to do those kinds of studies. We all agree they are really critical, and in fact will become more critical. I think we have to be open to any new structures that are developed to use this and any kind of mechanism that we have to support those kinds of trials, which are really critical."

NCI said accomplishments of the phase II contracts program include the following trials leading to randomized studies:

--Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck (University of Chicago). Of 52 patients enrolled, 47 were assessable for response. Half the cohort received ZD1839 as second-line therapy, with an observed response rate of 10.6% and a disease control rate of 54%. Median time to progression and survival were 3.4 months and 8.1 months, respectively. Performance status and skin toxicity were a statistically significant predictor of response and improved outcome. A randomized phase III trial is evaluating gefitinib versus methotrexate in recurrent head and neck cancer.

--Phase II trial of bortezomib in indolent non-Hodgkin's lymphoma and mantle cell lymphoma (MSKCC). In 21 evaluable patients, there were five partial responses and one complete response in eight patients with follicular lymphoma, and five PRs in 10 patients with mantle cell lymphoma. The promising activity in mantle cell lymphoma has led the industry sponsor to plan a multi-center trial.

--Phase II trail of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer (University of Chicago). The median survival of nine months and the 74% six-month survival in this trial were superior to historical data for single-agent gemcitabine. Response was not correlated with VEGF levels, but there was a borderline correlation of baseline VEGF level with survival (ASCO 2004 GI cancer symposium, abstract 86). The data from this study are the basis for Cancer and Leukemia Group B 80303, "A randomized phase III trial of bevacizumab plus gemcitabine versus gemcitabine plus placebo in patients with advanced pancreatic cancer."

Other accomplishments include trials with interesting correlative studies, exploration of new drug combinations, and trials leading to abandonment of unpromising approaches, according to NCI's concept statement. The excerpted text of the concept statement follows:

Early Therapeutics Development with Phase II Emphasis. Concept for recompetition of an RFP, proposed total $62 million over five years, to fund eight multi-institutional consortia. Project officer: James Zwiebel; co-officer: LeeAnn Jensen, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis.

The Early Therapeutics Development with Phase II Emphasis (referred to as the phase II contracts or the N01 program) and the Translational Research Initiative, which funds the correlative studies for N01 and other CTEP-sponsored trials, have created a flexible platform so that early clinical trials consortia are prepared to rapidly evaluate the biologic effects of NCI-sponsored anticancer agents or their molecular targets and to determine clinically-relevant correlates. This scalable mechanism, which permit the formation of flexible consortia as needed, have provided the majority of the essential clinical trials infrastructure and laboratory support to CTEP for complex phase II trials in its partnerships with academia and industry.

The NCI Developmental Therapeutics Program interacts with investigators from industry, academia, and internal NCI laboratories to prepare new investigational anticancer agents for human testing. Subsets of these agents are selected for sponsorship under NCI-held INDs. One critical role of CTEP is to bring the NCI-held anticancer agents into clinical trials. NCI also has collaborative agreements with 90 industry partners for 143 investigational agents. CTEP has filed approximately 15-20 IND applications annually in recent years and has 13 in preparation this year. All but two are for early clinical trials.

The phase II contracts program was begun in 2001. This program created consortia of investigators at geographically dispersed sites, and increased annual patient accrual to this mechanism within three years from 374 to 1,000. Each contract has continued to increase patient enrollment each year. The N01 program has more than doubled both the number of letters of intent approved each year, from 18, to more than 40, and the number of closed/completed trials, from 16 to 37.

Initially, eight N01 contracts were awarded for three years, with an option to extend each contract for an additional two years. Based upon their performance in enrolling patients and initiating and completing trials, seven N01 contractors were awarded the option to continue their contracts for two additional years, and their contracts will expire in December 2005. Unlike the previous phase II program (1995-2000), where a lump sum was provided to the sites for program activities, the N01 contracts are funded specifically when patients are enrolled to trials. Thus, 60-80% of each contract budget depends on per patient reimbursements, while the remaining 20-40% is intended for fixed, core costs, such as protocol planning and preparation, regulatory affairs and travel to national meetings to present results.

The increased capacity of the N01 program has permitted CTEP to approve more phase II trials than ever before and has provided a much-needed capability for early therapeutics development. We anticipate we will achieve the goal set in 1999 of enrolling 1,600 patients per year by

2005. Of 142 protocols activated in the first three years of the N01, 82 (58%) trials have been closed or completed. Data from more than 1,200 patients annually are being reported electronically to the NCI/CTEP Clinical Data Update System from all N01 contractors, which includes 14 NCI cancer centers.

The recompeted phase II contracts will fund eight multi-institutional consortia, each of which will commit to accruing a minimum of 150 to 250 patients per year (1,200 to 2,000 total patients) with different tumor types. These will provide sufficient patients for four to eight trials per contract, or 32 to 64 trials each year for the phase II program, testing a variety of new agents with different targets. These contracts will require rapid implementation and completion of trials and they will require the ability to carry out correlative studies testing the effects of the investigational agent on their target in tumors.

The recompeted RFP will encourage the assembly, when needed, of flexible "consortia within consortia" in order to bring together both a critical mass of patients as well as investigator expertise to carry out individual clinical trials. The re-issued RFP will include budgeting for multi-center trial coordination.

Another goal of the CTEP Early Clinical Trials Program is to increase participation of other qualified NCI cancer centers in phase II trials. One means to accomplish this would be to utilize the Clinical Trials Support Unit as is being done to facilitate investigator participation in phase III trials. The CTSU would allow NCI cancer centers access to phase II trials being carried out by N01 contractors. This approach will be piloted within the recompeted phase II contracts by opening eight phase II N01 trials within the CTSU.

The separately funded Translational Research Initiative provides investigators with funding to support the correlative studies needed to characterize the effects of new agents on their targets and to identify correlates of clinically-relevant endpoints. The TRI also provides funding directly to the phase II contractors or to other institutions that have unique expertise and that may function as centralized laboratories for studies of particular agents. The correlative studies must be linked to the clinical trials under CTEP INDs. The TRI funds the costs of personnel time, procedures directly related to the laboratory correlative investigations, and the laboratory studies, and is intended to supplement existing funding for assays already being performed in funded laboratories to leverage the existing NCI investment and permit that expertise to be used for specimens from clinical trial, and/or to support investigational imaging studies related to drug effect on its molecular target. It is anticipated that each of the clinical trials will have at least one correlative laboratory investigation, for a total of 32 to 64 laboratory correlates per year.

The RFP will solicit multi-institutional consortia of clinicians, statisticians, data managers, and research nurses with early phase clinical trial expertise with investigational agents in cancer. Offerors for these contracts must demonstrate that they have expertise in cancer drug development, and knowledge in the clinical management of specific tumor types, phase II clinical trials, pharmacology, and pharmacodynamics. They need to provide evidence of their own expertise, or access to such expertise, in diagnostic and functional imaging, interventional radiology, pathology, and other potentially relevant laboratory methodologies.

