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FDA Didn't Tell Advisors About Data Linking Obesity Drug With Precancerous Lesions

By Paul Goldberg

Many years and many experiments will be needed to determine whether microscopic lesions called aberrant crypt foci constitute an early manifestation of colorectal cancer.

Yet, it appears that this relatively obscure scientific question cannot await orderly resolution. Aberrant crypt foci, or ACF, have become a factor in a controversy over FDA's pledge to start relying on biomarkers to accelerate drug development.

Battered by Congress over cardiovascular side effects of the drug Vioxx and failure to make a decision on the Plan B emergency contraceptive, FDA has been trying to paint a picture of a future where drug discovery would become an engineering task. According to the agency, clinical trials of tomorrow would measure impact on biomarkers instead of waiting for disease to begin or progress. In theory, this would make trials cheaper and faster than they are today.

Aberrant crypts, which appear to be associated with the anti-obesity

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Von Eschenbach To Resign From NCI June 10; Niederhuber Named Acting NCI Director

By Kirsten Boyd Goldberg

After eight months in a controversial and unprecedented dual position as NCI director and acting FDA commissioner, Andrew von Eschenbach has set a date for his resignation from the institute.

Von Eschenbach plans to leave NCI on June 10, Christina Pearson, a spokesman for the Department of Health and Human Services, said in a May 31 announcement. He will continue as acting FDA commissioner and a senior advisor to HHS Secretary Michael Leavitt "while he awaits confirmation" by the Senate, she said.

Leavitt designated John Niederhuber as acting director of NCI upon von Eschenbach's resignation. Niederhuber, former director of the University of Wisconsin Comprehensive Cancer Center, is the NCI deputy director for clinical and translational research.

Von Eschenbach was selected as acting FDA commissioner upon Lester Crawford's sudden resignation last September. The NCI director initially stated that he would do both jobs.

His dual role as director of an institute that develops drugs and the head of an agency that regulates drugs raised questions of conflict of interest. After

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Group Urges FDA To Ban Sale Of Obesity Drug Orlistat

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drug Xenical (orlistat), point to a different scenario, where incompletely studied but potentially harmful biomarkers retard drug development and approval. Data from two separate studies point to this biomarker in animals exposed to orlistat, a drug Americans may soon be able to buy without a prescription.

The drug was approved in 1999 and has been sold by prescription by Roche. As sales dropped precipitously year after year, Roche licensed the drug to GlaxoSmithKline, which is preparing to make it available over-the-counter. After review by two advisory committees last January, FDA sent Glaxo an "approvable" letter, a document which usually means the drug would receive marketing approval after some undisclosed but often routine problems are resolved.

However, two respected pathologists who study ACF joined the advocacy group Public Citizen to file a citizen petition urging FDA to ban the sale of the prescription version of the drug and, by inference, rescind the approvable letter for over-the-counter sale. "Orlistat is a drug that has shown minimal efficacy coupled with both known and potentially important serious adverse events," states the petition by Case Western Reserve University pathologists Theresa Pretlow and Thomas Pretlow and the Public Citizen Health Research Group.

"Orlistat has been shown by two independent groups of investigators to cause the formation of ACF, the earliest identifiable neoplastic colonic lesion and putative precursor of colon cancer," reads the petition filed April 10. "FDA is now considering increasing the number of people exposed to the drug by allowing OTC use. There is no scientific justification for this decision. The FDA should not allow a drug, in this case orlistat, to remain on the market for the long-term treatment of a non-lethal condition when it combines so little efficacy coupled with a still unresolved potential to cause... colon cancer."

FDA became aware of animal data on orlistat's role in ACF in 1997, while performing the toxicology review of the Roche animal studies, agency documents show. Another study corroborating this link was recently published on the Web by a widely-read peer-reviewed journal, and could have been turned up in a simple library search. Yet, members of the advisory committee that met last January to consider the approval of Orlistat for over-the-counter sale were not asked to consider this potential toxicity.

Even scientists who are skeptical about the significance of aberrant crypts and extrapolation from animal data say that the studies should have been presented to the committee. "Regardless of my lukewarm feelings about ACF, if FDA had the data and they withheld it, I think there is a problem there," said C. Richard Boland, chief of gastroenterology at Baylor University Medical Center in Dallas. "Obviously, they are bringing the panel in to give them advice, and if you select the data you give them, they are going to give you whatever you've selected for."

Good Biomarkers vs. Bad Biomarkers

Biomarkers are first and foremost a political issue at FDA, as the agency promotes its Critical Path initiative to accelerate development of drugs.

"From FDA's standpoint, I can't emphasize enough how we need to move the paradigm toward scientific drug and device development," Janet Woodcock, FDA deputy commissioner for operations who heads the Critical Path program, said recently (The Cancer Letter, Feb. 17). "Right now, the development process is fraught with uncertainty. And that is because of a lack of enough scientific markers and mechanistic predictions that we can make about treatments."

When FDA Acting Commissioner Andrew von Eschenbach speaks of "molecular medicine," he, too, usually means greater reliance on biomarkers. Three years ago, the American Association for Cancer Research attempted to convince FDA to create an

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Founded Dec. 21, 1973, by Jerry D. Boyd.

approval category for drugs that treat "intraepithelial neoplasia," pre-cancer, to accelerate development of chemopreventive agents.

The IEN proposal met with strong opposition from skeptics, who argued that chemopreventive agents developed without proper testing could harm people who aren't diagnosed with cancer (The Cancer Letter, May 30, 2003). The idea has been dormant since the Celebrex and Vioxx trials demonstrated that such drugs can be unacceptably toxic for most patients.

Should biomarkers that appear on the toxicity side be treated differently than those that could represent surrogates for efficacy?

"It's is a no-brainer," said Robert Sandler, professor of cancer epidemiology and cancer prevention and control at the University of North Carolina Lineberger Cancer Center. "There are biomarkers for the good, and there are biomarkers for the bad. You have to be even-handed when you deal with them."

FDA officials declined to discuss the citizen petition. "We will be reviewing it and considering the matters before we respond to the petitioning party," said Crystal Rice, an agency spokesman. "We won't discuss the matter with anyone else." FDA has 180 days to respond to the petition. After that, petitioners have the option to sue the agency.

Public disclosure of this apparent lack of attention to a potential precursor to cancer could result in political trouble for the agency and legal problems for the drug's sponsor if patients who take orlistat, many of whom are at high risk of developing colon cancer because of their high-fat diets and obesity, proceed to develop the disease.

Chemoprevention Backwards?

Crypts are invaginations of the internal lining of the intestine into the underlying connective tissue of the gastrointestinal tract.

Aberrant crypt foci are either single crypts or groups of crypts that have specific alterations, such as increased size, a thicker layer of epithelial cells, and oval rather than round openings that can be observed in the intact tissue. They were described in animals in 1987 and in humans three years later.

An association between aberrant crypts, adenoma, and colorectal cancer was shown in a Japanese study published in The New England Journal of Medicine Oct. 29, 1998. The abstract is posted at http://content.nejm.org/cgi/content/short/339/18/1277.

Though aberrant crypt foci are far from being validatied as a biomarker for either cancer or polyps, "there are substantial data in carcinogen-induced animal models suggesting that ACF correlate with development of more advanced tumors," said Monica Bertagnolli, associate professor of surgery at Harvard University, a research scientist at Strang Cancer Prevention Center and the principal investigator in the NCI study of Celebrex for the prevention of recurrence of polyps.

"Human data to support this, however, are far from conclusive," Bertagnolli said. "The available studies suggest an association between human ACF and the presence of adenomas and/or cancers in the colorectum, but do not show that these lesions are causally linked.

