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Lilly Made False Claims About Raloxifene Reducing Breast Cancer Risk, Judge Rules

A federal judge found that Eli Lilly & Co. has systematically made false and misleading claims that its osteoporosis drug raloxifene has been proven to reduce the risk of breast cancer and is at least comparable to the AstraZeneca drug tamoxifen, the only drug approved for this indication.

In a July 15 ruling, Judge John Koeltl of the U.S. District Court for the Southern District of New York issued a preliminary injunction barring Lilly from making such claims.

The ruling also orders the pharmaceutical company to hold training

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In Brief:

Childhood Cancer Death Rates Decline, Incidence Stable, NCI Says In Report

CHILDHOOD CANCER statistical trends and risk factors are reported in a new NCI publication, "Cancer Incidence and Survival Among Children and Adolescents: United States SEER program 1975-1995." Since the 1970s, overall death rates for most childhood cancers have declined and survival rates have improved markedly, according to the monograph. Incidence rates for most types of childhood cancers, including brain cancer, have been stable since the mid-1980s. In 1998, an estimated 12,400 children under age 20 were diagnosed with cancer and 2,500 died. While cancer is the leading cause of death by disease among U.S. children, cancer remains rare in this age group, with an average of 150 out of 1 million children developing the disease annually. Cancer ranks fourth as a cause of death for children between ages 1 and 19 after injuries, homicides, and suicides. The monograph is available at http://www-seer.ims.nci.nih.gov. Print versions are expected to be available in November. . . . **MAYO CANCER CENTER** of Rochester, MN, has been designated an NCI comprehensive cancer center, and was awarded a renewal of its Cancer Center Support Grant. Mayo was one of the original centers that NCI designated "comprehensive" in 1973, but lost its status, moving back to the ranks of the clinical cancer centers. **Franklyn Prendergast** is the center director. . . . **VANDERBILT-INGRAM** Cancer Center has awarded the first Ingram Research Fellowships to eight current faculty members and two newly recruited faculty. The professorships are endowed at $1 million to $2 million, established through the fundraising campaign begun with a $56 million gift from the Ingram Charitable Fund. Current faculty members named Ingram Professors of Cancer Research: **Carlos Arteaga**, **David Carbone**, and **Robert Coffey**

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Zeneca Wins Suit Against Lilly Over Raloxifene Claims

(Continued from page 1)

sessions to educate the sales force about the clinical data on raloxifene and the meaning of its label.

"The evidence demonstrates that it is literally false for Eli Lilly to claim that raloxifene has been proven to reduce the risk of breast cancer or that raloxifene is comparable or superior to tamoxifen for that purpose," the ruling states.

The suit was filed by Zeneca Inc., of Wilmington, DE, the sponsor of tamoxifen, trade name Nolvadex, and Barr Laboratories Inc., a company that distributes generic tamoxifen under a license from Zeneca. Shortly after filing the suit, Zeneca merged with Astra and became AstraZeneca Inc. (**The Cancer Letter**, March 12).

The judge said the evidence did not support the plaintiffs' claim that Lilly sales force has been claiming falsely that raloxifene is approved for breast cancer risk reduction.

The judge didn't order Indianapolis-based Lilly to pay for corrective advertising, a remedy sought by the plaintiffs.

"The false information that Eli Lilly sales representatives have disseminated to physicians concerning raloxifene will be corrected by the revised detailing the sales representatives do after completing the training program," the ruling states.

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Founded Dec. 21, 1973 by Jerry D. Boyd

The 106-page ruling offers a detailed account of Lilly's unsuccessful efforts to convince FDA to broaden the labeled indications for raloxifene, trade name Evista, to include breast cancer data. Drawing on proprietary documents that were made public during litigation, the ruling traces the manner in which clinical information was communicated by Lilly sales representatives.

"Since at least October 1998, Eli Lilly representatives have been communicating to physicians that Evista has been proven to reduce the risk of breast cancer and that Evista is comparable or superior to tamoxifen in reducing the risk of breast cancer," the ruling states.

Lilly's marketing of raloxifene, trade name Evista, was based on data from the Multiple Outcomes of Raloxifene Evaluation trial and other studies that found a lower incidence of breast cancer on the raloxifene arm than on placebo. Breast cancer data from the MORE trial, which included 7,705 women and lasted three years, were published in the June 16 issue of the Journal of the American Medical Association.

However, the MORE protocol did not define breast cancer as a primary endpoint, didn't enroll women at high risk for the disease, and had short and inconsistent follow-up, FDA officials said repeatedly during two years of discussions with Lilly, the ruling states.

"The MORE data are insufficient to support [breast cancer risk reduction] claims," the ruling states.

The breast cancer risk reduction capabilities of raloxifene and tamoxifen are being compared side by side in the Study of Tamoxifen and Raloxifene, a trial being conducted by the National Surgical Breast & Bowel Project (**The Cancer Letter**, June 4).

By entering a preliminary injunction against Lilly, the judge ruled that, based on discovery and a five-day hearing, AstraZeneca and Barr would be likely to prevail in the litigation. The order against Lilly is intended to prevent further injury to the plaintiffs, and to protect the public, the judge said.

"Although off-label prescribing is not uncommon among physicians, it would be dangerous if physicians off-label prescribed Evista for breast cancer prevention, based on false information about whether Evista has been proven to reduce the risk of breast cancer," the ruling states. "It is important to the public interest and to the patients involved that truthful information be provided."

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FDA Said Breast Cancer Data Insufficient

For two years, Lilly sought to convince FDA that data from the MORE trial justified expanding the raloxifene label to include the breast cancer data, the ruling states.

"Based on its review, FDA has repeatedly determined… that the MORE study does not and cannot prove that Evista reduces the risk of breast cancer," the ruling states.

The company made its first effort to make breast cancer claims in August 1997, documents show. The FDA response to the company, dated Aug. 6, was unambiguous:

"The data provided appear to be grossly insufficient to support a claim that raloxifene reduces breast cancer risk… It is unlikely that more information will improve the acceptability of the methodology or the credibility of the data used by the sponsor to conclude that raloxifene reduces the risk of breast cancer."

Lilly persisted in its efforts to change the label to state that a statistically significant reduction in breast cancer was observed in the treatment arm of the MORE trial. In the fall of 1997, FDA reiterated its position: "Acceptance of this claim would effectively provide [Eli Lilly] with a second indication for raloxifene."

In subsequent discussions, the agency consistently reiterated its position, the ruling states. In a letter dated March 2, 1998, the agency said that any discussion of these data on the label would have to state that "the effectiveness of raloxifene in reducing breast cancer has not been established."

In December 1998, the agency allowed Lilly to alter the safety language to reflect the MORE data and the data from other trials to state that six cases of invasive breast cancer were reported among 7,017 women receiving raloxifene, compared to ten cases among 3,368 women receiving placebo.

However, these data were put in perspective in the language of the label. "The effectiveness of raloxifene in reducing the risk of breast cancer has not yet been established," the label states.

Twist MORE; Sell More

According to court documents, the claims of raloxifene's superiority figured prominently in the detailed scripts written to help Lilly sales force anticipate questions from physicians.

