THE CANCER LETTER INTERACTIVE

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ODAC Rejects Temodal For Melanoma After Discussion Of Approval Standards

The Oncologic Drugs Advisory Committee recommended against approval of Temodal (temozolomide) for the first line treatment of advanced metastatic malignant melanoma.

The application, filed Schering Plough Corp., was based on a study designed to demonstrate that Temodal was superior to DTIC (dacarbazine), a drug approved for the indication in 1975.

Unfortunately for Schering, the study failed to demonstrate superiority to DTIC, enabling the company to claim only that Temodal is

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In Brief:

Fidler Wins BMS Cancer Research Award; Thomas Cech To Head Howard Hughes Inst.

ISAIAH FIDLER was selected to receive the 22nd annual Bristol-Myers Squibb Award for Distinguished Achievement in Cancer Research for his work in founding the modern study of cancer metastasis. Fidler is the R.E. "Bob" Smith Chair in Cell Biology, chairman of the Cancer Biology Department, professor of urology, and director of the Cancer Metastasis Research Center at University of Texas M.D. Anderson Cancer Center. Fidler is to receive the $50,000 award and silver medallion on April 15 in New York. Fidler, in a 1978 paper in Science with Margaret Kripke, showed that metastatic cells preexisted in primary tumors. He subsequently showed that metastasis can arise from a single cell. More recently, Fidler identified metastasis-regulating genes in the tumors of recurrent Dukes B colon cancer patients, allowing for the identification and more aggressive treatment of patients whose tumors are more likely to recur. . . . **HOWARD HUGHES** Medical Institute trustees selected **Thomas Cech** of the University of Colorado at Boulder to become the next president of the institute, based in Chevy Chase, MD. Cech, who won the Nobel Prize in chemistry in 1989, will assume the presidency next January. He will succeed **Purnell Choppin**, president of the institute since 1987, who announced late last year that he would retire at the end of 1999. Cech, 51, has been an HHMI investigator since 1988 and a member of the faculty at University of Colorado since 1978. He is also a professor of biochemistry, biophysics and genetics at the University of Colorado Health Sciences Center in Denver. Cech shared the Nobel Prize in chemistry with Sidney Altman of Yale University for work that each had done independently on the "discovery that RNA in living cells is not only a

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Is A New Placebo Better Than An Old Placebo? ODAC Asks

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at least equivalent to DTIC.

In the course of considering the Schering study at a March 23 meeting, ODAC was forced to compare Temodal with a drug approved in accordance with the standards of nearly a quarter of a century ago.

DTIC was approved on the basis of objective tumor response. In a study involving 450 patients, the drug produced a 23 percent tumor response rate (6 percent of patients had complete responses, and 17 percent had partial responses). DTIC was not shown to prolong either progression-free survival or overall survival.

Though many oncologists describe DTIC as an ineffective treatment for metastatic melanoma, the drug is routinely administered to patients who wish to continue treatment.

"This takes us back to 1975," ODAC member David Johnson, director of the Division of Medical Oncology at Vanderbilt University Medical School, said at the committee meeting. "We saw the data on which FDA approved DTIC. I don't personally subscribe to the view that simply seeing the tumor shrink is sufficient."

Nonetheless, Schering chose the drug as a benchmark for the study of 305 patients, who were randomized to receive DTIC or Temodal. A much larger study would have been required to measure Temodal's effectiveness instead of comparing it with an existing treatment.

Johnson said Schering's comparison of Temodal with DTIC demonstrated tumor shrinkage only, failing to show that shrinkage was associated with any patient benefit.

"We can all agree that DTIC is at worst a bad placebo [for metastatic melanoma]," Johnson said. "So I think it was reasonable to construct a study to look for superiority." However, it is also important to consider the validity of your benchmark, Johnson said.

"Candidly, I would have warned [the sponsor] against doing [a superiority trial]," Johnson said. "I would have said that the question has been raised by a number of people, including myself, about the validity of using DTIC at all as a useful drug [in metastatic melanoma]."

DTIC, made by Bayer Corp. of West Haven, CT, is administered intravenously. Temodal is an oral drug. The two drugs are believed to have the same active metabolite, MTIC.

ODAC voted 10-0 with one abstention that Schering's study failed to demonstrate effectiveness of Temodal. That task accomplished, the committee turned to the next question: should the drug be approved?

First, the committee addressed the question that would appear peculiar in any field other than oncology: What does the apparent lack of effectiveness mean in terms of everyday clinical practice?

"For those of us who practice community medicine, the ease of administration is a factor to consider," said committee member James Krook, principal investigator at the Duluth, MN, CCOP. "Is this a form of a drug that is approved, that is going to be administered easily, more conveniently, for both the provider and the patient?"

A useless therapy conveniently administered is still useless, objected Richard Schilsky, director of the University of Chicago Cancer Research Center, who chaired the ODAC meeting.

"Perhaps I can just ask you, in view of your vote on the first question, what you are telling us is that you prefer an oral placebo to an IV placebo?" Schilsky asked Krook, one of the committee members who voted a few minutes earlier that temozolomide did not appear to be effective.

KROOK: "The answer is yes. All of us face this in practice. What do you do when somebody

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

Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg

Editorial: 202-362-1809 Fax: 202-362-1681
PO Box 9905, Washington DC 20016
E-mail: kirsten@cancerletter.com or paul@cancerletter.com

Customer Service: 800-513-7042
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wants to do something? I pass out—as a lot of people do—hormonal drugs, realizing that they may not do much, but the person who is taking it feels better."

SCHILSKY: "I would just comment that it seems to me that there are oral placebos available that are even less toxic than temozolomide."

KROOK: "Agreed. And I qualify myself by saying, 'If I reach the point of chemotherapy…'"

If approved, Temodal would make an illogical treatment choice more convenient, said committee member Derek Raghavan, associate director of the University of Southern California Norris Comprehensive Cancer Center.

"As a function of their frustration with the inability to offer an effective therapy for melanoma, recognizing that getting treatment helps the patient get through that crisis period, [oncologists] give DTIC," Raghavan said. "It just happens that they are giving a toxic drug.

"The reason many of us who are active clinicians are choking on this, is that we keep thinking that—given that this is a systemic error—maybe we can make the error less by having a less unpleasant mode of delivery of a useless drug," Raghavan said.

"That's the wrong way to think about it," he said.

It took a patient representative on the committee to point out that poor therapies, once they become available, are difficult to eradicate.

"As one sitting here hoping not to become stage 4, especially after this discussion, I wonder why we are not voting to outlaw DTIC," suggested Kenneth McDonough, a melanoma survivor from North Huntingdon, PA. "Faced with the possibility of the disease coming back and being told to consider DTIC, I am not going to have a hell of a lot of faith in it."

SCHILSKY: "Any comments on how we outlaw drugs?"

McDONOUGH: "My second point is, I don't see how you can leave one kid on the block who has a bad reputation, and not let the other one on the block, too. If you are going to purge, then you gotta purge."

"This is obviously an interesting and provocative question," said Robert Temple, director of the FDA Center for Drug Evaluation and Research. "I believe many of the older therapies that have been approved would have difficulty supporting their effectiveness in modern terms."