"For an endpoint to be validated, it must meet at least three criteria: 1) the presence of the endpoint correlates with the presence of the target disease; 2) the surrogate endpoint is modulated by agents that modulate the target disease; and 3) successful modulation of the surrogate directly correlates with a decrease in the target disease.

"In humans, ACF currently meet only the first of these criteria," Bertagnolli said.

FDA's rhetoric about Critical Path and "molecular medicine" notwithstanding, no biomarker for efficacy in cancer treatment or prevention has been universally accepted as valid. However, the agency routinely grants accelerated approvals to agents based on tumor shrinkage, which is also a biomarker.

Generally, the agency has been willing to accept biomarkers and even animal data for demonstration of toxicity. If a label states that a drug shouldn't be given to pregnant women, this warning is not based on conclusions from a clinical trial testing a potentially harmful agent in pregnant women. (Such trials for toxicity would be unethical and, possibly, criminal.)

Whenever studies suggest a "significant risk for humans, such as animal studies demonstrating mutogenicity, teratogenicity or carcinogenicity," sponsors are required to notify the agency and the investigators within 15 days. This regulation has the same level of urgency as an unexpected patient death or a life-threatening event on a study.

In the case of making orlistat available without a prescription, the agency should stay true to its tradition of caution, said Bernard Levin, vice president for cancer prevention at M.D. Anderson Cancer Center and a co-principal investigator in Pfizer's study of Celebrex for polyp prevention.

"ACF may be an incomplete surrogate marker, but it still points you in the direction that there is something there of concern," Levin said to The Cancer Letter. "The issue is, how much is it of concern?"

The citizen petition makes a compelling argument, Levin said. "I think they make a good point that this drug should be studied in follow-up for its impact on colon cancer," he said. "I feel strongly that this shouldn't be an over-the-counter drug for that reason. I think it should be sold [by prescription] with appropriate warnings. We need some long-term data. We need to know what happens to people who take this long-term."

Marc Bissonnette, a gastroenterologist at the University of Chicago agrees. "In my estimation, it's a reasonable intermediate biomarker to raise concern, if not alarm," said Bisonnette. "I don't know what the safety issues will really turn out to be, but the fact that we are seeing pre-malignant precursors in animals is worrisome to me. More studies need to be done, and, certainly, releasing it to the general public without any sort of real informed consent and knowledge is a hazardous thing to do."

Dueling Biomarkers

Orlistat triggers a conflict between two unvalidated biomarkers: ACF on one side, and obesity on the other.

While the association between obesity and cancer has been shown, it is less clear that elimination of obesity would reduce the risk of colon cancer, prevention experts say. This is noted in orlistat's label. "The long-term effects of orlistat on morbidity or mortality associated with obesity have not been established," the document states.

This contest of correlates could include vitamin E, suggests Sidney Wolfe, director of the Public Citizen's Health Research Group.

"Of further concern, in addition to ACF formation promoted by orlistat, is evidence that because it inhibits the absorption of fat-soluble vitamins such as vitamin E, this may also increase the risk of colon cancer," said Wolfe, citing a September, 1997, paper published in Cancer Causes Control. "A review of the relationship between colon cancer and vitamin E concluded that 'a randomized clinical trial, a cohort study, and a case-control study have all found inverse associations between colon cancer and vitamin E.'"

Asked to comment about ACF, Glaxo chose to address the question of colorectal cancer instead.

"We are preparing a response to the FDA," said Lori Lukus, a company spokesman. "The Public Citizen petition is recommending a change in the availability of orlistat based largely on one animal model, and it really ignores the data conclusion of the safety from previous years of clinical research and human exposure.

"FDA and other health authorities have used data from both animal and human tests in reaching their conclusion that orlistat is safe and effective when used as directed. The data we have is from Roche studies in human subjects taking orlistat for periods even up to four years that demonstrated that there is neither an association nor an increased risk for colon cancer."

Wolfe said the company's reference to cancer is misleading. "The explanation by Glaxo for the lack of any colon cancer in patients taking orlistat is not valid, because of the small number of people involved, as well as the relatively short time analyzed for cancer development," Wolfe said. "It is well known that the latency period for the development of human cancer from known carcinogens is usually at least ten or 20 years from the time of exposure."

Glaxo paid Roche $100 million plus a royalty on sales for the drug.

As a prescription drug, orlistat was not embraced by the market. Perhaps because of its unpleasant side effects, which include fecal incontinence and oily stools, the drug's U.S. sales dropped by 19% in 2002, 16% in 2003, 11% in 2004, and 15% in 2005. According to data from IMS Health, in 2005, gross sales were $86.6 million, about half of what they were four years earlier.

Data Not Presented to Advisory Committee

FDA chose not to consult its advisors about ACF either before approval of the prescription version in 1999 or during a January hearing of the application for the over-the-counter version.

In these public meetings, cancer was mentioned only as a correlate of obesity, in the context of the argument that a decrease in obesity could decrease cancer risk. Aberrant crypts weren't mentioned at all.

"This is the first I've heard of it," said Neal Benowitz, a member of the FDA Nonprescription Drugs Advisory Committee, professor of medicine, psychiatry, and biopharmaceutical sciences at the University of California, San Francisco, who took part in the advisory committee meeting Jan. 23. "This was not in any of the documents that we reviewed. Unless it gets reported by the manufacturer or FDA, or unless someone brings it up who gives testimony, we may not know about this."

The transcript and supporting documents are posted at www.fda.gov/ohrms/dockets/ac/cder06.html#NonprescriptionDrugs.

The FDA review of toxicology data Roche submitted prior to the 1999 approval notes that "there is a treatment-related increase in the number of colonic

aberrant crypt foci in rats on a high fat normal calcium diet for nine months."

However, the agency stated that "the significance of this finding is unknown and has not been detected in humans."

Documents show that the agency was sufficiently concerned to ask Roche to conduct additional studies and that the company convened a private advisory panel to review the data. "An expert committee was approached by the sponsor regarding colonic mucosal hyperproliferation and the possibility of colon cancer," the document states. "The panel concluded that overall the data available (preclinical and clinical) did not raise significant concerns regarding the effect of orlistat on colonic mucosal hyperproliferation," the agency report states.

The agency's summary of the orlistat rat data is posted at www.fda.gov/cder/foi/nda/99/020766a_xenical_phrmr_P5.pdf.

According to the Pretlows and Public Citizen, the rats in the Roche study were exposed to insufficiently high doses of orlistat. "The increase in ACF occurred even though the highest doses used in this study were only 40% (males) and 60% (females) of the human exposure, based on body surface area," the citizen petition states. "Normally, one would test at many times the human level to increase the sensitivity of the assay."

The petition argues that the agency didn't examine these data thoroughly. "Unfortunately, we cannot know the full story as to what occurred in rats because, in addition to the lack of adequately high doses, the FDA reviewer accepted the sponsor's conclusions without doing his own independent analyses," the document states.

The citizen petition is posted at www.citizen.org/publications/release.cfm?ID=7423.

There is no publicly available evidence that a toxicology review was repeated after Glaxo licensed the drug from Roche and applied for the OTC license.

"The evidence for aberrant crypts playing a role as precursors of cancer is certainly much stronger today than in 1997, when FDA did the pharmacology review of orlistat," Theresa Pretlow said. "In 1999, aberrant crypt foci were shown to be monoclonal or neoplastic lesions. You know that every [case of ACF] is not going to progress to cancer, but you don't know which one will. And the same is even true of polyps, and yet people do get concerns if polyps show up in a study. So they ought to be concerned if aberrant crypts show up."