In the industry jargon, these scripts are known as "verbatims."

According to court documents, before November 1998, a Lilly verbatim on breast cancer coached company reps to say only that Evista "may also prevent breast cancer."

However, after Zeneca received FDA approval for the risk reduction indication for tamoxifen, Lilly revised its verbatims to make stronger claims, court documents say.

According to a later verbatim, physicians asking Lilly reps to compare the breast cancer risk reduction capabilities of raloxifene and tamoxifen, received the following earnest answer:

"Dr.___, Evista is not approved for the prevention of breast cancer. However, let me share with you these data we currently have with regard to Evista reducing the incidence of breast cancer.

"Dr. ____, These data come from about 13,000 women age 45-80, enrolled in our osteoporosis prevention and treatment studies. Women who have taken Evista for an average of 29 months had a greater than 50 percent reduction in the incidence of newly diagnosed breast cancers, compared with the placebo group.

"While we do not currently have head-to-head trials, these results are similar to those for tamoxifen in women at high risk of breast cancer."

Physicians who asked for a comparison of the two drugs received the following answer:

"Dr. ___, a very distinct difference between Evista and tamoxifen lies in the uterine safety profile. In women, tamoxifen increases endometrial thickness, and increases the risk of polyps, and endometrial cancer. In contrast, Evista does not increase endometrial thickness or increase the risk of endometrial cancer."

Last December, after FDA allowed Lilly to expand the label to include the breast cancer data pooled from MORE and other studies, the company reps were given the following verbatim: "As you can see, this reflects a greater than 50 percent reduction in newly diagnosed breast cancer, compared to placebo."

Another verbatim prepared sales reps for an encounter with a physician who has a sufficient working knowledge of the package insert to note that the document clearly states that raloxifene's effectiveness in breast cancer reduction remains unproven:

"This is somewhat standard language included by the FDA to ensure that physicians understand that

studies are ongoing, and Evista is not indicated for the prevention of breast cancer."

"With All Due Respect, Dr. Dejarnatte…"

"Call notes" written by Lilly reps after their conversations with physicians indicate that at least some reps went beyond the verbatims in their marketing of the drug.

Call notes, which are intended to prepare sales people for subsequent sales calls to the doctor, were quoted in court documents.

"Hit him with strong Evista message," one rep wrote after a meeting with a physician. "He asked if we have a cancer indication or a treatment indication… told him the indication [sic.] are coming it's just a matter of time… but the data is [sic.] there and is strong."

Another rep reflected on an encounter with a skeptic:

"He basically said he doesn't believe the claims Ev. has made… w/ cancer (breast cancer reductions)… need to be confident in standing up for Ev. and telling him these claims are proven not suspected."

Yet another rep offered a creative explanation of the discussion of breast cancer data on the Evista label:

"He said Evista will be huge once we can say for sure that it protects women against breast cancer. I said 'with all due respect, Dr. Dejarnatte, that's what the package insert now states with the change that took place in December."

Notes cited in court documents indicate that at least some of the Lilly reps were not willing to wait for STAR to establish a comparison of raloxifene and tamoxifen:

"Asked if [STAR] will show Evista is better than Tamox. Told him already better—No endo. cancer," wrote one rep.

Based on a rep's account, at least one physician was won over by the raloxifene message:

"Informed him about a 63% reduction of breast cancer among women who have high risk of breast cancer compared to [tamoxifen]. He was pretty pleased with that."

In its response to the ruling, Lilly said the call notes quoted in the ruling represent a "small fraction of overall call volume." Altogether, Lilly reps have made 1.6 million sales calls involving Evista, the company said.

"As part of its ongoing training program, Lilly will ensure that its promotional message for Evista and the breast cancer data are communicated appropriately," the company said in a statement.

What It Would Take To Prove The Claim

After the label change last December, Lilly tried to convince the FDA Oncology Division staff that the MORE data could support a supplemental New Drug Application for breast cancer risk reduction in postmenopausal women with osteoporosis, documents state.

Once again, the agency disagreed. After hearing from the agency, Lilly ended the MORE trial, and initiated another trial, the ruling states. Dubbed CORE, for Continuing Outcomes of Raloxifene, that trial would continue for at least four years and would enroll many MORE participants.

According to court documents, FDA officials reviewed the CORE protocol last April, concluding that the trial would be insufficient to prove the breast cancer risk reduction claim.

"Data from a prospective randomized trial of raloxifene in which the reduction in the incidence of breast cancer is the primary endpoint will be needed, such as data from the STAR trial," FDA officials wrote on April 16.

Ultimately, the agency said, answers could be provided by a combination of three company-sponsored trials: MORE, CORE, and a trial called RUTH, which seeks to measure the cardiovascular effects of raloxifene. However, to be useful in proving the breast cancer risk reduction indication, RUTH would have to be redesigned, FDA officials said, according to the ruling.

CORE and RUTH would take four to five years to complete, court documents say. STAR, the only trial capable of producing a direct comparison of raloxifene and tamoxifen, is similarly expected to continue for five years.

Limits On Free Speech?

Though the ruling is clearly damaging to Lilly, the company said it was "pleased" about the court finding no evidence to back Zeneca's claim that Lilly represented Evista as a drug approved for the reduction of breast cancer risk.

The company said it was similarly pleased by the court's decision to deny Zeneca's request for corrective advertising by Lilly.

"Lilly does disagree with the court's opinion in several respects," the company said in a statement.

"Although the court recognized the importance of sharing recently published Evista breast cancer data, the court's decision emphasizes the importance of qualifying the discussion of these data."

Stopping just short of claiming a potential infringement on free speech, the statement continues: "This decision could have broader implications for emerging data from ongoing studies. For this reason, Lilly is reviewing all legal options."

If indeed the statement offers a glimpse of Lilly's legal strategy, the company may be weighing raising free speech issues in the next phase of this battle.

While the limitation of what drug companies can claim about scientific data is a matter of controversy, it is unclear how the First Amendment would apply in this case, several legal experts said to **The Cancer Letter**.

Judge Koeltl's ruling focused on the interpretations of Lilly's claims within the framework of the Lanham Act, a law that applies to false and misleading interpretations in advertising and promotion.

"If false and misleading claims are found under the Lanham Act, any First Amendment claim is probably futile," said a Washington attorney who spoke on condition that his name would not be used.

At this writing, another federal judge, Royce Lamberth, of the U.S. District Court for the District of Columbia, is reviewing the free speech implications of the FDA Modernization Act.

In an earlier ruling, on July 30, 1998, Lamberth's stated that free speech protection does not apply to false and misleading claims (**The Cancer Letter**, Aug. 14, 1998).

"Nothing in this opinion limits the FDA's ability to strictly enforce any rule, regulation, or guidance that sanctions the dissemination of information that is actually false or misleads," Lamberth wrote in that ruling.

NCI Programs:

HMO Research Network Wins $16M For Prevention Studies

NCI has awarded a four-year, $16 million grant to a consortium of researchers based at health maintenance organizations to study ways to increase cancer prevention and control among HMO enrollees.

