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At Its Launch, STAR Trial Inherits Baggage Of Its Predecessor, P-1 Tamoxifen Study

The tamoxifen v. raloxifene trial announced last week appears to have inherited the glory—and the baggage of controversy—from its predecessor, the Breast Cancer Prevention Trial, which tested the potential of tamoxifen to prevent cancer in women at high risk of developing the disease.

From its predecessor, the Study of Tamoxifen and Raloxifene inherits the opposition of some patient groups, the challenge to recruit underserved populations, the uncertainty over the significance of race, and a semantics dispute over the word "prevention."

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In Brief:

Strohl Leads Oncology Nursing Society; ONS Seeks Nominees For Consumer Panel

ROBERTA STROHL became president of the Oncology Nursing Society at the society's annual congress in Atlanta last month. Strohl is a clinical nurse specialist in radiation oncology and associate professor at the medical school at University of Maryland, in Baltimore. She succeeds **Linda Krebs**, assistant professor of nursing at University of Colorado School of Nursing. President-elect is **Paula Trahan Rieger**, nurse practitioner in the Human Clinical Cancer Genetics Program at M.D. Anderson Cancer Center. **Marcia Satryan**, of Bon Secours Holy Family Hospital, Altoona, PA, is secretary, and treasurer is **Luana Lamkin**, of Precedent Medical Center, Denver. Newly elected directors **are Barbara Rogers**, of Fox Chase Cancer Center; and **Patty Jassak**, of Illinois Masonic Medical Center, Chicago. **Carol Curtiss**, clinical specialist in cancer care and pain and symptom management in Greenfield, MA, received the ONS-Roche Laboratories Inc. Distinguished Service Award. **Marcia Grant**, director and research scientist at City of Hope National Medical Center, received the ONS-Bristol-Myers Squibb Oncology Division Distinguished Researcher Award. ONS Public Service Awards recognized the work of the late entertainer **Danny Thomas** and his daughter**, Marlo Thomas**, for their work in founding and supporting St. Jude Children's Research Hospital. ONS presented the International Award for Contributions to Cancer Care to **Shizko Kiba**, director of the Institute of Hospice Care in Tokyo. . . . **ONS BOARD OF DIRECTORS** said it is planning to assemble a volunteer panel of oncology healthcare consumers able to advise the society on consumer issues related to cancer

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Second Major Prevention Trial, STAR, Inherits Controversies

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In addition to having to confront these old issues in a new way, the STAR trial, which began May 25, will have to confront a great deal of commercial hype, ignorance, and confusion.

Potential participants in STAR will have to be convinced to forego the option of taking tamoxifen, trade name Nolvadex, a drug approved by FDA for reduction of breast cancer incidence in high-risk women.

Raloxifene, trade name Evista, is similarly available to potential STAR participants.

Taking a leap of faith, physicians are prescribing raloxifene, a drug approved by FDA for preventing bone loss in postmenopausal women, for the reduction of breast cancer risk. According to popular belief, raloxifene has the potential to prevent breast cancer without causing the side effects of tamoxifen.

Ironically, STAR will be comparing two drugs whose sponsors are in litigation. Earlier this year, in a federal suit, Zeneca alleged that Eli Lilly is improperly marketing raloxifene for breast cancer prevention. A New York federal court began hearing the case beginning June 1.

As if these challenges aren't enough, at least initially STAR will enroll only postmenopausal women. Premenopausal women may be added later, after NCI completes toxicity and pharmacology trials in that population. Ironically, enrollment of younger women at especially high risk of breast cancer allowed investigators to complete BCPT, also known as P-1, ahead of schedule. Not only will their initial absence from STAR present substantial problems, but if tamoxifen's risk-benefit ratio is an indication, younger, premenopausal women may have the most to gain from the drug.

How do investigators intend to overcome these formidable obstacles?

By sticking to the principles of evidence-based medicine, says Norman Wolmark, chairman of the National Surgical Adjuvant Breast and Bowel Project, the cooperative group conducting the trial.

"Clinical trials were designed to deliver us from the age of anecdotalism, when an individual, based on his charisma or the institution that he represented, in an authoritarian dictum could determine the therapy of a particular disease—breast cancer a case-in-point—for generations to come, " Wolmark said at a conference last week in Washington sponsored by the National Breast Cancer Coalition.

P-1 is widely viewed as a landmark trial in cancer prevention. "The results of this study are remarkable," NCI Director Richard Klausner said when the trial was unblinded (**The Cancer Letter**, April 10, 1998). "For women whose risk of developing breast cancer fall within the range of the study, tamoxifen can provide a first opportunity to reduce that risk, much as cholesterol-lowering medications can reduce the risk of heart attacks."

The STAR trial is expected to randomize 22,000 women through 400 centers across the US, Puerto Rico, and Canada. During the current fiscal year, NCI expects to spend $12 million on the trial, said Leslie Ford, associate director, clinical research, at the NCI Division of Cancer Prevention. Speaking at a press briefing, Ford estimated that the trial would take seven to 10 years to complete, and would cost $75 million to $100 million.

Another $34 million has been contributed to NSABP by Lilly, to cover risk assessments of potential participants, as well as other expenses not reimbursed by NCI. Zeneca did not make a monetary contribution to the trial, but is donating the drug, sources said.

Risk assessment in the STAR trial began the day of the announcement, and the first patients are expected to be randomized in June.

Once a woman chooses to participate, she will be randomly assigned to receive either 20 mg

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tamoxifen or 60 mg raloxifene daily for five years, and will have regular follow-up examinations, including mammograms and gynecologic exams.

Critics: Bring In The Placebo Arm

Cynthia Pearson, executive director of the National Women's Health Network and one of the critics the STAR trial inherited from P-1, said STAR should have a placebo arm, to establish whether either drug is better than no chemoprevention at all.

Pearson said a placebo arm in STAR would not amount to withholding an effective therapy since P-1 did not demonstrate a survival advantage, and since it remains to be proven whether breast cancer risk reduction from tamoxifen would be durable beyond completion of the trial.

"I believe that because we don't yet know what happens to the women who seem to have benefited in the relatively short term of four-and-a-half years, it is questionable ethics to conduct the STAR trial without a placebo arm," Pearson said.

At a May 24 debate with Pearson, NSABP chairman Wolmark said that in the absence of compelling rationale for dismissing the conclusions of P-1, the use of a placebo in the STAR trial would be unethical since it would withhold a proven therapy from a third of the participants.

"The use of a placebo would in essence be stating that we do not believe the observations that were generated through P-1," Wolmark said at a debate conducted by the National Breast Cancer Coalition at its annual Advocacy Conference in Washington.

"To go back to a placebo is not only counterproductive, but would dilute the sample size and not provide any additional information," Wolmark said. "From my perspective, this is unethical."

Pearson's view later was echoed in an NBCC statement. "NBCC believes that it is premature and unethical to conduct the STAR trial as it is currently designed," the statement reads. Pearson is a member of the NBCC board of directors.