One important paper—a rat study by Brazilian scientists—appeared on the Web site of the journal Cancer Letters on Dec. 27, 2005, nearly a month before FDA convened its advisory committee on orlistat.

The study by Brazilian researcher Sergio Britto Garcia and colleagues found that either a high fat diet or orlistat significantly increased the incidence of ACF in rats given the carcinogen dimethyl hydrazine. The highest level of ACF was found in rats that received a high-fat diet, orlistat and DMH.

Orlistat aids weight loss by blocking absorption of dietary fat by inhibiting its breakdown.

"There have been hypotheses for a while that fatty acids influence and stimulate colon cancer formation," Pretlow said. "The question has been whether it's the fat in your food, or the total body weight, or both, that act as promoters for colon cancer.

"But in that lab study, they showed that if you increased the fat in the diet of the animals, you increased the number of aberrant crypts by 60%," Pretlow said. "If you took a normal or lower-fat diet and added orlistat, you got the same increase. What makes this worse is that the reason people take orlistat is that they are overweight, and most likely have a diet that's too high in fat. The animals on a high-fat diet with orlistat had 2.4-fold more ACF than the animals on the normal diet.

"So, instead of just having a bad diet and probably having a higher risk for colon cancer, they are taking a drug which then increases their risk further."

The agency should have been aware of the Brazilian paper, critics say.

"If they are coming to the advisory committee in January, they should have been current on literature that cites orlistat," said Pretlow. "Since they knew from their original data that ACF were there after orlistat, they should have looked to see if there was anything published that substantiated the earlier data or claims.

"Orlistat is in the title of that paper. It's not so much that it's about aberrant crypts—which they have actually seen before—but if you are just on a search for orlistat, you would have come up with that paper."

The presence of ACF should have been discussed with the advisory committee earlier this year, Levin said. "The panel should have an opportunity to develop its conclusions based on all the evidence available," he said. "I respectfully suggest that it would have been prudent for the FDA to seek expert guidance."

Bissonnette said the agency's apparent decision not to consult advisors on ACF is consistent with its recent failures to detect toxicity in drugs. "That's clearly concerning," he said. "It reminds me of the Vioxx story, unfortunately, and lots of other stories like it."

NCI In Transition:

Von Eschenbach To Step Down As NCI Director On June 10

(Continued from page 1)

objections by members of Congress, scientists, and advocates, on Sept. 30, 2005, von Eschenbach took a leave of absence from "administrative duties" at NCI, but continued to make appearances as both NCI director and acting FDA commissioner.

Last March, President Bush nominated von Eschenbach as the nominee for FDA commissioner. Two Senators—Hillary Rodham Clinton (D-N.Y.) and Patty Murray (D-Wash.)—placed a hold on his confirmation until FDA acts on the Plan B emergency contraceptive.

As the months went by, cancer researchers expressed increasing dismay at the absence of a full-time, Presidentially-appointed director for NCI.

Harold Varmus, president of Memorial Sloan-Kettering Cancer Center, wrote in the May 26 issue of Science that, "the leadership of the nation's cancer efforts has been poorly defined in recent months and will remain so until a new NCI director is appointed."

President Bush appointed von Eschenbach, a urologic surgeon from M.D. Anderson Cancer Center, as NCI director in 2002. He led the institute with a corporate management style and stunned cancer researchers with his announcement of a "goal" for NCI to end the "suffering and death due to cancer" by 2015.

Even as scientists criticized the goal as an unattainable exaggeration of the state of science, von Eschenbach continued to trumpet "NCI's Challenge" or "Vision" in official documents.

However, since his nomination to the FDA post last March, von Eschenbach has conceded that, although he still believes in the goal, "what may be at issue is the time line of how long it will take us to accomplish that goal."

Niederhuber joined NCI last September and was named "chief operating officer" of the institute when von Eschenbach took his leave of absence.

As acting director, Niederhuber would be in the running for the Presidential appointment, but it's not clear whether he has wide support among cancer researchers, due to his close association with von Eschenbach.

Cancer researchers have forwarded to the White House the names of other possible candidates from academia, sources said.

In the Cancer Centers:

Levin To Retire In '07 As Head Of Prevention, M.D. Anderson

BERNARD LEVIN, vice president and head of the Division of Cancer Prevention and Population Science at M.D. Anderson Cancer Center, plans to retire Aug. 31, 2007, center officials said. A search committee will be appointed to help find a successor. "Under Dr. Levin's exemplary leadership, Cancer Prevention and Population Science has given rise to extraordinary advances in cancer prevention and is at the forefront of the field, receiving international attention from the scientific community, the public, media, and policy makers," Margaret Kripke, executive vice president and chief academic officer, and John Mendelsohn, president of M.D. Anderson, said in a joint statement. "We know his many colleagues and friends join us in expressing gratitude for all Dr. Levin has contributed during 22 years on our faculty and will continue to accomplish in the year ahead." . . . **KENNETH ZARET**, a cell and developmental biologist at Fox Chase Cancer Center, was selected for an NIH MERIT Award of more than $5.7 million over 10 years. MERIT (Method to Extend Research in Time) Awards recognize researchers who demonstrate superior competence and outstanding productivity in research. Zaret holds the W.W. Smith Chair in Cancer Research at Fox Chase. His research focuses on understanding how genes are activated and how early embryonic cells become specific cell types, such as the liver and pancreas, during the development of mammals. Zaret's MERIT Award is based on an NIH investigator-initiated grant that he has held continuously for 20 years. The grant was recently renewed for four more years. Based on Zaret's research progress, the NIH elected to extend the grant from four to 10 years. . . . **MARTIN ABELOFF** received the Marion I. Knott Directorship and Professorship of Oncology at the Johns Hopkins Kimmel Cancer Center on May 22. Abeloff, who has served as the director of the Hopkins cancer center since 1992, is the first recipient of the named endowment. Knott was the wife of Baltimore developer Henry Knott. . . . **STEPHEN FORMAN** was named the first Francis and Kathleen McNamara Distinguished Chair in Hematology and Hematopoietic Cell Transplantation at City of Hope. Forman, a stem cell transplantation and hematologic cancer scientist, is head of the Division of Hematology and Hematopoietic Cell Transplantation at City of Hope. He also is program leader for the Hematologic Neoplasia Program, and director of clinical research in the Division of Cancer

Immunotherapeutics and Tumor Immunology. The $2.5 million endowed chair was the gift of Kathleen and Francis McNamara. . . . **NCI PUBLIC AFFAIRS and Marketing Network**, an association of communications professionals working in cancer research and clinical organizations, elected its leadership at its 2006 annual meeting, hosted at Roswell Park Cancer Institute. **Cynthia Manley**, associate director for communications at Vanderbilt-Ingram Cancer Center, was elected to a two-year term as chairman of the steering committee. **Nancy Jensen**, executive director of external communications at M.D. Anderson Cancer Center, was elected vice chairman. Elected to the 2006-7 steering and planning committee: **Martin Beerman**, marketing director, University of Nebraska/The Nebraska Medical Center; **Don Clayton**, associate vice chancellor for medical public affairs, Washington University Siteman Cancer Center; **Laurel DiBrog,** vice president for marketing and planning, Roswell Park Cancer Center; **Dan Fischer**, senior marketing specialist, Holden Comprehensive Cancer Center/University of Iowa; **Mary Hawkins**, communications director, Norris Cotton Cancer Center at Dartmouth; **Kevin Koga**, associate vice president for marketing and communications, City of Hope Comprehensive Cancer Center; **Karen Mallet**, director of public affairs, Fox Chase Cancer Center; **Amy Mone**, director of public affairs, The Johns Hopkins Kimmel Cancer Center; **John Mugge**, communications manager, UCSF Comprehensive Cancer Center; **Dianne Shaw**, director of communications, UNC Lineberger Comprehensive Cancer Center; and **Arlinda Warren**, director of marketing, public relations and physician services, Washington University Siteman Cancer Center. PAN works with NCI Office of Communications to further public awareness of cancer research, prevention, detection and treatment. PAN members include representatives of NCI-designated cancer centers, American Association of Cancer Institutes cancer centers, and other related professional organizations such as American Society of Clinical Oncology, American Association for Cancer Research, and the Oncology Nursing Society. . . **IRELAND CANCER CENTER** of University Hospitals of Cleveland received a $250,000 grant from the Susan G. Komen Breast Cancer Foundation for the development of a new device to enhance breast cancer radiation treatment. The two-year grant will support research into the development of a high-precision positioning system for image-guided breast cancer radiation, led by **Jason Sohn**, in the department of radiation oncology.

