THE CANCER LETTER

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Study Attributes Drop In Breast Cancer To Decline In Hormone Replacement

By Kirsten Boyd Goldberg

Breast cancer incidence dropped sharply in 2003 in the U.S., probably due to the decision by an estimated 15 million women to stop taking hormone replacement therapy, according to an analysis by M. D. Anderson Cancer Center researchers

Using NCI data, the researchers found an overall 7 percent relative decline in breast cancer incidence between 2002 and 2003—the largest drop in breast cancer incidence in a single year ever recorded.

The steepest decline—12 percent—occurred in women between ages 50-69 diagnosed with estrogen receptor positive breast cancer, which depends

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In the Cancer Centers:

M.D. Anderson Wins $11M NCI Grant For Genetic Study Of Glioma Risk Factors

UNIVERSITY OF TEXAS M.D. Anderson Cancer Center received a $11 million grant from NCI to lead a genetic study on the causes and risk factors of adult and pediatric gliomas. The principal investigator is **Melissa Bondy**, professor of epidemiology at M. D. Anderson and director of the Childhood Cancer Epidemiology and Prevention Center—a joint effort among M. D. Anderson, Texas Children's Cancer Center at Texas Children's Hospital and Baylor College of Medicine. The study will incorporate the research of an international consortium of brain tumor specialists, who will examine DNA of families with multiple brain tumors in the U.S., the U.K., Sweden, Denmark, and Israel. **Beatrice Malmer**, associate professor at Umea University Hospital in Umea, Sweden, is the coordinating principal investigator of the European and Israeli study. The American Brain Tumor Association is funding the genetic analysis, which will be carried out in North America by **Ching Lau**, associate professor of pediatrics at Baylor College of Medicine. The genetic analysis of patients in Europe and Israel will be conducted at the Institute of Cancer Research in the U.K. Other American collaborators include Brigham and Women's Hospital; Duke University; Evanston Northwestern Healthcare; Mayo Clinic; Memorial Sloan-Kettering Cancer Center; University of California, San Francisco; and University of Illinois, Chicago. European partners include Umea University Hospital, Sweden; the Institute of Cancer Epidemiology, Denmark; the Institute of Cancer Research, U.K.; and Gertner Institute, Israel. . . . **VANDERBILT-INGRAM** Cancer Center

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As 15 Million Women Cut HRT, Breast Cancer Incidence Fell

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on hormones for tumor growth. The findings were presented at the San Antonio Breast Cancer Symposium Dec. 14.

As many as 14,000 fewer women were diagnosed with breast cancer in 2003 than in 2002, when an estimated 203,500 new cases were diagnosed, the researchers concluded.

"Something went right in 2003, and it seems that it was the decrease in the use of hormone therapy, but from the data we used, we can only indirectly infer that is the case," said Peter Ravdin, the study's lead author who presented the data at the San Antonio conference, and a research professor in the Department of Biostatistics at M. D. Anderson.

"But if it is true, the tumor growth effect of stopping use of HRT is very dramatic over a short period of time, making the difference between whether a tumor is detected on a mammogram in 2003 or not," Ravdin said.

In July 2002, NIH stopped the Women's Health Initiative study when the combination of estrogen and progestin was found, in the randomized trial, to significantly increase the risk of developing invasive breast cancer.

About 30 percent of women older than 50 were using HRT in the early years of this decade, that about half of these women stopped using HRT in the six months after WHI study results were reported, Ravdin said.

"Research has shown that ER-positive tumors will stop growing if they are deprived of the hormones, so it is possible that a significant decrease in breast cancer can be seen if so many women stopped using HRT," he said.

Mathematically, the finding holds up, Ravdin said in his presentation. If 30 percent of women older than 50 were taking HRT, and half stopped taking it, and for those women the risk of developing breast cancer the next year decreased by half, this can be shown by a simple calculation: 30 percent x 0.5 x 0.5 = 7.5 percent, the amount that breast cancer rates would fall.

The study's senior investigator, Donald Berry, said he was surprised by the size and speed of the decline in incidence. "The thing that's the most striking is the precipitous drop, but the fact that there was a drop associated with something that we understand—that is revealing and important, to me," Berry, professor and head of the Division of Quantitative Sciences at M. D. Anderson, said to The Cancer Letter.

Last year, Berry and colleagues published an analysis in the New England Journal of Medicine on the possible effect of screening, chemotherapy, and tamoxifen, on the decline in breast cancer mortality in the U.S. of about 24 percent between 1990 and 2000. As part of that analysis, the researchers also looked at breast cancer incidence during that period.

"Over the period 1975 to 2000, we had seen large increases in the incidence of breast cancer, and one of the influences was the introduction of screening mammography," Berry said. "But we subtracted out mammography and we were still left with about a 30 percent increase in incidence per capita, age-adjusted.

"What's causing this? People suggested environmental estrogens, or maybe it's obesity, and none of them seemed terribly plausible, except for the possibility that it was hormone replacement therapy, because the Women's Health Initiative had shown that breast cancer was fueled by HRT," Berry said.

"Now comes this big dip in 2002 immediately after WHI is published and 15 million women stopped taking HRT," Berry said. "It's pretty compelling evidence not only that HRT was the reason for the drop, but also the reason for the increase, or at least a major contributor to the increase over that period."

The effect of stopping HRT probably isn't taking place on the initiation of cancer, which takes years, but on small, pre-existing cancers that wouldn't have been found with mammograms, Ravdin and Berry said.

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"It takes breast cancer a long time to develop, but here we are primarily talking about existing cancers that are fueled by hormones and that slow or stop their growing when a source of fuel is cut," Berry said. "These existing cancers are then more likely to make it under mammography's radar."

A Cautionary Note

However, because the analysis is based solely on population statistics, the researchers said they can't know for certain why incidence declined. "We have to sound a cautionary note, because epidemiology can never prove causation," Berry said.

Even with that caveat, epidemiologists and public health advocates will find the M. D. Anderson team's analysis intriguing, because it appears that the epidemiologic finding may have, in effect, verified the result of the WHI randomized trial, said Otis Brawley, professor of oncology and epidemiology and deputy director of the Winship Cancer Institute at Emory University.

The WHI was controversial, because the randomized trial didn't confirm what was "known" from epidemiologic studies—that HRT was "good for the heart," though there was evidence that estrogen may increase the risk of getting breast cancer, Berry said.

"Many doctors had tremendous difficulty accepting the WHI findings, and many will have trouble accepting this finding, because they are struggling with scientific reality versus what their beliefs have always been," Brawley said.

"This may be one of the most important findings of the decade," Brawley said. "It should radically change medical practice. This finding, combined with the WHI finding, is going to prevent more breast cancer than tamoxifen could ever dream of preventing. From a public health perspective this is groundbreaking."

The analysis also may help explain why black women have fewer, but more aggressive breast cancers than white women, since studies have shown that white women are more likely than black women to use HRT, Brawley said.

"One of the questions this study brings up is, what about mortality?" Berry said. "These cancers may be not as aggressive as other cancers, and may be acutely susceptible to treatment with hormonal therapy. That still is an important consideration, because we don't want women out there with breast cancer, even if the breast cancer is not lethal. But the effect on mortality is as yet unknown. My own guess is the effect is not going to be great, if at all."