"Raloxifene needs to be compared with placebo," said Kay Dickersin, an associate professor of community health at Brown University School of Medicine, a member of the National Cancer Advisory Board, and an NBCC activist.

Ideally, the questions asked in STAR would need to be asked in two trials, Dickersin said. One trial would compare the drug with placebo, and another, subsequent, trial would compare it with the established treatment. The value of a decrease in incidence of breast cancer demonstrated in the prevention trial is unclear, Dickersin said.

"Had NSABP relied on recurrence instead of mortality, it would not have realized that lumpectomy is just as good as mastectomy," Dickersin said to **The Cancer Letter**.

Fran Visco, president of NBCC and a member of the President's Cancer Panel, agreed. "We all want to know how to prevent breast cancer, but we should be careful," Visco said to **The Cancer Letter**. "We should keep in mind that these are healthy women, and that's a different paradigm than treatment of a life-threatening disease."

Surrogate Endpoints v. Astronomic Costs

Ultimately, the debate boils down to the value of surrogate endpoints, the definition of the proof of principle, and the amount of money society would be willing to spend in pursuit of the definitive answer.

"I think with any trial you run, you first of all have to say to the people who are likely to use the therapy, 'What is the most important thing for you to know in order to decide whether to use this therapy?' That's what you want to answer," said Craig Henderson, adjunct professor at the University of California, San Francisco.

"I happen to be of the opinion that we haven't provided the answers to women on the most important question: 'Do you prolong survival? And, what's the size of the benefit?'" said Henderson, who was chairman of the FDA Oncologic Drugs Advisory Committee when it considered the trial.

"What percentage of women and their doctors believe that it's important we find out whether there is a survival benefit? I believe that as the years go by, more and more women are going to say, 'We want to know whether this improves survival.' As time goes on, more and more people are going to say, 'Why in hell didn't we do this right in the first place?'

"Should there be a placebo arm in the STAR study? My own answer would be, 'Yes,'" Henderson said. "But then you have to answer the second question: 'Could you complete the study?' The answer is, 'I doubt that there would be enough women willing to be randomized.' This has nothing to do with asking the question of raloxifene v. placebo. The question is, 'Does either one of these drugs change survival?'"

George Sledge, a professor of oncology at the Indiana School of Medicine, a member of the Oncologic Drugs Advisory Committee, and vice

chairman of the breast cancer committee of the Eastern Cooperative Oncology Group, said the ethical problem cited by Wolmark would have to be dealt with through disclosure in informed consent documents presented to participants.

"Informed consent would have to include the fact that a prospective randomized trial has already shown this drug to reduce the short-term incidence, compared to a placebo," Sledge said. "The patient coming onto the trial would have to say, 'I really want this drug to work. Am I willing to take a one-third chance that I am going to get something that has no effect?'"

While the ethical problem would go away, practical problems would be magnified, Sledge said. "You would have to significantly increase the accrual, and, frankly, the 13,388 patients [enrolled in P-1] really strained things for NSABP," Sledge said. "[STAR] may be a difficult trial to complete with two arms. It would be an extremely difficult trial to complete with three arms."

"From the practical standpoint, it would not be possible," Sledge said.

At the request of **The Cancer Letter**, Joseph Costantino, associate director of the NSABP biostatistics center, prepared a rough estimate of the enrollment targets and the expenditures involved in conducting a three-arm trial designed to show a survival benefit. According to Costantino, the trial would need to enroll 135,000 women to show a 30 percent survival benefit over seven years.

If the P-1 experience applies, to randomize this number of women, NSABP investigators would have to perform close to one million risk assessments. Extrapolated from the estimate for the STAR trial, the three-arm trial would cost about $800 million, Costantino said. The government's share would be about $614 million.

Recently, the conclusions of P-1 were upheld in a "technology assessment" by the American Society of Clinical Oncology. The technology assessment was presented at the ASCO annual meeting last month and published in the June issue of the Journal of Clinical Oncology. The trial is endorsed by the Susan G. Komen Breast Cancer Foundation and the National Alliance of Breast Cancer Organizations.

Raloxifene v. Tamoxifen In The Real World

Whatever its outcome, STAR could provide hard data as well as benefit assessment tools in the murky area of preventative use of hormonal agents.

Little is known about the risk-benefit profiles of estrogen replacement drugs that are routinely prescribed by family physicians, gynecologists, and endocrinologists. With tamoxifen and raloxifene now available for prescribing to healthy women, many oncologists over the past year have become aware of improper prescribing of raloxifene.

According to anecdotal accounts collected by **The Cancer Letter**, the osteoporosis drug is being commonly prescribed for breast cancer prevention, as a first-line therapy in the adjuvant setting, or sequentially after completion of five years of tamoxifen.

The only data on raloxifene in breast cancer comes from a toxicity study in which breast cancer prevention was not an endpoint.

"The patients I see are not on placebo," NSABP chairman Wolmark said at the NBCC conference. "Women in my practice who visited gynecologists come out with one of three things, never empty-handed: either a sample of raloxifene, a prescription for hormone replacement therapy, or a bill—or all three."

Sledge's experience is consistent with Wolmark's.

"Since the original data about raloxifene as a potential chemopreventive agent came out last year, I've had numerous patients, including one as recently as today, ask me whether they could switch from tamoxifen to raloxifene in the adjuvant setting," Sledge said to **The Cancer Letter.** "Of course, I explained to all of them that we have no data on raloxifene in the adjuvant setting. Having done that, I've had two patients who have told me that they didn't consider that answer acceptable, and basically fired me as their doctor, and presumably went off tamoxifen and got raloxifene."

One of the patients was acting on a recommendation from an endocrinologist, another from a gynecologist, Sledge said.

Last fall, Sledge served as an expert consultant to ODAC when that committee reviewed the results of P-1 to decide whether the trial establishes tamoxifen as a breast cancer "prevention." It doesn't, said Sledge, kicking off a discussion that led the committee—and ultimately FDA—to use the phrase "risk reduction" instead (**The Cancer Letter**, Sept. 11, 1998).

"Care More About Being a 1.7 than a 36B"

Critics of labeling tamoxifen for breast cancer

risk reduction warn that the drug may be prescribed to women who overestimate their breast cancer risk.

This has not happened, said the University of Pittsburgh oncologist Victor Vogel.

"I don't think tamoxifen is being prescribed indiscriminately," Vogel said to **The Cancer Letter.** "I certainly don't see it in the community. When I go around and talk to physician groups, I see a real reluctance to use this drug. They are not telling enough high-risk women about this. I don't know why. It's unstudied."

In 1998, the year when NSABP announced the findings of P-1 as well as B-24, a trial of tamoxifen in ductal carcinoma in situ, tamoxifen sales in the U.S. climbed to $368.6 million, a $58-million increase from the previous year's sales of $310.6 million, the company said.

The sales figures do not reflect the impact of the advertising campaign that began earlier this year, a Zeneca official said.

"It's a long-term educational process," said Mary Lynn Carver, communications manager at Zeneca Pharmaceuticals. "I am sure that when the first cholesterol-lowering and blood pressure-control drugs were introduced, education with these preventive, risk-reducing agents took a long time."

