THE CANCER LETTER

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Van Brings Free Brain MRIs To Capitol Hill; Experts See Enormous Potential For Harm

By Paul Goldberg

Over the past several months, over 1,000 New Yorkers have inserted their heads in an MRI unit mounted inside a truck operated by The Brain Tumor Foundation, a nonprofit started by a prominent neurosurgeon at New York University.

Earlier this week, the truck was parked at the base of Capitol Hill, and about 60 people—among them six legislators—stepped in to receive free scans.

Skeptics say these folks should have their heads examined.

"This is crazy," said Steven Woloshin, senior research associate in the Veterans Affairs Outcomes Group of White River Junction, Vt., and

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In the Cancer Centers:

Dana-Farber Opens Lurie Family Imaging Center; M.D. Anderson Offers Communcation Coaching

DANA-FARBER CANCER INSTITUTE'S Lurie Family Imaging Center opened April 27 with a ceremony at the center's home in the Marine Industrial Park on the South Boston waterfront. The ribbon-cutting ceremony, with Boston Mayor **Thomas Menino** and state **Sen. Jack Hart** in attendance, included tours of the facility where scientists will use specially designed MRI, CT, PET, ultrasound and optical scanners to visualize abnormalities in tumors of laboratory animals, speeding the development and testing of drugs targeted at cancer-specific changes. The 14,000 square-foot center was established with funds from Nancy Lurie Marks and the Nancy Lurie Marks Family Foundation. "Imaging technology provides a window into the inner workings of tumors, and in some cases can tell us whether drugs are working almost in real time," said **Andrew Kung**, director of the Lurie Family Imaging Center. "We'll be able to more quickly identify drugs that are effective against certain cancers and stop working on those that aren't." The center includes an MRI scanner specially designed for laboratory animals, a combined PET/CT scanner, an advanced ultrasound imaging system, and multiple optical imagers for studies that use light-emitting proteins to track disease. . . . **M. D. ANDERSON CANCER CENTER** has begun an online education program that coaches health care professionals on skills they may never have been taught in medical school. The I*CARE, or Interpersonal Communication and Relationship Enhancement, program is

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The Brain Tumor Foundation Screened Over 1,000 In NYC

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associate professor of medicine and of community and family medicine at Dartmouth Medical School. "No professional organization recommends this, and there is no credible evidence that this does more than good than harm, and there are lots of reasons to worry about harm. False alarms in the brain leading to biopsies can't be good for you."

The foundation that owns and operates the van was started by Patrick Kelly, a highly regarded neurosurgeon, who recently retired from practice at New York University School of Medicine.

"If you knew what I know, this would be so obvious to you, because this is not something that has come off the top of my head; this is after a 35-year career with more experience treating brain tumors than anybody else in the world," said Kelly, who claims to have set the world record for the largest number of brain tumor surgeries performed: 7,300. (An interview with Kelly appears on page 4.)

Though Kelly describes his approach is mainstream, several of his prominent colleagues in neurosurgery and neuro-oncology said that they wouldn't step into Kelly's van or recommend any asymptomatic person to do so.

Also, experts in cancer screening point out that brain tumors are relatively rare, that there is neither survival nor mortality data to justify screening, that prospectively identifiable risk groups are small, that there is no established methodology for screening, and that follow-up and treatment can be devastating.

Critics say that Kelly's campaign is another manifestation of the American belief in screening and insistence on the worst possible care at the highest possible price. "At a time when we are worried about healthcare costs, one must be responsible in screening and treatment recommendations," said Otis Brawley, chief medical officer of the American Cancer Society.

Of course, scarcity of resources isn't the only problem. Brawley said cancer screening can be feasible in more common diseases when data demonstrates that interventions brought by screening decreases mortality from the disease. "We don't have any of these things in the case of brain tumors," Brawley said.

People who agree to be screened could be harmed in many ways, Brawley said. "There is the potential that [Kelly] could cause something to be diagnosed which doesn't need to be diagnosed, and he could cause a medical intervention which clearly increases morbidity and might even be fatal," Brawley said.

A finding of uncertain clinical significance could also make the patient uninsurable. "If someone has an abnormality on one of these screening tests, even an abnormality that turns out to be a low-grade meningioma or something that doesn't need to be treated, it actually could make insurability a real problem for that person," Brawley said. "We are not just talking about the mental anguish. We are not just talking about needless surgery and interventions. We are talking about the future uninsurability."

The 60 asymptomatic individuals on Capitol Hill stepped into the van after receiving "Dear Colleague" letters from two congressmen.