Ten non-profit managed care organizations that are members of the HMO Research Network will participate in the NCI-funded project, called the Cancer Research Network. The HMO Research Network was formed in 1996 to encourage and coordinate research activities among HMO-affiliated researchers.

"The collaborative spirit represented by the commitment of these HMOs exemplifies a new paradigm for cancer research that will pave the way for greater progress in preventing disease," said Barbara Rimer, director of the NCI Division of Cancer Control and Population Sciences.

The project will be based at Group Health Cooperative's Center for Health Studies in Seattle. Other participants of the network are Fallon Healthcare System, represented by the Meyers Primary Care Institute (Worcester, MA), Harvard-Pilgrim Health Care (Boston), HealthPartners Research Foundation (Minneapolis), Henry Ford Health System/Health Alliance Plan (Detroit), and five Kaiser Permanente divisions, in Hawaii (Honolulu), Northern California (Oakland), Northwest (Portland, OR), Rocky Mountain (Denver), and Southern California (Pasadena).

A goal of the project will be to identify the patient, treatment and delivery system factors that may make a difference in health outcomes for cancer. By combining the data capacities of these large integrated health systems, researchers will be able to study health care patterns among millions of patients who mirror the diversity of the nation in terms of age, gender, income, education, cultural background and location.

The network plans to develop research tools to promote future studies of effective cancer control interventions that span the natural history of major cancers among diverse populations in various health care systems. Standardized data collection instruments, surveys and analytical methods will foster uniform databases and other research materials that can be shared across network institutions.

The project will be directed by Edward Wagner, of Group Health Cooperative. Wagner serves as chairman of the network's Steering Committee, which is comprised of the co-principal investigators from each of the participating organizations, and the NCI program director, Martin Brown, of the Applied Research Branch. An external advisory committee of collaborators from 10 academic institutions will review and advise the network.

"The network will put together the large populations, excellent researchers and superb data capabilities of these organizations to provide a rich

resource for studying important questions in the prevention and care of cancer," Wagner said.

The Data Coordinating Center is headed by Mark Hornbrook, of Kaiser Permanente Northwest.

The network plans to begin three research projects:

—Effectiveness of smoking cessation activities in HMOs, led by Victor Stevens, at Kaiser Permanente Northwest.

—Occurrence of late-stage breast and cervical cancer and factors that help prevent advanced disease, led by Stephen Taplin, of Group Health Cooperative.

—Efficacy of preventive strategies, such as mammography and prophylactic mastectomy, for women with a personal or family history of breast cancer, led by Suzanne Fletcher, of Harvard Pilgrim Health Care.

Researcher Made False Claims About EMF Effect On Cells

The HHS Office of Research Integrity has found that a researcher at the Lawrence Berkeley National Laboratory engaged in scientific misconduct by intentionally falsifying and fabricating data and claims about the purported cellular effects of electric and magnetic fields that were reported in two scientific papers.

Robert Liburdy, a former staff biochemist at the laboratory, agreed to submit letters to two journals retracting the claims, and is excluded from receiving federal grants and contracts for three years.

The research was supported by a grant from NCI.

The papers by Liburdy were: "Biological interactions of cellular systems with time-varying magnetic fields," Annals of the New York Academy of Sciences 649:74-95, 1992; and "Calcium signaling in lymphocytes and ELF fields," FEBS Letters 301:53-59, 1992.

The papers reported data indicating that EMF exert a biological effect by altering the entry of calcium across a cell's surface membrane.

Liburdy's claims were potentially important when published in 1992 because they purported to link EMF and calcium signaling, a fundamental cell process governing many important cellular functions.

Liburdy has entered into Voluntary Exclusion Agreement with ORI. As part of this agreement, Liburdy neither admits nor denies ORI's finding of scientific misconduct.

Liburdy also agreed to submit letters to the journals ANYAS and FEBS requesting retraction of Figure 12 of the ANYAS paper and of Figures 6 and 7 of the FEBS Letters paper within 30 days of the date of the agreement.

Funding Opportunities:

Leukemia Society Offers Center Research Grants

The Leukemia Society of America has begun a grants program titled Specialized Center of Research to bring together research teams on leukemia, Hodgkin's and non-Hodgkin's lymphoma, and myeloma.

The proposed center should be interdisciplinary, cohesive, and sharply focused. The center must be composed of at least three relevant scientific projects capable of interacting. The research may be fundamental or applied or an integrated combination of the two approaches. Basic research tied to a related translational research project is encouraged but not mandatory. The most promising ideas and the likelihood that the research will lead to a significant reduction in the morbidity and mortality of these diseases will be viewed favorably regardless of the particular approach. The center grant will also support scientific core laboratories required by the component research programs.

An application may be submitted by an individual holding a M.D., Ph.D., or equivalent degree, working in a domestic or foreign non-profit organizations, such as a university, college, hospital, institute or laboratory. Applications may be multi-institutional. Applicants need not be U.S. citizens, and there are no restrictions on applicant age, race, gender, or creed.

The center's maximal annual total cost, direct and indirect, cannot exceed $1.5 million. The aggregate costs over five years cannot exceed $7.5 million. The direct costs, if justified by the aggregate budget may be up to $1.25 million per year. The indirect or institutional costs can not exceed 20% of the direct costs per year.

Preliminary applications must be received by the Society by Nov. 15, and will be reviewed by the Society's Specialized Center of Research Program Grant Review Subcommittee.

Based on the review of the preliminary application, a smaller number of applicants will be notified by Dec. 15 and invited to submit full applications. Full application from selected investigators will be due on March 15.

Guidelines and Preliminary Application forms are available from http://www.leukemia.org or by contacting: Director of Research Administration, Leukemia Society of America 600 Third Avenue New York, NY 10016. Phone 212-450-8843, fax 212-856-9686, email: lermandb@leukemia.org.

NCI Program Announcements

PAR-99-127: Shared Resources For Scientists Outside NCI Cancer Centers

Letter of Intent Receipt Date: Oct. 21

Application Receipt Date: Nov. 18

The objective of this PA is to provide institutions that do not have NCI funded Cancer Centers or planning grants with additional shared resource support. This PA requests applications to establish cancer-related research resources to provide new sources of technical support and research materials to advance cancer research. To be eligible, applicants must identify six or more NCI funded investigators (principal investigators of R01 or P01 grants or NCI contracts) who will utilize the services of the proposed resource.

The resource should be made available to additional users at the applicant institution and may be opened to investigators at other institutions. Applications will only be accepted from institutions that currently are not supported by NCI Cancer Center Support Grants (CCSGs or P30) or Cancer Center Planning Grants (P20). There is also a cap on the direct cost amount of all applications from any applicant institution, based on the total NCI funding received by that institution.

This PA will use the NIH research resource grant (R24). Total project period may not exceed 5 years. The anticipated award date is July 2000.

Budget cap: An institution may submit more than one application, but the sum of all direct cost resource support, including third party indirect costs, requested cannot exceed 10% of its total NCI direct cost research base at the time of submission (funding for all grant and contract mechanisms). If multiple research grants are submitted, each must have a different principal investigator and must provide substantially different products or services. While the same individuals may be listed among the six NCI supported users on more than one application, their need for each resource must be clearly justified. This cap applies only to annual regular operating costs and does not include the one-time purchase of equipment.