Each contract applicant needs to show evidence of sufficient numbers of patients to be able to initiate, conduct, and complete four to eight trials each year using NCI-held IND anticancer agents. The size of each trial will vary depending upon whether the first phase demonstrates activity resulting in expansion from 12-20 to 35-50 patients. The average size of each trial is estimated to be 30 patients, necessitating approximately 150 to 250 patients per contract. Full contract credit will not be given unless patients are accrued and trials completed in the time specified, with electronic submission of high-quality data. Quarterly progress reports on accrual, safety, and response will be provided to CTEP, and future funding will be based on the numbers of patients accrued and reported.

CTEP will prepare solicitations for proposals to conduct clinical trials with specific NCI-held IND agents. N01 investigator-initiated proposals also will be welcome. Investigators will submit a letter of intent to conduct trials, which will undergo internal review by the Protocol Review Committee of CTEP. LOIs will be assigned a priority score based upon CTEP review criteria and will be rejected or approved, contingent upon incorporation of CTEP recommendations into the protocol. Upon final approval of an LOI (which requires concurrence by the industry partner), the contractor is asked to submit the clinical protocol to CTEP within 30 days. The protocol is reviewed by the PRC and a Consensus Review with both comments requiring a response and recommendations is sent to the investigators within one month of receipt of the full protocol. The protocol is approved by CTEP once the investigators have responded satisfactorily to CTEP reviewers' comments and the protocol has also been approved by the investigators' institutional review committees. After protocol activation, the contractor is expected to complete the trial within the time specified in the protocol.

AIDS Malignancy Consortium Grants To Be Consolidated

By Kirsten Boyd Goldberg

NCI plans to consolidate funding to the AIDS Malignancy Clinical Trials Consortium into one grant to a group chairman's institution, which would then parcel out subcontracts to members, in a similar manner as the cancer cooperative groups, Institute officials said last week.

The consortium has operated since 1995 through 14 grants to "main members," one grant to a data management center, and subcontracts to about 22

affiliates. The structure provided NCI "little ability to shift funds around from poorly performing sites," said Jodi Black, program officer in the NCI Division of Cancer Treatment and Diagnosis.

The change will take place when the grants are recompeted next year, a step the NCI Board of Scientific Advisors approved last week. The consortium's budget would be $4 million a year for five years.

The consortium also will work more closely with members of AIDS clinical trials network funded by the National Institute of Allergy and Infectious Diseases, Black said. None of the other cancer or AIDS clinical trials groups study AIDS-related malignancies, she said.

"We see our role in this is to be complementary to many of the other programs in AIDS and HIV, to take on the responsibility for not only dealing with the malignancies, but also the underlying mechanisms that could shed light on the entire cancer problem as it relates to the immune system," NCI Director Andrew von Eschenbach said.

In another action, the BSA approved on a vote of 11-9 the Institute's plan to set aside up to $50,000 the first year and $700,000 over the following two years to support a program that encourages alternative medicine practitioners to collect and submit data for evaluation.

Excerpts of the concept statements follow:

AIDS Malignancies Clinical Trials Consortium. Concept to reissue an RFA (cooperative agreement), one award, $4 million per year for five years, total $20 million. Program director: Jodi Black, Division of Cancer Treatment and Diagnosis.

The AMC was formed in 1995 to rapidly develop and conduct innovative and hypothesis-driven clinical trials aimed at improving the treatment and prevention of AIDS-associated cancers and related conditions and to identify and develop clinical and laboratory correlates that utilize the expertise of both NCI and National Institute of Allergy and Infectious Diseases sponsored scientists. It consists of 14 Clinical Trials Main Members, approximately 22 affiliated sites via subcontract to Main Member sites, and one Data Management, Operations and Statistical Center. The AMC is composed of basic and clinical investigators with expertise in oncology, infectious disease, pathology, radiology, gynecology, virology, molecular biology, and HIV-induced immune suppression with a focus on translational research.

Yearly deaths due to AIDS have dramatically decreased since the advent of highly active antiretroviral therapy (HAART). The number of patients living with AIDS in the U.S. has increased by about 50% since the introduction of HAART. Given the extension of life with HAART, the cumulative lifetime risk of an AIDS patient developing a malignancy is most likely increased. We can expect AIDS-associated tumors to become an increasing problem among the 900,000 persons currently living with HIV/AIDS in the U.S. as well as among the 40,000 newly diagnosed HIV/AIDS patients per year. The AIDS-defining malignancies are Kaposi's sarcoma, certain intermediate or high-grade B-cell non-Hodgkin's lymphomas, and cervical cancer. Most of these cancers have a viral etiology.

The AMC developed 43 concepts and 36 protocols of which 31 were approved. Five closed prior to enrollment due to new toxicity data or sponsor withdrawal and four are in the process of amendment or IRB review. A total of 825 patients were enrolled in 22 trials Thirteen trials are completed, six closed due to slow accrual, and three continue to enroll. Seven concepts or protocols are currently in development. Current therapeutic approaches include combination chemotherapy with monoclonal antibodies directed against B-cell target antigens, compounds that inhibit angiogenesis or improve immune function, therapeutic vaccines directed against viral targets, stem cell transplantation, and low morbidity anal lesion ablation techniques.

In addition to assessing potential anti-tumor activity and drug-drug interactions, the AMC members collaborate with investigators outside the network to develop and use laboratory correlates that help define the pathophysiologic basis of drug activity. This includes evaluating the impact of therapy on oncogenic viruses and HIV viral load, underlying immune function, apoptosis, and angiogenesis.

The purpose of the proposed initiative is to continue to provide support and to stimulate cooperative efforts to design and develop therapeutic clinical trials in patients with AIDS-related malignancies (ARM); to develop more effective management and therapies for ARM, to facilitate interaction between basic and clinical investigators towards translational studies, and to provide tumor tissue and other relevant biologic fluids to the AIDS and Cancer Specimen Resource, for tissue-based investigations. AMC structure and mechanisms for integrating and collaborating with the NIAID AIDS clinical trials networks will be altered significantly.

The project will use the cooperative agreement (U01) to fund one Leadership Group application, rather than multiple individual U01 grants. The Leadership Group will consist of the Group Chair, the operations, data management and statistics center PI and the PI of six to 10 main member core sites. The LG will be responsible for the organization and prioritization of studies and overall scientific management of the group. A single award will be issued to the Group Chair institution. The Group Chair will be required to commit a minimum of 25% effort. The operational, data management, and statistics activities will be subcontracted through the main CRO subcontract. Core site subcontracts will be capped at $100,000 direct costs consisting of the effort of the PI, travel to attend biannual group meetings, specimen acquisition for lab studies and donation to the ACSR, contracting with subspecialists/co-PI for needed services (high resolution anoscopy, gynecologic evaluations, pathology), study coordinator, data manager,

outreach/community representative interactions, laboratory personnel, and accrual of eight to 10 patients.