The agency takes drugs off the market if they cause unforeseen, severe adverse events, Temple said. FDA has no mechanism for weeding out therapies that can no longer be scientifically justified.

The committee voted 10-1 against approval, with McDonough casting the opposing vote.

In addition to the melanoma indication, DTIC is approved for second-line therapy, in combination with other agents, for Hodgkin's disease.

In January, ODAC recommended that Temodal receive accelerated approval for the treatment of anaplastic astrocytoma, based on the surrogate endpoints of time to progression and tumor response rate. Accelerated approval is conditional on the outcome of the sponsor's studies demonstrating patient benefit.

Also at the January session, the committee recommended against full approval of Temodal for recurrent glioblastoma multiforme in adults (**The Cancer Letter**, Jan. 22). Following that decision, FDA has been receiving a steady stream of letters and Congressional inquiries.

The correspondence appears to have been urged by Musella Foundation, a Hewlett, NY, based non-profit group that operates a web site distributing information on brain tumor trials (http://www.virtualtrials.com). The site displays a model letter addressed to FDA, with copies going to the House and Senate members. The letter urges the agency to "ignore the recommendation of the Oncologic Drugs Advisory Committee" to deny the glioblastoma indication for Temodal.

Capitol Hill:

Legislation Seeks Coverage For Treatment Of Underserved

For the third time in as many years, Congress has taken up the question of providing care for women diagnosed with breast or cervical cancers through a screening program intended for the medically underserved and operated by Centers for Disease Control and Prevention.

Bills to extend coverage for the treatment of cancers found through the CDC Breast and Cervical Cancer Screening Program were introduced in the Senate on March 18 and in the House on March 1.

Last year, similar bills were among other business left unfinished during the turbulent and abbreviated legislative session. In 1997, the measure was introduced as an amendment to the Senate spending bill, but did not survive the House-Senate conference.

The legislation is aimed at helping the working poor who qualify for screening through the CDC program, but have no health insurance and don't qualify for Medicaid coverage. If passed by Congress, the measure would give states the option of extending Medicaid to women who meet the criteria for being screened by CDC.

For two years, the bill has been the top legislative priority of the National Breast Cancer Coalition.

In its previous incarnations, the bill was shepherded through Congress by the former Sen. Alfonse D'Amato (R-NY). During the current session, Sen. John Chafee (R-RI), chairman of the Senate Finance Committee, emerged as the sponsor and key advocate of the bill. The Senate bill, S. 662, is co-sponsored by Chafee and Sens. Olympia Snowe (R-ME), Barbara Mikulski (D-MD), and Daniel Patrick Moynihan (D-NY).

The House bill, H.R. 1070, is co-sponsored by Rick Lazio (R-NY), Anna Eshoo (D-CA), and Ileana Ros-Lehtinen (R-FL). The bill has 95 co-sponsors in the House and 27 in the Senate.

Since its creation in 1990, the CDC program has screened about 794,400 women, finding 56,100 abnormalities and 4,100 cases of breast cancer.

It is unclear how many of these women were ineligible for Medicaid coverage and lacked health insurance.

According to a CDC survey of health officials in seven states, diagnostic and treatment services were found "for nearly all" women screened. "However, the strategies used to obtain those services [were] short-term solutions that were labor-intensive and diverted resources away from screening activities," CDC said in the March 27, 1998, issue of Morbidity and Mortality Weekly Report.

"What we have today is an ad-hoc system that is incapable of serving the future needs of the program and the women it serves," said Gloria Rogers-Bruse, a Washington area member of NBCC, speaking at a press conference announcing the House bill. "While the majority of woman get care, there is no reliable system of care. As a result, some women experience unnecessary delays, or are lost to follow-up care, and a few don't get treated at all."

Last year, Congress expanded the screening program to include coverage for diagnostic services, but treatment remains outside the boundaries of the program.

During the current session, the CDC bill is supported by the American Cancer Society, the NAACP, the National Coalition for Cancer Survivorship, YWCA, Y-ME, National Women's Health Network, Arm in Arm Oncology Nursing Society, American Association of Public Hospitals and Health Systems, National Partnership for Women and Families, the Association of Women's Health, Obstetric, and Neonatal Nurses, and the Rhode Island Breast Cancer Coalition.

Another breast cancer group, the Susan G. Komen Foundation, is evaluating the bill, said Diane Balma, senior counsel. "We are in the process of evaluating the legislation, and are considering all the options," Balma said to **The Cancer Letter**.

Clinical Trials:

Data Falsified In Two Studies; NCI Says Results Not Affected

The HHS Office of Research Integrity said it has found that a former data manager for Rush-Presbyterian-St. Luke's Medical Center committed scientific misconduct by falsifying research data collected at the center on several participants in two NCI-funded studies.

The ORI notice published in the Federal Register March 25 identified the data manager as Maria Diaz. Diaz is the second data manager from Rush-Presbyterian to have been cited for scientific misconduct related to NCI studies this year. The first, Thomas Philpot, was cited last month for having falsified entry data for three patients on studies conducted by the National Surgical Adjuvant Breast and Bowel Project (**The Cancer Letter**, Feb. 12).

An NCI official said the falsifications made by Diaz would not affect the results of the trials.

Based on a 1998 report by the Rush-Presbyterian Research Integrity Investigation Committee and additional information obtained by ORI during its review, ORI said it found that Diaz "intentionally fabricated and/or falsified research data and information collected at RPMC" for the Breast Cancer Prevention Trial and the Lung Cancer Prevention Trial.

"This problem was confined to one of the hundreds of institutions that participated in these trials and this misconduct does not affect the results of either of these studies," Leslie Ford, associate director for clinical research in the NCI Division of Cancer Prevention, said in a March 25 statement.

"Results from the lung cancer prevention trial have not yet been reported and the database that will

be analyzed has been corrected for the two of the 1,486 participants who were affected," Ford said. "Similarly, this falsification of data for three of the 13,388 participants in the BCPT does not change the results reported in September 1998."

The Lung Cancer Prevention Trial, also called Intergroup trial 0125, was a phase III double-blind randomized trial of 13-cis-retinoic acid vs. placebo to prevent second primary tumors in patients with totally resected stage I non-small cell lung cancer. The trial, led by M.D. Anderson Cancer Center and the Eastern Cooperative Oncology Group, included 1,486 registered and 1,267 randomized participants at 259 institutions. Participants were accrued between December 1992 and April 1997.

The Breast Cancer Prevention Trial (NSABP P-1) was a randomized, placebo-controlled phase III trial to determine the worth of tamoxifen for preventing breast cancer in women at increased risk. The trial included 13,388 participants at 345 institutions. Accrual took place between June 1992 and September 1997.

In a statement, NCI listed the instances of Diaz's falsifications or fabrications:

—Data were fabricated or falsified for two participants and a physician's signature was forged on informed consent documents for two participants in the lung cancer trial.

—False information was provided on several reports about a participant in the lung cancer trial who died from a recurrence before she started taking the study drug. "The participant was reported as alive, compliant with the protocol (taking the drug), and having no evidence of disease," the NCI statement said.

—A pill diary was falsified for another participant and physician signatures were falsified for this participant and another participant in the lung cancer trial.