"It has been estimated that half of all brain tumor patients could have their tumors successfully removed for good if they are detected early, before physical symptoms become apparent," said an email blast signed by Reps Eliot Engel (D-NY) and Robert Aderholt (R-Alabama). "The MRI scans will be free for all Members of Congress, Senators, congressional staff and the general public. Join us to help raise tumor awareness and to promote early detection."

According to a spokesman for the foundation, the event went well, and the van would likely return.

In an interview, Kelly claimed that owing to his standing as a surgeon, he has had no difficulty quelling skepticism among his colleagues. "Initially, I got a lot of disagreements," he said. "But you have to realize that… I personally have a lot of credibility, so not a whole lot of argument from my colleagues."

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However, Henry Brem, chairman of the Department of Neurosurgery at Johns Hopkins University, said his skepticism hasn't been deactivated.

"It's an untested hypothesis," Brem said. "One needs to gather data that an earlier diagnosis in an asymptomatic patient would change the natural histry of the disease, and we don't have data to that effect in neurosurgery at this point. General practice in neurosurgery is that there has to be an indication for doing a scan, which generally consists of a neurlologic symptom, including severe headaches. But something has to be wrong to get a scan."

Rolando Del Maestro, director of the Brain Tumor Research Centre at the Montreal Neurological Institute and Hospital, similarly described Kelly's approach as anything but mainstream. "Potentially, you could have a patient who is found to have a lesion that is benign, is operated on and has a complication that leaves that patient less well than before for no definite benefit," he said.

Kelly said the scanner in his van uses a sequence of three images and uses no contrasting agent. Both Brem and Del Maestro described this method of imaging as imprecise.

"Why would you do it without gadolinium [contrasting agent]?" said Brem. "I wouldn't consider myself screened if I didn't have gadolinium. If I were trying to determine, 'Do I or don't I have a brain tumor?' I'd need to get gadolinium. Otherwise, the question is not answered, because there are plenty of tumors that are missed without gadolinium under current techniques."

Del Maestro said that omission of the contrasting agent could make the screen miss up to 20 percent of tumors.

"That's not the typical MRI protocol that anybody would use if they were concerned about a tumor," he said. "If an individual were concerned about a tumor, they would do a proper MR with all the sequences and with gadolinium enhancement. So you are going to miss some tumors by doing this screen process. My guess would be you are going to miss 10 to 20 percent of people who really do have tumors."

Kelly acknowledges that no protocol exists for follow-up of radiographic findings and that the protocol he uses exists entirely in his head.

"If we found something, I would recommend a scan in three months time," he said. "If there is no change, then six months, and if there is no change, then a year, and then follow it annually for about five years, and after that, I think I would have to wing it, because we have no previous experience with this."

Other brain tumor experts said they use different approaches, noting that the issue is analogous to the controversy over follow-up of incidental findings. Brem estimates that as much as a third of his practice consists of follow-up of brain tumors that turn up on scans taken for reasons other than brain tumor diagnosis.

While Kelly's screening program in New York has found eight brain tumors, there have been no surgeries.

This doesn't surprise Del Maestro. "If you look at brain operations per se, they have a clear complication rate," he said. "What I tell people whom I operate on for a brain lesion is: One, there is somewhere around a one-percent chance of infection; Two, depending on your age, there is a risk that you could die after the operation from a heart attack, from pneumonia, from problems with your veins, from just the fact that you had an anesthetic. And the third thing is, if you are having a brain operation, there always is a risk that you will be worse after the operation than you are now. And that risk usually is in the range of two to three percent. So, if you put all those risks together, having a brain operation is not exactly a picnic."

In an interview, Kelly said patients wouldn't necessarily be taking a big risk. They could get a biopsy, "which in my hands had a risk of less than one percent and then treat it with radiosurgery, which is a noninvasive method of treating tumors, almost no risk."

The view that radiosurgery is risk-free is not widely shared.

"Radiosurgery has very little immediate risk, but, certainly, radiosurgery has an undetermined future risk, and I would not use it lightly, because we don't know what 35 or 40 years from now what the effect of very very high dose of radiation is going to be on the brain," said Brem. "We know that there are some patients who have difficulty with brain swelling as a consequence of radiation therapy. I would not say that it has no risk. In fact, for a tumor on the surface, I would say the risk of surgery is much lower than the risk of potential long-term consequences of radiosurgery."

Epidemiologists question Kelly's claim that as many as a million Americans and 25,000 New Yorkers are walking around without knowing that they have brain tumors.