NCI's CISNET Consortium

To conduct the study, Ravdin, Berry, and researchers at NCI and Harbor UCLA Medical Center, working as part of NCI's CISNET Consortium, analyzed data from nine regions across the country that contribute data to the NCI Surveillance Epidemiology and End Results database, from which national cancer incidence statistics are derived.

They examined rates of breast cancer in the U.S. from 1990 to the end of 2003 and found that while incidence increased at 1.7 percent per year from 1990 to 1998, it began to decrease, relative to other years, 1 percent each year from 1998 to 2002. When that 1 percent increase was adjusted for age in each of those years, incidence from 1998 to 2002 stayed about the same.

"There were more cases of breast cancer being diagnosed, but that was because women were getting older and entering the higher risk pool," Ravdin said.

But by the end of 2003, there was a 7 percent, age-adjusted decrease in the number of breast cancer cases diagnosed. With further analysis, the researchers discovered that decline in incidence was far greater in ER-positive breast cancer (8 percent) compared to ER-negative breast cancer (4 percent). When they looked at women 50-69 years old, the decline in ER-positive cancer was 12 percent, compared to 4 percent in ER-negative breast cancers. After adjusting for age, the researchers concluded that there was an absolute decline of about 14,000 fewer women diagnosed with breast cancer in 2003 than in 2002.

In his presentation, Ravdin said the results raise several questions that the researchers hope to address in future studies:

1. Will the patients on the WHI trials stopping HT experience a fall in breast cancer incidence rates?

2. How might the effects on incidence depend on the specific type of HT and the duration of use?

3. Might it be due to something other than HT ? (SERM use, anti-inflammatory agents, statins, or something else).

4. What will the time course of this effect be (will it be just 2003 or a multi-year effect)?

"The question is this: Why the drop?" Berry said. "Presumably, what is happening is that there is a set of cancers out there that are being fueled by hormones. Now you withdraw the hormones, what is the effect? Is it that it completely stops the growth? Is it that is slows the growth? Is it that, in fact, it might reverse the growth and these cancers would disappear? But we don't know which it is. We are going to try to address

that question in subsequent modeling in this CISNET consortium from NCI.

"If it is that [not using HRT] stops the growth and that this subset of breast cancers will not, in the future, be detected, then the decline will continue through 2004, although less dramatically, and then will level out," Berry said.

"If it is that [not using HRT] slows the growth, but that eventually these cancers will come back—unless the woman dies of other causes—then it will continue to dip for a while, but eventually will start to rise again. When that occurs depends on the extent of the slowing, maybe in 2005, 2006, 2010."

The research was conducted as part of CISNET, a consortium funded by NCI to mine cancer statistics for information that would help model the future of cancer incidence and mortality.

Coauthors include Kathy Cronin and Nadia Howlader from NCI, and Rowan Chlebowski, from Harbor UCLA Medical Center.

Capitol Hill:

NIH Reauthorization Approved In Last Hours Of Congress

By Kirsten Boyd Goldberg

Congress gave final approval Dec. 9 to a bill that authorizes budget increases for NIH and strengthens the role of the NIH director in setting scientific policy.

The National Institutes of Health Reform Act of 2006 (H.R. 6164) is the first reauthorization for the institutes since 1993.

The Act would:

—Authorize the NIH budget for fiscal years 2007-2009, including a $2 billion increase for FY 2007 and a $2.5 billion increase for FY 2008.

—Launch an electronic reporting system to catalogue all of the research activities of the NIH in a standard format.

—Limit the size of the NIH to the current 27 institutes and centers.

—Establish a "common fund" to support promising research that cuts across multiple institutes or centers.

—Create a Scientific Management Review Group, composed of institute and center directors and other experts, to evaluate NIH's structural organization at least once every seven years and propose any restructuring plans it deems necessary.

House Energy and Commerce Committee Chairman Joe Barton (R-Tex.) had introduced the bill in the House, which passed it on a 414-2 vote Sept. 26.

"This legislation will strengthen the research efforts of the NIH and will provide the foundation for future scientific and medical advancement," Barton said in a press release. "For 13 years, this program has remained unauthorized despite a Republican-led effort to double the NIH budget. Meanwhile, the science has sped past. We can help the NIH catch up by providing it with not just twice the money, but the tools it needs to reorganize and revitalize.

"We can accomplish all that and do the taxpayers a good turn, too, with increased transparency and improved strategic planning on how research funds are allocated at NIH," he said. "Increased transparency of NIH research activities can only serve to improve research portfolio management, provide greater accountability of research dollars, and spur creative thinking about new scientific approaches."

NIH Director Elias Zerhouni said the bill would help the institutes modernize. "I commend Congress for its overwhelming bipartisan show of support and confidence in the National Institutes of Health," he said. "The passage of the 2006 NIH reauthorization bill is an affirmation of the importance of NIH and its vital role in advancing biomedical research to improve the health of the Nation. The legislation preserves the core authorities of NIH, while adding new tools to maximize NIH's effectiveness. Congress has taken an important step towards modernizing the operation of NIH, in conformance with a new era of science. It brings greater hope for the many people across the nation and around the world suffering from disease and disability. It also increases our future potential for pre-empting disease before it strikes and improving people's health.

"This support from Congress could not have come at a better moment," Zerhouni said. "We are at a pivotal point in the history of medical research—now is the time to take full advantage of the tremendous momentum in science to help revolutionize medicine and health in this country."

The legislation was endorsed by 46 scientific societies, research institutions, and patient-advocacy groups, including the Association of American Medical Colleges, the Federation of American Societies for Experimental Biology, and the Association of American Universities.

"Our nation will be well served by this legislation, which emphasizes the cornerstone of medical breakthroughs, investigator-initiated research, as well as providing commonsense transparency and sustainable levels of funding for NIH," said Leo Furcht, president of the Federation of American Societies for Experimental

Biology.

"We want all people to live longer, healthier lives," Furcht said. "NIH is key to discovering the treatments and cures to the debilitating diseases and injuries suffered by millions of Americans. We strongly urge the President to sign this bill as quickly as possible, and support the authorization levels specified for NIH in his FY2008 budget proposal to Congress."

Jon Retzlaff, FASEB director of legislative relations, said the bill's passage sends a strong message of support for NIH. "Medical research has always been a high priority for the American people and NIH reauthorization will demonstrate that it remains a priority for Congress, too," Retzlaff said. "The NIH budget has lost purchasing power over the past four years, and we look forward to working with Congress through the upcoming fiscal years to realize the vision they have outlined for NIH."

In a statement, FASEB thanked Barton for his "tireless leadership," as well as Rep. John Dingell (D-Mich.), Sen. Mike Enzi (R-Wyo.), Sen. Edward Kennedy (D-Mass.), Sen. Arlen Specter (R-Penn.), and Sen. Tom Harkin (D-Iowa).