—Data were falsified or fabricated for three participants and a physician's signature was forged on a follow-up informed consent amendment document for 12 participants in the BCPT.

—Laboratory reports were falsified for two BCPT participants and documentation of follow-up breast and gynecologic exams were falsified or fabricated for a third participant.

M.D. Anderson notified NCI of a "potential misconduct problem" in April 1997, and NCI notified ORI, the NCI statement said. In May 1997, NCI audited all data that Diaz handled from the LCPT and the BCPT.

Rush-Prebyterian conducted an internal investigation. Based on NCI's investigation, Rush-Presbyterian was suspended from entering additional participants on the BCPT. The lung cancer trial had already closed.

ORI has instituted administrative actions which limit the data manager's participation in research funded by the Public Health Service for three years.

Science Policy:

NCI, DOD Begin Pilot Project For Coding Of Cancer Grants

NCI and the Department of Defense Office of Congressionally Directed Medical Research Programs, of the U.S. Army Medical Research and Materiel Command, said they have begun a pilot program to test a common scientific outline for evaluating each agency's cancer research portfolio.

The outline, developed by NCI, will provide the agencies with a common method for coding cancer research projects.

The outline is the product of NCI's Prostate and Breast Cancer Progress Review Groups and its Prostate and Breast Cancer Task Forces.

In the pilot testing, the Army programs will compare self-coding of research grants from submitting investigators to coding by staff and peer reviewers. This will be followed by full evaluation of the overall portfolios of the Army programs.

Information about the DOD research programs can be found at http://cdmrp.army.mil

Funding Opportunities:

Administrative Supplements For Mouse Models Of Cancer

Submission Deadlines: April 15, June 1

NCI announces the availability of administrative supplements to NCI-funded research project (R01), FIRST Award (R29), cooperative agreement (U01), and program project (P01) grants to assist with unanticipated costs associated with the development and validation of mouse models of human cancer. In addition, NCI-funded investigators whose research involves investigations of mouse models and who require supplemental support to take advantage of new opportunities afforded by these cancer models may submit a request detailing the basis for the needed supplement. To support this activity, the NCI has set aside funds for administrative supplements in the area of research on mouse models of human cancer.

Any inadequate support or unanticipated costs in this broadly defined area may be the basis for a supplement request under this program.

Requests must meet the criteria required for all administrative supplements: (1) the supplement funding may not exceed the project period for the grant; and, (2) the work proposed must be within the scope of the research originally approved.

Because funds are limited, the NCI will give highest priority to administrative supplement requests that meet the following criteria:

1. The grantee has substantial evidence that an existing model may be a good preclinical model for human cancer.

—Funds are needed to develop or refine the model further through additional studies, such as detailed molecular or genetic characterization, or in-depth pathobiology.

—Funds are needed for pilot experiments to determine a model's suitability for testing therapy or prevention modalities.

2. Studies to develop or refine or validate existing mouse models that may be useful as preclinical models for cancer will take priority over plans to derive new models for this purpose, because the latter experiments will likely exceed the limited scope of an administrative supplement.

3. Grantees may request 1 to 4 years of support; however, the funding request may generally not exceed $50,000/year of direct costs, and the requested budget must be appropriately justified.

4. Requests should contain enough detail to allow the NCI to judge the merit of the research opportunity and the need for additional funds. All requests require an itemized budget and must be countersigned by the grantee institution business office.

A request for an administrative supplement under this program should be sent directly to the NCI program director responsible for administration of the grant and identified on the latest Notice of Grant Award. Grantees are strongly encouraged to discuss with their NCI program directors the specific reasons for their supplements before submission. The requests will be first evaluated by the program director for the grant, then by an internal NCI review committee of extramural program staff. NCI expects to make decisions about these supplements within about 60 days of the submission deadlines.

Inquiries: Cheryl L. Marks, Ph.D., Division of Cancer Biology, NCI, Executive Plaza North Room 501, Bethesda, MD 20892-7381, phone 301-435-5226, fax 301-496-8656, email: cm74v@nih.gov

NCI Request For Applications

RFA CA-99-003: Special Populations Networks For Cancer Awareness Research And Training

Letter of Intent Receipt Date: June 11

Application Receipt Date: July 16

The NCI Office of Special Populations Research invites applications for cooperative agreement awards from eligible institutions to develop and implement a variety of community-based cancer control and prevention activities. The goal is to establish a robust and sustainable infrastructure to promote cancer awareness within minority and medically underserved communities, and to launch from these more research and cancer control activities aimed at specific population subgroups. Examples of cancer awareness activities appropriate for this project include health fairs, lectures to community groups, healthy cooking workshops, campaigns to encourage cancer screening, and the establishment of survivor support groups. Other key activities involve facilitating collaborative interactions among academic institutions with substantial minority student enrollments, cancer research centers, clinical cooperative groups, and NCI funded independent researchers.

An information session for investigators planning to submit applications to this RFA will be held April 12, noon-4 pm in Room 6C6, NIH Building 31, Bethesda, MD. Transcripts will be available upon request for investigators who are unable to attend. Contact the NCI program staff member listed under Inquiries by April 5 to confirm attendance.

Approximately $6 million will be available per year for five years to fund several large, multi-site projects at approximately $1.4 million total costs each (direct and indirect), and a series of small, single-site projects at up to $350 thousand total costs each. The anticipated award date is March 1, 2000.

Inquiries: Frank Jackson, Office of Special Populations Research, NCI, Executive Plaza South Room 320, Bethesda, MD 20892, phone 301-496-8589, fax 301-435-9225, email: fj12i@nih.gov

Program Announcement

PA PAR-99-077: Clinical Oncology Research Career Development Program

Letter of Intent Receipt Date: Sept. 7, 1999, May 1, 2000, May 1, 2001

Application Receipt Date: Oct. 1, 1999; June 1, 2000; June 1, 2001

The purpose of the NCI Clinical Oncology Career Development Program is to increase the number of medical doctors (MDs, DOs) and doctorally degreed Oncology registered nurses who are motivated and properly prepared to: (1) communicate and coordinate clinical research activities with basic/behavioral research scientists in order to expedite the translation of basic/ behavioral research information into patient-oriented research; (2) perform independent clinical research that develops and tests rational scientific hypotheses based on fundamental and clinical research findings for improving the medical care of cancer patients; and (3) design and test innovative clinical protocols and manage all phases of clinical trial

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research. Awards are made to institutions for up to five years for the development and implementation of training programs providing clinicians with all of the information and training needed to design, implement and manage all phases of cancer clinical trials research. Clinicians would be appointed to the training program, and would likely have more than one mentor. Support will be through the NIH Mentored Clinical Scientist Development Program (K12) mechanism.