Professional Societies & Advocacy:

India And Korea Join IARC

INDIA and **KOREA** have joined the International Agency for Research on Cancer. "Both countries are expected to make a significant scientific contribution to global cancer research in joining the World Health Organization cancer research agency, as we need to identify and apply cost-effective, culturally acceptable and innovative measures to cancer prevention in diverse low- to medium-resource settings," said **Peter Boyle**, IARC director. . . . **ONCOLOGY NURSING Certification Corp.** honored two individuals and one institution May 5. **Carol Brueggen** was selected the 2006 Advanced Oncology Certified Nurse of the Year. She is assistant professor of nursing at Mayo Clinic College of Medicine and an oncology clinical nurse specialist at St. Mary's Hospital in Rochester, MN. **Sherry Looker** received the 2006 OCN of the Year. She is a nursing supervisor in the medical oncology unit at the Mayo Clinic. ONCC presented the 2006 Employer Recognition Award to **M.D. Anderson Cancer Center** of Orlando for support of oncology nursing certification. Currently, 75 percent of the eligible nurses at the cancer center are ONCC certified, and the goal is to reach 100 percent by 2007.

NCI & NIH In Brief:

Udey Appointed CCR Deputy; Carl Wu Chosen By NAS

MARK UDEY, chief of the NCI Dermatology Branch, was named deputy director of the NCI Center for Cancer Research. Udey majored in chemistry at the University of Wisconsin-Madison and received his M.D. and Ph.D. degrees from Washington University. He completed medical and dermatology residencies at Barnes Hospital and was a faculty member in dermatology at Washington University before coming to NIH in 1989. His research focuses on elucidating aspects of epidermal Langerhans cell and dendritic cell biology. He recently expanded his area of interest into developing vaccines for cancer. . . . **CARL WU**, chief of the NCI Laboratory of Molecular Cell Biology, was one of 72 new members chosen by the National Academy of Sciences on April 25. Wu obtained his Ph.D. in 1979 and conducted postdoctoral research at Harvard University. In 1982, he joined the NCI Laboratory of Biochemistry. He was appointed chief of the Laboratory of Molecular Cell Biology in 1996. . . . **PAUL MELTZER** was named chief, Genetics Branch, and head, Clinical Molecular

Profiling Core at the NCI Center for Cancer Research. He joins CCR from the Cancer Genetics Branch of the National Human Genome Research Institute. Meltzer is internationally recognized for his work on genes and mechanisms in cancer cell development. He and his colleagues advanced studies of gene expression profiles in cancer cells to better understand the progression and prognosis of cancers. Meltzer earned his Ph.D. from the California Institute of Technology and M.D. from the University of Tennessee. He received postdoctoral training in genetics at the University of Cambridge and the University of Arizona. . . . **JOSEPH FRAUMENI JR.**, director of the NCI Division of Cancer Epidemiology and Genetics, was presented the Medal of Honor from the International Agency for Research on Cancer on May 17 in recognition of his "outstanding contributions to the field of cancer epidemiology." He also delivered the third Richard Doll Lecture, titled "Genes and the Environment in Cancer Causation: An Epidemiologic Perspective." . . . **NATIONAL INSTITUTES OF HEALTH** dedicated the C.W. Bill Young Center for Biodefense and Emerging Infectious Diseases at its Bethesda campus May 3. **Rep. C.W. Bill Young** (R-FL) was honored for his support of biomedical research. Young is chairman of the House Appropriations Subcommittee on Defense. The $182.6 million center will house 250 National Institute of Allergy and Infectious Diseases staff. . . . **HEALTH AND HUMAN SERVICES** awarded five contracts of more than $1 million for the development of a cell-based influenza vaccine. The contracts also would support modernization and strengthening of the influenza vaccine production by creating an alternative to influenza vaccines produced in eggs. The awards include: GlaxoSmithKline, $274.75 million; MedImmune, $169.46 million; Novartis Vaccines & Diagnostics, $220.51 million; DynPort Vaccine, $40.97 million; and Solvay Pharmaceuticals, $298.59 million. The funds are part of $3.3 billion proposed by the President and appropriated by Congress to HHS for FY 2006. . . . **PAUL ROGERS**, chairman of The Friends of the National Library of Medicine and a former member of Congress, announced the launch of NIH MedlinePlus Magazine. The quarterly publication will be distributed free in the waiting rooms of practicing physicians, the institutes said in a press release. "The American people have made a long-term investment in the crucial medical research being carried on by NIH," NIH Director **Elias Zerhouni** said. "NIH MedlinePlus magazine is an important way to make this research and healthcare information even more accessible and useful to health professionals and patients alike." The magazine will also serve as an introduction to http://www.MedlinePlus.gov, Zerhouni said. The first issue includes an interview with athlete **Lance Armstrong**, a member of the President's Cancer Panel.

Obituary:

ANITA ROBERTS, 64, biochemist and chief of Laboratory Cell Regulation and Carcinogenesis at NCI until 2004, died of cancer May 26 in Bethesda. She did postdoctoral work as an NIH fellow at Harvard Medical School before becoming staff chemist at Aerospace Research Applications Center in Bloomington, Ind. After teaching chemistry at Indiana University, Roberts joined NCI in 1976. By 1990, she rose to deputy chief, then acting chief, and finally in 1995, chief of the LCRC. Known for her work on TGF-beta, she and her research partner Michael Sporn of Dartmouth Medical School, won the 2005 Komen Foundation Brinker Award for Scientific Distinction for research on molecules that can turn a healthy cell cancerous. Roberts also won the Federation of American Societies for Experimental Biology's 2005 Award for Excellence in Science.

Funding Opportunities:

RFP N02-CP-61010-66: Database Support for the Chornobyl Thyroid Study in Ukraine. Response Due Date: July 17. Full text: http://www.fbodaily.com/archive/2006/05-May/28-May-2006/FBO-01058020.htm.

Inquiries: Sharon Miller at 301-435-3783.

RFA-TW-06-006: International Tobacco and Health Research and Capacity Building Program. R01. Full text: http://grants.nih.gov/grants/guide/rfa-files/RFA-TW-06-006.html. Letter of Intent Receipt Date: Aug. 25; Application Receipt Date; Sept. 25. Inquiries: Michele Bloch, 301-402-5284; blochm@mail.nih.gov.

PA-06-440: Basic and Preclinical Research on Complementary and Alternative Medicine. R01. Full text: http://grants.nih.gov/grants/guide/pa-files/PA-06-440.html. Inquiries: Wendy Smith, 301-480-0075; smithwe@mail.nih.gov.

PAR-06-406: In Vivo Cellular and Molecular Imaging Centers. P50. Full text: http://grants.nih.gov/grants/guide/pa-files/PAR-06-406.html. Letters of Intent Receipt Date: July 16; July 16, 2007. Application Receipt Date: Aug. 16; Aug. 16, 2007. Inquiries: Anne Menkens, 301-496-9531; menkensa@mail.nih.gov.