The vote came hours after a senior NIH researcher, Trey Sunderland, pled guilty in federal court to violating conflict of interest rules. A review conducted by the Energy and Commerce Subcommittee on Oversight and Investigations concluded that Sunderland improperly shared thousands of valuable human tissue samples with Pfizer, and received $285,000 from the drug company. Sunderland appeared at a June 14 subcommittee hearing and invoked his Fifth Amendment right against self-incrimination.

FDA News:

Deputy FDA Commissioner To Depart For Think Tank

SCOTT GOTTLIEB, FDA deputy commissioner for medical and scientific affairs, said he plans to leave Jan. 16 to return to the American Enterprise Institute, a Washington-based think tank where he was a resident fellow prior to joining the agency in 2005. He will be working with **Mark McClellan**, former FDA commissioner and CMS administrator who joined AEI after leaving CMS in October. FDA Commissioner **Andrew von Eschenbach** said Gottlieb "helped to create a forward-thinking policy agenda that bolstered our efforts to transparently provide more timely information to patients and providers so they can have the tools they need to make informed medical decisions."

NCI Programs:

NCAB Members Urge Board To Take A More Active Role

By Kirsten Boyd Goldberg

Several members of the National Cancer Advisory Board urged the board to play a more active and visible role in support of the National Cancer Program.

The appointment of a new NCI director and six new NCAB members in recent months appears to have awakened the board from a quiet period of uncertainty over the institute's leadership. Now the new board members, as well as some veterans, say it's time for the NCAB to make public statements on important issues such as tobacco and Congressional appropriations for biomedical research.

"This is my second meeting and what I see here is a typical board meeting," NCAB member Donald Coffey said at the board's Nov. 30 meeting. "You hear reports, but you take no action."

Coffey, a former president of the American Association for Cancer Research and a urology professor at Johns Hopkins University, asked NCI Director John Niederhuber to give the board some guidance.

"What did we actually decide as a group at our last meeting that would have been helpful…to the NCI?" Coffey said. "I could not identify anything that we made a decision on. Tell us some specific ways we could be more helpful."

Niederhuber, who served as chairman of the NCAB for two years before he joined the institute, said he was "sympathetic" to Coffey's concern. "When I came on the board in 2002, I had the same kind of sense, that we wanted to have more opportunity to help make decisions," he said. As board chairman, he held a retreat to discuss "how could we be more helpful," he said.

"The way that I see it now coming from the other side is [that] you are hugely important to us in communicating our message—hugely important," Niederhuber said to the board. "You are able to do things when you are not here—working in your own universities, with your university boards and the powerful people who sit on them, the powerful and influential people who sit on cancer center boards, and patients—to impact on the national story about cancer.

"You communicate that national story to legislators," Niederhuber said. "We know that we need to increase the investment in cancer. That's what we really need to do."

The 18-member board was created by the National

Cancer Act of 1971. Twelve of the members must represent health and scientific disciplines relevant to the institute, while six are public representatives from fields such as cancer patient advocacy, public policy, and management. Board members serve six-year terms and a third of the membership is replaced every two years.

"Too Much Niceness"

The NCAB could be "a little more active," said Carolyn Runowicz, the board chairman and director of the Neag Comprehensive Cancer Center at University of Connecticut. "I certainly support that," she said to Niederhuber. "We can go back to our communities and we can advocate for more research funding. The brainpower around this table is very impressive, and we can provide input on whatever you need."

The board's Planning and Budget Subcommittee could examine research funding issues, she said. "Things like more stamps," she said. "The American public has voted with their feet and are willing to pay 8 or 10 cents more per stamp to support breast cancer research. That's been a windfall. Maybe we need to do one in prostate, or lung, or ovary, or something else. I think we can do more than what we are doing."

Also, the subcommittee could look at areas where NCI could economize, Runowicz said. "For example, information services," she said. "The American Cancer Society is probably the most trusted source in cancer information services, and maybe we need to re-evaluate how much money we, meaning the NCI, put into cancer information services, and maybe we want to partner or collaborate with somebody who does it as great as we do it, or better, and pool those resources, and then take those resources and put them into training grants, for example, where our future is. That's just a wild thought."

Franklyn Prendergast, director of the Mayo Clinic Comprehensive Cancer Center and an NCAB member for the past three years, said the NCAB should define its "advisory" role.

"You look around the table and the people who are involved at this table, and the purpose I would imagine here is some sort of cerebral function," Prendergast said. "If so, then advisory meetings [should] provide substantive advice on substantive matters that justify coming to Washington in the middle of December."

The board has "too much diffidence" toward NCI, Prendergast said. "There is too much niceness and cuteness in all of this, rather than trenchancy without stridency," he said. "I think we need some more direct and tangible engagement. I think it's time that the National Cancer Advisory Board stand for something more than sitting and having lunches at the big table.

"If this seems out of line, it isn't meant to be," Prendergast said. "It's meant to be a call for action on the part of this board to stand up and be counted. It is not sufficient to be a scribe or an amanuensis. We have got to be a voice, it seems to me, on behalf of both the investigators and of the pubic on matters that are germane [to] the overall responsibility of the National Cancer Institute."

NIEDERHUBER: "I can't say that I disagree with anything you said. I get a report from each board meeting that itemizes in great detail what each of our scribes sitting around this room feel were constructive comments, action items, and we talk about that at our staff meetings, or Executive Committee meetings, and we try to meet those suggestions. Maybe we haven't done as good a job of giving you back a PowerPoint that says with a checkmark off on each of those things."

PRENDERGAST: "What Don says is right. We are your voice and we amplify that voice, in terms of reporting back to our institutions, to the public, and the scientists. But that amplification, in my view, has been muted, not by you, but by virtue of circumstance, by virtue of the culture of the institution, that has permeated the very walls and that inflicts us with some sort of strange virus. It strikes me that we can find a way to very effectively amplify what you want to do by validating our opinion of what you want to do, we could be a much more impressive voice, especially back to the legislature."

NIEDERHUBER: "I hope that you do use it that way."

"Speak Up For The Good Of The Nation"

NCAB members can't lobby when they are working on government time, at government expense, noted Paulette Gray, director of the NCI Division of Extramural Activities and executive secretary of the board.

"Are we prohibited as a board to communicate a consensus on a particular topic, bill, etc.?" asked board member Lloyd Everson, vice chairman of US Oncology Inc.

"No you are not prohibited, but the discussion about that particular issue must occur in an open session of this meeting," Gray said.

COFFEY: "I'm not so interested in our political action at the Capitol, we can do that on the outside. But what I would like to ask you is, can we get into the political process of the NIH? There must be some place where we as a board can go in and weigh in.… There are

sensitive institutional issues, but there are times when this group could speak up for the good of the nation and the good of cancer, on the politics within the NIH and within the NCI, that I think would be very beneficial. What do you think, John?"

NIEDERHUBER: "I'm assuming that I could probably find a job after this."

COFFEY: "Is that an advisory role?"

NIEDERHUBER: "Yes, that is advisory. Absolutely. You may, and the board has spoken out, and I'd also emphasize two things. One is that I feel I have a very, very good relationship with my former Hopkins colleague [NIH Director] Elias [Zerhouni], and we are able to sit and really give and take on issues. I feel he actually has a real interest in what I think about certain issues. Secondly, he is also very, very committed to NCI in many ways, though he does have to love all of his children, but he is committed to the NCI and as you know, served on the BSA before becoming director of NIH, and he willing to come here anytime."