Both Zeneca and Lilly have been told by FDA that their marketing claims are inconsistent with their drugs' labels. Lilly was told to stop making the breast cancer prevention claim. Zeneca has been told on several occasions that its advertising downplayed the risks of tamoxifen (**The Cancer Letter**, March 12).

Initially, Zeneca was not interested in testing tamoxifen in asymptomatic women. During the P-1 trial, the Investigational New Drug license was held by the NSABP. With approval in hand, Zeneca appears to have overcome this reluctance and is aggressively promoting the indication in direct-to-consumer ads.

So far, the company's "educational campaign" has not gone smoothly.

Last December, Zeneca placed an unusual ad in Mamm, a magazine for breast cancer survivors. The ad contained nothing but the photographs of seven women and the words, "There is something you can do… Nolvadex."

By running the ad, the company managed to step into two bear traps at once.

First, there was the race issue. Both NCI and NSABP have been frequently—and severely—criticized for failure to enroll non-white women in P-1. However, Zeneca apparently overlooked this deficiency in the trial and included pictures of four women of color, implying that the drug has been tested in a variety of populations.

This implication triggered a complaint from activist Pearson to FDA. Looking over the ad flagged by Pearson, FDA didn't act on the race issue. However, the agency determined that information-free ads violate the Food Drug and Cosmetic Act.

"It fails to provide adequate information regarding Nolvadex's approved indication and usage," the agency said in a Jan. 22 letter to Zeneca. By limiting content to the photos, the ad failed to include any risk information or present even a summary of side effects, contraindications, or effectiveness, the letter said.

In the same letter, FDA told the company to stop using another promotional tool, a "reprint carrier" produced to accompany a reprint of the 1998 paper on the results of P-1, published in the Journal of the National Cancer Institute.

Distributed to physicians, such folders summarize materials in the paper. Accentuating the positive, the text on the folder played down the side effects of tamoxifen, improperly claimed a lower risk of fractures, said that endometrial cancer was "uncommon" among high-risk women who took the drug, and inaccurately described the risk assessment criteria, the FDA letter said. The summary also failed to define women at high risk, and presented information on side effects in a manner that "lacks the prominence, readability, scope, and depth that Zeneca dedicated to the presentation of efficacy information," the letter said.

Most recently, Zeneca took out a three-page ad that features a woman in undergarments, sitting with her back to the camera.

"If you care about breast cancer, care more about being a 1.7 than a 36B," the ad states, juxtaposing a breast cancer risk assessment score in the NCI risk model and a bra size.

The Thromboemboli Of Olmstead County

In preparation for the STAR trial, NCI and NSABP have developed a method for assessing risks and benefits of tamoxifen. The approach uses a population model to project adverse events and balance them against the benefits of tamoxifen.

Potential participants in STAR will be given a single number which would allow them to assess whether they stand to benefit from taking tamoxifen

in the trial. This number will be used in conjunction with the Gail Model, a risk assessment method that measures only the risks.

The model, developed by NCI biostatistician Mitchell Gail, was used to establish eligibility for P-1 and is now widely used by women considering tamoxifen for the reduction of breast cancer risk. Volunteers entering the STAR trial would have to have the risk of at least 1.67 percent of developing breast cancer within five years.

While the Gail Model weighs a woman's risk factors for developing the disease, the new approach attempts to go one step further and use the data from P-1 as well as population data to quantify both risk and benefit of tamoxifen.

The new system produces a single number that shows potential usefulness of the therapy for a range of risk categories and age groups. If the number is large and positive, tamoxifen is a worthwhile risk. If the number is large and negative, the risk is probably not worth taking.

The system was developed as follow-up to an NCI-sponsored workshop on breast cancer risk assessment, held last July. A paper describing the new model has been submitted to JNCI, sources said. The authors include Gail and NSABP biostatistician Costantino.

To assess the risks of tamoxifen, statisticians had to find a reliable data set that would reflect the incidence of stroke, pulmonary embolism, and deep vein thrombosis. Since the U.S. has no national surveillance of the incidence of cardiovascular diseases, researchers had to find data that could be extrapolated to the U.S. population.

The best data set on these events—the Women's Health Initiative—is still blinded. Thus, statisticians had to make do with the incidence data from Olmstead County, MN, published in the journal Stroke in 1989.

Since the population of Olmstead County is overwhelmingly white, the next step was to project the incidence in African Americans.

Here, statisticians had to make a projection based on the mortality data. To achieve this, they compared mortality rates of black women with mortality rates of white women from cardiovascular diseases associated with tamoxifen. The resulting ratio was then used to predict the incidence of these cardiovascular events in blacks.

To estimate risk and benefit, the new model uses an index to correlate "life threatening" and "severe" events prevented—and caused by—tamoxifen. In the category of "life-threatening" events, tamoxifen decreases the probability of invasive breast cancer and hip fracture. However, the therapy increases the odds of endometrial cancer, stroke, and pulmonary embolism. In the index, these life-threatening events are given the value of one.

In another, not life-threatening category of events, tamoxifen reduces the risk of in situ breast cancer, but increases the risk of deep vein thrombosis. In the index, these events are given the value of one-half.

In the tables, adverse events are subtracted from events prevented, and calculated for every 10,000 women followed over five years. The result was a model for assessing the risk and benefits one would expect in the general population.

However, people who enroll in clinical trials are healthier than the general population. Comparing these population projections with the actual adverse events observed in P-1, the statisticians measured the so-called "healthy volunteer effect" in the trial. Overall, the P-1 participants experienced about half the number of adverse events one would expect to find in general population.

Thus, potential volunteers for the STAR trial will be shown the risk-benefit data based on the P-1 trial, in which incidence of stroke, pulmonary embolism, and deep vein thrombosis would be extrapolated from the Olmstead County data.

Of Race And Risk

Overall, the tables, which were obtained by **The Cancer Letter**, show that younger women stand to gain the most from tamoxifen, and the risk of adverse events increases with age.

The risk-benefit ratio was much better for women who did not have a uterus, since that eliminates the risk of endometrial cancer.

Another factor was race. Based on extrapolations on the population data, black women had less to gain and more to lose from taking tamoxifen.

To consider the significance of these findings, NCI convened a "working group" to examine the assumptions on which the risk-benefit assessment system was based, as well as to consider possible reasons for disparity associated with race. The working group, which included epidemiologists, physicians, and patients, met at NCI on May 5 to review the STAR consent documents.

After considering the options, the most drastic

of which included instituting different eligibility criteria based on race, the group decided that in the context of eligibility criteria for the trial, race should be viewed as a surrogate for health conditions that can be attributed to diet, culture, and lifestyle.

"A black woman who leads a healthy lifestyle and has no history of hypertension, diabetes, or obesity has the same risks as a white woman; same risks for breast cancer; same risks from taking tamoxifen; same risks from not taking tamoxifen," said Otis Brawley, director of the NCI Office of Special Populations Research, who took part in the meeting. "Race is not a factor. Hypertension and diabetes are."