Inquiries: Roger Aamodt, Ph.D., Division of Cancer Treatment and Diagnosis, NCI, 6130 Executive Blvd Room 700, Bethesda, MD 20892-7399, Rockville, MD 20852 (for express/courier service), phone 301-496-7147, fax 301-402-7819, email: ra32u@nih.gov

PAR-99-128: Insight Awards To Stamp Out Breast Cancer

Letter of Intent Receipt Date: Sept. 15

Application Receipt Date: Oct. 13

Breast cancer is the most commonly diagnosed cancer of women and the second leading cause of cancer deaths among women. In 1998, NCI convened a panel of basic and clinical researchers from academia, industry, and the government, and representatives of the patient advocacy community to develop a national plan for the next decade of breast cancer research. In addition to identifying specific areas where breast cancer research should be focused, the Breast Cancer Progress Review Group also recommended that NCI initiate a program to develop new and innovative insights in the area of breast cancer research. The purpose of this program announcement is to directly address the recommendations in the BC-PRG report (http://wwwosp.nci.nih.gov/planning/prg/bprgtableofcontents.htm) by encouraging the submission of applications for new "Insight Grants" directed against breast cancer. Both new and established investigators from a variety of disciplines who want to explore research topics related to breast cancer in new and innovative ways are encouraged to apply.

"Insight Grants" are a new initiative designed to support innovative pilot studies that will generate new understanding of breast cancer. It is designed to encourage investigators to explore new research areas. Features of this initiative include:

—Support of novel or innovative research that is considered high risk/high payoff

—Minimal preliminary data required

—Maximum of two years with limited budgets

—Condensed application format with page limitations

—Review within NCI Division of Extramural Activities by ad hoc review panel

—Applications are not renewable

Applications that represent only incremental change in already established research programs will not be considered. Applications that propose projects that are particularly innovative and/or carry a substantial degree of risk but potentially great reward are especially welcomed.

Support of this program will be through the NIH exploratory/developmental grant (R21) mechanism. Applications will be limited to $75,000 in direct costs and appropriate facilities and administrative costs per year for up to two years. These grants are non-renewable, and continuation of projects developed under this program will be through the traditional unsolicited investigator-initiated research grant program.

In 1997 Congress passed the "Stamp Out Breast Cancer Act" to help support breast cancer research and to raise public awareness about the disease. This act authorized the sale of breast cancer postage stamps by the US Postal Service with a portion of the proceeds to fund breast cancer research at NIH. The program described herein will be funded through these monies. To date, approximately $4 million is available to support applications submitted in response to this PA. It is estimated that NCI will be able to fund 20 to 25 two-year awards.

Inquiries: Dan Gallahan, Ph.D., Division of Cancer Biology, NCI, Executive Plaza North Room 513, Bethesda, MD 20892, phone 301-496-7028, fax 301-402-1037, email: dg13w@nih.gov

In Brief:

Vanderbilt-Ingram Awards 10 Endowed Professorships

(Continued from page 1)

Jr., professors of medicine and cell biology; **Graham Carpenter**, professor of biochemistry and medicine; **Lynn Matrisian**, professor and interim chair of cell biology; **J. Robert Roberts**, assistant professor of cardiac and thoracic surgery; **Mace Rothenberg**, associate professor of medicine; and **Earl Ruley**, professor of microbiology and immunology. Two newly recruited faculty members have been named Ingram Professors of Cancer Research: **Friedrich Schuening**, who will direct Vanderbilt's Bone Marrow Transplant Program beginning Aug. 1; and **Andrew Link**, who will join the faculty in October as assistant professor of microbiology and immunology. Schuening was a professor of medicine at University of Wisconsin and head of the Bone Marrow Transplant Division. Link, a scientist with Millennium Predictive Medicine Inc. in Cambridge, MA, was previously a senior research fellow in molecular biotechnology at University of Washington in Seattle. The professorships are awarded for five years and are renewable. The funds cannot be used to pay the investigator's salary. "The income from the endowments provides discretionary funding for the faculty member's laboratory to allow innovative, cutting-edge research that cannot be easily funded through research grants," cancer center director **Harold Moses** said. . . . **AFFYMETRIX INC**. has entered into a broad GeneChip technology access agreement with six institutes of the NIH, including NCI. NIH researchers will gain broad access to Affymetrix' standard and custom GeneChip arrays, instrumentation, and software to monitor gene expression for use in research, the company said. The terms and conditions for use of the GeneChip technology by NIH researchers allow for broad publication of scientific results and collaborations with academic, governmental, and commercial scientific colleagues, Affymetrix said July 22. . . . **TEEN SMOKING RATES** have declined from 1998, according to the third annual Federal report, "America's Children: Key National Indicators of Well-Being." The percentage of 10th and 12th graders who smoked daily dropped in 1998 after having gradually increased since 1992. The report, issued by the Federal Interagency Forum on Child and Family Statistics, is available at http://childstats.gov. Printed copies are available through the National Maternal and Child Health Clearinghouse, 2070 Chain Bridge Road Suite 450, Vienna, VA 22182; phone 703-356-1964. . . . **AMERICAN-ITALIAN** Cancer Foundation was awarded a three-year, $240,000 grant from the Avon Breast Health Access Fund to promote breast health awareness and education. The grant supports the AICF Free Mobile Mammography Program for underserved New York area women. Founder of the screening program is **Harold Freeman**, chairman of the President's Cancer Panel and the recently appointed president and chief executive officer of Harlem's North General Hospital. Freeman has been North General's director of surgery and was director of surgery at Harlem Hospital Center. . . . **CANCER CARE INC.** is moving its national office Aug. 9. The new location is 275 Seventh Ave., New York, NY 10001, but phone number remains the same: 212-221-3300, website: http://www.cancercare.org. . . . **COLD SPRING** Harbor Laboratory's DNA Learning Center, creator of the world's first portable genetics laboratory—the Vector Van—plans to unveil another novel educational vehicle. With a $500,000 grant from the Howard Hughes Medical Institute, the center is developing the VectorNet Computer Laboratory, the first mobile bioinformatics laboratory, for educating students and teachers about the use of computers in biological research, said **David Micklos**, director of the DNA Learning Center (http://vector.cshl.org). The center, in collaboration with Mount Sinai School of Medicine, developed DNA laboratories in five New York metropolitan high schools. During the academic year, the mobile lab will deliver a program called New York City Genes to these schools. During summer, the lab will travel the U.S. to train high school science teachers in modern genetics instruction. The lab includes a presenter workstation, 10 participant computers, and a server with satellite access to the Internet. . . . **SUPER UPGRADE:** NCI has signed a three-year, $6.5 million agreement with Silicon Graphics Inc. to lease a Cray SV1 supercomputer. The machine, expected to be operational by the end of the year, will provide about 48 times the computing capacity and 96 times the disk and memory of the Cray Y-MP supercomputer in use since 1991 at the NCI Advanced Biomedical Supercomputing Center in Frederick, MD. **Stanley Burt** is director of the ABSC and **Jacob Maizel Jr.** is chief of the NCI Laboratory of Experimental and Computational Biology.