COFFEY: "I was not directing that at any person, but policy and process."

Other Comments

NCAB member David Koch, executive vice president of Koch Industries, urged NCI to do more to streamline the grant applications process. "What I don't understand is, if the rest of the NIH institutes aren't willing to do it, why can't NCI take the lead and set up streamlining on the grant applications here, and the rest of the institutes can follow?" he said. "Are there any rules in the NIH that all the institutes have to go in lock-step? Can't the NCI break free and do it on their own?"

GRAY: "Within the NCI, we have streamlined the review of certain mechanisms that are assigned directly to NCI, for instance, the Program Project grant reviews. We brought those to you and reported to you exactly how we were going to streamline those."

NIEDERHUBER: "We're primarily talking about a set of funding instruments called RPGs. If we really thought about it, we would understand that this really needs to be a corporate mechanism at that level. The reason I say that is that, remember our investigators may have one grant from NCI, one grant from NIAID, and one grant from the Institute of Aging. At that level, you have to act in a corporate way, both in terms of the instruments that are used and the funding policies that are set, so there aren't inequities in the process."

NCAB member Bruce Chabner, clinical director of the Massachusetts General Hospital Cancer Center, said he was concerned about NCI's increasing use of the Foundation for NIH to fund research at the same time that cancer centers are having to do more fundraising.

"With the leveling of the budget, it became apparent that we would have to do more fundraising ourselves to make up for the gap in our expectations about funding for the cancer centers in the future," Chabner said. "This included, for us, targeting the same people that you are targeting for [NIH] foundation fundraising.

"I'm worried that we are going to be colliding in this sphere, and I'm not sure that this is the way a government agency should be solving its budget problems," Chabner said. "I know these are very worthwhile projects, but I would suggest that there should be some very frank discussion with the cancer center directors particularly about this issue, because we can't all try to feed at the same trough at the same time."

"That's a very good point, and one that I'm probably as sensitive to as you are, Bruce, having worked in a university environment with our cancer center also competing with the university, competing with the medical school, and always this kind of tension," Niederhuber replied. "I'm familiar with that. I would think we would have most of the potential collisions around the foundations, and we kind of stay away from that. It's more that the foundations come to us, looking for investment, because they recognize that we have that very important peer review component. I constantly get visited by some of the key foundations looking for advice and help on what they can do. We process that through the foundation. But most of my work with the foundation is, I promise you, and will be, where we can be proactive to the extent that I can legally be proactive, is through the foundation to work with industry. We are working mostly with biotech and big pharma, because that's where the bigger dollars are for us to do the bigger projects."

In the Cancer Centers:

(Continued from page 1)

and AstraZeneca have developed a master scientific agreement to streamline and integrate collaborations in basic, translational and clinical cancer research. "Our goal is to shorten the time to approval of more effective new drugs and new combinations," said **Carlos Arteaga**, the Vice Chancellor's Chair in Breast Cancer Research and director of the Breast Cancer SPORE at Vanderbilt-Ingram. Common goals include identifying molecular targets for therapy and biomarkers to assess and predict response to treatment.

NIH Funding Opportunities:

RFA-CA-07-031: Early Clinical Trials of New Anti-Cancer Agents with Phase 1 Emphasis. U01. Letters of Intent Receipt Date: Feb. 26. Application Receipt Date: March 26. Full text: http://www.grants.nih.gov/grants/guide/rfa-files/RFA-CA-07-031.html. Inquiries: S. Percy Ivy, 301-496-1196; ivyp@ctep.nci.nih.gov.

PA-07-106: Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research. F31. Application Receipt Date: April 13, Aug. 13, Dec. 13. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-106.html. Inquiries: H. Nelson Aguila, 301-496-7344; Aguilah@mail.nih.gov.

PA-07-107: Ruth L. Kirschstein National Research Service Awards for Individual Predoctoral Fellowships to Promote Diversity in Health-Related Research. F32. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-107.html.

PA-07-140: Research on Sleep and Sleep Disorders. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-140.html. Inquiries: Ann O'Mara, 301-496-8541; ao45s@nih.gov.

PAR-07-160: Innovations in Biomedical Computational Science and Technology Initiative SBIR R43/R44. Application Receipt Date: Feb. 9; May 24; Sept. 24; Jan. 24, 2008; May 24; Sept. 24; Jan. 24, 2009. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-160.html. Inquiries: Peter Lyster, 301-451-6446: lysterp@mail.nih.gov.

PAR-07-161: Innovations in Biomedical Computational Science and Technology Initiative SBIR R41/R42. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-161.html.

PA-07-148: Understanding Mechanisms of Health Risk Behavior Change in Children and Adolescents. R01. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PA-07-148.html. Inquiries: Linda Nebeling, 301-451-9530; nebelinl@mail.nih.gov.

PAR-07-145: Tools for Zebrafish Research. R01. Application Submission/Receipt Date: Sept. 19. Full text: http://www.grants.nih.gov/grants/guide/pa-files/PAR-07-145.html. Inquiries: Lorette Javois, 301-496-5541; lj89j@nih.gov.

Request for Information: Tools and Resources for Human Embryonic Stem Cell Research in the Nervous System. Response Due Feb. 2, to BlueprintESC@mail.nih.gov. Full text: www.grants.nih.gov/grants/guide/notice-files/NOT-DC-06-004.html.

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THE CANCER LETTER

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Business & Regulatory Report

Product Approvals & Applications:

Eli Lilly Applies for FDA Approval of Evista In Postmenopausal Invasive Breast Cancer

Eli Lilly and Co. (NYSE:LLY) of Indianapolis said it submitted a New Drug Application to the FDA Division of Drug Oncology Products for Evista (raloxifene HCl) for invasive breast cancer in postmenopausal women with osteoporosis and postmenopausal women at high risk for breast cancer.

Evista is indicated for osteoporosis in postmenopausal women, the company said.

The filing includes data from four clinical trials representing data from three different patient populations: Postmenopausal women at increased risk for invasive breast cancer in the Study of Tamoxifen and Raloxifene (STAR) trial; Postmenopausal women with known or at increased risk for coronary disease in the Raloxifene Use for The Heart (RUTH) trial; Postmenopausal

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Clinical Trials:

Bayer, Onyx Say Phase III Trial Of Nexavar In Melanoma Didn't Meet PFS Endpoint

Bayer Pharmaceuticals Corp. (NYSE:BAY) of West Haven, Conn., and **Onyx Pharmaceuticals Inc.** (NASDAQ:ONXX) of Emeryville, Calif., said a phase III trial administering Nexavar (sorafenib) or placebo tablets in combination with the chemotherapeutic agents carboplatin and paclitaxel for advanced melanoma did not meet its primary endpoint of improving progression-free survival.

The treatment effect was comparable in each arm, the companies said. The international, double-blind, randomized, placebo-controlled trial evaluated Nexavar when administered in combination with a standard dosing schedule (21-day cycles) of carboplatin and paclitaxel.