As a consequence of the meeting, NCI and NSABP decided to exclude women with uncontrolled diabetes and uncontrolled hypertension from taking part in the trial.

In the States:

Illinois, Virginia, Approve Bills Mandating Coverage In Trials

State legislatures in Illinois and Virginia recently approved bills mandating insurance coverage of routine care costs for patients enrolled in cancer clinical trials.

The Illinois House of Representatives gave its unanimous final approval May 21 to a bill requiring health insurance companies to offer coverage for patients participating in cancer treatment trials.

"After many years of negotiations, it is truly satisfying that the General Assembly has approved this plan to give people the opportunity to obtain insurance coverage for clinical trials," said James Wade, immediate past president of the Illinois Medical Oncology Society.

Several organizations, including the Medical Oncology Society, the American Cancer Society, and the Illinois State Medical Society worked for the legislation. Blue Cross and Blue Shield of Illinois endorsed the legislation, HB 1622, sponsored by Rep. Kevin McCarthy of Orland Park and Sen. Kathleen Parker of Northbrook.

Virginia Gov. Jim Gilmore signed a bill April 6 requiring that insurers including health maintenance organizations and the health plan for state employees provide coverage for "patient costs incurred during participation" in cancer treatment trials. The clinical trials provision was attached to HB 871, a "patient's bill of rights" measure.

The legislation, effective July 1, applies to patient costs for phase II, III, and IV treatment trials. Coverage for phase I costs is possible on a "case-by-case" basis under the bill.

Trials covered by the legislation include those approved by NCI, FDA, the Department of Veterans Affairs, or an institutional review board of an institution in Virginia that has approval of the NIH Office of Protection from Research Risks.

MD To Use Tobacco Funds For Anti-Cancer Programs

Maryland Gov. Parris Glendening announced a $1 billion, 10-year program that proposes to spend a significant portion of the state's share of the national tobacco lawsuit settlement on cancer research, prevention, and efforts to reduce smoking.

The state expects to receive $1.7 billion from the settlement over the next decade.

"I see the tobacco settlement not as an infusion of money, but rather as a unique opportunity—a once-in-a-lifetime opportunity—to positively and permanently re-shape public policy," Glendening said at the June 3 announcement. "I see this as an opportunity to take the tobacco industry's blood money and make Maryland a healthier state for everyone."

The state plans to allocate $50 million per year on cancer research and prevention, and $30 million per year for smoking education, prevention, and cessation programs. Of the $30 million, at least $10 million per year would be targeted to reach minority communities.

Glendening asked the University of Maryland and Johns Hopkins University to develop a plan for cancer education, prevention, research, and treatment that would use $15 million annually for each institution over 10 years.

Another $100 million would be committed over the next 10 years for substance abuse programs. Also, $83.5 million would be set aside for financial assistance programs for tobacco farmers.

The state also plans to provide the Maryland Health Care Foundation with $15 million over the next decade to suport the foundation's efforts to provide health care for the uninsured.

Glendening also announced the formation of three task forces: the Task Force on tobacco Crop Conversion in Maryland, the Task Force to End Smoking in Maryland, and the Task Force to Conquer Cancer in Maryland.

Funding Opportunities:

Avon Offers Breast Health Education, Screening Grants

The Avon Breast Health Access Fund is seeking grant applications for programs to facilitate breast health education and screening services. Two types of grants are funded:

—Outreach grants to community based programs that provide medically underserved women with direct access to breast cancer education and screening.

—Inreach grants to medical providers using their existing client databases to recruit underserved women for breast cancer education and screening.

Application deadline is July 15. Applications are available on the website of the National Alliance for Breast Cancer Organizations at http://www.nabco.org or contact Hilary Colwell at 212-889-0606 ext. 3010 or email hcolwell@interport.net.

NCI Extends NCDDG Deadline

NCI has extended the application deadline for RFA CA-99-010, National Cooperative Drug Discovery Groups, http://www.nih.gov/grants/guide/rfa-files/RFA-CA-99-010.html. The previous receipt date of July 14 has been changed to Oct. 13.

In Brief:

ONS Foundation Raises $9.8M To Form Leadership Center

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care. To be considered for membership, send letter describing interest, background, and relevant skills to Consumer Advisory Panel, ONS Board of Directors, 501 Holiday Dr., Pittsburgh, PA 15220-2749 or email marym@ons.org. . . . **ONS FOUNDATION** said it has raised more than $9.8 million to form a Center for Leadership, Information, and Research at ONS headquarters in Pittsburgh. The center is to provide a forum for nurses to increase leadership skills and provide research to enhance their work. Chairman of the capital campaign is **Helene Brown**, director of community applications of research at the Jonsson Comprehensive Cancer Center at University of California, Los Angeles. President of the foundation is **Barbara Carlile Holmes**. . . . **INDUCTED** as charter members into the National Breast Cancer Coalition's "Hall of Fame" last week during the NBCC annual advocacy conference in Washington were **Sens. Ted Kennedy** (D-MA), **Patrick Leahy** (D-VT), **Tom Harkin** (D-IA), and **Rep. Nita Lowey** (D-NY). NBCC also recognized other Members of Congress for their commitment to the fight against breast cancer. They were: **Sens. Barbara Mikulski** (D-MD), **John Chafee** (R-RI), **Ted Stevens** (R-AK), **Reps. Rick Lazio** (R-NY), **Ileana Ros-Lehtinen** (R-FL), **Anna Eshoo** (D-CA), **Michael Bilirakis** (R-FL), and **Tom Bliley** (R-VA). "These Members of Congress have shown us by their actions that they support the Coalition's efforts and that they're committed to working with us to ensure an end to this dreaded disease," said **Fran Visco**, NBCC president. . . . **LUSTGARTEN FOUNDATION** for Pancreatic Cancer Research has awarded grants of $150,000 each to researchers at three institutions: **Michael Goggins**, Johns Hopkins University; **Robert Radinsky**, M.D. Anderson Cancer Center; and **Margaret Tempero**, UNMC Eppley Cancer Center at the University of Nebraska Medical Center. The foundation is accepting applications for the next round of grants. Contact foundation president Robert Vizza, c/o DeMatteis Center of St. Francis Hospital, Northern Blvd., Old Brookville, NY 11545, phone 516-629-2103, fax 516-629-2183. . . . **NCI CANCER PREVENTION** Fellowship Program, a postdoctoral training program, provides Master of Public Health training, a summer academic course in cancer prevention and control, mentored research at NCI, and brief field experiences. Application deadline is Sept. 1. Contact Barbara Redding, phone 301-496-8640, fax 301-402-4863, email br24v@nih.gov. . . . **TWO NEW REPORTS** from the National Academies of Sciences and Engineering and the Institute of Medicine: One finds the U.S. leads the world in most areas of immunology research, primarily due to funding by federal, state, and private sources. The report, "International Benchmarking Of U.S. Immunology Research" is available at no charge from the Committee on Science, Engineering, and Public Policy, phone 202-334-2424. The second report says the health of the federal science and technology enterprise depends on a balanced investment strategy across a broad range of research fields. While funding for NIH has increased 31.2 percent since FY1994, funding for the Department of Defense science and technology budget has decreased 19.8 percent during the same period, the report said. Copies of "Observations on The President's Fiscal Year 2000 Federal Science and Technology Budget," are available at $12 per copy plus shipping from the National Academy Press, phone 202-334-3313 or 800-624-6242. Information: http://www.nas.edu.