Failure to meet accrual goals after year 1 will result in reduction of award for the following year. Restricted patient accrual and retention funds will be available for approximately 25-30 non-core sites on a capitation basis (average of $5,000 per patient). Reserve funds for laboratory correlative, translational, training, community representatives, and international studies will be available and also restricted in the budget. In addition, these funds will be available for tissue procurement and shipping to the ACSR or to labs for specialized assays. Unexpected funds will be used as an offset to a future year award. Funds for four future years (total of five years) are requested.

This RFA will recompete the AMC within the context of the new structure for AIDS Therapeutics Groups being developed in collaboration with NIAID and will set the stage for leveraging existing NIAID cooperative group infrastructure for patient referral. Collaborative interactions between clinicians and laboratory scientists and with the clinical research groups funded by the NIAID and the NICHD are essential features of these investigations. Members of this consortium will interact with each other, the AIDS therapeutics research groups, CTEP and NIAID staff in a concerted way to conceive, create, and evaluate new approaches to prevention and treatment of cancer in HIV+ individuals. The clinical trials objectives and approaches will be investigator-initiated but consistent with the program aims of improving the survival and quality of life for persons with AIDS and cancer and providing fundamental insights into the biology of these tumors. This competition will subject the incumbent awardees to peer review to evaluate their progress.

HIV+ patients are excluded from other NCI-funded clinical trials cooperative group protocols. The NIAID AIDS Therapeutics Groups are not conducting studies on AIDS-associated malignancies. With the support of the NIH Office of AIDS Research, NCI has assumed the scientific leadership of clinical trials in AIDS malignancies.

NCI Best Case Series Program: Developmental Support and Prospective Research Projects. Concept for a new Broad Agency Announcement, proposed phase I funding $50,000 for one year, phase II proposals of up to $350,000 per year for two to three years. Project officer: Jeffrey White, director, Office of Cancer Complementary and Alternative Medicine.

The focus of the BAA is to solicit projects that enhance the state of the science on cancer treatment. The NCI Best Case Series (BCS) Program is designed to seek out alternative approaches to cancer treatment, and this BAA will support the development of BCS submissions as well as additional research when warranted.

We propose an announcement calling for collaborative projects which would pair a clinical cancer investigator with a complementary and alternative medicine practitioner. Phase I of the contract would provide limited support funds to prepare a BCS submission to NCI and develop researcher/practitioner partnerships. This type of contract would support travel, documentation development, and support staff necessary to document informed consent and other administrative activities.

The anticipated products of a successful phase I contract would be 1) documentation of a series of patients that fully meets the NCI Best Case Series Program criteria and 2) a proposal with budget for an appropriate prospective research project (preclinical, clinical, or both) which would be submitted for review prior to phase II funding.

Phase I/II Fast Track contracts would support both a phase I and phase II project (based upon some of the characteristics of the SBIR model). Phase II funds would be restricted based upon phase I assessment by NCI. This mechanism allows for quicker transition from successful BCS to research project. These contract proposals would undergo initial peer review by NCI special emphasis panels. Fast Track proposals would be subject to internal review prior to release of phase II funding support.

We also propose a BAA program to support the follow up of research projects of "successful" spontaneous submissions to the NCI Best Case Series Program.

Phase II contracts would provide funding to conduct specific types of studies on topics that have come through the Best Case Series Program and that are deemed warranting of further study with NCI resources.

HHS News:

HHS Opens National Quitline, Bans Tobacco From Campuses

A national smoking cessation telephone service will provide information and advice to U.S. smokers to help them kick the habit, HHS officials said.

The service, 1-800-QUITNOW (784-8669), provides a single access point to the National Network of Tobacco Cessation Quitlines. Callers are routed to a state-run service if one is available, or to NCI.

The department also announced plans to make all HHS campuses tobacco-free as of Jan. 1, and to provide cessation programs for its employees.

HHS Secretary Tommy Thompson made the announcements after a meeting with members of the CEO Roundtable on Cancer and the tobacco control community. "I ask all doctors and nurses to encourage every tobacco user they see to call this number as a supplement to any medication they recommend," he said. "Americans want to quit smoking, and they should quit smoking."

HHS also has a smoking cessation Web site, www.smokefree.gov. The site offers instant messaging text chat with an NCI specialist in tobacco cessation, during specified hours of operation.

Funding Opportunities:

Program Announcement

PAR-05-011: NCI Transition Career Development Award to Promote Diversity

NCI Comprehensive Minority Biomedical Branch invites applications from recipients of the NCI Mentored Career Development Award for Underrepresented Minorities or from advanced postdoctoral or newly independent research scientists representative of groups underrepresented in biomedical, behavioral, clinical, or social sciences. Awards will be made through the K22 mechanism for a total project period not to exceed 3 years. Eligible candidates must: Possess a research or health professional doctoral degree (or equivalent) suitable for a productive research career; have been in or currently be in a mentored research postdoctoral position and completed 2 years of research in this capacity at the time of the application, or be in a suitable independent position for less than 2 years with continuous previous postdoctoral research training at the time of the application; intend to conduct a research project relevant to cancer biology, etiology, pathogenesis, prevention, diagnosis, and treatment that has the potential for establishing an independent research program; and be U.S. citizens or non-citizen nationals, or must have been lawfully admitted for permanent residence by the time of award. The PA is available at http://grants1.nih.gov/grants/guide/pa-files/PAR-05-011.html.

Inquiries: Belinda Locke, phone 301-496-7344; fax 301-402-4551; e-mail lockeb@mail.nih.gov.

NCI Supplemental Funding

NOT-CA-05-005: Activities to Promote Research Collaborations.

Receipt Date: Feb.15

NCI Division of Cancer Biology will provide funds to supplement existing DCB-supported research projects in FY05 for scientific collaboration among DCB grantees and other scientists. The initiative can support collaborative activities that bring together ideas and approaches from disparate scientific disciplines, including those not currently supported by DCB. Examples include, but are not limited to, new collaborative research projects, sharing resources and reagents, developing novel technologies, and organizing cross-disciplinary meetings/workshops. It is essential that proposed activities be within the overall scope of the active parent award and that the collaborative activity is new.

Four areas of special scientific emphasis for FY05: structural biology; integrative cancer biology; tumor microenvironment; and mouse models. Applications focused on other cancer biology topics will be accepted. Requests must be submitted as described in the program guidelines. Investigators funded by DCB must contact their DCB program director prior to submitting an application.

Inquiries: John Sogn, deputy director, NCI Division of Cancer Biology, phone 301-594-8782; fax 301-496-8656; e-mail js150x@nih.gov.