The trial enrolled 270 patients progressing after one previous systemic chemotherapeutic treatment with either dacarbazine (DTIC) or temozolomide. The study measured the safety and efficacy of the drug when co-administered with chemotherapy, and had PFS as its primary endpoint.

PFS is defined as the time that a patient lives without meaningful tumor growth. The safety profile of these agents in combination (Nexavar with carboplatin/paclitaxel) was comparable to those previously reported for the agents in combination, the companies said.

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Cleveland BioLabs Inc. (NASDAQ:CBLI) of Ohio said it has begun a phase II efficacy study for Curaxin CBLC102 in advanced, hormone-

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FDA Grants Full Approval Of Velcade For Lymphoma

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women with osteoporosis in the Multiple Outcomes of Raloxifene Evaluation (MORE) and Continuing Outcomes Relevant to Evista (CORE) trials, the company said.

The NDA includes data from 37,000 postmenopausal women from four studies that have spanned nearly 10 years, the company said.

The most commonly reported side effects are hot flashes and leg cramps. Side effects with Evista are usually mild, the company said.

* * *

Millennium Pharmaceuticals Inc. (Nasdaq: MLNM) of Cambridge, Mass., said FDA has granted full approval of Velcade for mantle cell lymphoma where there has been at least one prior therapy.

The approval marks the first indication for Velcade for lymphoma, the company said.

"Mantle cell lymphoma is the most challenging lymphoma to treat because it is commonly resistant to chemotherapy in the relapsed setting," said André Goy, chief of The Division of Lymphoma, The Cancer Center at Hackensack University Medical Center.

The approval is based on data from the PINNACLE trial, a prospective, multi-center, single-arm, open-label study for MCL where the disease progressed following at least one prior therapy, the company said. Response rates to treatment were determined according to the International Workshop Response Criteria and based on independent radiologic review of CT scans.

Results include: overall response rate of 31 percent; complete response (CR + CRu) rate of 8 percent; median duration of response of 9.3 months; 15.4 months in patients achieving a complete response; and median time to progression of 6.2 months, the company said.

The most commonly reported adverse events were asthenic conditions (72 percent), peripheral neuropathy (55 percent), constipation (50 percent), diarrhea (47 percent), nausea (44 percent), decreased appetite (39 percent), rash (28 percent), edema (28 percent), vomiting (27 percent), dizziness (23 percent), dyspnea (23 percent), insomnia (21 percent) and thrombocytopenia (21 percent), the company said.

Two U.S. cooperative groups are studying Velcade, the company said. The first study, conducted by the Southwest Oncology Group, is in the front-line setting. The second study, conducted by the Cancer and Leukemia Group B, is evaluating the combination with R-CHOP as consolidation or maintenance following transplant.

Earlier this year, Millennium and co-development partner, Johnson & Johnson Pharmaceutical Research & Development, began an international phase III trial with the agent in combination with rituximab for relapsed or refractory follicular lymphoma.

More than 170 clinical trials with Velcade are ongoing in various disease settings, both company sponsored and investigator initiated, the company said.

In a related development, Millenneum said Velcade (bortezomib) for Injection, for relapsed multiple myeloma, has been added to the updated National Comprehensive Cancer Network treatment protocol for newly diagnosed MM.

* * *

Medarex Inc. (NASDAQ:MEDX) of Princeton said FDA has granted Fast-Track designation for ipilimumab (also known as MDX- 010) used in combination with chemotherapy (dacarbazine) for untreated (first-line) metastatic melanoma.

FDA also has granted Fast-Track designation for ipilimumab used as a monotherapy in treated (second-line) metastatic melanoma patients, the company said.

Ipilimumab is an investigational fully human antibody against human CTLA- 4, a molecule on T cells that suppresses the immune response, the company said. The drug is under investigation in registrational clinical trials under Special Protocol Assessment agreements with FDA for metastatic melanoma--as a first-line

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treatment in combination with dacarbazine, as a second-line monotherapy and as a second- line treatment in combination with MDX-1379, the company said.

* * *

ACCESS Pharmaceuticals Inc. (OTC Bulletin Board: ACCP) of Dallas said it had received 510(k) clearance from FDA to market MuGard, its proprietary oral rinse product for oral mucositis, in the U.S.

Studies of the rinse prevented significant mucositis in over 40 percent in a population where the incidence of mucositis normally exceeds 90 percent, the company said. In addition to the management of mucositis, the approved indication for MuGard includes all types of oral wounds, including aphthous ulcers and traumatic ulcers, such us those caused by oral surgery or ill-fitting dentures or braces.

* * *

Advanced Magnetics Inc. (NASDAQ:AMAG) of Cambridge, Mass., said **Guerbet S.A.** of France, its European partner, submitted a marketing authorization application, the European equivalent of an NDA, to the European Medicines Agency for Combidex, an investigational functional molecular imaging agent used with magnetic resonance imaging to differentiate normal from metastatic lymph nodes.

The functional molecular imaging agent consists of iron oxide nanoparticles, the companies said.

Guerbet said the MAA was submitted seeking approval of Combidex under the trade name Sinerem for pelvic cancers, including prostate, bladder and uterus cancer.

Advanced Magnetics and Guerbet said they are parties to a supply and distribution agreement whereby Advanced Magnetics granted Guerbet an exclusive right to manufacture and sell Combidex in countries in the European Union, South America, the Middle East, Southeast Asia, South Africa, Mexico and Eastern Europe.

Clinical Trials:

Cleveland Clinic Begins Study Of Curaxin For Prostate Cancer

(Continued from page 1)

refractory prostate cancer at the Cleveland Clinic and Case Western Reserve University Hospital.

Curaxin CBLC102 is an oral drug used for malaria that demonstrates efficacy in vitro, in animal models, and in live tumors, the company said.

Test results indicate the treatment can be effective against malignancies, including hormone refractory prostate cancer, renal cell carcinoma, and soft-tissue sarcoma, the company said. FDA permitted Cleveland BioLabs to advance directly to phase II studies, based on CBLC102's historic safety profile.

The 31-patient study dosing regimen includes a 300 mg loading dose three times daily for seven days, followed by a 100 mg maintenance dose administered once daily for an additional 23 weeks, the company said. Primary endpoints are reduction in PSA levels, reduction in tumor size, and disease-free survival. The duration of the study is two years, however certain preliminary data may be available earlier.

The CBLC102 mechanism of action simultaneously hits two cancer targets: p53 and NF-kB; which research indicates would be effective in the majority of cancers, the company said. The mechanism of action was identified at Cleveland BioLabs and the Cleveland Clinic Foundation, which was published in the November 14, 2005 issue of the Proceedings of the National Academy of Sciences .

* * *

Generex Biotechnology Corp. (NASDAQ: GNBT) said the results of clinical studies on a novel cancer vaccine being developed by its wholly owned immunotherapeutics subsidiary, Antigen Express Inc., will be presented at the 29th Annual San Antonio Breast Cancer Symposium. The results of the studies will be presented by Col. George Peoples, a collaborator of Antigen Express who has been directing the trials at the Walter Reed Army Medical Center.