THE CANCER LETTER

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Business & Regulatory Report

Formerly "Cancer Economics"

Oncology Management:

US Oncology Is Proposed Name For Firm Resulting From Merger Of AOR, PRN

Houston-based American Oncology Resources Inc. and Dallas-based Physician Reliance Network Inc. will become **US Oncology,** following stockholder approval, the companies said.

The two companies entered a definitive agreement to merge. Closing of the transaction is anticipated on June 15, the companies said.

Under the merger agreement, stockholders of the company and PRN will each own approximately 50 percent of the combined company on a

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Clinical Trials:

ILEX Begins Trial Of Vitamin D3 Analog; Matrix To Study Agent In Colorectal Cancer

ILEX Oncology Inc. (Nasdaq: ILXO) of San Antonio said it has begun patient enrollment into a phase I trial of its vitamin D3 analog, ILX23-7553.

The study, at the University of Medicine and Dentistry of New Jersey, is designed to define the optimum dose and to evaluate the potential of the compound in the treatment of a number of malignancies.

The activity of ILX23-7553 has been documented in preclinical models of acute myelogenous leukemia, as well as breast and prostate cancer cell lines, the company said.

* * *

Matrix Pharmaceutical Inc. (Nasdaq: MATX) of Fremont, CA, said it has begun a phase II study in advanced or recurrent cancer of the colon or rectum for its anticancer agent FMdC.

The study will assess the efficacy and safety of FMdC in this patient population as well as the impact on quality of life and disease symptom relief, the company said. Trials will be conducted at several medical centers in the U.S., and will enroll up to 30 patients.

Since February 1999, FMdC has also been studied in a phase II trial in non-small cell lung cancer. That trial of up to 30 patients is expected to be completed later this year, the company said.

The trial in colorectal cancer is open to patients with stage III or IV disease. Patients may have received one prior course of chemotherapy as well as previous surgery or radiation. Patients will receive an intravenous infusion of FMdC once every 15 days during a two-month

(Continued to page 3)

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PRN Will Become Subsidiary Of AOR Under Merger Plan

(Continued from page 1)

diluted basis. Following the merger, PRN will be a wholly owned subsidiary of AOR.

During the first quarter ended March 31, the AOR net income was $8.5 million ($0.17 per share) on revenues of 139.8 million, the company said. In 1998, net income was $6.5 million ($0.14 per share) and revenues $100.9 million.

PRN earned $8 million ($0.15 per share) on revenues of $114.3 million for the first quarter ended March 31. Last year's first quarter income was $6.7 million ($0.13 per share) and revenues $90.5 million.

* * *

APN-IMPATH Research Co., LLC, of Fort Lee, NJ, said it has executed an agreement with Novartis Pharmaceuticals Corp. of East Hanover, NJ, to conduct an outcomes research study on the usage of the Novartis product Aredias (pamidronate disodium for injection) in its network of oncology physicians.

The study is designed to retrospectively examine physician practice patterns, the company said.

"By understanding current practice patterns and evaluating the patient care outcomes of alternative treatment regimens, we can provide valuable information to our physicians in order to help them make optimal treatment decisions," said Joseph Welfeld, CEO of APN-IMPATH Research.

APN-IMPATH Research Co., LLC is a joint venture formed last year by Affiliated Physicians Network Inc., a network of more than 150 community-based oncology specialists, and IMPATH Inc.

APN-IMPATH Research provides research services, including clinical trials and outcome studies, to the pharmaceutical and biotechnology industries.

APN was founded in 1996 by privately practicing oncologists. IMPATH provides cancer information and analyses, including patient-specific cancer diagnostic and prognostic information. The company said it serves over 4,500 physicians specializing in the treatment of cancer patients, in over 1,740 hospitals and 290 oncology practices.

* * *

Myriad Genetics Inc. (Nasdaq: MYGN) of Salt Lake City said a breast cancer genetic testing follow-up study performed by the Dana-Farber Cancer Institute found that, contrary to the general concern over the potential for discrimination by insurance companies, not a single participant has had their health insurance rates raised or canceled.

The study, led by Fred Li of Dana-Farber, reported the results of 131 patients who had BRCA1/2 genetic testing performed by Myriad Genetics. Participants volunteered to join the study and consented to have their responses to questionnaires linked to the genetic testing results, after all patient identifying information had been removed.

The study, supported with a sponsored research contract by Myriad Genetics, was presented at the 1999 annual meeting of the American Society of Clinical Oncology.

The study found that participants with both positive and negative results expressed a high rate of satisfaction with the test, fully 95 percent of them were glad to have had BRACAnalysis genetic testing.

Additionally, patients who had undergone genetic testing were more likely to seek chemoprevention and less likely to consider prophylactic mastectomy as cancer prevention options.

"In order for society to achieve the greatest benefit from these promising new approaches to preventing and curing disease, concerns such as discrimination by insurers must be put to rest," said Peter Meldrum, president and CEO of Myriad Genetics. "We are very pleased with these data demonstrating positive outcomes for women following

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BRACAnalysis testing, including the lack of any insurance discrimination."

Matrix Begins Phase II Study Of FMdC In Colorectal Cancer

(Continued from page 1)

period. Patients who respond after two months of treatment will continue treatment for at least two more months.

Study endpoints include objective tumor response, duration of response, time to progressive disease, survival and safety.

FMdC is a nucleoside analog. The agent is believed to inhibit DNA synthesis directly by incorporation into DNA strands and indirectly by blocking the action of an enzyme, ribonucleotide reductase, that is important to the formation of nucleotides, the building blocks of DNA, the company said.

* * *

Dana Farber Cancer Center, Columbia Physicians and Surgeons Hospital, and **Cell Therapeutics Inc.** (Nasdaq: CTIC) of Seattle have initiated phase II trial of Apra (CT-2584) in metastatic or unresectable soft tissue sarcomas.

Forty patients initially will be randomized to one of two treatment schedules of Apra, the company said. If one response is observed among the first 20 patients, an additional 20 patients will be enrolled in that treatment arm.

Enrollment is expected to be completed early next year, the company said. Columbia and Dana Farber are primary referral treatment centers for sarcoma.

Data on one of the company's two phase I trials of Apra in sarcoma, conducted at the Christie Hospital in the UK, were presented at the American Society of Clinical Oncology meeting earlier this month.

"Among the 17 patients who had advanced sarcomas in our phase I study, 6 patients (35 percent) had a demonstrable response with 5 of those 6 patients (83 percent) still alive an average of 18 months following treatment with Apra," said Carolyn Paradise, head of medical affairs at CTI. "That's encouraging activity given that all but one of these 17 patients had failed multiple courses of radiation and/or chemotherapy."