PAR-06-394: Global Research Initiative Program, Basic/Biomedical Sciences. R01. Full text: http://grants.nih.gov/grants/guide/pa-files/PAR-06-394.html. Letters of Intent Receipt Date: Aug. 21, Aug. 21, 2007; Aug. 21, 2008; Application Receipt Date: Sept. 21; Sept. 21, 2007; Sept. 21, 2008. Inquiries: Susan McCarthy, 301-496-7815 or 301-594-8785; mccarths@mail.nih.gov.

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THE CANCER LETTER

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Business & Regulatory Report

Product Approvals & Applications:

Genentech Submits sBLA For Avastin As Treatment For Metastatic Breast Cancer

Genentech Inc. (NYSE: DNA) of South San Francisco said it has submitted a supplemental Biologics License Application with FDA for Avastin (bevacizumab) in combination with taxane chemotherapy for chemotherapy-naïve patients with locally recurrent or metastatic breast cancer.

Genentech has requested Priority Review of the application, which means that if accepted, the FDA would make its decision on the application within six months of the agency's receipt of the submission, or in November 2006. Avastin is approved as a first-line treatment for metastatic colorectal cancer in combination with intravenous 5-FU-based chemotherapy.

The sBLA submission is based on results from a randomized, controlled,

(Continued to page 2)

Oncology Management:

CMS Approves Registry To Collect Data, Provide Medicare Coverage Of PET Scans

American College of Radiology and the **American College of Radiology Imaging Network** said the National Oncologic PET Registry would expand Medicare coverage of positron emission tomography scans.

Managed by the ACR and ACRIN, and sponsored by the Academy of Molecular Imaging, NOPR is now formally approved by the Centers for Medicare and Medicaid Services and the ACR Institutional Review Board, the groups said.

Previously, Medicare only reimbursed for PET scans for several common cancers, but the opening of the NOPR means that participating Medicare beneficiaries will now have PET scans covered for cancers including, but not limited to, brain, cervical, small cell lung, pancreatic, testicular, and ovarian cancers, the groups said.

More than 600 PET facilities nationwide have registered to take part in the NOPR and can now be reimbursed by CMS and CMS contracted Medicare Advantage plans for PET indications currently not covered for payment, the groups said.

"NOPR affords oncologists, and nuclear medicine physicians, a unique opportunity to make PET available to Medicare beneficiaries and to improve our understanding of the role of PET in oncology practice," said Barry Siegel, ACRIN researcher and co-chairman of the NOPR Working Group.

* * *

Oncology Therapeutics Network of South San Francisco said it

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Genentech Submits sBLA For Avastin In Breast Cancer

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multicenter phase III trial (E2100) that enrolled 722 patients with previously untreated, locally recurrent or metastatic breast cancer.

The trial assessed treatment with paclitaxel, a standard chemotherapy, with or without Avastin, and the primary endpoint was progression-free survival. In the trial, patients treated with Avastin plus paclitaxel had a 52 percent reduction in the risk of disease progression or death, based on a hazard ratio of 0.48, compared to those treated with paclitaxel alone.

Patients receiving Avastin plus paclitaxel had a median PFS of more than a year while patients receiving paclitaxel alone had a median PFS of approximately six months.

"In this study, Avastin, when added to paclitaxel chemotherapy, doubled the time that women with metastatic breast cancer lived without their cancer advancing, without significant added toxicities, compared to patients who received only paclitaxel," Kathy Miller, associate professor of medicine, Indiana University School of Medicine and principal investigator for the study, said in a statement. "This is the first time progression-free survival has been observed beyond one year in a phase III U.S. clinical trial in patients with metastatic breast cancer."

In a related development, Genentech announced a decision by Roche, following a recommendation from an independent Data Safety Monitoring Board, to resume patient recruitment into AVANT, an international phase III study of Avastin, XELOX and FOLFOX chemotherapy regimens in early-stage colon cancer. Patient recruitment will resume upon clearance by the relevant Independent Review Boards and European Health Authorities.

The DSMB based its recommendation to resume enrollment on a detailed analysis of safety data from the trial. The halt in enrollment was implemented in order to conduct a 60-day safety review for recently recruited patients and assess occurrences of cardiac and unknown deaths in one of the treatment arms. The DSMB concluded that the current safety profile and overall mortality observed in AVANT are consistent with those seen in other early-stage colon cancer trials.

Currently, there is no indication of an imbalance of cardiac events between the treatment arms of the AVANT study. However, in order to gain further insight on the overall occurrence of cardiac events and sudden deaths, the AVANT study protocol will be amended to include a cardiac monitoring plan that will involve an enhanced baseline cardiac assessment and additional basic cardiac investigations.

"Following rapid patient enrollment into the AVANT study, we believe the temporary halt of recruitment to assess safety was the right thing to do for patients," said Hal Barron, Genentech's senior vice president for development, and chief medical officer. "The U.S.-based adjuvant trial, NSABP C-08, has continued to enroll as planned with no changes to its protocol. The AVANT and NSABP C-08 trials, which have different treatment arms, provide an opportunity to investigate whether adding Avastin to standard chemotherapy as adjuvant therapy may be safe and effective in patients with early-stage colon cancer."

* * *

Roche of Basel, Switzerland, said the European Commission has approved Herceptin (trastuzumab) for patients with early-stage HER2-positive breast cancer following surgery and standard chemotherapy.

The decision is based on results from the international HERA (HERceptin Adjuvant) study, which showed that the treatment, following standard chemotherapy, significantly reduces the risk of cancer recurrence by 46 percent compared to chemotherapy alone, the company said.

"The remarkably quick manner in which Herceptin has received European approval in early-stage breast cancer is commendable," William Burns, CEO of

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Roche's Pharmaceuticals Division, said in a statement. "Herceptin has clearly demonstrated that it provides the best chance of long-term survival when used as early as possible in the course of the disease, and this decision is great news for patients and the medical community. We will now work with national authorities to ensure that this treatment is accessible to physicians and patients throughout Europe."

Herceptin was previously approved in the EU for the treatment of metastatic HER2-positive breast cancer, so this new approval allows women with all stages of this aggressive disease, including early-stage breast cancer, to access this life-extending treatment option.

Herceptin was recently granted approval status in New Zealand and Australia, and several countries over the past year have developed clinical guidelines and committed funding to allow eligible patients faster access, prior to license.

* * *

Bayer Pharmaceuticals Corp. (NYSE: BAY) of West Haven, Conn., and **Onyx Pharmaceuticals Inc.** (Nasdaq: ONXX) of Emeryville, Calif., said they have received a positive opinion from the European Committee for Medicinal Products for Human Use of Nexavar (sorafenib) 200 mg film-coated tablets for advanced renal cell carcinoma, or kidney cancer, failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy.

The companies said Nexavar tablets were approved by the Mexican Ministry of Health for advanced renal cell carcinoma, or kidney cancer.

Nexavar, an oral multi-kinase inhibitor, targets both the tumor cell and tumor vasculature, the company said.

In a related development, **Bayer Pharmaceuticals Corp**. and **Onyx Pharmaceuticals Inc.** said FDA has granted Nexavar tablets orphan drug status for hepatocellular carcinoma.

"Liver cancer is such an aggressive disease that patients diagnosed with it rarely live beyond two years," said Jordi Bruix, head of the Barcelona Clinic Liver Cancer Group at the University of Barcelona in Spain, and co-primary investigator of the phase III trial along with Joseph Llovet, senior scientist of the Division of Liver Disease at Mount Sinai School of Medicine.