In an interview, Kelly said he got that number by extrapolating the findings of an NIH study of MRI scans performed in 1,000 healthy volunteers who enrolled in control groups on various protocols. The study found two brain tumors, or 0.2 percent. (Katzman et al., JAMA. 1999; 282:36-39).

Even if one were to accept this extrapolation as valid, this would mean that 600,000—not a million—Americans may be walking around with asymptomatic brain tumors. The paper cites an earlier study, where an examination of MRI scans from 3,672 patients found no primary CNS neoplasms.

In a more recent study, researchers in Rotterdam prospectively scanned 2,000 healthy people and found that asymptomatic brain abnormalities are relatively common. Mostly, these were subclinical vascular pathologic changes, which were found in 7.2 percent of the subjects. Benign primary tumors were found in 1.6 percent of the population. There was also one possibly malignant primary brain tumor, a low-grade glioma that was not histologically confirmed (http://content.nejm.org/cgi/content/full/357/18/1821).

The American Cancer Society estimates that 18,500 people would be diagnosed with brain cancer and that 12,760 men and women would die of brain cancer in the U.S. in 2005, the most recent year for which such projections are available..

"The question is what is the best use of resources to deal with the brain tumor population?" Del Maestro said. "The incidence of brain tumors in a population per year is in the range of 6 to 10 per 100,000 population. So what you would have to do is perform MR scans on 100,000 people to find somewhere between 6 and 10 brain tumors, and of those 6 to 10, about half of those lesions would be benign.

"It wouldn't seem to be a reasonable expenditure of resources."

Q & A:

Should I Get My Head Examined? TCL Editor Seeks Medical Advice

The Cancer Letter asked neurosurgeon Patrick Kelly to explain his rationale for using MRI to perform mass screening for brain tumors in of asymptomatic people.

The controversial screening program has been focused on New York, but on May 4 and 5, a van operated by Kelly's non-profit, The Brain Tumor Foundation, was parked on Capitol Hill. About 60 people, including as many as six lawmakers, prompted by a "dear colleague" letter, dropped in to get a free scan.

Were these people helped or harmed?

Kelley, who is the Joseph Ransohoff Professor of Neurosurgery at NYU School of Medicine, retired from surgery last year.

The interview was conducted by The Cancer Letter editor Paul Goldberg.

TCL: *If I were to consider sticking my head in an MRI, would you suggest I do it?*

KELLY: Yes, sure, why not, unless you look at your body like a 1949 Studebaker and you don't want to open the hood.

TCL: *It's a 1959 Coupe DeVille.*

KELLY: There are some people who would rather not know what's going on. But sure, just to be sure everything is okay. I think that in the future it might be the way medicine is going to be practiced, where people step into an MRI and scan the whole body and an on-board computer system will come out and say "You better go see a doctor" or "Congratulations, you are normal."

TCL: *I guess I would be worried about the possibility of a false-positive.*

KELLY: You shouldn't be operating based on everything you see there, but what we are doing is establishing a population at risk. There are probably lots of people walking around with asymptomatic brain tumors that may be in a quiescent state and would never grow. The thing to do then is to follow it closely with serial MRIs.

TCL: *I would be asymptomatic. So I guess everyone would have to do it.*

KELLY: That's right. As a matter of fact, I think everybody should, just because once they produce symptoms, most of them ultimately are incurable, unless they are benign tumors like meningiomas or acoustic neuromas, which we can cure with surgery. If they are gliomas, by the time they start destroying brain tissue to cause symptoms, many of them are surgically incurable and incurable by any other means.

TCL: *So everybody in America needs to do this?*

KELLY: In my opinion, yes.

TCL: *It's quite a screening effort.*

KELLY: Sure it is, but you know, for the first three months of the Iraq war, you could have screened every man, woman, and child in the U.S. three times over.

TCL: *You are talking about yanking out a lot of tumor.*

KELLY: In reality, there would be probably a very small percentage that would be tumors that should be operated on. The rest of them would probably be followed. But then you'd have a chance, because if we found a small, 1-cm tumor and notice a little growth or a little change, that's an indication that something needs to be done.

TCL*: Is there a protocol for follow-up?*

KELLY: At this point, there isn't, except in my own head. If we found something, I would recommend

a scan in three months time. If there is no change, then six months, and if there is no change, then a year, and then follow it annually for about five years, and after that, I think I would have to wing it, because we have no previous experience with this.