THE CANCER LETTER

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Business & Regulatory Report

Formerly "Cancer Economics"

Oncology Managment:

Salick Replaces CEO, Medical Director, Eliminates 12 Positions In Headquarters

Salick Health Care Inc. of Los Angeles said it has replaced its CEO and medical director, and eliminated 12 other positions in its Los Angeles corporate headquarters.

In the shakeup, Ronald Jessup, an attorney who formerly served as the executive vice president and general counsel, replaced oncologist Lawrence Piro as CEO.

The company said the shakeup at Salick, a unit of **AstraZeneca**, was designed to reduce the strategic role of the headquarters and give

(Continued to page 2)

Product Approvals & Applications:

FDA Approves Doxil For Ovarian Cancer, Ethyol For Dry Mouth Following Radiation

ALZA Corp. (NYSE: AZA) of Palo Alto, CA, said FDA has approved Doxil (doxorubicin HCl liposome injection) for the treatment of refractory ovarian cancer.

The agency also approved Ethyol (amifostine) for the reduction of moderate-to-severe xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer, where the radiation port includes a substantial portion of the parotid glands.

In the U.S. Ethyol is marketed by ALZA and co-promoted by **U.S. Bioscience** (Amex: UBS) of West Conshohocken, PA.

Doxil is indicated for ovarian cancer that is refractory to paclitaxel- and platinum-based chemotherapy regimens. Refractory ovarian cancer is defined as disease that progresses during treatment or within six months after completing treatment.

The new indication for Doxil was based on objective tumor response rates. No results are available from controlled trials that demonstrate a clinical benefit resulting from this treatment, such as improvement in disease-related symptoms or increased survival.

The drug was given accelerated approval from FDA, which means the company would be obligated to demonstrate a patient benefit from the therapy at a later date.

With the new indication, Doxil is the first and only liposomal cytotoxic agent approved to treat a solid tumor, the company said. Doxil also was granted orphan drug status for ovarian cancer, which provides for seven years of market exclusivity upon approval.

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Piro, Zeneca Said To Disagree Over Direction Of Salick

(Continued from page 1)

greater autonomy to the cancer centers. "I believe these moves will allow for greater autonomy for our operating units and greater delegation of decision-making," Jessup said in a statement June 29.

Sources close to the company said Piro and Zeneca leadership had been in disagreement over the direction of the company. During his tenure, Piro sought to change the company's emphasis from operation of cancer centers to a disease management strategy less reliant on cancer centers.

Among his priority projects was development of a data management system called OMAR. Piro did not return calls from a reporter.

As a business executive with legal training assumes the CEO position, medical issues in the company will be handled by oncologist John Macdonald, who was named chief medical officer, the company said.

Jessup's appointment represents a break with tradition at Salick, a company founded by nephrologist-entrepreneur Bernard Salick. The tradition continued after Salick sold the company to Zeneca in 1995.

"I don't think the attorney issue is relevant," said Sheldon King, executive vice president for business strategies, commenting on Jessup's professional background. "There is a sense of Mr. Jessup as a manager, that he can provide the kind of leadership needed at this time in the healthcare market."

Medical issues don't have to be handled by the CEO, King said.

"I don't think the fact that [Jessup] is not a physician is important," King said. "That's where the Jack Macdonald role comes in. Macdonald's appointment gives oncologists at Salick centers an oncologist of international reputation to work through clinical issues. It's a chance to draw closer to our physicians at our cancer centers. It really wasn't done directly."

The chief medical officer's position is a second concurrent position for Macdonald within the company. He will continue as director of the cancer center at St. Vincent's Hospital in New York. That cancer center, estimated to cost well over $40 million, was scheduled to be completed in August 1998, and is now expected to be completed next month.

King said the company intends to continue development of the OMAR system. "There was a substantial software development program," he said. "That will continue as a discreet business unit within Salick Health Care."

Another prominent oncologist ousted last month was Robert Gale, corporate director for transplantation. Announcing the changes, the company said its chief operating officer Anthony LaMacchia also resigned. LaMacchia did not return calls from a reporter.

King, too, said he plans to retire in the near future. "My intent is to retire relatively soon," King said. "I am not part of any streamlining or downsizing."

Over four years, the odd coexistence of Salick and Zeneca has had the flavor of a long-running soap opera. Back in 1995, the decision by the multinational pharmaceutical company to pay a premium price for Salick shocked many in oncology. While some observers thought the purchase signaled an erosion of boundaries between the businesses of making drugs and providing medical care, others thought the British company made a $438-million mistake.

After Zeneca bought a stake in his company, founder Bernard Salick proved to be something other than the stereotypical Zeneca company man. With cash behind him, he trotted the globe and made big plans matched by big pronouncements to the press (**The Cancer Letter**, April 4, 1997).

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Two years after buying a stake in the company, Zeneca assumed complete control and staged an elaborate coup to oust Salick (**The Cancer Letter**, May 8, 1997). With that accomplished, Zeneca found itself running day-to-day operations of an idiosyncratic company that had gross sales of $100 million at the time it changed hands.

Over the past two years, Zeneca trimmed the size of its small subsidiary. It sold the Van Nuys Breast Center, abandoned plans to build a transplantation center at the Westlake Hospital in Los Angeles, terminated a deal with Temple University to build a cancer center in downtown Philadelphia, and sold the Salick dialysis business.

Now, the company's key holdings include outpatient centers at the Cedars Sinai Hospital in Los Angeles, Alta Bates in Berkeley, as well as centers in Palm Springs, the University of Kansas, and the Mount Sinai Hospital in Miami. With reimbursement shrinking, these centers are expected to finance the development of the St. Vincent's center, a facility in the ferociously competitive New York market.

Now that Zeneca Group PLC has merged with Astra AB to form AstraZeneca PLC, a company with gross sales of $15.8 billion a year, will the new giant be able to muster the attention to detail to run a relatively small US operation?

Is Salick for sale?

"It is definitely not on the market," King said to **The Cancer Letter.** "It is not for sale. The intent is to make it go."

* * *

MetroWest Medical Center of Framingham, MA, and **Beth Israel Deaconess Medical Center** of Boston said they have signed a letter of intent to develop a community-based cancer program at the MetroWest Cancer Center.

Under the agreement, the MetroWest Cancer Center will retain current physicians and staff, who will work with their counterparts at BI-Deaconess.

BI-Deaconess will collaborate with MetroWest Cancer Center physicians and staff on combined programs for medical and radiation oncology, quality review standards and academic affiliations. BI-Deaconess will assist MetroWest in the establishment of new cancer-related programs. In addition, MetroWest Cancer Center patients will be eligible to participate in clinical research programs through BIDMC.

MetroWest's cancer care affiliation with BI-Deaconess replaces a relationship that existed between MetroWest's former owner, Columbia HCA, and Dana-Farber Cancer Institute.

MetroWest Medical Center consists principally of the 281-bed Framingham Union Hospital in Framingham and the 194-bed Leonard Morse Hospital in Natick. The Medical Center has more than 2,500 employees and more than 400 affiliated physicians.