The presentation is entitled "Results of a phase I clinical trial of an Ii-Key/Her2/neu MHC class II peptide-based vaccine in breast cancer patients" and reports clinical data from the phase I clinical trial of the Antigen Express cancer vaccine being conducted at the Walter Reed. The clinical studies were initiated in April of 2005.

The immunotherapeutic vaccine being developed at Antigen Express, AE37, is designed to elicit a specific response against a protein encoded by the HER-2/neu oncogene, which is expressed in a high percentage of various types of cancer. The trials have shown that the vaccine is safe, well-tolerated and produces a significant immune response in breast cancer patients.

While the target of AE37 is the same as that of the marketed cancer drug Herceptin, the activity of AE37 relies on its ability to stimulate a patient's own immune system to recognize the cancer target rather than by interacting with the target directly. The advantage of this is that the immune system, once activated, is capable of detecting lower levels of the target protein than is

Herceptin and that the anti-tumor activity lasts long after termination of AE37 treatment.

"The phase I studies have been successful both in establishing the safety of AE37 as well as in determining an optimal biological dose," said Eric von Hofe, president of Antigen Express. "The results of these studies provide a solid foundation both for subsequent Phase II studies designed to look at the efficacy AE37 and for upcoming clinical trials on the use of AE37 in prostate cancer patients."

* * *

Dynavax Technologies Corp. (NASDAQ:DVAX) of Berkeley said it has begun a phase I dose escalation trial of its TLR9 agonist in combination with a standard chemotherapeutic regimen for metastatic colorectal cancer.

The enrollment target of 15 patients, previously treated for colorectal cancer but had a recurrence of the disease, would be conducted at three centers in the U.S., the company said. The trial would identify the optimum dose and yield safety and tolerability data for escalating doses of the TLR9 agonist administered with irinotecan and cetuximab.

"In preclinical studies, TLR9 agonist has shown anti-tumor activity when administered alone and in combination with monoclonal antibodies or chemotherapeutic agents," said Eduardo Martins, vice president, clinical development at Dynavax.

The trial is the first of several funded by Symphony Capital, which committed $50 million to Dynavax to advance the cancer program and other therapeutic indications into clinical trials, the company said.

An ongoing phase II trial funded by NIH is evaluating a TLR9 agonist with Rituxan in non-Hodgkins Lymphoma, the company said.

* * *

Genmab A/S of Copenhagen said it has begun a phase II study of HuMax-CD20 (ofatumumab) in combination with fludarabine and cyclophosphamide for chronic lymphocytic leukemia.

The 56-patient study will be randomized into two treatment groups of 28 each, the company said. Each patient will receive 6 monthly infusions of either 500 or 1000 mg of HuMax-CD20 in combination with FC. Disease status will be measured every 4 weeks until week 24 according to the NCI Working Group Guidelines and every 3 months thereafter until disease progression or 24 months. Patients not having progressed on their disease at 24 months, will be followed for disease progression at 6 month intervals until 48 months.

The study objective is efficacy of HuMax-CD20 in combination with FC in previously untreated CLL patients, the company said. The primary endpoint is complete remission measured at any time during the treatment period.

* * *

Genta Inc. (Nasdaq: GNTA) of Berkeley Heights, N.J., said it has begun a pilot study of Genasense (oblimersen sodium) Injection for advanced melanoma.

The trial is the first follow-on study to the Genta randomized phase III trial of Genasense plus dacarbazine that showed benefit across multiple clinical endpoints for advanced melanoma with no prior chemotherapy, the company said.

Preclinical results demonstrated marked anticancer synergy when Genasense was combined with Abraxane (paclitaxel protein-bound particles; Abraxis Oncology Inc.) and Temodar (temozolomide; Schering Plough Inc.), the company said. Both of the chemotherapy agents have recently entered phase III trials for advanced melanoma.

The new pilot study would evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of the three-drug combination in chemotherapy-naive patients whom have normal levels of a key biomarker, serum lactate dehydrogenase, the company said. Anna Pavlick, director, NYU Melanoma Program, assistant professor of medicine and dermatology, New York University Cancer Institute, would lead the study.

"Genasense has demonstrated significant benefit in melanoma patients compared with dacarbazine chemotherapy used alone," said Pavlick.

The drug inhibits production of Bcl-2, a protein made by cancer cells that is thought to block chemotherapy-induced apoptosis, the company said.

* * *

Keryx Biopharmaceuticals Inc. (NASDAQ: KERX) of New York said it has begun a corporate-sponsored phase II program to evaluate KRX-0401 (perifosine) for rare sarcomas.

The study will be conducted by the Sarcoma Alliance for Research through Collaboration multi-center network, throughout the U.S.

Dejka Steinert, assistant professor, Department of Sarcoma at MD Anderson Cancer Center, is principal investigator, the company said.

The single agent activity of KRX-0401 is being evaluated for chondrosarcoma, alveolar soft part sarcomas and extra-skeletal myxoid chondrosarcomas, the company said. Treatment will be with KRX-0401 (100 mg oral daily) until disease progression. Phase I

and phase II trials of perifosine for chemo-insensitive sarcoma that showed experiences of very little toxicity and the duration of responses observed on both weekly and daily dosing schedules varied from 6 months to more than 18 months. Furthermore, some of the partial responses occurred with sarcoma subtypes that have been traditionally unresponsive to conventional therapy, the company said.

KRX-0401 is in-licensed by Keryx from Aeterna Zentaris Inc. in the U,S., Canada and Mexico, the company said.

* * *

Progen Industries (NASDAQ:PGLA) Brisbane, Australia, said it has received notification from FDA that the appropriate CMC procedures have been put in place to continue its phase III trials for its anti-cancer drug PI-88.

The notification allows Progen to manufacture the drug for its upcoming trial, the company said. Manufacturing the first step of PI-88 in-house saves Progen AUD$7.8 million in outsourcing fees to a contract manufacturing organization.

At the end of the phase II CMC meeting, the details on the specifications, stability and release procedures for the active ingredient and the final product were reviewed and discussed, the company said. No issues were identified that would delay the manufacture of the product. Holding the meeting now avoids manufacturing related delays for the phase III trial and forms the basis for submitting PI-88's CMC section of the NDA.

Following the FDA meeting, Progen said it now has the PI-88 manufacturing and quality control schedule defined, and would fill excess capacity by renewing contract manufacturing services for the pharmaceutical and biotechnology industries.

* * *

Roche of Nutley, N.J., said that a large, international phase III study (NO16967) for 627 previously treated patients with advanced colorectal cancer met its primary endpoint of progression-free survival.

Study results showed that the chemotherapy combination Xelox (oral Xeloda plus oxaliplatin) is as effective in delaying disease progression as the chemotherapy combination FOLFOX-4 (infused 5-FU/ leucovorin plus oxaliplatin), the company said.

"Our data complement the findings of the NO16966 study, suggesting that Xelox is a very reasonable treatment option for patients with recurrent colorectal cancer," said Mace Rothenberg, lead investigator and professor of medicine at Vanderbilt University Medical Center and Ingram Professor of Cancer Research at Vanderbilt-Ingram Cancer Center. "By demonstrating that Xeloda in combination with oxaliplatin was as effective as FOLFOX-4, these two studies provide the strongest evidence yet that Xeloda may be used in place of IV 5-FU for advanced colorectal cancer."