Inquiries: Dr. Lester S. Gorelic, Training and Resources Program, NCI, 6130 Executive Blvd MSC 7390, Bethesda, MD 20892-7390, phone 301-496-8580, fax 301-402-4472, email: lg2h@nih.gov

In Brief:

Attention! It's *Admiral* Rick; Klausner Gets PHS Promotion

(Continued from page 1)

molecule of heredity but also can function as a biocatalyst," according to the Royal Swedish Academy of Sciences. Cech is a member of the National Academy of Sciences and the American Academy of Arts and Sciences. He has received numerous prizes and awards, including the Lasker Award and the National Medal of Science. With an endowment currently valued at $11.4 billion, HHMI is among the largest philanthropies in the world. Its operating budget this year is $556 million, including $424 million for its scientific program and $99 million for grants. . . . **NCI DIRECTOR RICHARD KLAUSNER** has been promoted in the Commissioned Corps of the Public Health Service to the rank of Assistant Surgeon General, **The Cancer Letter** has learned. Assistant Surgeon General is equivalent to the Navy rank of Rear Admiral, lower half. Traditionally, the Navy ranks are used when referring orally to PHS officers, according to the Corps. Other NCI officials who previously achieved the rank of Rear Admiral include NCI Deputy Director **Alan Rabson**, Division of Epidemiology and Genetics Director **Joseph Fraumeni**, and Division of Cancer Prevention Director **Peter Greenwald**. There are about 6,100 commissioned corps officers in the PHS (http://www.os.dhhs.gov/phs/corps/). Klausner also recently received the Herbert J. Block Memorial Lectureship for Distinguished Achievement in Cancer, from the James Cancer Hospital and Solove Research Institute at Ohio State University. Klausner's March 18 lecture was titled, "Hereditary Cancer Syndromes: Kidney Cancer as a Case Study." . . . **PROMOTIONS** at M.D. Anderson Cancer Center: **David Callender** was named senior vice president and chief medical officer, **Margaret Kripke** was named senior vice president and chief academic officer, and **Janet Bruner** was appointed chairman of the Department of Pathology and deputy head of the Division of Pathology and Laboratory Medicine. Callender and Kripke join the center's seven-member Management Committee. Callender, who joined the M.D. Anderson faculty in 1990, serves as the physician partner with the center's executive vice president and chief operating officer, Kevin Wardell, to oversee patient care. Clinical and basic science divisions and departments will report to Kripke on research and education, and she will oversee appointments, reviews, and promotions of all faculty. Kripke joined the center's faculty in 1983 and holds the Vivian L. Smith Chair in Immunology. Bruner is the first woman to be appointed a clinical department chairman and full-time deputy division head at M.D. Anderson. She joined the faculty in 1984 and is a professor of neuro-oncology as well as pathology. Bruner also leads the laboratory core for the Brain Tumor Center program project grant investigating molecular genetics of gliomas. . . . **MERRILL EGORIN** was appointed professor of medicine and pharmacology at University of Pittsburgh School of Medicine. He will lead the University of Pittsburgh Cancer Institute's work in anticancer drug development and evaluation, according to UPCI Director **Ronald Herberman**. Egorin was professor of medicine, pharmacology, and experimental therapeutics and oncology at University of Maryland School of Medicine in Baltimore. He remains an adjunct professor of medicine there. . . . **DAVID CHANG** won a Presidential Early Career Award for Scientists and Engineers, a federal award for professionals at the beginning of their independent research careers. Chang is an assistant professor of medicine and microbiology, immunology and molecular genetics at University of California, Los Angeles, School of Medicine. The award includes a $972,000 five-year grant from NIH to investigate metastasis. . . . **SUSUMU OHNO** received the first Royal Danish Association of Science Research Prize for his research in genetics. The prize of $100,000 was presented by Queen Margrethe of Denmark. Ohno retired in 1996 from City of Hope National Medical Center and Beckman Research Institute after a 40-year career. . . . **J. DOUGLAS RIZZO** was appointed assistant professor of medicine in the division of hematology/oncology and assistant

scientific director of the Statistical Center of the International Bone Marrow Transplant and the Autologous Blood & Marrow Transplant Registries at Medical College of Wisconsin. He was senior clinical fellow in oncology and hematology at Johns Hopkins University School of Medicine. . . . **UNIVERSITY OF WISCONSIN** Medical School's Center for Tobacco Research and Intervention will lead a project to update the Smoking Cessation Clinical Practice Guideline released April 1996 by HHS. **Michael Fiore** will serve as chairman of a panel of about two dozen experts involved in the preparation of the original guideline. The project is expected to be completed late this year.

Professional Societies:

AACR Awards Honor Eight Cancer Scientists, Clinicians

The American Association for Cancer Research will honor eight cancer investigators with its annual research awards and lectureships at the association's 90th annual meeting in Philadelphia April 10-14.

The 1999 Clowes Award will be presented to Mina Bissell, director of the Life Sciences Division of the Lawrence Berkeley National Laboratory at the University of California. Bissell is being honored for her demonstration that the extracellular matrix in breast tissue is a complex system of interacting control signals that determine whether the cells grow, die, remain normal, or become malignant.

The AACR-Pezcoller International Award for Cancer Research will be awarded to Carlo Croce, director of the Kimmel Cancer Center and professor and chairman of the Department of Microbiology and Immunology, Jefferson Medical College of Thomas Jefferson University. Croce is being recognized for revolutionizing the understanding of cancer genetics.

Dennis Slamon, director of the Revlon/UCLA Women's Cancer Research Program at UCLA's Jonsson Cancer Center, will receive the Richard and Hinda Rosenthal Foundation Award for his research establishing the relationship of the HER-2/neu gene to the prognosis for patients with an aggressive form of breast cancer.

The Cornelius P. Rhoads Memorial Award will be presented to John Kuriyan, investigator at Howard Hughes Medical Institute and Patrick E. and Beatrice M. Haggerty Professor at Rockefeller University. Kuriyan is being honored for his pioneering biophysical studies into the structure and interactions of critical genes and control factors.

The Bruce F. Cain Memorial Award will be awarded to J. Martin Brown, professor and director of the Division of Radiation Biology and director of the Program in Cancer Biology at Stanford University. The award honors Brown for developing and applying the concept that it is possible to exploit the fluctuations in oxygenation in a tumor due to variations in blood flow.

The AACR American Cancer Society Award for research excellence in cancer epidemiology and prevention will be presented to Alice Whittemore, professor and chief of the Division of Epidemiology at the Northern California Cancer Center at Stanford University, for her contributions to the field of cancer epidemiology. Specifically, she developed and applied improved statistical methods to handle multiple sets of data that are essential for the design and conduct of definitive epidemiological studies involving hereditary predisposition and modifiable lifestyle characteristics.

The Joseph H. Burchenal AACR Clinical Research Award will be presented John Mendelsohn, president and professor of medicine at University of Texas M.D. Anderson Cancer Center, for an extraordinary list of accomplishments that range from fundamental contributions in basic and translational cancer research to building and fostering some of the strongest clinical cancer research programs in the U.S.

The DeWitt S. Goodman Lecture will be awarded to Bandaru Reddy, chief, Division of Nutritional Carcinogenesis at the American Health Foundation, and research professor of microbiology at New York Medical College. Reddy is honored for his contributions to the understanding of the role of nutrition and other protective factors in relation to colon cancer.