In the Cancer Centers:

Karen Fields To Succeed Coltman As CTRC President

(Continued from page 1)

of Vanderbilt-Ingram's Board of Overseers and son of the center's namesake, the late E. Bronson Ingram, said DuBois will continue the center's momentum. "He has a lot of the same characteristics as Hal, and I look forward to working with him to make Vanderbilt-Ingram the best cancer center in the country," Ingram said. Having received his doctorate in biochemistry at the University of Texas Southwestern Medical School, DuBois was awarded his medical degree from the University of Texas Health Science Center at San Antonio, and completed his post-graduate training at Johns Hopkins. DuBois serves on the NCI Board of Scientific Advisors, the Board of Directors of the American Association for Cancer Research, is a scientific advisors to the National Colorectal Cancer Research Association. DuBois said his goals include nurturing translational team science, working with the medical center to solidify a clinical base that will support that translational research, and continuing to build a world-class program in cancer research. "Retaining the successful faculty that Hal has brought together will be a challenge because they are highly sought-after, but that is a must," DuBois said. "We have a wonderful foundation to work from, and Hal has my greatest respect for what he has created here in Nashville." . . . **KAREN FIELDS** was appointed president and CEO of the Cancer Therapy & Research Center effective Jan. 5, said **Mark Watson Jr**., chairman of CTRC. She is medical director of Total Cancer Care and medical director of affiliations and referring physicians at the Moffitt Cancer Center and Research Institute at the University of South Florida. CTRC President and CEO **Charles Coltman Jr**. will become president emeritus. The San Antonio Breast Cancer Symposium, founded by Coltman in 1978, will be renamed the Charles A. Coltman Jr. San Antonio Breast Cancer Symposium. Coltman also is a professor of medicine at the University of Texas Health Science Center at San Antonio and chairman of the Southwest Oncology Group. "The strong relationships between CTRC, the Health Science Center, and the San Antonio Cancer Institute will be helpful as we work on drugs, the pathology of cancers, cancer prevention, and so many more collaborative programs," said Fields. CTRC is a partner in the San Antonio Cancer Institute, a collaborative research effort between CTRC and the University of Texas Health Science Center at San

Antonio. . . . **JOANNE MORTIMER** was appointed deputy director for clinical oncology at the Rebecca and John Moores University of California, San Diego, Cancer Center, said Center Director **Dennis Carson**. She was professor of medicine and chief of the Division of Medical Oncology and Hematology at Eastern Virginia Medical School, and medical director of the Sentara Cancer Institute. Her faculty appointment at UCSD School of Medicine is pending. . . **HILLMAN CANCER Center** of University of Pittsburgh Medical Center raised over $3 million in sponsorships and contributions at its annual gala. The funds, which include a $1 million challenge grant from the Wheeler family of Somerset, Pa., will go to patient care and research. The event included an eBay auction to support the center. The center received a $1 million gift from **Mark Pasquerilla**, president, CEO and chairman of Crown American Enterprises, for genomics and proteomics cancer research. **Ronald Herberman** is director of UPCI and the UPMC Cancer Centers. . . . **ANDREW THORBURN** joined the University of Colorado Cancer Center as the associate director for basic science. He was director of the Cell Growth and Survival Program at Wake Forest University School of Medicine. . . . **UNIVERSITY OF OKLAHOMA** Cancer Center has recruited **Chinthalapally Rao** to the Cade Chair for Cancer Research and associate professor of medicine. Rao was associate chief of the Division of Nutritional Carcinogenesis and head of the Cancer Prevention Laboratory at the Institute for Cancer Prevention in Valhalla, NY. His research interest is clinical prevention of colorectal cancer and other aerodigestive tract cancers. He also works on understanding the molecular mechanisms involved in the pathobiology of colorectal cancer, and identifying and developing molecular targets for chemoprevention of colon cancer.

* * *

NIH STATE-of-the-SCIENCE Conference on Improving End-of-Life Care is scheduled for Dec. 6-8, at the NIH Natcher Conference Center. Experts will present the latest research findings on end-of-life care to an independent panel. The panel will draft a statement, presented on the final day of the conference. Registration is available at http://consensus.nih.gov. . . . **THE CANCER LETTER** will not be published next week, due to the Thanksgiving holiday in the U.S. Publication is scheduled to resume with the Dec. 3 issue. Subscriptions to **The Cancer Letter** make outstanding gifts to colleagues. Contact us for information on group rates or institutional site licenses.

Copying Policy for The Cancer Letter Interactive

The software that comes with your issue allows you to make a printout, intended for your own personal use. Because we cannot control what you do with the printout, we would like to remind you that routine cover-to-cover photocopying of The Cancer Letter Interactive is theft of intellectual property and is a crime under U.S. and international law.

Here are guidelines we advise our subscribers to follow regarding photocopying or distribution of the copyrighted material in The Cancer Letter Inc. publications in compliance with the U.S. Copyright Act:

What you can do:

--Route the printout of the newsletter to anyone in your office.

--Copy, on an occasional basis, a single story or article and send it to colleagues.

--Consider purchasing multiple subscriptions. Contact us for information on multiple subscription discounts.

What you can't do without prior permission:

--Make copies of an entire issue of the newsletter. The law forbids cover-to-cover photocopying.

--Routinely copy and distribute portions of the newsletter.

--Republish or repackage the contents of the newsletter.

We can provide reprints for nominal fees. If you have any questions or comments regarding photocopying, please contact Publisher Kirsten Boyd Goldberg, phone: 202-362-1809.

We welcome the opportunity to speak to you regarding your information needs.

THE CANCER LETTER

Vol. 19 No. 10
November 2004

Business & Regulatory Report

Product Approvals & Applications:

FDA Approves Tarceva For Advanced Or Metastatic Non-Small Cell Lung Cancer

FDA approved Tarceva (erlotinib) for locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen.

Tarceva, sponsored by **OSI Pharmaceuticals Inc.** (Nasdaq: OSIP) of Melville, NY, and **Genentech Inc.** (NYSE: DNA) of South San Francisco, is an oral tablet indicated for daily administration. It is the only drug in the epidermal growth factor receptor class to demonstrate in a phase III trial an increase in survival in advanced NSCLC.

"The FDA approval of erlotinib marks an important new treatment

(Continued to page 2)

Oncology Management:

ASCO: Aromatase Inhibitors Appropriate For Postmenopausal HR+ Breast Cancer

American Society of Clinical Oncology issued a "technology assessment" concluding that adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor.

ASCO's assessment states that aromatase inhibitors are appropriate either following a course of tamoxifen or used as initial treatment. Options include treatment with tamoxifen for two to five years, followed by treatment with the aromatase inhibitors, or treatment for five years with an aromatase inhibitor alone.

"The findings show a modest but consistent improvement in disease-free survival among women who received an aromatase inhibitor compared to those who did not," said Eric Winer, director of the Breast Oncology Center at the Dana Farber Cancer Institute and lead author of the ASCO technology assessment.

"In women with hormone receptor-positive early breast cancer, hormones can influence the growth of the cancer," Winer said in a statement. "In postmenopausal women, aromatase inhibitors can block estrogen production and reduce estrogen levels by more than 90 percent."