* * *

Bioniche Life Sciences Inc. (TSX: BNC) of Belleville, Ontario, said FDA has granted Fast-Track designation to its Mycobacterial Cell Wall-DNA Complex (urocidin) for non-muscle invasive bladder cancer refractory to Bacillus Calmette-Guerin.

The company said the open-label phase III 105-patient trial would demonstrate the efficacy of Urocidin as a therapy in non-muscle invasive bladder cancer refractory to BCG.

The refractory trial is one of two in the Bioniche phase III program with the agent, the company said. The second trial, of 630 patients, is a randomized, double-blind multi-centre study comparing the drug to BCG as first-line therapy in non-muscle invasive bladder cancer at high risk of recurrence or progression.

MCC is formulated from Mycobacterium phlei, a non-pathogenic strain of mycobacteria and has been shown to have immune stimulatory and apoptosis activity against cancer cells. the company said.

* * *

Celgene Corp. (Nasdaq: CELG) of Summit, N.J., said FDA granted accelerated approval to its Supplemental New Drug Application for Thalomid (thalidomide) in combination with dexamethasone for the treatment of newly diagnosed multiple myeloma.

The approval was based on response rates.

The safety profile for Thalomid in multiple myeloma has shown an increase in side effects with Thalomid and dexamethasone as compared to dexamethasone alone, the company said. The most common adverse events were constipation, sensory neuropathy, confusion, hypocalcemia, edema, dyspnea, thrombosis/embolism, and rash/desquamation, occurring in 20 percent of patients with a frequency less than or equal to 10 percent in patients treated with Thalomid/dexamethasone compared with dexamethasone alone.

* * *

Cell Genesys Inc. (Nasdaq: CEGE) of South San Francisco said FDA has granted Fast-Track designation for GVAX immunotherapy in advanced prostate cancer.

The product is in two phase III trials of 1200 patients with metastatic hormone-refractory prostate cancer, one of the largest phase III programs ever conducted, the company said. The first trial, VITAL-1, for chemotherapy naïve, asymptomatic patients without cancer-related pain, will compare the immunotherapy to Taxotere chemotherapy plus prednisone. The second trial,VITAL-2, for symptomatic cancer-related pain, will compare GVAX cancer immunotherapy plus Taxotere to Taxotere plus prednisone. Each trial of 600 enrollees, would demonstrate a survival benefit compared to Taxotere plus prednisone. Cell Genesys said it received Special Protocol Assessments from FDA for each of the VITAL studies.

GVAX immunotherapy for prostate cancer is

comprised of two prostate cancer cell lines that have been modified to secrete GM-CSF--granulocyte-macrophage colony stimulating factor--, an immune stimulatory hormone, which is then irradiated for safety, the company said. The immunotherapy for prostate cancer is being developed as a non patient-specific, off-the-shelf pharmaceutical product.

* * *

Cytogen Corp. (Nasdaq: CYTO) of Princeton said FDA has cleared an Investigational New Drug application for CYT-500 in prostate-specific membrane antigen.

The company said it would begin the first U.S. phase I trial for hormone-refractory prostate cancer subject to Institutional Review Board approval.

The product candidate uses the same monoclonal antibody from the Cytogen Prostascint (capromab pendetide) molecular imaging agent. CYT-500 enables the targeted delivery of a cytotoxic agent to PSMA-expressing cells, the company said.

Cytogen said it retains full and exclusive development rights to CYT-500.

* * *

Gendux AB of Stockholm and a wholly owned subsidiary of **Introgen Therapeutics Inc.** (Nasdaq: INGN) of Austin said Gendux AB has submitted an Orphan Drug Designation request to the European Medicines Evaluation Agency for Advexin p53 therapy for cancer patients with Li-Fraumeni Syndrome.

"We intend to provide Advexin on a compassionate use basis to qualifying patients in Europe as well as other countries including the U.S.," said Max Talbott, senior vice president of worldwide commercialization at both Gendux and Introgen.

The drug is a targeted molecular therapy with applicability in a range of tumor types and clinical settings because it targets abnormal p53 tumor suppressor function, associated with cancer initiation, progression and treatment resistance, the company said.

Gendux is a wholly owned subsidiary of Introgen Therapeutics Inc.

* * *

Pharmacyclics Inc. (Nasdaq: PCYC) of Sunnyvale, Calif., said it would submit an NDA to FDA to market Xcytrin (motexafin gadolinium) Injection for non-small cell lung cancer with brain metastases.

The phase III SMART trial, Study of Neurologic Progression with Motexafin Gadolinium And Radiation Therapy, compared the safety and efficacy of whole brain radiation therapy alone to WBRT plus Xcytrin, the company said. The primary endpoint was time to neurologic progression as determined by a blinded events review committee.

"New data from the SMART trial, will be included in an NDA filing," said Richard Miller, president and CEO of Pharmacyclics.

The treatment is an anti-cancer agent that selectively concentrates in tumors and induces apoptosis, the company said.

* * *

MGI Pharma Inc. (Nasdaq: MOGN) of Minneapolis and **SuperGen Inc**. (Nasdaq: SUPG) of Dublin, Calif., said FDA has approved Dacogen (decitabine) for Injection for myelodysplastic syndromes including previously treated and untreated, de novo, and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia), and Intermediate-1, Intermediate-2, and High-Risk International Prognostic Scoring System groups.

"FDA approval of Dacogen marks an important advancement for patients who suffer from MDS," said John Bennett, chairman of The Myelodysplastic Syndromes Foundation. "Patients are often anemic, experience fatigue and weakness and, in certain cases with an increase in leukemic blast cells, MDS can result in bone marrow failure."

Results from a phase III trial demonstrated an overall response rate of 21 percent in Dacogen-treated patients considered evaluable for response, defined as having been pathologically confirmed MDS at baseline who received at least 2 cycles of treatment, compared to 0 percent in the supportive care arm, the company said. All patients who responded to Dacogen treatment became or remained transfusion independent during the time of the response. The most commonly occurring adverse reactions include neutropenia, thrombocytopenia, anemia, pyrexia, fatigue, nausea, cough, petechiae, constipation, and diarrhea, the company said.

Dacogen is a hypomethylating agent that exerts its antineoplastic effects by incorporation into DNA and inhibition the enzyme DNA methyltransferase, the company said.

* * *

Pfizer Inc of New York said FDA has approved its anti-smoking pill, Chantix (varenicline).

Chantix is the first prescription medication approved for smoking cessation in nearly a decade, the company said.

The agent partially activates the nicotinic receptor

and reduces the severity of the smoker's craving and the withdrawal symptoms from nicotine, the company said. Moreover, if a person smokes a cigarette while receiving treatment, Chantix could diminish the sense of satisfaction associated with smoking.

The approval was based on a comprehensive clinical trial program including four trials of more than 2,000 cigarette smokers, the company said. Subjects on average had smoked about 21 cigarettes per day for an average of approximately 25 years. In two identically designed studies, patients receiving a 12-week course of Chantix therapy (1 mg twice daily) nearly quadrupled the likelihood of quitting than those taking placebo and had nearly twice the likelihood of quitting than those patients taking buproprion (150 mg twice daily), after the 12-week course of therapy. Patients were provided with educational materials. Patients were followed for an additional 40 weeks without treatment. After one year, one-in-five patients who received the 12-week course of Chantix remained smoke-free, the company said. For those who quit at the end of 12 weeks, an additional course of 12 weeks treatment with Chantix resulted in a greater likelihood of long-term success in quitting smoking.

"The results suggest Chantix is a significant advancement," said Cheryl Oncken, clinical investigator of Chantix and associate professor of medicine at the University of Connecticut Health Center.