Meet Us In Philadelphia

The Cancer Letter editors Kirsten Boyd Goldberg and Paul Goldberg invite readers attending the American Association for Cancer Research annual meeting April 10-14 in Philadelphia to stop by our display in the exhibit hall (booth #1025) of the Pennsylvania Convention Center. Share your latest news with us, pick up copies of the newsletter to pass along to colleagues, and view a demonstration of our new e-mail edition, **The Cancer Letter Interactive**.

THE CANCER LETTER

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Business & Regulatory Report

Formerly "Cancer Economics"

Clinical Trials:

NCI Selects Wisconsin, M.D. Anderson To Conduct Phase I Trials Of Endostatin

NCI has selected the University of Wisconsin, Madison, and the University of Texas M. D. Anderson Cancer Center to conduct initial clinical trials of the anti-angiogenesis drug endostatin.

Both sites will conduct a phase I trial of approximately 15 to 25 patients each, expected to begin later this year, NCI said in a March 24 statement. The studies will involve people with advanced solid tumors that include, but which are not limited to, lung cancer, lymphoma, breast cancer, colon cancer, and prostate cancer.

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Oncology Management:

ASCO Testifies For Medicare Coverage Of Patient Care Costs In Clinical Trials

American Society of Clinical Oncology President Allen Lichter said Medicare has "no basis for Medicare to refuse coverage of patient care costs for cancer clinical trials."

Lichter was a witness at a public forum sponsored by the Institute of Medicine.

The forum, titled "Reimbursement of Routine Patient Care Costs for Medicare Patients Enrolled in Clinical Trials," was organized to receive public input on what criteria the Health Care Financing Administration should use to determine which clinical trials should be covered by Medicare.

"Medicare is not being asked to pay any pure research costs—only those that it is legally obliged to cover," Lichter said. "Medicare beneficiaries who have paid premiums and taxes should be entitled to expect coverage of their hospital and physician costs and routine diagnostic tests that would be administered regardless of whether the patient was enrolled in a trial."

The Clinton Administration recently announced its support of Medicare coverage for trials approved by the National Institutes of Health, and a bipartisan legislative initiative led by Senators Jay Rockefeller and Connie Mack would guarantee Medicare coverage of federally-approved cancer clinical trials. It would also cover trials sponsored by non-governmental research entities who meet peer-review standards set by the National Institutes of Health.

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Endostatin Phase I Trials To Begin Later This Year

(Continued from page 1)

The NCI-sponsored studies will be designed to evaluate the safety of endostatin alone. Initial drafts of the protocols for these clinical trials will not be finalized for several weeks, NCI said.

For information on participation in the studies, contact: University of Wisconsin Cancer Connect Line, 800-622-8922 or 608-262-5223; or M.D. Anderson Information Line, 800-392-1611, select option 3.

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Celgene Corp. (Nasdaq: CELG)of Warren, NJ, announced the initiation of a phase II pilot trial by NCI to administer Thalomid (thalidomide) to patients with recurrent and metastatic squamous cell carcinoma of the head and neck.

The trial is sponsored by the NCI Cancer Therapy Evaluation Program, and will be conducted at M. D. Anderson Cancer Center under a Clinical Trials Agreement between the NCI and Celgene, the company said. Researchers will collect primary data on evidence of disease stabilization and response in approximately 35 patients, the company said.

Celgene also said NCI has initiated a pilot trial of Thalomid in patients with advanced non-small cell lung cancer.

The trial will evaluate Thalomid in concurrent therapy with paclitaxel and carboplatin, the company said.

The trial will be conducted at the University of Wisconsin Comprehensive Cancer Center under a Clinical Trials Agreement between the NCI and Celgene.

Investigators will collect data on toxicity and tolerability of the regimens in 10 patients. In addition, researchers will assess the patients for objective response, disease stabilization, time-to-disease progression and overall survival, the company said.

Celgene received FDA clearance to market Thalomid for erythema nodosum leprosum in leprosy, on July 16, 1998. The drug has been commercially available since October 1, 1998. In December 1998, Celgene licensed from EntreMed Inc. (Nasdaq: ENMD) the rights to thalidomide as an antiangiogenic agent.

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Genzyme Molecular Oncology (Nasdaq: GZMO) of Framingham, MA, said it has initiated a phase I/II trial of a vaccine for melanoma. The vaccine utilizes dendritic cells and combines two of the most widely expressed melanoma tumor antigens, MelanA/MART1 and gp100, the company said.

Approximately 24 patients with stage IV melanoma will be enrolled in the study. It is anticipated that the study will be completed in 2000. Frank Haluskaat, of the Massachusetts General Hospital Cancer Center, is the lead investigator for the trial.

The trial will evaluate the combination of two tumor antigens to increase the potency of the vaccine, the company said. The vaccine will also capitalize on the immune stimulating abilities of dendritic cells by specifically targeting the vaccine to those cells.

Since the vaccine is gene-based, as opposed to the protein or peptide vaccines used in many previous tumor vaccine trials, there will be a more prolonged presentation of the antigens to T-cells, the company said. This allows the T-cells to make a more powerful attack on the tumor cells. The immune response may also be sustained for a longer period of time because the vaccine contains the whole genes for the tumor antigens. Some patients will also receive low dose IL-2.

Genzyme Molecular Oncology has completed two phase I cancer vaccine trials in melanoma, the company said. According to the company, the studies demonstrated that treatment with either the MelanA/Mart1 or the gp100 antigen was safe and well-tolerated, the company said. In addition, a number of

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patients showed significant tumor regression.

In the phase I/II trial, patients will be treated with both the MelanA/Mart1 and gp100 antigens. Genzyme Molecular Oncology said it plans to initiate additional vaccine trials in breast cancer and ovarian cancer later this year.

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ImClone Systems Inc. (Nasdaq: IMCL) of New York said the company will receive a $5 million milestone payment from **Merck KGaA** (DAX: MERCK) of Darmstadt, Germany, its partner in the development of C225.

The milestone payment is based on FDA permission for ImClone to initiate a phase III of advanced squamous cell head and neck cancer using C225, a monoclonal antibody which inhibits activity of epidermal growth factor receptor associated with cancer cell growth in a number of solid tumors, the company said.

The phase III trial will enroll 416 advanced squamous cell head and neck cancer patients in over 25 clinical sites in the US and Europe, the company said.

In a randomized double-arm, phase III trial, patients with locally advanced head and neck cancer will be treated with radiation therapy alone or radiation therapy plus weekly infusions of C225. The primary endpoint of the trial will be the ability to control locoregional disease.

In a phase Ib/IIa study of C225 in combination with radiotherapy, 13 of 15 treated head and neck cancer patients experienced 100 percent tumor regression, the company said. Two additional patients experienced greater than 50 percent tumor regression.

In December 1998, Merck KGaA and ImClone initiated a collaboration under which Merck KGaA received the exclusive license to develop and commercialize C225 outside North America. ImClone retained North American rights. The companies will co-develop the product in Japan.

The collaboration agreement also established that ImClone would receive up-front fees, early cash-based milestones, late-stage equity-based milestones, and a $30 million credit line for the build-out of a manufacturing facility by ImClone for the commercial production of C225.