* * *

Open Text Corp. (NASDAQ:OTEX) of Chicago said the Dana-Farber Cancer Institute is deploying Livelink to manage an extranet that links scientists and physicians at Harvard-affiliated medical facilities in the Boston area. Dana-Farber is also deploying Livelink to manage their intranet to improve the institute's administrative efficiency and flow of information.

The cancer research extranet will provide an information sharing platform for the Dana-Farber/ Harvard Cancer Center, a new collaboration among the Dana-Farber Cancer Institute, the Harvard Medical School, the Harvard School of Public Health, Massachusetts General Hospital, Brigham and Women's Hospital, Children's Hospital Medical Center and the Beth Israel Deaconess Medical Center. Livelink will make it possible for scientists and physicians at these institutions to share research documents, participate in online workgroup discussions, and maximize existing lab resources.

Livelink is a scaleable, collaborative knowledge management application for intranets and extranets. Livelink's richly-featured enterprise document management, virtual team collaboration, business process automation, enterprise group scheduling and information retrieval services are tightly integrated into an off-the-shelf application that is easily customized and extended to fill a broad range of information and knowledge management needs.

Livelink servers are fully Web-based and open-architected to ensure rapid deployment, requiring just a standard Web browser on users' desktops to access its full functionality. Livelink runs on Microsoft Windows NT and the leading UNIX platforms and supports most popular relational database management systems.

* * *

Response Oncology, Inc. (Nasdaq NMS:ROIX) MEMPHIS, Tenn.- announced that it has executed a Loan Agreement with AmSouth Bank as lead bank providing the Company with a $42 million secured credit facility.

NationsBank of Tennessee, N.A. and Union

Planters Bank, N.A. are also participants in the financing. The portion of the facility dedicated to working capital and general corporate purposes, amounting to $7 million, matures June 2002. The remaining $35 million term portion will become due in quarterly installments of $1.25 million to $1.5 million beginning July 1999.

* * *

Innovative Clinical Solutions Ltd.(Nasdaq: PHMX) of Providence, RI, and **Pharmacia & Upjohn** (NYSE: ICSL) said they have entered into a service agreement with which will include clinical and outcomes research and disease management projects.

Innovative Clinical Solutions Ltd. is the former PhyMatrix Corp.

The company, through its wholly-owned subsidiary, Clinical Studies Ltd., will conduct phase I-IV clinical research for Pharmacia & Upjohn across multiple therapeutic areas.

CSL will utilize its 36 fully-staffed clinical research locations, 72-bed phase I unit and Oncology Research Network to provide physician investigators, clinical staffing and study participants for clinical research programs aimed at reducing drug development timelines.

Two Drugs Marketed By ALZA Approved In Cancer Treatment

(Continued from page 1)

Doxil was originally approved in 1995 for the treatment of AIDS-related Kaposi's sarcoma in patients with disease that has progressed on prior combination therapy or in patients who are intolerant to such therapy.

"In an area that lacks effective and tolerable alternatives, Doxil represents a major advance for patients who are unresponsive to currently available regimens," said Maurie Markman, chairman of the Department of Hematology and Medical Oncology at the Cleveland Clinic Taussig Cancer Center. "There is a great need for more options to offer these patients because so many women experience disease progression while receiving paclitaxel- and platinum-based chemotherapy. The approval of Doxil is truly encouraging news for women with ovarian cancer and physicians alike."

Studies evaluating Doxil included three phase II trials conducted among women with relapsed or refractory ovarian cancer, as well as preliminary results of a phase III randomized trial.

Patients in the phase II studies with refractory ovarian cancer demonstrated a 13.8 percent partial response rate.

In clinical trials, the most common side effects reported with Doxil therapy included (neutropenia), (anemia), nausea, hand-foot syndrome, (stomatitis), vomiting, diarrhea, constipation, appetite loss, tiredness, weakness, rash, and mild hair loss. Some patients experienced infusion-related reactions and skin reactions. In some patients, heart-related side effects were reported, some of which were severe, the company said.

Ethyol Approval

Data supporting the safety and efficacy of Ethyol for the reduction of xerostomia included data from a phase III, open-label, prospective multi-center randomized trial involving more than 300 patients with head and neck cancer.

In clinical trials, improvements in subjective measurements of oral dryness were supportive of Ethyol's effectiveness, the company said.

Approximately one month following treatment, 78 percent of patients given radiation alone experienced moderate to severe xerostomia, compared with 51 percent of patients treated with Ethyol prior to radiation.

This represented a 35 percent reduction in the incidence of moderate to severe xerostomia with the use of Ethyol ($p=<0.0001$). Moreover, nine to 12 months after radiation therapy, 57 percent of the patients in this trial who had been treated with radiation alone were still experiencing moderate to severe xerostomia, as compared to 34 percent of the patients in the Ethyol arm ($p=0.0016$).

Side effects reported by patients receiving Ethyol plus radiation in the phase III study were nausea and vomiting, which were sometimes severe, hypotension, fever, allergic-type skin reactions, dizziness/lightheadedness, fatigue/lethargy, rigors/chills, sneezing, sleepiness/somnolence and flushing. Of the 26 patients who discontinued Ethyol due to side effects (17 percent), all but one continued radiation treatment following discontinuation of Ethyol.

"Ethyol is the first therapy to help limit the degree of xerostomia that many patients suffer as a result of radiation therapy," said Walter Curran, chairman of the Radiation Therapy Oncology Group, professor and chairman of radiation oncology and clinical director of the Kimmel Cancer Center at

Jefferson Medical College.

The approval applies to patients undergoing post-operative radiation therapy, and Ethyol should not be administered in patients receiving definitive radiation therapy except in the context of a clinical trial, the company said.

* * *

Ligand Pharmaceuticals Inc. (Nasdaq: LGND) of San Diego said it has submitted a New Drug Application to FDA, seeking marketing clearance for Targretin (bexarotene) capsules for once daily oral administration of Targretin capsules for the treatment of early stage cutaneous T-cell lymphoma in patients who have not tolerated other therapies, patients with refractory or persistent early stage CTCL, and patients with refractory advanced stage CTCL.

Ligand has received approval from the FDA to file Targretin capsules under orphan drug designation for this indication and has requested priority review status of the NDA filing. If the Targretin capsules NDA is granted priority review status, the FDA is expected to respond to the application within six months of the submission.

Based on the results from two multicenter, multinational clinical trials involving 152 patients with CTCL, the dose regimen recommended in the NDA is a single daily oral dose of Targretin capsules at an initial dose level of 300 mg/m2 of body surface area, administered with a meal. In both clinical trials, this initial dose level provided efficacy that exceeded the protocol-defined targets of response rates of at least 20% and a lower bound of the 95% confidence intervals statistically superior to a theoretical spontaneous remission rate of 5% or less.

Ligand has the worldwide rights to Targretin. If approved, Ligand will market and sell Targretin capsules in the U.S., Canada and selected European markets through its specialty oncology sales and marketing group. In Spain, Portugal, Greece, and Central and South America, Ferrer Internacional, S.A., will market and distribute, if approved in the respective jurisdictions, Targretin and other oncology products.