In trials, the drug was generally well tolerated, with overall discontinuation rates similar to placebo, the company said. The most common side effects included nausea, changes in dreaming, constipation, gas, and vomiting.

In another development, **Pfizer** said the Committee for Human Medicinal Products issued a positive opinion recommending conditional marketing authorization for Sutent (sunitinib malate) for metastatic renal cell carcinoma, or advanced kidney cancer, after failure of interferon alpha or interleukin-2-based therapy.

The positive opinion was also granted for gastrointestinal stromal tumors resistant or intolerant to imatinib mesylate, the company said.

This is the first time the CHMP has used the new directive intended for drugs for patients with an unmet medical need, the company said. Additional data will be submitted to confirm the risk-benefit of the drug for mRCC patients.

Sutent is an oral therapy belonging to a class of multi-kinase inhibitors that attack cancer by inhibiting both tumor growth and blood supply.

Oncology Management:

OTN To Buy Cardinal Health's Oncology Distribution Unit

(Continued from page 1)

has agreed to purchase the oncology distribution unit of **Cardinal Health Inc.** (NYSE: CAH) of Dublin, Ohio.

OTN said it would acquire the distribution business, as well as contract services and physician distribution businesses. As a result of the sale, Cardinal Health will participate in the market as a minority owner in the OTN parent company, Oncology Holdings Inc, the company said. The acquisition increases the number of OTN customers to more than 4,000 specialty practices nationwide, including oncology and rheumatology practices.

In other developments:

—OTN and IMPAC **Medical Systems Inc**., of Mountain View, Calif., entered into a co-marketing alliance in which IMPAC will become the OTN preferred oncology electronic medical records vendor.

The agreement will enable the two companies to combine their offerings of inventory management, practice management, drug distribution and a full-spectrum of oncology information management solutions to deliver even greater value to their respective customers, the companies said.

—OTN and **Owens & Minor Inc.** of Richmond, Va., said they have entered into an exclusive two-year distribution agreement to offer medical and surgical supplies to community-based infusion practices.

Under the agreement, OTN said it customers will have access to the Owens & Minor selection of medical/surgical products customized for the office-based infusion setting.

Clinical Trials:

EntreMed Begins Phase Ib Of Panzem For Breast Cancer

EntreMed Inc. (Nasdaq: ENMD) of Rockville, Md., said it has begun a phase Ib study to test Panzem NCD (2ME2) in combination with paclitaxel for metastatic breast cancer.

The single-center study will be conducted at the Duke University Medical Center under a grant from the Susan G. Komen Breast Cancer Foundation. Kimberly Blackwell, director, clinical trials in breast cancer at the Duke University Medical Center, is principal investigator.

The study, for clinical stage IV or inoperable stage III breast cancer, would evaluate the biologic effects on tissue and plasma in treatment with paclitaxel alone and in combination with Panzem NCD (2-methoxyestradiol or 2ME2). The safety and tolerability of Panzem NCD in combination with weekly paclitaxel will also be evaluated, the company said.

Panzem NCD is part of a next generation of antimitotic cancer drugs that bind to tubulin and work through multiple cellular pathways, the company said.

* * *

GPC Biotech AG (Frankfurt Stock Exchange: GPC; TecDAX index; Nasdaq: GPCB) of Martinseied/ Munich said patient accrual has begun in a phase I study evaluating satraplatin in combination with Xeloda (capecitabine) for advanced solid tumors.

Xeloda is an oral form of 5-FU, a marketed chemotherapy treatment used for cancers, including metastatic breast and colorectal cancers.

The trial is an open label 24-patient study being conducted at Northwestern University Medical Center in Chicago under the direction of William Gradishar, professor of medicine, director breast medical oncology. The primary objective is to determine the maximum tolerated dose for satraplatin in combination with Xeloda for advanced solid tumors.

* * *

GTx Inc. (Nasdaq: GTXI) of Memphis said it has attained its enrollment goal for the phase III trial of Acapodene for prostate cancer with high-grade prostatic intraepithelial neoplasia, or PIN.

The study enrolled 1,260 patients at 150 clinical sites in the U.S. Canada, Mexico and Argentina, the company said. To participate, patients had to have a diagnosis of high grade PIN confirmed by David Bostwick, the central pathologist. They were then randomized to receive daily for three years either Acapodene (toremifene citrate) in a 20 mg dose or placebo. The primary endpoint is a reduction in prostate cancer incidence.

The trial, which is being conducted under a Special Protocol Assessment from FDA, is designed as a 36-month study, but provides for an interim efficacy analysis after a sufficient number of cancer events have occurred.

* * *

Genitope Corp. (Nasdaq: GTOP) of Redwood City, Calif., has begun a multicenter trial of MyVax idiotype immunotherapy, an idiotype active immunotherapy, for chronic lymphocytic leukemia.

The therapy is based on the genetic makeup of the individual tumor, and is designed to activate the immune system, the company said.

The phase I/II trial will be conducted at nine cancer centers and will register 70 patients, the company said. The study also may include those with Rai stage 0, I and II, who are untreated. They would receive a series of 16 injections of their custom-made vaccine over a 52-week period.

* * *

NeoRx Corp. (Nasdaq: NERX) of Seattle said it has begun a phase I/II trial of picoplatin for front-line treatment of colorectal cancer.

The phase I/II colorectal cancer study would determine the safety and efficacy of picoplatin when combined with fluorouracil and leucovorin for newly diagnosed metastatic disease, the company said.

The phase I/II study will evaluate picoplatin newly diagnosed hormone refractory prostate cancer and would determine the safety and efficacy of picoplatin when combined with docetaxel.

The ongoing open-label, multi-center phase II trial of the agent for small cell lung cancer would confirm and expand data supporting the efficacy of picoplatin as a single agent for platinum refractory or resistant SCLC, the company said. Efficacy endpoints are being assessed, including response rate, progression-free survival, overall survival, improvement in disease-related symptoms and disease control—defined as complete response, partial response and stable disease rates combined. The trial is being conducted at 30 sites in Eastern Europe and 30 sites in North America.

The company also said it is changing its corporate name to Poniard Pharmaceuticals Inc. effective June 16 and will relocate its corporate headquarters to San Francisco. Its new Nasdaq trade name will be PARD.

* * *

Telik Inc. (Nasdaq: TELK) of Palo Alto said it has begun ASSIST-5, an international phase III trial comparing the combination of Telcyta and Doxil to Doxil alone in platinum refractory or resistant ovarian cancer.

Telik said it would enroll 244 with 122 randomized to each treatment arm. Trial endpoints include objective response rate, progression-free survival and overall survival. ASSIST-5 is based on the positive results reported from a multicenter phase II study of the combination of Telcyta plus Doxil in platinum refractory or resistant ovarian cancer.

Telik has two additional phase III trials ongoing in platinum refractory or resistant ovarian cancer, ASSIST-1 and ASSIST-3. The ASSIST-1 trial is evaluating

Telcyta in third line platinum refractory or resistant ovarian cancer. Enrollment has been completed on the ASSIST-3 trial evaluating the combination of Telcyta plus carboplatin versus Doxil in platinum refractory or resistant ovarian cancer, the company said.

* * *

YM BioSciences Inc. (AMEX: YMI)(AMEX: TSX: YM)(AMEX: AIM: YMBA) of Mississauga, ON, said its partner, **Oncoscience AG**, has begun a phase III trial of nimotuzumab in combination with radiation in children with diffuse, intrinsic pontine glioma.

The trial is a single-arm study whose primary clinical endpoints will be progression-free survival with median survival as secondary endpoint, the company said. Clinical sites will be located in Germany, Italy, Belarus, and Russia.