The ASCO panel recommends the following guidelines for aromatase inhibitors:

--Postmenopausal women with hormone receptor-positive breast cancer may substitute an aromatase inhibitor for tamoxifen as initial adjuvant

(Continued to page 4)

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

Tarceva Approved For NSCLC, Improved Survival In Trial

(Continued from page 1)

option for patients in the United States with advanced non-small cell lung cancer after chemotherapy has failed," Alan Sandler, associate professor of medicine at Vanderbilt University and medical director of the Thoracic Oncology Department said in a statement. "Physicians will now be able to offer patients a new therapy that has been proven to increase survival and that is different from traditional cytotoxic chemotherapy treatment."

FDA based the approval results from a randomized double-blind, placebo-controlled phase III trial of patients with second and third-line advanced NSCLC. The trial included 731 patients with advanced NSCLC for whom one or more chemotherapy regimens had failed.

The primary endpoint for the study was survival. In addition to achieving this primary endpoint, Tarceva also met all secondary endpoints of the trial. The study was conducted by the National Cancer Institute of Canada Clinical Trials Group based at Queen's University in collaboration with OSI Pharmaceuticals.

Patients receiving Tarceva had a median survival of 6.7 months compared to 4.7 months in patients who received placebo (a 42.5 percent improvement). A hazard ratio (HR) of 0.73 and a p-value of less than 0.001 were determined for comparisons of overall survival. In addition, 31.2 percent of patients receiving Tarceva in the study were alive at one year versus 21.5 percent in the placebo arm.

Results from two earlier randomized, placebo-controlled clinical trials in first-line advanced NSCLC patients showed no clinical benefit with concurrent administration of Tarceva with doublet platinum-based chemotherapy (carboplatin and paclitaxel or gemcitabine and cisplatin) and its use is not recommended in that setting.

In the pivotal trial, the most common adverse reactions in patients receiving Tarceva were rash and diarrhea. Grade three/four rash and diarrhea occurred in nine and six percent of Tarceva-treated patients, respectively. Rash and diarrhea each resulted in discontinuation of one percent of Tarceva-treated patients. Six and one percent of patients needed dose reduction for rash and diarrhea, respectively.

In the phase III trial, severe pulmonary reactions, including potential cases of interstitial lung disease, occurred in 0.8 percent of patients, and were equally distributed between treatment arms. The overall incidence of ILD in Tarceva-treated patients from all studies was approximately 0.6 percent.

The Tarceva NDA was granted Pilot 1 Status under the FDA "program for continuous marketing applications." The Pilot 1 program was designed for investigational products that have been given Fast Track status, such as Tarceva, and that have demonstrated significant promise in clinical trials as a therapeutic advance over available therapy for a disease or condition.

Under Pilot 1 status, FDA commits to reviewing each unit of the NDA within six months of each unit submission. Tarceva is one of the first drugs to be granted and approved under the program.

A phase III clinical trial of Tarceva has been completed in pancreatic cancer, and additional early-stage trials of Tarceva are being conducted in other solid tumors, the companies said.

Prescribing information is posted at www.tarceva.com.

* * *

BioAlliance Pharma of Paris said the European Commission has granted the company an orphan medicinal product designation for doxorubicin Transdrug for hepatocellular carcinoma.

The decision follows the favorable opinion of the Committee for Orphan Medicinal Products of the European Medicines Agency.

Doxorubicin Transdrug is a proprietary nanoparticle

THE CANCER LETTER

Member, Newsletter and Electronic Publishers Association

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

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

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016

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

Business & Regulatory Report is a supplement to The Cancer Letter and available separately for $175 per year. ISSN 1053-9611.

formulation that is in a phase I/II trial in HCC at seven clinical sites in France.

The company said it will also file an application this month with FDA to obtain orphan drug designation in the U.S.

The EMEA's orphan designation promotes development of drugs to treat rare diseases or conditions, which would otherwise be unprofitable to pursue. The actual definition of an orphan drug within the EU is one for a disease that affects fewer than five people in every 10,000.

The designation provides EU market exclusivity, for a particular indication, against drugs with the same principal molecular structural features and which act via the same mechanism.

The market exclusivity is for a 10-year period if the sponsor complies with certain EMEA specifications. The EMEA represents 25 EU countries, including France, Germany, Italy, Spain and the United Kingdom.

In addition to marketing exclusivity, designation as an orphan drug provides other incentives including EMEA protocol assistance to optimize drug development in preparing a dossier that will meet regulatory requirements; facilitating access to the Centralized Procedure for the application for marketing approval; complete or partial waiver of fees associated with applying for marketing approval and protocol assistance; and, access to EU research funding for rare diseases.

The rationale for testing doxorubicin Transdrug in HCC is based on the ability of the drug to bypass multi-drug resistance in vitro and to increase the efficacy in vivo by increasing tumor necrosis and tumor cell apoptosis, the company said.

As a result of its preferential hepatic distribution, proven efficacy in numerous susceptible or resistant tumor models, especially hepatic tumor models, Doxorubicin-Transdrug is being studied in a phase I/II clinical trial utilizing the hepatic intra-arterial route of administration

* * *

Marshall Edwards Inc. said FDA has granted Fast Track status for the investigational anti-cancer drug phenoxodiol for recurrent ovarian cancer.

In approving phenoxodiol, the letter from FDA the following reasons for granting the status: "1. Recurrent ovarian cancer that is resistant or refractory to platins and taxanes is a life-threatening condition. 2. Phenoxodiol intravenous demonstrates potential to address an unmet medical need by restoring chemo-sensitivity in resistant/refractory ovarian cancer."

The Fast Track application contained clinical data including tumor measurements based on radiographic examination, the company said. The data are from the phase Ib/IIa study where patients with recurrent ovarian and primary peritoneal cancers are receiving phenoxodiol (intravenous dosage form) in combination with paclitaxel where the cancer is refractory or resistant to taxanes, or in combination with cisplatin where the cancer is refractory or resistant to platinum-based drugs, the company said.

Phenoxodiol regulates signal transduction pathways in cancer cells resulting in the break down of the intra-cellular proteins—XIAP (X-linked Inhibitor of Apoptosis Protein) and FLIP (Fas Ligand Inhibitory Protein)—which block the ability of the cancer cell to undergo apoptosis via the death receptor mechanism.

Pre-clinical studies have shown that by targeting the anti-apoptotic proteins, phenoxodiol is able to promote death of ovarian cancer cells that are resistant to standard anti-cancer drugs, as well as being able to restore sensitivity in the cells to standard anti-cancer drugs such as taxanes, the company said.

Phenoxodiol works selectively on tumor cells because of its interaction with the tumor-specific NADH oxidase, which is restricted to cancer cells, the company said.

The phase Ib/IIa study is an open label, randomized study being conducted at two sites, Yale-New Haven Hospital, and Royal Women's Hospital, Melbourne, VIC, Australia, for recurrent ovarian cancer that is either resistant or refractory to taxane- and/or platinum-based drugs, the company said.