The NDA is based on two phase II/III multicenter, open-label, historically controlled clinical studies conducted in the U.S., Canada, Europe and Australia. A total of 200 patients with CTCL have been treated with Targretin capsules.

Although some toxicities (i.e., hypertriglyceridemia, hypothyroidism and, less frequently, neutropenia) often warranted concurrent administration of an additional drug, the required concurrent therapy was easily administered and monitored, and the toxicities were generally well-tolerated, easily managed, nearly always lacked clinical complications, and were reversible upon dose reduction, suspension or discontinuation.

"Targretin capsules are an effective and well-tolerated oral treatment for patients with all stages of CTCL that has been refractory or persistent following prior therapy," said Madeleine Duvic, Chief, Section of Dermatology at the University of Texas M.D. Anderson Cancer Center.

"A rapid onset of response was observed in over 50% of patients at M.D. Anderson, and the duration of responses have been long-lasting, even in patients with large cell transformation and in erythrodermic patients with Sezary syndrome. I would expect that Targretin capsules would be used at some point in almost all patients with CTCL and believe that additional clinical evaluation with Targretin capsules in combination therapeutic regimens with other agents would prove to be very productive."

* * *

Coulter Pharmaceutical Inc. (Nasdaq: CLTR)of South San Francisco and SmithKline Beecham (NYSE:SBH) announced the submission of a Biologics License Application to FDA for Bexxar (tositumomab, iodine I-131 tositumomab).

The companies are seeking marketing approval of Bexxar for the treatment of relapsed or refractory, low-grade or transformed low-grade B-cell non-Hodgkin's lymphoma.

Last December, Bexxar was designated a Fast Track Product for which the FDA would take appropriate actions to expedite development and review. The designation was awarded because one of the targeted indications for the therapy is transformed, low-grade non-Hodgkin's lymphoma, a life-threatening disease with an unmet medical need. The companies have requested a Priority Review, or review within a six-month period, of the license application under the Food and Drug Administration Modernization Act.

Bexxar is a radioimmunotherapy involving an antibody conjugated to iodine 131 that attaches to a protein found only on the surface of B-cells, including non-Hodgkin's lymphoma B-cells. Through Bexxar's targeted approach, the tumor cells receive a greater concentration of the therapeutic radiation relative to normal tissues.

Coulter and SmithKline Beecham established a partnership to jointly develop and market Bexxar in the U.S. following regulatory approval with the two companies sharing equally in profits. Outside the U.S., excluding Japan, Coulter has granted SB exclusive marketing and distribution rights in return for product royalties.

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Rhone-Poulenc Rorer Inc. of Collegeville, PA, and **Guilford Pharmaceuticals Inc.** (Nasdaq: GLFD) of Baltimore said GLIADEL 7.7 mg Implant, (polifeprosan 20 with carmustine), the first commercially available brain cancer treatment to deliver chemotherapy directly to the tumor site, has successfully completed the Mutual Recognition Procedure in 10 European countries.

This is one of the two European registration procedures used to obtain marketing authorization in Europe. Consequently, Germany, Italy, the United Kingdom, Austria, Greece, Ireland, Luxembourg, Portugal, Spain, and the Netherlands are expected to grant national marketing authorization within the next six months.

The first marketing authorization of GLIADEL in Europe was granted in France in December 1998.

GLIADEL was approved by the FDA in 1996 for use as an adjunct to surgery to prolong survival in patients with recurrent GBM for whom surgical resection is indicated. In 1996, Guilford and Rhone-Poulenc Rorer entered into a worldwide marketing and distribution rights agreement granting RPR worldwide marketing rights (currently excluding Scandinavia and Japan), for GLIADEL.

Deals & Collaborations:

EntreMed Contracts For GMP Production Of Angiostatin

EntreMed Inc. (Nasdaq: ENMD) of Rockville, MD, said it has signed a contract with **Covance Biotechnology Services Inc.**, of Research Triangle Park, NC, to provide Good Manufacturing Practices production of Angiostatin protein for phase I trials projected to commence early next year.

EntreMed and Covance began technology transfer for the production of Angiostatin protein in the first quarter of this year. With the technology transfer process now complete, EntreMed and Covance have jointly demonstrated success in numerous small and medium-scale fermentation runs.

Larger GMP fermentations of Angiostatin protein at the 2,000 liter scale are scheduled to commence at Covance early this quarter. Under the terms of the agreement, Covance will produce enough recombinant human Angiostatin protein for the Phase I clinical trials as well as further preclinical studies.

"After EntreMed's initial evaluation of five separate recombinant expression systems in 1995 and 1996, the Pichia pastoris yeast system emerged as the clear choice for the scale-up expression of Angiostatin protein for human clinical trials," John Holaday, EntreMed Chairman, President and CEO.

"As a result of the molecular engineering of the Angiostatin molecule, and the knowledge gained from biochemical studies performed by EntreMed scientists, we can now report that recombinant human Angiostatin protein is being readily synthesized and purified at Covance," Holaday said.

In 1995, EntreMed signed a Research, Collaboration and License Agreement with Bristol-Myers Squibb Co. for Angiostatin protein. Last February, the agreement was modified to grant EntreMed development rights for Angiostatin protein and rights to future partnering and commercialization of the protein.

Angiostatin protein, a naturally occurring antiangiogenic substance, was discovered in 1994 by Judah Folkman and Michael O'Reilly of Children's Hospital, Boston.

In another development at EntreMed, Tetrionics Inc. of Madison WI, will manufacture 2-methoxyestradiol (2ME2) for preclinical testing.

EntreMed has a CRADA in place with the National Cancer Institute to further develop 2ME2. Preliminary data indicate 2ME2 is an effective, orally-active antitumor compound.

Tetronics is a privately held company.

EntreMed said it anticipates submission of an Investigational New Drug application to FDA later this year.

Tetrionics is expected to manufactures 2ME2 to purities greater than 99.9%.

"2ME2 is the first product candidate from EntreMed to attack both compartments of cancer, the tumor cells and their blood supply," said Shawn Green, EntreMed's Vice President of Discovery Research. Shawn Green.

The agent is orally active at inhibiting the growth of metastatic and primary cancerous tumors in experimental rodent models, and in preclinical models, 2ME2 has shown no overall toxicity at therapeutically effective doses, the company said.

* * *

Titan Pharmaceuticals Inc. (Amex: TTP) of South San Francisco said its Ingenex subsidiary has executed a cross-license agreement acquiring rights to a tumor targeting technology developed by **Selective Genetics Inc.,** of San Diego, a privately held company.

Under the agreement, Titan will have exclusive rights to develop cancer therapies using Selective's proprietary cancer cell targeting technology in conjunction with the anti-cancer gene RB, including Ingenex's proprietary tumor suppressor gene RB94. Selective will have exclusive rights to use Ingenex's RB94 gene with its therapeutic device and targeting technologies in non-cancer applications, including restenosis.

Titan said it plans to combine the targeting technology with its proprietary RB94 based anti-cancer gene therapy. RB94 is a modified version of the naturally occurring RB tumor suppressor gene.

In a related event, Titan announced the issuance of U.S. Patent No. 5,912,236 covering the use of its RB94 gene in cancer therapy.