ImClone's other late stage clinical development program is an anti-cancer vaccine, BEC2, also partnered with Merck KGaA in limited disease small cell lung cancer patients. ImClone and Merck KGaA initiated a phase III multinational trial in December 1997 to study BEC2. In addition, in preclinical research, the company is evaluating the therapeutic potential of its anti FLK-1/KDR monoclonal antibody as an anti-angiogenic agent against tumors known to secrete vascular endothelial growth factor.

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Transgene (Nasdaq: TRGNY) (Nouveau Marche: TRANSGENE) of Strasbourg, France, announced the initiation of a second phase II trial of its Vero-IL2 product in Freiburg, Germany, in the laboratory of Professor Mertelsmann, with the enrollment of the first two patients.

The study will include 20 patients with malignant mesothelioma, a form of lung cancer arising in the pleura (lining) of the lung.

Transgene's Vero-IL2 product is an immortal cell line genetically modified to produce interleukine-2, a natural cytokine that helps to stimulate the body's immune system. Earlier studies in cats and dogs showed Vero-IL2 to be beneficial in the treatment of spontaneously occurring tumors.

More recently, two phase I clinical trials completed in France and Switzerland have suggested some anti-tumor activity and demonstrated preliminary evidence of safety and tolerance to this therapy. In addition, the first phase II trial with this product began in spring 1998 in patients with malignant melanoma, the most aggressive form of skin cancer.

Transgene's objective is to use its Vero-IL2 or a second vector, Adenovirus-IL2, to encourage the human immune response to reject cancer cells, thus providing the potential for a less toxic alternative to current chemotherapy and radiation treatments of advanced cancer.

Another direction in Transgene's anti-cancer program is continuing efforts for the development of anti-cancer vaccines, where tumor specific antigens are produced by vaccinia viruses in an effort to boost the body's immune response.

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Medarex (Nasdaq: MEDX) of Annandale, NJ, and **BankInvest Biomedical Development Venture Fund** of Copenhagen said they have formed a new Danish company to develop and commercialize a portfolio of fully human antibodies derived from Medarex's HuMAb-Mouse technology.

The new company, Genmab, has received initial funding of DKK 35,420,000, approximately $5.5 million with BankInvest VF as lead investor with A/S Dansk Erhvervsinvestering and others, as co-

investors. Genmab will be jointly owned by Medarex and these investors.

Genmab will conduct clinical trials of human antibody products. Genmab will also have the opportunity to contract with Medarex for product development resources, including its manufacturing and antibody development expertise. Genmab will focus primarily on developing several products to treat inflammatory conditions, such as rheumatoid arthritis and psoriasis, and has received a license to certain of Medarex's rights to MDX-CD4, a fully human antibody in phase I/II trials for rheumatoid arthritis.

BankInvest, founded in 1969, is headquartered in Copenhagen, and currently has $2 billion under management in a variety of mutual funds. BankInvest is a leading European biotechnology investor and currently manages approximately $200 million in two biotechnology funds. The BankInvest Biotechnology Mutual Fund holds positions in publicly traded companies worldwide. The BankInvest Biomedical Development Venture Fund, which invests in biotechnology start-up companies, has invested in seven ventures to date.

A/S Dansk Erhvervsinvestering is a Danish venture capital firm, founded in 1984, to inject capital into Danish companies, with the goal of supporting the growth and development of the Danish economy in the areas of job growth, productions, and exports. The firm currently has DKK 325,000,000, approximately $50 million, under management and a portfolio that consists of 23 companies. The firm invests in established companies, as well as start-ups, with an emphasis on biotechnology and information technology.

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Resolution Pharmaceuticals Inc. of Mississauga, ON, announced that it is initiating a phase I/II clinical trial of RP527, an imaging product.

The trial, which is designed to determine the safety, dosimetry and preliminary efficacy of the product, will be conducted in patients with prostate, small cell lung cancer and suspicion of breast cancer. The trial will be conducted in several sites in Europe and will start later this month.

RP527, which was developed in conjunction with the University of Missouri, is a technetium labeled radiopharmaceutical, designed to target tumors expressing the gastrin releasing peptide (GRP) receptor.

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MethylGene Inc. of Montreal said it has begun phase I trials of MG98, a second generation antisense oligonucleotide which inhibits messenger ribonucleic acid (mRNA) produced by the DNA methyltransferase gene.

The trials will be conducted in collaboration with the Clinical Trials Group of the National Cancer Institute of Canada. According to the company, four cancer centers will participate in the studies: Johns Hopkins Oncology Center; Ottawa Regional Cancer Centre; Princess Margaret Hospital, Toronto; and the British Columbia Cancer Agency, Vancouver.

MG98, a second generation antisense oligonucleotide, is composed of synthetic DNA which is chemically capped on each end of the molecule.

Patents:

Patents For Collagen Gel Process, Equipment Awarded

Matrix Pharmaceutical Inc. (NNM:MATX) of Freemont, CA, said it has obtained two patents for the processes and equipment for manufacturing collagen gels, key components of the company's injectable gel drug delivery systems.

The company said the technology is employed in the manufacture of IntraDose (cisplatin/epinephrine) Injectable Gel and MPI 5020 Radiopotentiator, a collagen-based product candidates currently in clinical development.

U.S. Patent No. 5,874,006 covers a new method for concentrating dilute collagen dispersions into more viscous preparations using vortex-flow microfiltration. U.S. Patent No. 5,875,620 covers improvements to the equipment used for this process.

IntraDose, Matrix's lead product candidate, is a collagen-containing gel that combines the widely used anticancer drug cisplatin with epinephrine. IntraDose is injected directly into tumors, where it provides and retains high concentrations of drug.

IntraDose is in phase III trials for head and neck cancer and in phase II studies in primary and metastatic liver cancer. MPI 5020, a locally injected gel containing the anticancer agent fluorouracil, is designed to enhance the cytotoxic effects of radiation therapy.

MPI 5020 is in a phase I/II trial in recurrent and metastatic breast cancer. The company is also developing FMdC, a systemically-administered chemical entity currently under evaluation in a phase II trial in non-small cell lung cancer.

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Xechem International Inc. (OTC BB: ZKEM) of New Brunswick, NJ, said it has obtained U.S. Patent No. 5,854,278 containing broad coverage of several novel paclitaxel analogs.

The company said preliminary studies have shown strong anti-neoplastic efficacy of these compounds against a wide array of cancer tumor cells and leukemic cells rivaling.

The company said the analogs are produced by semisynthesis involving selective halogenation of paclitaxel's close analog cephalomannine, to produce dihaloisomers of cephalomannine including (2"R, 3"S) and (2"S, 3"R) dichlorocephalomannine, (2"R, 3"S) and (2"S, 3"R) dichloro 7-epi-cephalomannine.

In addition to the paclitaxel analogs, the patent contains claims which very broadly cover pharmaceutical formulations comprising these compounds, a method for administering the compounds for treating both animal and human tumors, and a method for production of the novel compounds.

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Cytoclonal Pharmaceutics Inc. (Nasdaq: CYPH, CYPH, CYPHZ) of Dallas announced the issuance of a broad patent (U.S. Patent # 5,861,302) for the production of paclitaxel, the active ingredient in Taxol, by microorganisms isolated from the Yew Tree.