TCL: *There are no studies whatsoever. You are bringing up comparisons with breast and even prostate, where it's still extremely unclear.*

KELLY: Let's look at that. There is one major difference between breast tumors, and prostate, and breast, and colon, and lung cancer. And you know what that difference is? It's a very important difference. You know what it is?

TCL: *No.*

KELLY: A lot of doctors don't know it, so don't feel bad. It is the fact that brain tumors don't metastasize. They grow by local extension. Which is why it makes a lot of sense to screen for brain tumors where it might be questionable to screen for other types of tumors, even though they are doing it. Everybody goes out to get a colonoscopy for almost $2,000 a pop, but then they worry about getting an MRI, which is a couple hundred bucks.

TCL*: But in this case you can get it for free.*

KELLY: We were doing it for free. Ultimately it may not be. Maybe some day you would walk into a mall, sweep a credit card, and it might charge you $20 to get an MRI scan. Right now, we are just trying to increase awareness.

TCL: *Is that a standard scan?*

KELLY: There is no contrasting agent. Right now, we are using tree-image sequences, and it takes about three to five minutes. It's not the same as the diagnostic scan, where they do a lot of image sequences and contrast.

TCL: *And the cost is?*

KELLY: Of course, we are doing this for free. The actual costs of it are probably $300-400 for the Brain Tumor Foundation. Of course, this is why we need to raise money to be able to afford it.

TCL: *How many people have you scanned so far?*

KELLY: Over 1,000 in less than a year.

TCL: *So you park the truck in the middle of New York, and they come out?*

KELLY: Actually, we go out to the five boroughs. And if you go to the website roadtoearlydetection.org, you can see where the truck is any particular week.

TCL: *How many tumors have you found?*

KELLY: Eight tumors within the brain, and there are several pituitary tumors. You might say, that's not very much. Actually, that is an astounding statistic. It's about 100 times what you'd expect.

TCL: *Where do your numbers come from? [The BTF brochure claims that a million Americans and 25,000 New Yorkers are "walking around with a brain tumor and don't even know it."]*

KELLY: That is from a study done at NIH, where they did 1,000 scans on health volunteers and found three brain tumors. We are finding more… Basically we are looking at the tip of the iceberg, where incidence is only the tip of the iceberg. But under the water there is much larger prevalence, and the question is going to be is what factors make an asymptomatic tumor become a malignant tumor.

TCL: *How many of those eight tumors did you operate on?*

KELLY: None. These people will be followed. We notify the person and their doctor.

TCL: *Who reads the scans?*

KELLY: It's read by a neuroradiology group. It's part of Alliance Imaging, which is part of the administrative support for this project. The Brain Tumor Foundation owns the MRI scanner and the truck, but we need someone to run it, which means technicians and various logistics. That's what Alliance Imaging provides. They provide MRI units to various hospitals.

TCL: *In New York, does Medicare work with you?*

KELLY: It's absolutely free. You just make an appointment and get a scan. The data gets sent to the central reading facility for Alliance Imaging, and their radiologists generate a report, which goes to the physician of record of to the person.

TCL: *And there is no referral?*

KELLY: That is what the patient has to consult their doctor about. The doctor would make a referral if they thought it was appropriate.

TCL: *So this goes to the primary care physician. If they have one; right?*

KELLY: If they have one. If not, they call the Brain Tumor Foundation and we make a referral.

TCL: *How do your colleagues react to this? Do you feel like you are getting a lot of agreement with this or a lot of disagreement?*

KELLY: Initially, I got a lot of disagreements. But you have to realize that I have operated on more brain tumors than anybody in the world. I have operated on 7,300 brain tumors. So, I've got a lot of credibility with my colleagues, just by virtue of the fact of my academic positions, what I've written—I've written about 300 papers and a couple of text books. I personally have a

lot of credibility, so not a whole lot of argument from my colleagues.

TCL: *The neurosurgeons?*

KELLY: Neurosurgeons. The general public, obviously, is probably smarter than the medical profession. They say, "Yes, it's a good idea." Because wouldn't it be better to find a problem very early on than later on when it's incurable and it costs $500,000 to give somebody another six months of survival. The medical profession had made a whole industry out of treating incurable diseases, which is what we basically do—90 percent of your health care costs are consumed in the last year of your life. If we were to find tumors earlier, I suppose that cost would go down, as opposed to what people are worried about, that it increases costs.

But, to answer your question, I think initially I had some arguments, which were very easy to quell. And lately, I've had a lot of people agreeing with me that this is certainly something that should be tried.

TCL: *And you are not at all concerned about false-positives?*

KELLY: What do you mean by false-positives?