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Introgen Therapeutics Inc. of Austin, TX, said Rhone-Poulenc Rorer (NYSE: RP) will make a $6 million equity milestone payment to the company under the terms of their collaboration agreement.

The companies recently completed three phase II clinical trials on their lead product, RPR/INGN 201 (Adenoviral-p53), in head and neck cancer and are planning to initiate phase III trials.

Since the commencement of their collaboration, Introgen Therapeutics and Rhone-Poulenc Rorer have initiated 17 trials of Introgen's p53 therapeutic in 8 different cancer indications. The clinical studies include systemic, intravenous administration as well as p53 used alone and in combination with surgery, radiotherapy and chemotherapy. Clinical research has demonstrated activity in prostate cancer and non-small cell lung cancers.

In October 1994, Rhone-Poulenc Rorer and Introgen entered into a $50 million strategic alliance to develop and commercialize gene therapy cancer products based on the p53 pathway and K-RAS inhibition. Under the agreement, Introgen provides discovery, pre-clinical and phase I clinical development while RPR is responsible for later stage clinical trials.

* * *

Enzon Inc. (NASDAQ: ENZN) of Piscataway, NJ, and **Schering-Plough Corp.** (NYSE: SGP) Madison, NJ, announced a revision of their 1990 PEG-INTRON licensing agreement, which entitled Enzon to royalties for product sales and specific milestone payments.

The revised agreement calls for Schering-Plough to pay Enzon royalties on sales at a higher effective rate than provided for in the original agreement in exchange for the return to Schering-Plough of Enzon's exclusive U.S. manufacturing rights for the product.

In addition, Enzon grants to Schering-Plough a non-exclusive worldwide license, with a limited right to sublicense, under Enzon's patents covering another form of PEG called "Branched PEG," which uses a different proprietary PEG technology than PEG-INTRON.

PEG-INTRON is a modified form of Schering-Plough's INTRON A (interferon alfa-2b, recombinant) that was developed using Enzon's PEG technology to have longer-acting properties. PEG-INTRON is in phase III clinical trials for two cancer indications, malignant melanoma and chronic myelogenous leukemia, as well as in early stage trials for various solid tumors.

The patent licensed to Schering-Plough under terms of the revised agreement is the subject of a patent infringement suit brought by Enzon against Shearwater Polymers Inc. earlier this year.

Clinical Trials:

Anti-Angiogenesis Compound Completes Phase I Trials

Ribozyme Pharmaceuticals Inc. (Nasdaq: RZYM) of Boulder, CO, and **Chiron Corp.** (Nasdaq: CHIR) announced the completion of phase Ia and Ib trials of the anti-angiogenesis cancer compound, Angiozyme.

The phase Ia trial demonstrated excellent tolerability of low single doses of Angiozyme administered either intravenously or subcutaneously to healthy volunteers, the company said.

The subsequent phase Ib trial, performed with cancer patients, extended to higher single doses of Angiozyme up to 300 mg/m^2 to help define appropriate dosing for future phase II and III trials. The trial demonstrated no clinically significant drug-related side effects were observed at any dose in the phase Ia and Ib studies in normal volunteers or cancer patients, the company said.

In addition to studying tolerability, the phase I trials were designed to compare the pharmacokinetics of Angiozyme administered either intravenously or by subcutaneous injection. PK data showed that Angiozyme was detectable in patient serum up to 24 hours after subcutaneous injection, and at levels exceeding those predicted to be necessary to achieve an anti-angiogenesis effect based on preclinical studies.

"These results further suggest ribozymes will be safe when given on therapeutic schedules," said Ernest Borden of the Center for Cancer Drug Discovery and Development at The Cleveland Clinic Foundation. "Because of its antitumor effects in mouse models and targeted, selective mechanism of action, we look forward to initiation of more extended clinical trials in cancer patients of this novel molecule."

Angiozyme is the first chemically synthesized ribozyme to be studied in human clinical trials.

Based on preclinical data, the compound specifically inhibits angiogenesis and resulting cancer tumor growth and metastases by inhibiting production of the Vascular Endothelial Growth Factor receptor (VEGF-r), a key component that regulates the growth of new blood vessels that nourish malignant tumors, the company said.

By minimizing the new blood supply to tumors, Angiozyme was shown in preclinical studies to halt tumor growth and prevent the growth and spread of metastases, the company said.

"We now know that single doses as high as 300 mg/m^2 can be given intravenously or subcutaneously to patients without any clinically significant side effects," said Ralph Christoffersen, CEO and president of RPI. "If subsequent clinical studies confirm the results observed in preclinical models, the persistence of ANGIOZYME seen in the blood after subcutaneous administration may ultimately permit home treatment of cancer by self-administration, in a manner similar to current outpatient treatment of diabetes with insulin."

The next round of clinical studies is slated to begin within six to nine months, the company said.

* * *

NeXstar Pharmaceuticals Inc. (NASDAQ: NXTR) of Boulder, CO, said it has enrolled the first patient in a US-based phase I study of the investigational anticancer drug NX 211, a proprietary liposomal formulation of lurtotecan, a topoisomerase I inhibitor.

The study, which will take place at two clinical sites, is part of a worldwide phase I development program designed to evaluate the safety and pharmacokinetics of NX 211 in patients with advanced-stage solid tumors.

In addition to the U.S. study, patient enrollment has begun in two separate phase I clinical trials in Canada and The Netherlands. Further phase I studies are planned to evaluate NX 211 in combination with other cytotoxic agents. Subsequently, NeXstar plans to initiate a phase II development program.

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TRANSGENE (Nasdaq: TRGNY; Nouveau Marche: TRANSGENE) of Strasbourg, France, said it has initiated a phase I trial using adenovirus-IFN-Gamma in advanced malignant melanoma.

The trial is conducted at the University of Rochester in Rochester, NY, and in Europe.

The product is designed to produce interferon-Gamma.

* * *

GLYCODesign of Toronto is expanding its phase II trial of GD0039 in renal cell carcinoma and 5-FU resistant colorectal cancer by adding a third site, the Jewish General Hospital in Montreal.

The trial will be under the direction of Gerald Batist, director of the McGill University Centre for Translational Research in Cancer, based at the Jewish General Hospital.

Phase II trials of GD0039 in patients with advanced or metastatic renal cell carcinoma and 5-FU resistant colorectal cancer have been underway since September and November 1998, respectively, at Sunnybrook Regional Cancer Centre in Toronto and the Group Health Centre in Sault Ste. Marie, Ontario. The study calls for 15 patients per tumor type. GD0039 is an orally-administered inhibitor of the enzyme Golgi alpha-mannosidase II.

* * *

The Cancer Research Campaign of London has selected for phase I testing of polyglutamate paclitaxel **Cell Therapeutics Inc.'s** water soluble form of paclitaxel.

In a presentation before the CRC's phase I/II Clinical Trials Committee, Jack Singer, Research Program Chairman for Cell Therapeutics, Inc. presented data suggesting that polyglutamate, a novel biodegradable polymer, is capable of increasing the maximum tolerated dose of paclitaxel by up to 400 percent over the non-polyglutamate version of paclitaxel.

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