The technology was developed by Gary Strobel of Montana State University and Andrea and Donald Stierle of Montana College of Science and Technology. In 1994, a patent was issued for the original fungal strain that produced paclitaxel. This new broad patent establishes a strong proprietary position for the technology.

Cytoclonal obtained exclusive rights to this technology and established a program with the Montana researchers to develop a cost-effective system to produce paclitaxel and related compounds using microbial fermentation, which is the basis for efficient production of many drugs, including antibiotics. Taxol is presently produced from components of the rare Yew Tree.

In 1998 Cytoclonal signed an agreement with Bristol-Myers Squibb (BMS) concerning production of paclitaxel, employing its microbial fermentation as well as paclitaxel-specific genes isolated by Rodney Croteau at Washington State University.

The agreement covers production of paclitaxel, Bacatin and other Taxanes that could be used for a second-generation version of paclitaxel and new cancer compounds from microorganisms furnished by Cytoclonal. In 1998 BMS generated $1.25 billion in sales of Taxol, which is approved for the treatment of breast, ovarian and lung cancers.

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Corixa Corp. (Nasdaq: CRXA) of Seattle said the US Patent and Trademark Office has issued to the University of Washington in Seattle a patent, which is licensed exclusively worldwide to Corixa, for treating disease where Her-2/neu is associated with the malignancy.

The patent covers methods for the ex vivo treatment of patients whose tumors express Her-2/neu.

Patent No. 5,876,712 covers therapy of patients bearing Her-2/neu positive tumors with patient T-cells that have been harvested and stimulated outside of the body with Her-2/neu protein. Corixa has previously sponsored clinical trials with Her-2/neu peptide vaccines and announced in October of 1998 the license of its these vaccines to SmithKline Beecham.

Corixa is providing microsphere-encapsulated Her-2/neu peptide vaccines for a phase I trial at the University of Washington. In the study, breast, ovarian, prostate and non-small cell lung cancer patients are receiving microsphere-encapsulated Her-2/neu peptide vaccine.

In another development, Corixa was issued three patents granting composition and method claims covering Corixa's proprietary vaccine adjuvant protein Leishmania elongation Initiation Factor, or LeIF. LeIF has been found to stimulate and enhance immune responses to antigens, including tumor antigens, in a variety of preclinical studies, the company said.

LeIF stimulates a protective Th1 immune response that may be useful in improving the efficacy of various prophylactic and therapeutic vaccines.

The patents issued cover the composition of matter of LeIF as a polypeptide and further provide patent coverage to portions of the LeIF molecule that are useful for stimulating immune responses.

The patents stem from Corixa experimentation conducted and directed by Steven Reed, executive vice president and chief scientific officer of Corixa. Patent No. 5,876,966 entitled "Compounds and Methods for the Stimulation and Enhancement of Protective Immune Responses and IL-12 Production" covers the LeIF protein encoded by specific gene sequences. Patents No. 5,876,735 and

5,879,687 both entitled "Methods for Enhancement of Protective Immune Responses," cover methods of enhancing or eliciting immune responses to antigens by using LeIF as a vaccine adjuvant. SmithKline Beecham has an option to license LeIF as an adjuvant for use in therapeutic vaccine products developed under its collaboration with Corixa.

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IVAX Corp. (Amex: IVX) of Miami said its Baker Norton Pharmaceuticals subsidiary has received a patent from the Commonwealth of Australia's Patent Office for an oral method of administering paclitaxel. The patent for oral administration of the drug is the company's first.

"The new technology utilized in this patent represents a breakthrough in the oral delivery of anti-cancer drugs," said Phillip Frost, IVAX chairman and CEO. The company's oral system for paclitaxel is currently undergoing human trials.

Last month, IVAX received a recommendation by the European Committee for Proprietary Medicinal Products for centralized approval in the 15 member-countries of the European Union of its proprietary drug, Paxene, an injectible form of paclitaxel. Additionally, IVAX has an ANDA pending in the U.S. for a generic form of Taxol.

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ImmunoGen Inc. (Nasdaq: IMGN), of Norwood, MA, said it has obtained U.S. Patent No. 5,846,545, covering a new form of its novel tumor-activated prodrugs for treating cancer. TAPs combine cancer-specific monoclonal antibodies and cyclopropylbenzindole (DC1).

The company said animal studies have shown that the specificity of the monoclonal antibody component of ImmunoGen's TAPs results in the delivery of DC1 to tumor cells, sparing healthy tissue.

ImmunoGen said it is developing two TAPs using the cytotoxic compound, DM1, a member of a family of chemotherapeutic agents called maytansinoids, which act by a mechanism similar to established chemotherapeutic drugs such as the Vinca alkaloids. The company is co-developing its lead TAP product, huC242-DM1 for colorectal cancer, with SmithKline Beecham.

FDA Approvals & Applications:

Theragyn Granted Orphan Drug Status For Ovarian Cancer

Antisoma plc (EASD: ASOM) of London said it has received notification from the FDA Office of Orphan Products Development that its lead product candidate, Theragyn, has been granted orphan drug designation in the US for adjuvant treatment of ovarian cancer.

The designation grants the sponsor a 7-year period of market exclusivity following approval of the drug.

Theragyn is in a phase III trial in North America, Europe and Australia. The study aims to enroll 300 patients to measure survival of ovarian cancer patients who receive Theragyn after standard treatment regimens. Theragyn entered a UK phase II study with gastric cancer patients at the end of February, the company said.

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Bigmar Inc. (Nasdaq SmallCap Market: BGMR) of Johnstown, OH, said it has received Abbreviated New Drug Application approval from FDA for Fluorouracil Injection, USP 50 mg/mL, a therapy for palliative management of carcinoma of the colon, rectum, breast, stomach and pancreas. The product will be co-marketed and distributed by IVAX Corp. in the U.S., the company said.

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Digene Corp. (Nasdaq: DIGE) of Beltsville, MD, said FDA has given marketing clearance for the Digene HPV Test, Hybrid Capture II, a DNA-based technology to detect the human papilloma virus.

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Chiroscience Group plc of London announced that it has received an Approvable Letter from FDA for Chirocaine, a long-acting local anesthetic. The company said it is in discussions with FDA regarding final printed labeling.

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Bigmar Inc. (Nasdaq SmallCap Market: BGMR/Boston Stock Exchange: BGM) of Johnstown, OH, announced that it has received its first Abbreviated New Drug Application approvals from FDA for the following products:

—Methotrexate for Injection USP, 1g/vial (lyophilized)

—Methotrexate Injection USP, 25 mg/mL, (Preserved)

—Methotrexate Injection USP, 25 mg/mL, (Preservative-free)

—Leucovorin Calcium for Injection USP, 200 mg/vial (lyophilized)

—Leucovorin Calcium for Injection USP, 500 mg/vial (lyophilized)

Deals & Collaborations:

EntreMed Arranges For Larger Production Of Angiostatin

EntreMed Inc. (Nasdaq: ENMD) of Rockville, MD, said it has signed a letter of intent with Covance Biotechnology Services Inc., of Research Triangle Park, NC, to provide large-scale Good Manufacturing Practices production of Angiostatin protein for further preclinical studies and early human clinical trials.

Since 1995, EntreMed has been engaged in the development of Angiostatin protein at its Rockville facility.