The NO16967 trial is a large, international phase III trial randomized 627 patients who had received chemotherapy and whose disease had returned or continued to progress, the company said. Xelox (oral Xeloda plus oxaliplatin) was compared vs. Folfox-4 (intravenous bolus and infusional 5-fluorouracil/ leucovorin plus oxaliplatin) as first line colorectal cancer treatment. The primary objective was whether the Xelox regimen was as effective as Folfox-4 in terms of progression-free survival. The secondary outcomes included overall survival, overall response rates and safety profile. There were no unexpected safety findings in the study, the company said.

* * *

Semafore Pharmaceuticals Inc. of Indianapolis said it had received a grant award from the Multiple Myeloma Research Foundation for a phase l trial evaluating its Pl3K inhibitor SF1126 in multiple myeloma.

This is the second clinical trial grant awarded to Semafor---last week the company said it received a grant from Cancer Treatment Research Foundation to for a phase l trial of SF1126 in solid cancers.

"The PI3 kinase pathway plays a key role in the signaling processes that are vital to cancer cell proliferation, invasion and metastasis, yet there currently are no PI3K inhibitors in clinical trials," said Joseph Garlich, president and chief scientist of Semafore. "Cancer trials of our lead Pl3K inhibitor scheduled to begin in the new year."

MMRF has awarded Semafore a $996,380 grant to help fund both the drug manufacturing and the patient costs of the phase l trial in relapsed and refractory multiple myeloma, the company said. The grant award is from the new MMRF LEAD program, which encourages myeloma clinical trials for promising drugs being developed by young companies.

"The growing interest in the anti-cancer potential of our Pl3K approach is also highlighted by the fact that data from preclinical studies of SF1126 in myeloma were selected for an oral presentation at the upcoming ASH meeting, a noteworthy occurrence for a preclinical study." said Kathi Giusti, founder and CEO of MMRF.

Deals & Collaborations:

City of Hope, Sangamo Enter IP, Research Agreements

City of Hope of Duarte, Calif., and **Sangamo BioSciences Inc.** (NASDAQ:SGMO) of Richmond, Calif., said they have entered into an exclusive, worldwide license agreement for intellectual property related to a chimeric immunoreceptor for cancer treatment.

Sangamo and COH said they also have entered into a research collaboration to develop a cell therapy combining the technology with the Sangamo proprietary zinc finger DNA-binding protein nuclease technology for glioblastoma multiforme.

Sangamo said it is collaborating with Michael Jensen, associate chairman, Division of Cancer Immunotherapeutics and Tumor Immunology, City of Hope, who has developed zetakines, which are chimeric immunoreceptors, engineered into human immune cells to generate a population of cells that can recognize and destroy cancer cells. Jensen is using the engineered cells in clinical trials for malignant gliomas and lymphoma.

The collaboration would use the Sangamo ZFN gene modification technology to delete the glucocorticoid receptor, a gene that limits the benefit of the therapy, the groups said. The deletion of GR in the zetakine, anti-glioma T-cells will allow the immune therapy to be used in the presence of glucocorticoids, steroids used for glioma.

Jensen has developed an IL-13 zetakine that, when expressed in cytotoxic or killer T-cells, enables them to seek out and destroy glioblastoma cells, the groups said. In his clinical protocol, T-cells are removed with GM and modified to express the zetakine. The modified cells are infused into the brain following surgery for the targeted elimination of residual tumor cells. Frequently, however, glucocorticoids must be administered post-surgery to stop the brain from swelling. Glucocorticoids inactivate or kill the desirable T-cells through a protein on the T-cell surface known as the glucocorticoid receptor. Cells without a functional GR are drug-resistant and are therefore available to destroy tumor cells. Jensen and his colleagues are collaborating with Sangamo scientists to generate zetakine positive, GR-negative T-cells, the groups said.

"This is an exciting opportunity to apply a technology for gene modification to T cell immunotherapy of brain cancers to create a cell product which can be used in combination with glucocorticoids to treat GM," Jensen said.

Under the license agreement, Sangamo said it would pay COH an up-front license fee and annual maintenance fees. COH is also eligible for payments relating to clinical milestones, royalties and a portion of any revenue that Sangamo may realize from sublicensing agreements.

The license granted to Sangamo is exclusive for the treatment or prevention of disease in humans using a combination of the zetakine and disruption of the expression or function of an endogenous gene.

* * *

Aarhus University Hospital of Aarhus, Denmark, said it is using image-guided brachytherapy technology together with **Varian Medical Systems** of Palo Alto technology for gynecological cancers.

The radiotherapy center at the hospital said it is able to treat patients more precisely with higher, more effective radiation doses using the Varian technology.

Data has demonstrated the technique showed that optimization using high quality MRI scans and the planning capabilities of the Varian BrachyVision treatment planning system significantly improved the brachytherapy treatments, the collaborators said.

"Without image-guidance we were unable to see and plan treatment that protected healthy anatomy as much as we wanted to," said Jacob Lindegaard, radiation oncologist. "With image guidance we have a powerful new tool that enables us to precisely deliver the dose from brachytherapy in the tumor while avoiding the bladder, rectum and intestines."

Aarhus University Hospital said it is carrying out the work as part of a European network of cancer centers led by the Medical University of Vienna. The objective at Aarhus is to reduce the cervical cancer recurrence rate and decrease severe complications by 50 percent.

Standard gynecological cancer treatments at Aarhus involve a combination of brachytherapy and external beam radiotherapy, the hospital said. A total dose of 30 Gy is delivered in three 10 Gy fractions using a GammaMed Plus PDR afterloader, a computer-controlled device that automatically inserts the radioactive source. The other 50 Gy is delivered using external beam treatments on Varian linear accelerators.

The use of MRI-compatible applicators is crucial to the Aarhus technique, and Varian has developed a new titanium applicator as a more rigid alternative to existing plastic versions, the hospital said. Such applicators are needed for more precise brachytherapy treatments because they are rigid and do not flex or move, offering a more reproducible and accurate setup.

* * *

ADITUS Medical AB of Lund, Sweden, **and IGEA s.r.l.,** of Carpi, Italy, said they have entered into a long-term agreement to develop intelligent Electro Chemo Therapy.

ECT is utilized for cutaneous and sub-cuteaneous cancer by increasing the effect of chemotherapeutic drugs, thereby providing an alternative to traditional radiation therapy and or surgery, the companies said.

The agreement forms an alliance within the electroporation area of research and development as well as sales and marketing, the companies said.

* * *

Avanade Inc. of Seattle and **The University of Texas M.D. Anderson Cancer Center** said they have entered into a partnership to develop an Electronic Medical Records system that would unify electronic patient records.

The initiative would bring together clinical data with patient-specific information, representing a shift toward personalized medicine, the groups said.

"While many U.S. healthcare organizations are implementing commercial EMR software packages to create unified records, integration of patient care and clinical research data—a process that is critical to M.D. Anderson—can be challenging," said Lynn Vogel, vice president and chief information officer for M.D. Anderson.