Apra kills cancer cells by a process associated with altering their phospholipid composition, the company said. By altering the phospholipid composition of tumor cells, Apra appears to have more activity against a broad variety of cancers including those that are resistant to conventional chemotherapeutic drugs, without the toxicities that commonly accompany treatment with those agents, the company said.

In addition to soft tissue sarcoma, Apra is being investigated in an 80-patient phase II study for hormone- and chemotherapy refractory prostate cancer. Additional phase II trials investigating the use of Apra along with standard chemotherapy for lung cancer are scheduled to begin later this year, the company said.

* * *

EntreMed Inc. (Nasdaq: ENMD)of Rockville, MD, announced the three medical centers that will become the first sites for phase I human clinical trials of recombinant human Endostatin protein. The announcemment was made at the ASCO annual meeting.

The first phase I trial to begin human safety testing and evaluation of Endostatin protein will be through Dana-Farber/Partners CancerCare, the joint-venture between Dana-Farber Cancer Institute, Brigham and Women's and Massachusetts General Hospitals in Boston.

"We have the unique opportunity to initiate the first human safety trial with this novel new protein," said principal investigator Donald Kufe, of Dana-Farber. Judah Folkman, of Children's Hpspital, will be part of the team selected to evaluate phase I data, the company said.

The additional phase I sites are the M.D. Anderson Cancer Center and the University of Wisconsin Comprehensive Cancer Center in Madison. These centers were selected by NCI and will commence their Phase I clinical trials under an NCI-sponsored Investigational New Drug application to FDA.

The Dana-Farber/Partners CancerCare study will be conducted under an EntreMed-sponsored IND.

* * *

Isis Pharmaceuticals (Nasdaq: ISIP) of Carlsbad, CA, has initiated phase II testing of ISIS 2503 as a single-agent in colon, breast, pancreatic, and non-small cell lung cancers.

Approximately ten sites in the US and Europe will enroll between 15 and 30 patients per tumor type, the company said. Phase I trials examining the use

of ISIS 2503 in combination with approved chemotherapies are also planned in 1999.

In phase I studies, ISIS 2503 was well-tolerated, with no clinically significant toxicities observed among 22 patients with a variety of solid tumors who received the drug by 14-day continuous infusion repeated every 21 days, the company said. The schedule will be used in the phase II trials. Prolonged stable disease was observed in four patients on this trial, including one patient with pancreatic cancer who had disease stabilization for eight treatment courses administered over six months.

ISIS 2503 is a selective antisense inhibitor of H-ras gene expression.

* * *

Techniclone Corp. (NASDAQ: TCLN) of Tustin, CA, said it has initiated patient enrollment for a phase I/II trial of Tumor Necrosis Therapy, a chimeric monoclonal antibody radiolabeled with Iodine-131, under the trade name Cotara.

The company said the agent will be tested in pancreatic, prostate and liver cancer patients and will be conducted at the Salvador Zubrian National Nutrition Institute in Mexico City, under the direction of Gabriella Cesarman, of the Department of Hematology and Oncology.

Cotara, which to necrotic cells found in the core of solid tumors, is in phase II trials in the U.S. for malignant glioma, the company said.

* * *

SunPharm Corp. (Nasdaq: SUNP) of Ponte Vedra Beach, FL, said its partner, the Parke-Davis research division of **Warner- Lambert** (NYSE: WLA) of Morris Plains, NJ, will expand clinical trials of the cancer drug, CI-1006 (diethylnorspermine [DENSPM]), a polyamine analogue for the treatment of solid tumors.

This decision follows the demonstration of a modest degree of tumor shrinkage in patients with renal cell carcinoma in an ongoing multicenter phase II study, the company said.

Interim results from the trial were included in the published proceedings of the ASCO annual meeting.

In a related development, Parke-Davis said it decided to expand the clinical studies by combining CI-1006 with other approved anti-tumor agents. "We saw striking synergy in animal studies with CI-1006 in combination with alpha interferon and look forward to starting expanded trials shortly," said W.R. Leopold, Parke-Davis senior director, cancer research. The upcoming studies will enroll 50-100 additional patients into Phase I and Phase II clinical trials over the next year and will include new dosing regimens and combination studies with other anticancer drugs.

CI-1006 is an analogue of a naturally occurring polyamine, which starves the tumor cell of the natural polyamines necessary for rapid growth and eventually kills the tumor cell, the company said. CI-1006 was invented and characterized by Raymond Bergeron at the Department of Medicinal Chemistry at the University of Florida. The drug was then licensed to the Parke-Davis Research Division of Warner Lambert Company from SunPharm Corp.

* * *

Immunex Corp. (Nasdaq: IMNX) of Seattle said it has launched a phase II trial of CD40 Ligand (CD40L) in renal cell carcinoma. The company is continuing the development of CD40L based on results of a multi-dose phase I trial of the drug in advanced cancer patients.

The phase I study, which evaluated escalating doses of CD40L in patients with recurrent solid tumors and lymphoma, has been completed and the objectives of the study were met.

The study, being conducted in three cancer treatment centers across the US, will evaluate the safety and efficacy of the drug in metastatic renal cell carcinoma.

CD40L is a protein primarily expressed on the surface of activated CD4+ T cells. Its receptor, CD40, is expressed on B cells, antigen presenting cells such as dendritic cells, macrophages and on some other normal and tumor cells. The company said pre-clinical research shows that CD40L can stop tumor growth and actually kill many tumor cell types. It does this in two ways: by binding to its CD40 partner present on many tumor cell types generating a signal for the tumor cell to either stop growing or apoptose, or by stimulating specific immune responses to the tumor.

Immunex said it plans to conduct a second phase II trial of CD40L in a separate solid tumor type. Pre-clinical studies have also suggested potential for the compound in HIV and other immunodeficiency diseases. Immunex holds the exclusive global rights CD40L.

* * *

Ligand Pharmaceuticals Inc. (Nasdaq: LGND) of San Diego said the Eastern Cooperative Oncology Group has initiated a phase II study of

ONTAK (denileukin diftitox, DAB389 IL2) in non-Hodgkin's lymphoma. Ligand is marketing ONTAK for CTCL in the U.S.

The primary purpose of the multi-center study is to determine the objective response rate to ONTAK administered to patients with certain types of low- and intermediate-grade NHL who have been previously treated with at least one systemic cancer therapy, the company said.

Specific NHL diagnoses included are: small lymphocytic lymphoma or follicular lymphoma (small cleaved, mixed or large cell) as classified by the International Working Formulation Classification; or small lymphocytic, lymphoplasmacytoid, marginal, or follicular lymphoma as categorized by the Revised European-American Lymphoma classification of the International Lymphoma Study Group.

Malignant cells from study patients will be tested for the presence of the CD25 sub-unit of the receptor for interleukin-2 (IL-2R) to establish whether screening for CD25 is a meaningful criterion for the use of ONTAK.

"The rationale for using ONTAK in this trial includes its novel mechanism of action, its lack of cross-resistance with known mechanisms of drug resistance, and the activity observed in low- and intermediate-grade NHL in the earlier phase I/II trial," said Timothy Kuzel, of Northwestern Medical School, chairman of the study.