Randomization is occurring to one of three treatment groups: phenoxodiol + cisplatin; phenoxodiol + paclitaxel; and paclitaxel only, converting to phenoxodiol + paclitaxel after disease progression has been demonstrated, the company said.

The treatment is administered by intravenous infusion on two consecutive days per week and the second drug administered intravenously immediately following the second phenoxodiol administration. Treatment is weekly on a continuous basis until either disease progression or complete response as determined by the absence of detectable disease.

There are 20 subjects per treatment group. Phenoxodiol is being administered at a dosage of 3 mg/kg; the dosages of paclitaxel and cisplatin are standard but adjustable to ensure that toxicity is no greater than Grade 1,4 being the least toxic grade, the company said.

* * *

Threshold Pharmaceuticals Inc. of South San

Francisco said FDA has granted Fast Track status to one of the company's drug candidates, glufosfamide, for injection, to treat unresectable locally advanced or metastatic pancreatic adenocarcinoma previously treated with gemcitabine.

Glufosfamide was designated as a fast track product both because of the severity of pancreatic cancer and because glufosfamide may provide a therapeutic benefit to the intended patient population, the company said.

There are currently no approved therapies for metastatic pancreatic cancer refractory to gemcitabine. These patients have an expected survival of approximately three months.

"Glufosfamide's fast track status underscores the urgency of developing new treatment options for pancreatic cancer patients and the potential of glufosfamide to improve current survival rates for this devastating disease," said George Tidmarsh, founder and president of Threshold Pharmaceuticals. "Threshold will continue to work closely with the FDA to expedite the development of Glufosfamide."

Data from the company's phase III trial, currently under enrollment in the U.S., will be submitted to FDA as part of Threshold's marketing application, should the study meet its primary endpoint.

The study, for which Threshold has received a Special Protocol Assessment from FDA, will evaluate the survival of patients treated with Glufosfamide in conjunction with best supportive care versus those receiving BSC.

Oncology Management:

ASCO Finds DSF Improved With Aromatase Inhibitors

(Continued from page 1)

therapy. Alternatively, women can still begin treatment with tamoxifen and plan to switch to an aromatase inhibitor after two to five years. It's not clear at this time which strategy is superior, ASCO said.

--Postmenopausal women who are taking tamoxifen may considering switching to an aromatase inhibitor after two to five years of tamoxifen therapy.

--Women who switch to an aromatase inhibitor may continue this therapy for two to three more years, but no longer than five years. Women are advised that the result of treatment with an aromatase inhibitor for longer than five years has not been studied and should only be done in the context of a clinical trial.

--There are no data to recommend taking tamoxifen after an aromatase inhibitor.

--Women who develop invasive hormone receptor-positive breast cancer while taking tamoxifen for breast cancer risk reduction, and women who cannot take tamoxifen because of high risk of severe side effects, or who have tried tamoxifen and had to stop because of severe side effects, might be advised to consider using an aromatase inhibitor.

The three types of aromatase inhibitors included in the assessment are anastrozole (Arimidex), letrozole (Femara), and exemestane (Aromasin). It's not known whether these drugs can be used interchangeably. The long-term side effects of aromatase inhibitors are not known.

Early data suggest that when compared with tamoxifen, aromatase inhibitors may reduce the risk of blood clots and uterine cancer, but may increase the risk of osteoporosis and fractures, the society said.

* * *

Broadlane of San Francisco said it has acquired **National Oncology Alliance Inc**. of San Rafael, Calif., a privately held company that provides services for oncology physician practices.

"Reining in the rapidly rising cost of drugs in the treatment of cancer and other diseases involving high-cost specialty drugs is a critical issue for everyone," said Charles Saunders, CEO of Broadlane. "With NOA's industry-leading specialty pharmaceutical sourcing capabilities, combined with clinical expertise in cancer drug utilization, Broadlane will enhance its capability to help hospitals and physicians control this important driver in the cost of care, and do so in a manner that is complementary to and collaborative with physicians and the way they practice."

NOA, founded in 2000, serves more than 50 percent of the physician office-based oncology market, the company said. The client base includes 3,500 physicians in 1,600 locations in all 50 states.

After becoming a wholly owned subsidiary of Broadlane, NOA will continue its relationships with its physician practice customers, the company said.

* * *

International Physician Networks of King of Prussia, Penn., announced a collaboration with **ProMetrics Consulting Inc**. of Baltimore to provide support services, including market research, to pharmaceutical and biotechnology firms in the oncology, rheumatology, and orthopedic markets.

International Oncology Network and International Musculoskeletal Network, both divisions of IPN, will collaborate with ProMetrics to enable management to

make quicker decisions, the companies said.

The support services will include ready access to physicians that would allow a team to respond to the time line of a client and provide real-time data. Along with the accessibility advantage, the technology would provide data collection involving the use of on-line surveys that automatically compile results for speed and efficiency. Many of the products being developed will contain a CD-ROM searchable database that will allow the user to conduct in-depth analysis, the companies said.

"With many of the sudden changes in product development, administration, and reimbursement taking place, particularly in the field of oncology, the demand for the services that we will be providing is at an all-time high," said Jeffery Scott, president of IPN. "The added resources of the ProMetrics market research and consulting team will enable us to leverage our internal capabilities across many more programs than we could have on our own to satisfy this demand for clinical information."

Clinical Trials:

NeoPharm Begins Phase I Trial In Phoenix of C-raf Inhibitor

NeoPharm Inc. (Nasdaq: NEOL) of Lake Forest, Ill., said the first patient has been dosed in a phase I study of LErafAON (Liposome Entrapped c-raf Antisense Oligonucleotide) for the treatment of advanced cancers.

"We are pleased that dosing has begun in this important dose-escalation study of our new LErafAON formulation," said Gregory Young, NeoPharm's president and CEO. "The LErafAON formulation utilizes our proprietary NeoPhectin cationic cardiolipin technology which has potential application for other antisense oligonucleotides and siRNA delivery."

The study is being conducted at the Arizona Cancer Center, Greater Phoenix Area located in the Virginia G. Piper Cancer Center at Scottsdale Healthcare. The drug is being developed in collaboration with the Translational Genomics Research Institute, a non-profit biomedical research institute whose mission is to make and translate genomic discoveries into advances in human health. TGen is also located in Phoenix.

LErafAON is designed to interfere with the expression by tumor cells of a protein known as c-raf. The protein is expressed at higher levels in various tumors including breast, ovarian and prostate cancers. By inhibiting expression of the c-raf protein, LErafAON may have independent anti-tumor activity and may render tumor cells more susceptible to radiation or chemotherapy.

"The technology underlying LErafAON has the possibility to enable the formulation of therapeutic agents which are difficult to deliver into tumor cells. Intracellular delivery of oncology therapeutics has been a hurdle that needs to be overcome," said Daniel Von Hoff, executive vice president and director of the Translational Drug Development Division and head of the Pancreatic Cancer Research Program at TGen.