EntreMed's development of the Angiostatin protein have focused solely upon the production of the protein in the Pichia pastoris yeast expression system.

In 1998, EntreMed scientists produced over 50 biologically active lots of Angiostatin protein up to the 100-liter scale. Now, through the collaboration with Covance, GMP production of the protein is anticipated to advance to the 2,000-liter fermentation scale by mid-year.

"We anticipate that our relationship with Covance will enable the production of sufficient clinical grade Angiostatin to meet our aggressive development timetable," said Edward Gubish, EntreMed senior vice president, research and development.

EntreMed and Covance said they have have begun the work for the set-up and production of Angiostatin protein in the Pichia yeast expression system. In 1997, EntreMed first reported that Pichia-derived recombinant human Angiostatin protein inhibited primary and metastatic cancer in preclinical testing (Cancer Research 57, 1329-1334, April 1, 1997, Sim et al).

In 1998, EntreMed first reported on a newly defined version of Angiostatin that was smaller, less complex, and yet still conferred all of the potent tumor inhibitory activity of the larger molecule (Abstracts of the 89th Annual Meeting of the AACR, March 1998, Liang et al). It is that version of the molecule that is now being scaled-up for human testing.

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SkyePharma PLC (Nasdaq: SKYEY; LSE: SKP) of London announced the completion of its acquisition of **DepoTech Corp.** (Nasdaq: DEPO) of San Diego. DepoTech shareholders approved the acquisition at a shareholder meeting March 8, the cpmpany said.

DepoTech develops and manufactures injectable sustained-release therapeutic products based on the DepoFoam technology for cancer and pain management. In November 1998, FDA Oncologic Drugs Advisory Committee recommended that DepoTech receive an accelerated approval for its compound DepoCyt for neoplastic meningitis from lymphomas. The product is an injectable sustained release formulation of cytarabine.

In conjunction with the acquisition, SkyePharma stated that it would integrate the clinical development, finance and regulatory affairs functions of its U.S. subsidiary Brightstone into DepoTech, and discontinue its generic sales and marketing functions.

SkyePharma said it will seek potential collaborative partners with significant existing generic capabilities in the U.S. to sell and distribute the company's generic product portfolio.

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AutoCyte Inc. (Nasdaq: ACYT)of Burlington, NC, said it has executed a definitive agreement to acquire the entire intellectual property estate of **Neuromedical Systems Inc.** (Nasdaq: NSIX) of Wilmington, DE.

Concurrently with the transaction, Neuromedical Systems filed a Chapter 11 petition in the U.S. Bankruptcy Court for the District of Delaware. If the agreement is approved by the court after a hearing that allows for competitive bids, AutoCyte will acquire the assets for $4.0 million in cash and the issuance of 1.4 million common shares of stock, the companies said.

Neuromedical Systems develops interactive, neural net technology for the computer screening of conventional Pap smears. The company's first product, the PapNet Testing System, increases the accuracy of cervical screening by displaying potentially abnormal cells for review and analysis by a cytology professional, the company said.

AutoCyte develops, manufactures and markets an integrated, automated sample preparation and image analysis system which supports cytotechnologists and pathologists in cervical cancer screening. The company's integrated system is comprised of the AutoCyte Prep sample preparation system and the AutoCyte Screen computerized image analysis system. AutoCyte is pursuing regulatory approval of its products for sale in the United States and has begun sales in several foreign countries.

"Together, these technologies allow us to offer the entire range of interactive methods for cytology

screening, including interactive methods for primary and adjunctive screening of both conventional Pap smears and LBP's," said James Powell, AutoCyte president and CEO.

Neuromedical Systems said the sale and the filing were necessitated by the escalating losses, from $13.8 million in 1994 to $36.6 million 1997.

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Chiroscience Group plc said it has reached final agreement with **Zeneca Group PLC** for the return to Chiroscience of rights to the long-acting local anaesthetic, Chirocaine.

The agreement, which has been concluded as a direct consequence of Zeneca's proposed merger with Astra AB, has been approved by the U.S. Federal Trade Commission and follows the similar approval by the Commission of the European Union, the company said.

The deal relates to all territories, excluding Japan, where Chiroscience has licensed Chirocaine rights to Maruishi Pharmaceutical Co. Ltd. Under the agreement Zeneca will:

—Make a payment of 10 million punds to Chiroscience to compensate for the near-term impact on the commercialization of Chirocaine as a result of Zeneca ceasing to be the licensee.

—Provide transitional funding and resources to ensure the optimum continuation of the development of Chirocaine in all territories excluding Japan, pending agreement with a new marketing partner in such territories. This will be used for:

—pre- and post-marketing clinical studies;

—the filing of regulatory documentation;

—marketing support; and

—continuing the product development already underway to create a number of line extensions. Zeneca is obliged to fully fund the completion of these elements of Chirocaine's commercialization.

Chiroscience estimates that this will cost an additional 10 million pounds.

Under the FTC Consent Decree, Zeneca will be obliged to dispose of its its 3.53 million ordinary shares (3.12 % of all outstanding shares) in Chiroscience. Zeneca acquired its holding of in Chiroscience when the original Chirocaine licensing agreement between the two companies was signed in March 1998.

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Gilead Sciences Inc. (Nasdaq:GILD) and **NeXstar Pharmaceuticals Inc.** (Nasdaq:NXTR) announced a definitive agreement whereby Gilead will acquire NeXstar in an all-stock, tax-free pooling-of-interests transaction.

Under the agreement, NeXstar stockholders will receive 0.425 of a share of Gilead for each share of NeXstar, subject to adjustment based on the trading range of Gilead stock prior to completion of the merger.

"The combined company will have three commercial products with total annual revenue of over $100 million, a strong pipeline, and the international infrastructure to introduce a number of important near-term products," said John Martin, president and CEO of Gilead Sciences.

The three currently marketed products are AmBisome (liposomal amphotericin B), an injectable treatment for serious fungal infections; DaunoXome (daunorubicin citrate liposome injection), an anticancer agent approved for the treatment of AIDS related Kaposi's Sarcoma; and Vistide (cidofovir injection), an antiviral agent used to treat AIDS related cytomegalovirus. NeXstar's currently approved product, DaunoXome, is in development for the treatment of leukemia and lymphoma.

Oncology Management:

Quality Oncology To Provide Specialized Cancer Care In FL

(Continued from page 1)

and Blue Shield of Florida, said it is launching a cancer treatment program in eight South Florida counties.

The program, administered by **Quality Oncology**, an independent cancer disease management company based in Sunrise, FL, will provide more than 300,000 Health Options members in South Florida with access to specialized care for all forms of cancer, including breast, prostate, colon, lung and gynecological.

The program is voluntary with no additional cost to Health Options members. Benefits include continuity of care, fewer hospital admissions, reduction in the use of inappropriate chemotherapy, decreased emergency room visits, and enhanced provider communication and education.

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Response Oncology Inc. (Nasdaq:ROIX) of Memphis, TN, lost $17.4 million on revenues of $128.2 million for the year ended Dec. 31, the company said. Last year, the company's earnings were $4.2 million and revenues $101.9 million.

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