TCL: *Treating tumors that do not need to be treated, that will just sit there, and people will die of something else. I guess it's a question of survival vs. mortality studies.*

KELLY: I think brain tumor is different. You can categorize tumors with MR spectroscopy. Somebody who has a positive scan—something that looks like a tumor—would need further study. And that would mean all the imaging sequences and contrast, and then MR spectroscopy to better characterize it as a tumor. Let's say you have a 4 cm meningioma. This is not something that somebody was born with. This something has been growing and will ultimately kill the patient. That person should be operated on. But let's say you have a 1 cm glioma. I would recommend following that. Some people might say, if it's close to the surface and the risk of doing it is small, they might recommend a surgery. But I think it's always going to be a question of risk vs. benefit. They could also do a biopsy, which in my hands had a risk of less than 1 percent and then treat it with radiosurgery, which is a noninvasive method of treating tumors, almost no risk. It's a little different than false positives in CT scans of the chest.

TCL: *There are no survival studies in early detection for brain tumors.*

KELLY: No, not for brain tumors.

TCL: *That's where this thing is complicated, and you really don't know it until you've done the mortality studies.*

KELLY: I think those mortality studies done with breast tumors and that sort of thing are very flawed studies, and they are usually sponsored by some group that doesn't want to pay for screening, be it the government, like in the UK and Canada, or various insurance agencies. They are trying to avoid paying for screening.

I'd be curious to see what you write. But if you knew what I know, this would be so obvious to you, because this is not something that has come off the top of my head; this is after a 35-year career with more experience treating brain tumors than anybody else in the world.

In the Cancer Centers:

Free Site Offers Coaching On Communication Skills

(Continued from page 1)

designed to help teach clinicians, especially oncologists, the communication and relationship skills necessary to managing challenging patient or family encounters. Focused chiefly on cancer care and related issues, the site is free to any physician, nurse, physician's assistant, health care provider, patient or caregiver, and is available at www.mdanderson.org/icare. The site is accredited by the Health on the Net Foundation. **Walter Baile**, a practicing psychiatrist, is the program director. . . . **RUTH O'REGAN** was named to the Louisa and Rand Glenn Family Chair in Breast Cancer Research in Emory Winship Cancer Institute. O'Regan is associate professor of hematology and medical oncology and director of Emory Winship's translational breast cancer research program. O'Regan, a Georgia Cancer Coalition Distinguished Scholar, joined Emory from Northwestern University in Chicago. O'Regan also is co-director of the Jean Sindab Endowment Research Team, which focuses on developing scientific research on breast cancer in African-American women. O'Regan and her colleagues have worked closely with the Avon Foundation to build a multidisciplinary breast cancer team at the Georgia Cancer Center of Excellence at Grady Hospital. She is also principal investigator of the first statewide breast cancer clinical trial run through the Georgia Center for Oncology Research and Education. . . . **UMDNJ-GRADUATE SCHOOL** of Biomedical Sciences at Robert Wood Johnson Medical School has announced a new advanced degree program designed for professionals who want to broaden their career opportunities in science and medicine. The Master's in Clinical and Translational