The custom-built application, ClinicStation, would be fully operable in 2007 and would integrate research and clinical data more seamlessly, improve patient care and save the institution considerable costs associated with physician efficiency.

Avanade said it is a global IT solutions consultancy using the Microsoft platform.

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Clarient Inc. (NASDAQ:CLRT) of Aliso Viejo, Calif., said the final milestones for the ACIS III development agreement with **Dako** of Denmark, have been completed, triggering payment of $750,000 to Clarient.

Also, Clarient said it filled the first order for the commercial units to be used for the new ACIS III.

The ACIS III is a automated cellular imaging system featuring improved image resolution, faster scanning, interface to Dako automated stainers, improved user interface and remote viewing capabilities, the company said.

Dako A/S provides system solutions for cancer diagnostics and cell analysis, the company said.

In another development, **Clarient Inc.** and **Natural Selection Inc.** said they have entered into a three year agreement for in vitro diagnostics development in oncology.

The agreement grants Clarient an exclusive, worldwide, non-transferable license to apply the NSI algorithms to diagnostic analysis and services, the companies said.

"The advent of personalized medicine and the resulting gap between therapeutics and diagnostics has fueled a 'and grab in the area of cancer biomarkers that would increase the market for cancer diagnostics by as much as $1 billion in the coming 3 to 5 years," said Ron Andrews, president and CEO of Clarient. "The NSI biological and advanced mathematical knowledge integrated with Clarient's medical experience positions Clarient to bridge the gap between large, cumbersome data and a usable panel of cancer tests."

* * *

Innovive Pharmaceuticals (BULLETIN BOARD: IVPH) of New York said it acquired exclusive North American rights from **TMRC, Co. Ltd.** to develop and commercialize Tamibarotene, a synthetic retinoid for acute promyelocytic leukemia.

Tamibarotene was developed for APL resistance and the high rate of toxicity for all-trans retinoic acid, the company said.

ATRA is the standard of care for first-line treatment of APL in combination with chemotherapeutic agents, the company said. National Comprehensive Cancer Network guidelines also recommend undergoing one to two years of maintenance therapy with ATRA following disease remission. However, ATRA therapy is associated with toxicities, including retinoic acid syndrome, a serious and sometimes fatal complication that occurs in up to 25 percent. Additionally, resistance to treatment with ATRA may develop.

In a phase III study in Japan, effectiveness of orally administered Tamibarotene was evaluated daily for eight weeks in 39 patients with APL, including those who were treatment-naive and previously treated, the company said. The overall response rate was 61.5 percent. In recurrent disease the overall response rate was 81 percent. RAS was reported in 7.3 percent. An additional phase III study is underway in Japan comparing ATRA to Tamibarotene for the maintenance treatment of APL.

INNO-406 , formerly known as NS-187, is an orally bioavailable, rationally designed, dual Bcr-Abl and Lyn-kinase inhibitor in phase I studies.

* * *

Lentigen Corp., of Baltimore and Philadelphia said it has received NIH Small Business Innovation

Research funding to develop a therapy for chronic lymphocytic leukemia and other hematological malignancies.

The project would demonstrate the ability of the Lentigen lentiviral vector to provide a delivery system for CD40-ligand (CD154), a stimulator of T cells in CLL, the company said. Lentiviral vectors deliver genes or RNAi into cells with up to 100 percent efficiency and stability. Previous viral vector systems such as non-viral, adenoviral and adeno-associated viral vectors could achieve high, but not stable gene delivery into cells. Other vectors such as murine retroviral vectors can deliver genes stably, but not efficiently.

Laboratory Products:

Abbott Offers Six DNA Tests In Europe For Leukemia

Abbott Molecular of Delkenheim, Germany, said it has introduced six CE-marked DNA tests in Europe that identify chromosomal abnormalities associated with leukemia.

The tests are based on the Abbott proprietary fluorescence in situ hybridization technology and employ DNA probes used to detect genetic abnormalities, such as extra or rearranged chromosomes, common in acute lymphocytic leukemia, chronic myeloid leukemia and chronic lymphocytic leukemia, the company said.

DNA probes are molecules stained with fluorescent dyes that recognize and bind to specific target molecules in patient samples, the company said. The fluorescent probes can be viewed under a special microscope, enabling the detection of chromosome gains, deletions or translocations.

The FISH tests supplement conventional cytogenetics and provide additional information not detected by other test methods, the company said.

"Combining traditional cytogenetics with FISH testing provides doctors with the accurate information they need to make better decisions regarding treatment options and quality of life," said Christine Harrison, director, Leukaemia Research Fund Cytogenetics Group, Southampton General Hospital, UK

The following six probes have received CE mark certification, allowing them to be commercially marketed in the European Union, the company said. They include the Vysis LSI p53/LSI ATM and LSI D13S319/LSI 13q34/CEP 12 Multi-Color Probe Sets; Vysis LSI BCR/ABL Dual Color, Dual Fusion Translocation Probe Set (20 assays and 50 assays); Vysis LSI BCR/ABL ES Dual Color Translocation Probe Set; Vysis LSI BCR/ABL Dual Color, Single Fusion Translocation Probe Set; Vysis LSI MLL Dual Color, Break Apart Rearrangement Probe; and Vysis LSI 21 SpectrumOrange Probe. The six probes are already available in the U.S.

* * *

Genzyme Corp. (NASDAQ:GENZ) of Cambridge, Mass., said it has made commercially availability the KRAS Mutation Analysis, a laboratory test that identifies non-small cell lung cancer patients who may not respond to targeted therapies.

The test identifies NSCLC patients who test positive for specific KRAS mutations, the company said. Mutations in the KRAS gene have been associated with resistance to drugs, including the tyrosine kinase inhibitors Tarceva (erlotinib) and IRESSA (gefitinib).

"Between 15 and 30 percent of tumors from NSCLC have mutations in the KRAS gene and clinical studies show that this information plays an important role in making treatment decisions," said Mara Aspinall, president of Genzyme Genetics, the business unit of Genzyme Corp.

Clinical studies have shown that mutations in the KRAS gene are found more frequently in patients who show limited clinical response or who have a shorter time to disease progression with TKI treatment. A retrospective study demonstrated a decrease in time to disease progression and in overall survival in KRAS mutation-positive patients when treated with Tarceva plus chemotherapy, versus chemotherapy treatment alone. Conversely, with TKI treatment, NSCLC patients with mutations in the epidermal growth factor receptor gene have shown improved response rates, and longer time to disease progression.

Oncology Management:

US Oncology To Offer $190M Dividend To Stockholders

US Oncology Holdings Inc. of Houston said it would offer an aggregate of $150 million of its common and preferred stock to Morgan Stanley Strategic Investments Inc. in a private offering.

The net proceeds of the issuance of the stock, together with the cash-on-hand of US Oncology Inc., its wholly owned operating subsidiary, would be used to pay a dividend of $190 million to the stockholders and to pay fees and expenses related to the offering, the company said. Subject to finalization of the terms and conditions of the offering and satisfaction of the other conditions, the offering would close prior to the end of 2006.