The trial will include up to 74 patients, the company said.

Ligand is developing a second multi-center trial protocol for ONTAK in patients with low-grade NHL who have been previously treated with at least one chemotherapy regimen and at least one monoclonal antibody therapy. The trial is in final development and is expected to begin later this year.

* * *

ImClone Systems Inc. (Nasdaq: IMCL) of New York said FDA has agreed to allow the company to initiate a second phase III pivotal trial of its lead cancer therapeutic, C225, in patients with advanced squamous cell head and neck carcinoma. C225, a monoclonal antibody, inhibits activity of epidermal growth factor receptor (EGFr) associated with cancer cell growth in a number of solid tumors.

Achievement of this milestone is triggering a $3 million milestone payment to ImClone from its corporate partner for C225, **Merck KGaA** (DAX: MERCK) of Darmstadt, Germany.

The trial will evaluate the effect of C225 in combination with cisplatin in approximately 114 patients with advanced squamous cell head and neck carcinoma. Under the trial protocol, patients with advanced squamous cell head and neck carcinoma and metastatic disease will be treated with cisplatin alone or cisplatin plus weekly infusions of C225. The primary endpoint of the trial will be response and time to disease progression.

In addition to C225, ImClone's other late stage clinical development program is an anti-cancer vaccine, BEC2, 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, especially against tumors known to secrete vascular endothelial growth factor.

* * *

Magainin Pharmaceuticals Inc. (Nasdaq: MAGN) of Plymouth Meeting, PA, said phase II studies of its anti-angiogenic inhibitor squalamine in non-small cell lung cancer in combination with the leading chemotherapeutic regimen are planned to begin this quarter.

Data from the ongoing phase I trials were presented at the American Society for Clinical Oncology meeting.

The phase I trials were designed to investigate the safety of squalamine as a single agent, at increasing doses and over multiple courses of treatment. Company investigators reported that squalamine is very well tolerated in advanced cancer patients enrolled to date in the studies.

Thirty-nine patients with advanced cancer have been treated in two phase I dose escalation studies, at the Lombardi Cancer Center at Georgetown University (under the direction of John Marshall), and at the Cancer Therapy and Research Center in San Antonio (under the direction of Gail Eckhardt).

"Squalamine has been very well tolerated in our patients in this single agent phase I trial," said Eckhardt. "Squalamine has shown promising anti-angiogenic activity in animal models, and further clinical investigation in combination with cytotoxic chemotherapy is warranted."

Squalamine was discovered in 1992 in the body tissues of the dogfish by a team led by Michael Zasloff, executive vice president and vice chairman of Magainin. The agent uses a class of naturally

occurring, pharmacologically active, small molecules known as aminosterols which are under development at Magainin as human therapeutics.

Product Approvals & Applications:

European Committee Supports Temodal For Astrocytoma

Schering-Plough Corp. (NYSE: SGP) of Madison, NJ, said the Committee for Proprietary Medicinal Products of the European Agency for the Evaluation of Medicinal Products has issued a positive opinion recommending approval of Temodal (temozolomide) capsules for anaplastic astrocytoma.

The CPMP opinion serves as the basis for a European Commission approval, which is typically issued within three to four months, the company said.

Commission approval of the centralized Type II variation to the Marketing Authorization for Temodal would result in one single Marketing Authorization with unified labeling that would be immediately valid in all 15 European Union-Member States.

In January, the European Commission granted centralized marketing authorization to Temodal for glioblastoma multiforme, and in March, Schering-Plough submitted a Type II variation to CPMP seeking approval of Temodal as a first-line treatment of advanced metastatic melanoma, the company said. The application is currently pending regulatory review.

Earlier this year, the FDA Oncologic Drugs Advisory Committee recommended accelerated approval of temozolomide capsules for the treatment of adult patients with refractory anaplastic astrocytoma. The committee recommended against approval for glioblastoma and metastatic malignant melanoma.

* * *

Crescendo Pharmaceuticals Corp. (Nasdaq: CNDO) of Palo Alto, CA, said **ALZA Corp.** (NYSE: AZA) has submitted an NDA to FDA for Duros leuprolide.

The product, which is being developed by ALZA on behalf of Crescendo, is designed to provide a once-yearly dosing regimen of leuprolide for the palliative treatment of advanced prostate cancer, the company said.

ALZA has an option to license the Duros leuprolide product on a country-by-country or worldwide basis. If ALZA exercises its option, Crescendo will receive payments from ALZA based on sales of the product.

Crescendo Pharmaceuticals Corporation was formed by ALZA for the purpose of selecting and developing human pharmaceutical products for commercialization, most likely through licensing to ALZA, the company said.

* * *

Matrix Pharmaceutical Inc. (NNM: MATX) of Fremont, CA, said FDA has granted fast track review status to the company's lead cancer product candidate, IntraDose (cisplatin/epinephrine) Injectable Gel.

FDA guidelines include a six-month goal for the review of new product applications identified as fast track. The fast track review process was authorized by the FDA Modernization Act of 1997 to expedite the review of treatments that have the potential to address unmet medical needs for serious life-threatening disease.

Matrix said it plans to submit a New Drug Application in last half of the year 2000, following completion of the two double-blind, placebo-controlled phase III trials currently enrolling patients with recurrent and refractory head and neck cancer who are considered incurable with surgery or radiation. The planned NDA submission will also include the data from completed open-label phase III studies of IntraDose in other solid tumors, including recurrent breast cancer, malignant melanoma, and esophageal cancer.

IntraDose is designed to provide and retain high concentrations of the potent anticancer drug cisplatin within tumors through direct intratumoral injection while reducing the significant side effects normally associated with intravenous administration of cisplatin, the company said.

* * *

SkyePharma PLC (LSE: SKP; Nasdaq: SKYEY) of London, said its DepoCyt product, a controlled release injectable form of cytarabine, has been launched in the United States.

DepoCyt, which utilizes SkyePharma's DepoFoam sustained-release injectable technology, was approved by FDA in April. The agent is indicated for lymphomatous meningitis.

Deals & Collaborations:

AVAX, University of Tokyo To Collaborate On Vaccine

AVAX Technologies Inc. (Nasdaq: AVXT) of Kansas City, MO, said it has entered into a

collaborative research agreement with the University of Tokyo to evaluate the application of the company's patented AC Vaccine technology to the treatment of breast cancer.

Under the agreement, AVAX will provide the university with access to its technology in order to manufacture the vaccine for a clinical trial in Japan. The trial will be conducted under the direction of Masazumi Eriguchi, of the Department of Surgery, Institute of Medical Science, University of Tokyo, and will be supported in part by a grant from the Noguchi Medical Foundation.

The AC Vaccine technology was invented by David Berd, professor of medicine at the Kimmel Cancer Center, Thomas Jefferson University, in Philadelphia.