Von Hoff also holds an appointment of Professor of Medicine, Molecular & Cell Biology and Pathology at the University of Arizona College of Medicine.

* * *

ADVENTRX Pharmaceuticals Inc. (Amex: ANX) of San Diego said it has started accruing patients to the second stage of its phase II trial of CoFactor to modulate the effect of 5-fluorouracil for metastatic colorectal cancer.

Based on the submission of 23 initial patients recruited as part of the Simon Two-Stage trial design, FDA granted authorization to proceed to the second stage and enroll an additional 25 patients, the company said.

The phase II trial is an open-label single arm study to evaluate safety, tumor response, time-to-tumor-progression and overall survival, the company said. Eligible patients have surgically incurable, metastatic colon or rectal adenocarcinoma, and no prior chemotherapy for metastatic disease.

CoFactor (5,10-methylenetetrahydrofolate), a biomodulator designed for use with 5-FU, is the active metabolite of leucovorin that bypasses the chemical pathway required by leucovorin to deliver the correct form of folate to cancer cells, allowing 5-FU to work more effectively, the company said.

In European phase II trials, the agent was administered for metastatic colorectal cancer 20 minutes before intravenous administration of 5-FU. In the trials, the treatment improved survival and time-to-tumor-progression while lowering toxicity for metastatic colorectal cancer.

* * *

Gemin X Biotechnologies Inc. of Montreal said it has begun phase I testing for GX15-070, a small-molecule inhibitor of Bcl-2 proteins for solid tumors.

The open-label, dose-escalation study, which is being conducted at the Lombardi Comprehensive Cancer Center at Georgetown University, is designed to evaluate the safety and tolerability of multiple doses of the inhibitor, the company said.

The protocol will include pharmacokinetic sampling and pharmacodynamic evaluation.

In preclinical studies, GX15-070, administered as a single agent, inhibited tumor growth in mouse models of melanoma as well as of breast, cervical, prostate and colon cancers, the company said.

"Preclinical studies with GX15-070 have shown strong activity at levels well below the maximum tolerated dose, which indicates that a targeted therapy like GX15-070 could potentially avoid the toxicities associated with less specific cancer treatments such as chemotherapy and radiation," said Jean Viallet, vice president of clinical development at Gemin X. "If reflected in clinical studies, such a profile would make GX15-070 a very attractive alternative to burdensome combination therapies."

GX15-070 induces apoptosis by inhibiting members of the Bcl-2 protein family, the company said. When over-expressed in cancer cells, Bcl-2 proteins stop apoptosis by blocking Bax and Bak, two elements of the cell-death pathway.

The over-expression of Bcl-2 proteins has been observed in cancers, including lymph, breast, lung, prostate and colon.

Because of the redundancy in the Bcl-2 family, inhibition of a single protein in the group is unlikely to result in a therapeutic effect, the company said. Instead, inhibition of all proteins in the family is needed to allow the cell death program to proceed. To address this issue, GX15-070 targets the entire group, instead of a single member, by exploiting the structural similarity of Bcl-2 proteins.

Separate phase I trials in chronic lymphocytic leukemia should begin both in the US and Canada, the company said.

* * *

Helix BioPharma of Aurora, Ontario, said it has initiated a phase II study of Interferon-alpha Cream for low-grade squamous intraepithelial lesions that are positive for human papilloma virus infection.

The 18-month study, which will evaluate the efficacy and safety of Interferon-alpha Cream for LSIL, represents the mild-to-moderate forms of cervical dysplasia, the company said.

Study subjects will self-administer Interferon-alpha Cream intravaginally three times per week for six weeks, the company said. The primary study endpoint will be cytological in nature, whereby subjects will be evaluated for evidence of resolution of their abnormal Papanicolaou smear.

Other study assessments will include pre- and post-treatment histological examinations by way of colposcopy and qualitative assessment of HPV+ status using PCR.

The trial will take place at the Friedrich-Schiller-University of Jena in Germany, under the direction of Achim Schneider, the company said.

Interferon alpha-2b is an immune system modulator active against HPV-induced lesions, the company said. The treatment triggers an antiviral response within infected cells by activating certain intracellular enzymes, which cause degradation of viral RNA, and by mobilizing the immune system to destroy the infected cells.

Interferon alpha-2b has been used commercially for ano-genital warts, but is not generally favored because of the painful intradermal injection that conventional administration requires. In addition, intradermal injection is restricted to visible lesion administration, while HPV infection is often characterized by both visible and non-visible lesions.

The cream would offer a discreet, self-administered, pain-free therapy that can be broadly applied across the entire affected tissue area, the company said.

Deals & Collaborations:

NIDA Awards $2.1 M Contract To Perlegen For SNP Analysis

The National Institute on Drug Abuse awarded a $2.1 million contract to **Perlegen Sciences Inc.** of Mountain View, Calif., to investigate the human genome for DNA variations and candidate genes associated with nicotine addiction.

"This partnership, which combines NIDA support and cutting-edge private-sector technology, will help us better understand the significance of genetic influences in smoking," NIDA Director Nora Volkow said in a statement. "As we learn more about genetic influences on nicotine addiction and treatment response, we will be able to individually tailor the treatments for people who are addicted to this powerful drug."

NIDA-supported scientists at Washington University in St. Louis will use Perlegen's technology to analyze more than 1.5 million single nucleotide polymorphisms (SNPs) across the genome in people who are highly addicted to nicotine, and compare these findings with those from people who are not addicted to the drug.

* * *

EXACT Sciences Corp. (NASDAQ: EXAS) said it has amended its exclusive licensing agreement with

the **Johns Hopkins University** to include the PIK3CA gene.

Scientists at the Kimmel Cancer Center and the Howard Hughes Medical Institute at JHU published research findings in the March 11 online issue of Science identifying the link between mutations in PIK3CA and colon and other cancers.

Through its relationship with JHU, EXACT Sciences has received exclusive, long-term rights to the PIK3CA gene for use in connection with colorectal cancer screening from stool samples. EXACT Sciences believes that the addition of the PIK3CA gene to a reconfigured PreGen-Plus assay may result in greater assay sensitivity.

"This exclusive right that we received from JHU for PIK3CA is a reflection of our continued collaboration with Dr. Vogelstein's lab," said Anthony Shuber, EXACT Sciences Chief Technology Officer.

"Mutations in PIK3CA appear to be strongly correlated with colon cancer, and we believe that the addition of this gene to the PreGen-Plus panel could result in an assay with even higher sensitivity than that previously demonstrated," Shuber said. "In fact, we recently presented preliminary research at a conference in Bar Harbor, Maine hosted by the Jackson Laboratory, which described the substantial increase in performance in detecting mutations in colorectal cancer tissues through use of a reconfigured PreGen-Plus panel that included the PIK3CA gene. We are moving forward with the validation of these preliminary findings."