Science degree will be offered for the first time in September, providing innovative training for doctors, nurses, pharmacists, dentists and research scientists, as well as others who want to learn the complexities of translational research, or how research is transformed into clinical diagnoses and treatments to improve patient care. "The Master's in Clinical and Translational Science degree program is a unique curriculum designed to train the next generation of leaders by providing students with the knowledge, skills and experience to significantly advance healthcare solutions and lead the research teams of the future," said **Terri Goss Kinzy**, associate dean for the Graduate School of Biomedical Sciences. "This degree will enhance a professional's employment value and strengthen his or her opportunities for career advancement." The degree was developed to complement the goals of the NIH Roadmap for medical research, designating clinical and translational science as a major initiative. "The course of study focuses on breaking down barriers to collaborative research and stimulating innovative thinking," said **Ramsey Foty**, associate professor of surgery and director for the master's program. "Prominent researchers, clinicians and industry professionals at the forefront of clinical and translational research will provide students with a global and comprehensive understanding of the complex continuum of translating hypothesis-driven basic research discoveries into clinically useful and commercially viable tests or treatments." Further information is available at http://rwjms.umdnj.edu. . . . **OHIO STATE UNIVERSITY** Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute has hired **R. Michael Townsend** as chief information officer, with responsibility for all cancer information management, including strategic planning and execution of informatics projects that support operational and strategic goals. Townsend was the CIO and an IT management and planning consultant for RIK Data Solutions in Manalapan, N.J. He has also served as director of information technology for the Cold Spring Harbor Laboratory, and as director of Advanced Research Systems and the director of the Physical Sciences Numerical Calculations Laboratory at the University of Chicago. . . . **BRYAN SCHNEIDER**, assistant professor in the Division of Hematology/Oncology at Indiana University School of Medicine and a physician/researcher with the Indiana University Melvin and Bren Simon Cancer Center, received a $5.8 million Promise Grant from Susan G. Komen for the Cure for his research that attempts to establish biomarkers to better predict which breast cancer patients will benefit from bevacizumab. The researchers will study genetic biomarkers in the IU-based E5103 phase III trial that is evaluating whether adding bevacizumab to standard chemotheraphy will improve disease-free and overall survival for women with potentially curable disease. The grant will allow Schneider to use a genome wide association study to uncover the most clinically accurate biomarkers possible and to conduct quality of life studies. . . . **DAVID GERSHENSON**, professor and chair of the Department of Gynecologic Oncology at The University of Texas M. D. Anderson Cancer Center, has been tapped to lead the Gynecologic Cancer Foundation. GCF is a nonprofit organization established in 1991 by the Society of Gynecologic Oncologists to support research and training in gynecologic cancers and promote public awareness of prevention, early detection and treatment. . . . **JOHNS HOPKINS** pediatric oncologist **Donald Small** received the Frank A. Oski Award from the American Society of Pediatric Hematology/Oncology on April 24, at the society's annual meeting in San Diego. The award honors clinicians and basic science investigators in pediatric hematology and oncology who have made significant research contributions to the field. Small and his team were the first to clone the human FLT3 receptor gene, the most frequently mutated gene in acute myelogenous leukemia. The FLT3 mutation is a predictor of poor survival for patients with this mutation. Small found small molecules capable of inhibiting the receptor and showed that these drugs would kill leukemia cells with the FLT3 mutation, while leaving normal blood cells unharmed leading to a new targeted therapy for acute leukemia. He led the design of clinical trials using one of these drugs. Most recently, the drug has entered clinical trials through the Children's Oncology Group for children with FLT3 mutant AML and infants with acute lymphocytic leukemia.

NCI Programs:

NCI, Foundation Fund Studies Of Early Lung Cancer Detection

NCI and The Canary Foundation have begun a research partnership to find biomarkers for lung cancer in people who have never smoked.

NCI's Early Detection Research Network and the Canary Foundation will provide initial funding of $1 million each.

"Efforts to study the disease in never-smokers have been limited, and no screening tests or approaches for

identifying individuals at increased risk are available today," said Samir Hanash, of the Fred Hutchinson Cancer Research Center, and team leader for Canary Foundation-funded projects. "This inability to recognize non-smokers who are at risk often leads to delays in diagnosis and results in cancer identification at an advanced stage, and this problem is what we're tackling with this new study."

Global estimates suggest that as many as 25 percent of all lung cancers worldwide are not attributable to smoking. "If you consider lung cancer in never smokers as a separate category, it ranks as the seventh most common cause of cancer deaths worldwide, even before cancers of the cervix, pancreas and prostate," commented Adi Gazdar, of the University of Texas Southwestern Medical Center, Dallas, and team leader for the NCI-funded studies.

Using lung cancer cell lines, tissue, and blood specimens, researchers at five institutions will undertake a coordinated approach to biomarker discovery by studying the same sets of specimens by different methods. The researchers will deposit the data in a single repository, and integrate the results to find the most promising biomarkers. Because of this design, this project will also serve as a pilot study to demonstrate the feasibility of the approach. If it is successful, the researchers plan to open the project to additional collaborators from the EDRN.

The NCI-EDRN will fund most of the tumor studies, and the Canary Foundation will provide funding for the cell culture studies. Projects funded by NCI include:

—Protein biomarker discovery: In-Depth Proteomic Analysis of Plasmas from Subjects with Lung Cancer Arising in Current, and Never Smokers (Principal Investigator: Hanash)

—Genome analysis: Mining the Genome and Transcriptome in Lung Cancer from Never Smokers (PI: Gazdar)

—Cellular alterations: Mitochondrial Mutations in Lung Cancer from Never Smokers (PI: David Sidransky, Johns Hopkins University School of Medicine)

—Genome analysis: Genomic Studies of Lung Cancer Arising in Current, and Never Smokers (PIs: Wan Lam and Stephen Lam, British Columbia Cancer Agency)

Projects funded by the Canary Foundation include:

—Protein biomarker discovery: Proteomic Analysis of Lung Cancer Cell Lines (PI: Hanash)

—Tumor biomarker discovery: Biomarker Discovery for Lung Cancer in Never Smokers (PI: Gazdar)

—Genome analysis: Genomic Studies of Lung Cancer Cell Lines from Lung Cancers Arising in Current, and Never Smokers (PIs: Lam and Lam)

—RNA analysis: MicroRNA Profiles of a Lung Cancer Cell Line Panel (PI: Muneesh Tewari, Fred Hutchinson Cancer Center)

—Genome analysis: Genome-Wide DNA Methylation Profiling of Lung Adenocarcinomas from Never Smokers and Current Smokers (PI: Ite Laird-Offringa, University of Southern California)

Funding Opportunities

Recovery Act Grand Opportunities GO Grant Submission Deadline Moved to May 29. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-090.html

Extended Error Correction Window for Electronic Submission of NIH Challenge Grants and Funding Opportunities with Submission Deadlines From April 27 Through May 1. http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-091.html

Delays in Grant Application Submission Due to Closure of Institutions because of 2009 H1N1 Flu Concerns http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-092.html

Administrative Supplements to Study Economic Impact of Interventions Targeting Cancer Survivors and/or their Families http://grants.nih.gov/grants/guide/notice-files/NOT-CA-09-023.html

Notice of Opportunity for Fast Track Entry of Assay Projects for High Throughput Screening into the NIH Roadmap Molecular Libraries Probe Production Centers Network http://grants.nih.gov/grants/guide/notice-files/NOT-RM-09-011.html

Website for RFA-RR-09-009: Recovery Act 2009 Limited Competition: Enabling National Networking of Scientists and Resource Discovery (U24) http://grants.nih.gov/grants/guide/notice-files/NOT-RR-09-012.html

Minority-Based Community Clinical Oncology Program (U10) (RFA-CA-09-023) Application Receipt Date: July 08 http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-023.html

Pediatric Device Consortia Grant Program (P50) (RFA-FD-09-007) http://grants.nih.gov/grants/guide/rfa-files/RFA-FD-09-007.html

Modeling the Scientific Workforce (U01) (RFA-GM-10-003) http://grants.nih.gov/grants/guide/rfa-files/RFA-GM-10-003.html

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Business & Regulatory Report

Clinical Trials:

Genentech Says Phase III Trial Of Avastin In Colon Cancer Didn't Meet Endpoint

Genentech Inc. said a phase III study of Avastin (bevacizumab) plus chemotherapy following surgery in patients with adjuvant colon cancer did not meet its primary endpoint of improving disease-free survival.

Results were obtained are from a planned final analysis of the C-08 trial conducted by the National Surgical Adjuvant Breast and Bowel Project. This represents the first result of an Avastin adjuvant trial.

Data from the trial have been submitted for presentation at the upcoming

(Continued to page 2)

Drug Approvals & Applications:

OncoGenex In Agreement With FDA On Design Of Prostate Cancer Trial

OncoGenex Pharmaceuticals Inc. (NASDAQ: OGXI) of Bothell, Wash., said it has reached an agreement with FDA on the design of a second phase III registration trial of OGX-011, an agent targeting castrate-resistant prostate cancer (CRPC), via the Special Protocol Assessment process.

FDA has agreed that the design and planned analysis of the trial featuring durable pain palliation as the primary endpoint adequately addresses the objectives necessary to support a regulatory submission.

"We have now received confirmations on two separate phase III trial designs from the FDA via the SPA process, each in second-line treatment of advanced prostate cancer," said Scott Cormack, president and CEO of OncoGenex Pharmaceuticals. "One trial design evaluates overall survival benefit while the second trial design evaluates reduction in pain as the primary endpoint. Having evaluated both of these endpoints in our phase II trials, we are well positioned to re-evaluate each of these endpoints in larger phase III registration trials."

"The FDA's acknowledgement of pain in addition to survival as key endpoints for market approval supports the basis of our OGX-011 development program for advanced prostate cancer," Cormack said. "Although we observed a positive effect on PSA in our Phase II trials of OGX-011, we recognize that PSA response has not been shown to correlate to a clinical benefit and therefore is not an acceptable endpoint for FDA approval. Our focus remains on survival and pain palliation, both endpoints

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NSABP's C-08 Didn't Meet Primary Endpoint For Avastin

(Continued from page 1)

ASCO annual meeting, May 29-June 2.