The company said the vaccine is made from a patient's own cancer cells by modifying the tumor cells with a molecule called a "hapten." This process, known as "haptenization," alters the tumor cells and makes them appear foreign to the patient's immune system. When the hapten-modified cells are reinjected into patients, they stimulate the immune system to recognize the cancer cells and destroy them, the company said.

AVAX is conducting a trial of the vaccine in malignant melanoma (M-Vax) and a phase I/II trial in ovarian cancer (O-Vax) in the U.S. The collaborative research agreement with the University of Tokyo extends clinical development of the technology to a third indication, the company said.

* * *

Corixa Corp. (Nasdaq: CRXA) of Seattle, and **Zambon Group spa**, said they have entered into a multi-year research collaboration and license agreement covering Corixa's lung cancer antigen discovery program.

The agreement provides Zambon with exclusive rights to vaccine products aimed at treating lung cancer in Europe, the countries of the former Soviet Union, Argentina, Brazil and Colombia, as well as co-exclusive rights in China. Corixa retains its exclusive rights with respect to the rest of the world.

Under the agreement, Zambon also receives certain rights to develop vaccine products containing Corixa's lung cancer antigens, including antigens formulated using Corixa's microsphere delivery system and proprietary adjuvant technologies.

Zambon agreed to purchase $2 million in shares of Corixa common stock at a premium to its market value. If all milestones are reached, Corixa may receive over $21.5 million, the company said.

* * *

The Cord Blood Registry, in collaboration with the **Cord Blood Donor Foundation**, is participating in a Stanford University School of Medicine study which seeks to examine potential links of the prenatal environment to the risk of breast cancer. The study is funded by the Susan G. Komen Breast Cancer Foundation

Prenatal CBR clients who know they are expecting baby girls will be offered the opportunity to donate plasma for the study. The donated plasma is a component of cord blood that is routinely discarded after the processing and storage of a baby's cord blood stem cells.

"The major goal of this study is to compare estrogen levels in cord blood among female babies of the four racial/ethnic groups whose breast cancer risk varies significantly," said Atsuko Shibata, assistant professor of Health Research and Policy at Stanford. "The study relates to the hypothesis that the formation of breast cancer could start very early in a woman's life. This is an important research question, and yet difficult to study."

Shibata, the principal investigator, will be testing samples from baby girls that are among African-American, Asian, Caucasian, and Hispanic groups.

Cord Blood Registry, an umbilical cord blood bank, is a founding member of the Cord Blood Donor Foundation, a not-for-profit organization dedicated to building an ethnically balanced stem cell bank and providing education and medical research.

* * *

The Immune Response Corp. of Carlsbad, CA, said it has reached agreement on key terms of a collaboration with the University of Maryland Biotechnology Institute, whereby IRC will exclusively license rights from UMBI for chemokine and HAF (hCG associated factor) technology discovered by Robert Gallo and his associates at the Institute of Human Virology. The IHV is directed by Gallo.

IRC will issue restricted stock to UMBI as an initial license fee and will sponsor a five-year renewable research program at IHV. In addition, IRC will initiate a research effort of its own at the UMBI facility.

"This relationship creates a vehicle for Dr. Gallo to commercialize the scientific discoveries made at the Institute, and at the same time, it allows IRC to concentrate its efforts and resources on product development and the clinical evaluation of these early

stage products," said Dennis Carlo, IRC president and CEO. "This relationship not only expands IRC's pipeline, but immediately gives the company access to what we believe are some of the most important scientific discoveries made in the last few years. In addition, it builds upon our scientific leadership by having Dr. Gallo play a key role in the scientific direction of the partnership."

HAF is a naturally occurring peptide discovered by Gallo and his associates, the company said.

Gallo's group has generated data in vitro and in vivo that demonstrate HAF may have clinical applications in the direct treatment of cancer, as an adjunct to chemo or radiation therapy by promoting bone marrow cell growth and differentiation, and in HIV prevention and treatment.

IRC will have a right of first refusal to license all new technology related to HAF and chemokines that is subsequently developed by the IHV,

IRC said it will use reasonable efforts to commercialize these products, and will incur the associated cost of patenting the new technology.

* * *

Introgen Therapeutics Inc. of Austin, TX, and RPR Gencell, a division of Rhone-Poulenc Rorer of Colleheville, PA, said they have signed a Cooperative Research and Development Agreement with NCI.

Under the CRADA, NCI will evaluate and develop Adenoviral-p53 (RPR/INGN 201) as a potential anti-cancer agent. The agent will be evaluated in breast, ovarian, bladder, liver, lung, and brain cancers.

Trials for RPR/INGN 201 have been planned throughout the US. Treatment has begun in the ovarian, liver, and bladder trials, and enrollment is expected to begin shortly for other cancer indications.

The trials, conducted under a NCI-sponsored Investigational New Drug Application, which cross-referenced Introgen Therapeutics' existing IND application, will evaluate RPR/INGN 201 alone and in combination with other anti-cancer agents. The companies said Introgen will manufacture the clinical-grade materials for all CRADA trials.

Three phase I trials for RPR/INGN 201, testing the product candidate in head and neck and non-small cell lung cancers, have been completed, and the companies are conducting phase II studies in the U.S., Canada, and Europe for these indications. To date, more than 300 patients have been treated with RPR/INGN 201, yielding critical pharmacokinetic, safety and efficacy data relative to the product candidate and the clinical use of viral vectors in humans, the companies said.

Patents:

Compound To Treat Infections Patented By SafeScience Inc.

SafeScience Inc. (Nasdaq: SAFS) of Boston said it has received U.S. Patent No. 5,891,861 covering composition and method for CAN-296, a naturally-derived carbohydrate compound under development to combat antifungal infections. CAN-296 is a naturally occurring complex carbohydrate extracted from arthropod shells and fungal cell walls.

The company said CAN-296 has demonstrated pre-clinical activity against the fungal infection Candida and Aspergillus, including a rapid killing of fungus, typically within fifteen minutes of exposure, and has shown effectiveness against species and strains that are resistant to conventional antifungal agents. The preclinical studies also indicated that no cross-resistance occurred between CAN-296 and conventional treatments.

SafeScience said it plans to develop CAN-296 for both topical and systemic anti-fungal applications. This is a novel mechanism of action suggesting CAN-296 belongs to a new class of antifungal drugs.

The patent covers CAN-296 for use in treating fungal disease in animals and humans. CAN-296 contains oligomers comprised of repeating units of beta glucosamine.

The claims include analogs of CAN-296, including a broad range of linked repeat units of beta glucosamine, and acetylated beta glucosamine sub units.

* * *

Cytoclonal Pharmaceutics Inc. (Nasdaq: CYPH, CYPHW, CYPHZ) of Dallas announced a patent allowance for the gene coding for Taxadiene Synthase, an enzyme in paclitaxel synthesis. Cytoclonal has been developing a method of making paclitaxel through fermentation and genetic engineering.

The company signed agreements with Bristol-Myers Squibb, the sponsor of Taxol, regarding licensing and further development of these technologies last year. The Taxadiene Synthase gene and other paclitaxel-related genes were isolated by Rodney Croteau of Washington State University, under work sponsored by Cytoclonal.

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