* * *

Ligand Pharmaceuticals (Nasdaq: LGND) of San Diego said it has restructured its agreement with **Eli Lilly and Co**. (NYSE: LLY) on royalties payable to Lilly on sales of the Ligand marketed cancer drug Ontak (denileukin diftitox) in the U.S.

Ligand said it recorded sales of $34.3 million for Ontak in calendar year 2003.

Under the revised agreement, Ligand and Lilly will each have two options. Ligand will have an independent option exercisable in January 2005 and another independent option exercisable in April 2005 to buy down a portion of the Ontak royalty stream on net sales in the U.S.for a total consideration of $33 million, the company said. Lilly will have options in 2005 to trigger the same royalty buydown on Ligand's part for a total consideration of up to $37 million, dependent on whether Ligand has exercised one or both of its options and Ontak has achieved certain sales levels.

The first option provides that Ligand will make to Lilly a one-time cash payment of $20 million in exchange for elimination of the Ontak royalties due to Lilly on net sales in the U.S for 2005 and a reduced reverse-tiered royalty scale on net sales thereafter, the company said. The second option in April 2005 provides that Ligand will make a one-time cash payment of $13 million in exchange for the elimination of the Ontak royalties due to Lilly on net sales in the U.S. in 2006 and a reduced reverse-tiered royalty scale thereafter.

If both Ligand options are exercised, Ligand would make total payments of $33 million for elimination of all royalty payments due on U.S. sales through year-end 2006 and elimination of all royalties on U.S. sales of $38 million or less going forward, the companies said.

Beginning in 2007, Ligand would pay royalties to Lilly on a reverse-tiered scale (from 20 percent to 10 percent) only on annual U.S. sales in excess of $38 million for the minimum tier and in excess of $72 million for the maximum tier threshold for the remaining patent life (through 2014).

Sales outside the U.S. (if Ontak gains marketing approval in other geographies) will be excluded from this restructured agreement and will continue at the previous non-tiered contract royalty rate of 20 percent. Neither party is obligated to exercise either of its options and the options will expire if not exercised by the specified dates.

"The restructuring of the Ontak royalty stream to Lilly has important strategic and financial value for Ligand and our stockholders," said Paul Maier, senior vice president and chief financial officer at Ligand. "The restructured Ontak arrangement provides flexibility to Ligand to make the commercial and development investments to continue to grow the brand while also contributing to improved EPS.

In another development, Ligand and **Royalty Pharma** of New York said they have amended their royalty agreement for three selective estrogen receptor modulator products.

Under the agreement, Royalty Pharma will purchase for $32.5 million an additional 1.625 percent of the SERM products net sales, the companies said.

The amendment reflects an acceleration of the previous option timetable and an increase in the royalty amount and aggregate purchase price. Previously, two options were exercisable as NDA acceptance and approval milestones were achieved in 2004 and 2005 for a total of $26.5 million in two equal payments for a total of 0.8 percent of the SERM products net sales.

The recent Pfizer NDA filing for lasofoxifene for osteoporosis triggered the first of the two previous options during the fourth quarter of 2004.

Under the revised agreement, payments from the royalty purchase are non-refundable, regardless of whether the products are ever successfully registered or marketed, the companies said. Milestone payments owed by Ligand's partners as the products complete development and registration are not included in the Royalty Pharma agreement and will be paid to Ligand as earned, the companies said.

As a result of the transaction, Royalty Pharma said it increased its rights to a total of 3.0125 percent of net sales of each of the three SERM products for a period of ten years following first commercial sale of each product and has no further options.

Ligand retains an approximately equal portion of lasofoxifene and other SERM net sales going forward and for periods that may exceed ten years. For the royalties just purchased, the royalty rates owed to Royalty Pharma may be reduced by one third if SERM product sales exceed certain thresholds.

Ligand said it has formed a portfolio of partnerships with 11 pharmaceutical companies, including Pfizer and Wyeth.

The companies have in clinical studies or on development track more than a dozen products, which include two phase III products (in addition to lasofoxifene, under FDA review), four phase II products, four phase I products, and four compounds on IND track.

* * *

Seattle Genetics Inc. (Nasdaq: SGEN) of Bothell, Wash., said **Genentech Inc**. (NYSE: DNA) has agreed to pay a technology access fee of $1.6 million to designate additional antigen targets under their drug conjugate collaboration agreement.

Under the agreement, Genentech has rights to use the ADC technology with antibodies against targets selected by Genentech, the companies said.

Seattle Genetics said it has received $20 million in upfront payments, research and material supply fees and equity investments from Genentech, pursuant to the ADC collaboration, which was established in 2002 and expanded in 2003, the companies said.

Genentech said it has also agreed to make progress-dependent milestone payments and pay royalties on net sales of ADC products. Genentech said it is responsible for research, product development, manufacturing and commercialization of any products resulting from the collaboration.

The SG ADC technology utilizes monoclonal antibodies to deliver cell-killing payloads to specific cells, the companies said. The technology employs synthetic drugs that can be attached to antibodies through proprietary linker systems.

The linkers are designed to be stable in the bloodstream but to release the drug payload under specific conditions once inside target cells, thereby sparing non-target cells of the toxic effects of chemotherapy, the companies said.

* * *

Reata Discovery Inc. of Dallas said it has completed a license agreement with **Dartmouth College** and **M. D. Anderson Cancer Center**, providing Reata with exclusive worldwide rights to anticancer compounds.

The selection of a clinical candidate, designated RTA 401, for advanced development would lead to clinical testing in 2005, the company said.

RTA 401, also known as CDDO, was synthesized by investigators at Dartmouth College and developed in cooperation with M. D. Anderson and NCI, the company said. The compound and its analogues are based on compounds found in medicinal plants, but have much greater potency. The compounds have been shown to have a profile of antitumor, anti- inflammatory, and anticarcinogenic properties.

Data show that RTA 401 and its analogues induce apoptosis in a variety of cancer cells but are less toxic to normal cells, the company said. In cancer cell lines, treatment reduced expression of apoptosis resistance factors and growth-promoting factors, while increasing expression of proapoptosis factors and growth-inhibiting factors.

RTA 401 and its analogues have shown activity in animal models of solid tumors and hematological cancers and were active against cancer cells taken from myeloma and leukemia patients who were unresponsive to standard and targeted therapies. The compounds have also shown anti-inflammatory activity in cell and animal studies, suggesting they may have a role in cancer prevention and treatment of inflammatory diseases, the company said.

"Years of scientific collaboration between Michael Andreeff, chief of the section of molecular therapy and hematology at M. D. Anderson, Marina Konopleva, assistant professor of bone marrow transplantation, and their colleagues at Dartmouth have resulted in the preclinical development of the compounds into valuable intellectual property," said Kevin Casement, director of technology assessment and licensing at M. D. Anderson. "The subsequent business partnership between M. D. Anderson and Dartmouth has enabled a successful technology transfer."