YM BioSciences also said it and its majority owned subsidiary, CIMYM Inc., propose to file for authorization to conduct a trial in a similar patient population in North America.

Deals & Collaborations:

Two Research Institutes Plan Collaboration On Nanotech

Cleveland Clinic Lerner Research Institute and **Rensselaer Polytechnic Institute** of Troy, N.Y., said they have entered into a biomedical research collaboration to undertake research in areas including nano-medicine, nano-bio materials, smart orthopaedic implants, biomolecular imaging, biocomputation and bioinformatics, bio-MEMS and the development of drug delivery devices.

Together, the Lerner Research Institute and Rensselaer Polytechnic Institute said they would develop joint research proposals and secure funding from federal and non-federal funding sources, such as corporations, foundations and private philanthropists.

The institutions also would establish a visiting scientist program and a summer internship program for undergraduate and graduate students. The institutes would hold joint research retreats, fund a joint seed grant program, offer joint seminars and workshops, and facilitate joint proposals and briefings to NIH in areas of mutual interest.

* * *

Gynecologic Cancer Foundation and the **Gynecologic Oncology Group** have joined to make information about GOG phase III trials available on the Web.

The GOG Clinical Trials page, found on the GCF, at http: //www.wcn.org/, provides information on how to enroll in each trial. Each section also provides a detailed description of the trial, including the purpose of the study, how it works, eligibility requirements as well as risks and benefits, the groups said.

"The GOG is committed to promoting excellence in research in the gynecologic oncology field," said Philip DiSaia, GOG chairman. "Working with GCF to promote clinical trial enrollment allows us to reach more women interested in trial participation and in turn, complete valuable research studies in a more timely fashion."

* * *

Novogen Ltd. (Nasdaq: NVGN) of Washington and **Marshall Edwards Inc.** (Nasdaq: MSHL) of Sydney, Australia, said they have concluded a license agreement for MSHL to develop and commercialize two oncology compounds NV-196, oral form for pancreatic and bile duct cancer, and NV-143, for melanoma, also in oral dosage form.

Marshall Edwards Inc. said it holds an option license agreement with Novogen that entitles it to make the first and last offer from Novogen for oncology compounds that have entered clinical trials.

Under the agreement, the licenses consist of a single upfront payment to Novogen of $1 million, a series of payments for each compound upon reaching the milestones of U.S. Investigational New Drug approval, entering testing at phases II and III and receipt of a NDA for marketing and a royalty on sales of five per cent, the companies said. Marshall Edwards Inc. said it would fund the ongoing clinical programs and is responsible for the commercial development of the drugs.

Marshall Edwards Inc., said it is also the licensee of the Novogen developed investigational anti-cancer drug phenoxodiol in phase II trials for ovarian and prostate cancer. The company is concluding the protocol for phenoxodiol to enter a phase III trial for chemotherapy resistant ovarian cancer, the development program for which the FDA has granted Fast-Track status.

Marshall Edwards Inc. is majority owned by Novogen.

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Peregrine Pharmaceuticals Inc. (Nasdaq: PPHM) of Tustin, Calif., said the Department of Defense has awarded a $460,000 grant to its collaborators at the University of Texas Southwestern Medical Center to study the Peregrine first-in-class anti-phospholipid agent bavituximab (formerly Tarvacin) as an imaging and therapeutic agent for recurrent breast cancer.

In the study, bavituximab will be labeled with

radioactive isotopes to assess as it as an imaging agent to identify tumor metastases and as a radioimmunoconjugate for metastatic disease, the company said.

Bavituximab is a monoclonal antibody that binds selectively to cells that line tumor blood vessels, the company said. Data demonstrated that a mouse equivalent of bavituximab in combination with docetaxel resulted in a 93 percent inhibition of human breast cancer growth in mouse cancer models. Researchers reported that combination treatment with a bavituximab equivalent and cisplatin doubled survival time in a preclinical model of cisplatin-resistant breast cancer, the company said. The Bavituximab phospholipid target was amplified when exposed to radiation, and recent preclinical studies demonstrated that bavituximab plus radiation was more effective in a brain cancer model than either therapy alone, the company said.

"The DOD project will enable us to assess bavituximab's utility for both tumor detection and therapy in breast cancer," said Ralph Mason, professor of radiology at UT Southwestern and a principal investigator. "Since bavituximab's unique target is expressed on blood vessels in tumors but not in normal tissues, it may have both safety and efficacy advantages compared to other antibodies. We are eager to assess the utility of a bavituximab radioimmunoconjugate for the identification and treatment of metastatic breast disease."

The drug also is in a phase I trial for advanced refractory solid tumors, the company said.

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Cytogen Corp. (Nasdaq: CYTO) of Princeton and **Savient Pharmaceuticals** (Nasdaq: SVNT) of East Brunswick, N.J., said they have executed a distribution agreement granting Cytogen exclusive marketing rights for Soltamox (tamoxifen citrate) in the U.S.

Soltamox, a cytostatic estrogen receptor antagonist, is the first oral liquid hormonal therapy approved in the U.S, the companies said. It is indicated for breast cancer in adjuvant and metastatic settings and to reduce the risk of breast cancer in women with ductal carcinoma in situ or with high risk of breast cancer, the companies said.

Under the agreement, Cytogen said it would pay an upfront licensing fee of $2 million to Savient and would also pay contingent sales-based milestone payments totaling $4 million to Savient and its wholly owned subsidiary, Rosemont Pharmaceuticals Ltd. Savient and Rosemont would also receive royalties on net sales of Soltamox. Also, Cytogen has entered into a supply agreement with Rosemont for manufacture and supply of the agent.

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Oxford Genome Sciences Ltd of Oxford, England, and **Medarex Inc**. (Nasdaq: MEDX) of Princeton said they have entered into a strategic collaboration to discover and develop human antibody therapeutics for cancers, including colorectal cancer.

OGeS said it would provide colorectal cancer targets, against which Medarex would generate fully human monoclonal antibodies using its proprietary UltiMAb Human Antibody Development System. OGeS said it would use its Oxford Genome Anatomy Project database, a human protein database that integrates genomic, proteomic and clinical information derived from blood and tissue studies from 50 different human tissues and represents 60 diseases.

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R2 Technology Inc. Sunnyvale, Calif., said it has entered into a multi-year agreement with **GE Healthcare**, a division of the General Electric Co. (NYSE: GE).

Under the agreement, GE Healthcare will distribute the R2 proprietary ImageChecker D mammography CAD system with the GE Senographe 2000D, Senographe DS full-field digital mammography systems in the GE international markets outside the USA, and the GE Senographe Essential FFDM system once commercially available, the company said.

Five independent prospective clinical studies showed that the use of the R2 mammography CAD resulted in 6.6 percent to 19.5 percent more cancers detected, the company said.

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XA Ltd. (Nasdaq: XA) of Berkeley, Calif., and **AVEO Pharmaceuticals Inc**. said they have entered into an agreement for XA to use its Human Engineering technology to humanize AV-299, the AVEO anti-HGF monoclonal antibody.

AVEO will pay XA an up-front license fee, development milestones and royalties.AVEO retains all development and commercialization rights to AV-299.

"AV-299 is an antagonist of hepatocyte growth factor/scatter factor which has demonstrated excellent efficacy in preclinical models of human cancer," said Tuan Ha-Ngoc, president and CEO of AVEO. "Our clinically-validated HE technology is intended to accelerate product development timelines for the AV-299 program, while increasing the potential for clinical and commercial success."

AV-299 is a high-affinity antibody whose binding to HGF potently neutralizes the biological activities of HGF in vitro and in vivo, the companies said.