"While we are disappointed the C-08 study did not meet its primary endpoint, our initial review of the data leads us to continue to believe Avastin may be active in patients with early-stage colon cancer and look forward to NSABP's presentation at ASCO," Hal Barron, senior vice president, development, and chief medical officer at Genentech, said in a statement.

"We remain fully committed to the ongoing Avastin adjuvant programs in early-stage colon, breast and lung cancers," Barron said.

The C-08 study was conducted by NSABP and sponsored by NCI under a Cooperative Research and Development Agreement.

C-08 was a a randomized multi-center phase III study designed to evaluate the effect of FOLFOX (5-fluorouracil, leucovorin and oxaliplatin) chemotherapy with or without Avastin on disease-free survival in patients with resected stage II or III adenocarcinoma of the colon.

The trial was conducted primarily in the U.S. Patients enrolled in the two-arm study were randimized after surgery to receive either FOLFOX chemotherapy alone for six months or FOLFOX in combination with Avastin (intravenous every two weeks) for six months, followed by an additional six months of Avastin monotherapy. The secondary endpoint was overall survival.

Results are expected in 2010 from a separate Roche-sponsored international Phase III study (AVANT) assessing Avastin in combination with chemotherapy for early-stage colon cancer, the company said. The three-arm trial is evaluating Avastin in combination with the chemotherapy regimens XELOX (capecitabine and oxaliplatin) or FOLFOX chemotherapy versus FOLFOX alone.

Avastin is being studied as an adjuvant treatment in other early-stage diseases: HER2-negative breast cancer, HER2-positive breast cancer and non-squamous, non-small cell lung cancer. Approximately 26,000 people are expected to participate in Avastin adjuvant studies.

Genentech is a unit of the Swiss company **Roche**.

Genomic Health Inc. (NASDAQ: GHDX) of Redwood City, Calif., announced that the QUASAR validation study met its primary endpoint to predict the likelihood of recurrence for stage II colon cancer patients following surgery, and that the colon cancer Recurrence Score provided additional independent clinical value beyond standard measures of risk.

Based on these positive results, Genomic Health is initiating the necessary work in its Clinical Reference Laboratory and proceeding with commercialization plans to make the Oncotype DX colon cancer Recurrence Score available to physicians and patients in early 2010. Detailed results from the QUASAR study are scheduled to be presented during the upcoming ASCO annual meeting in Orlando, Florida.

While meeting the primary endpoint in predicting recurrence, the study did not meet a second endpoint evaluating a separate score, with a distinct set of genes, designed to predict which patients experience greater relative benefit of 5-fluorouracil/leucovorin (5FU/LV) following surgery.

"The positive findings of this large QUASAR validation study represent a significant step forward in better understanding the biology of a disease that is a leading cause of cancer related death," said Steve Shak, chief medical officer of Genomic Health. "With these results, we believe we can introduce the promise of genomics into clinical practice for colon cancer as we did in breast cancer, and are pleased that the study has been accepted for presentation at the upcoming ASCO annual meeting in Orlando, Florida."

The oncology community widely recognizes the need for better prognostic tools in stage II colon cancer

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(also known as Dukes' Stage B) that can more accurately predict the likelihood of disease recurrence. Currently, selection of stage II patients for chemotherapy following surgery relies on a limited set of clinical and pathologic markers that do not always adequately assess individual risk. As a result, determining the optimal treatment of stage II patients is a significant challenge in clinical practice.

For its colon cancer program Genomic Health and its collaborators used the same rigorous clinical development strategy and standardized quantitative assay technology designed for the company's Oncotype DX breast cancer assay. More than 1,800 colon cancer patients and 760 candidate genes were evaluated in four clinical studies to select the genes for the Oncotype DX colon cancer assay. The resulting genes were then studied in more than 1,200 stage II colon cancer tumor samples from the landmark QUASAR study (Lancet 370:2020, 2007).

Infinity Pharmaceuticals Inc. (Nasdaq: INFI) today announced that, based on the recommendation of its independent data monitoring committee (IDMC), Infinity has elected to terminate the RING trial, a double-blind, placebo-controlled international Phase 3 registration trial of IPI-504 (retaspimycin hydrochloride) in patients with refractory gastrointestinal stromal tumors (GIST).

The IDMC's recommendation to halt the trial was based on an early review of safety data from the first 46 patients enrolled in the study, which showed a higher than anticipated mortality rate among patients enrolled in the treatment arm. While the RING trial had similar entry criteria to the earlier study of IPI-504 in patients with refractory GIST, a preliminary review of the data suggests that the patients enrolled in the RING trial had more advanced disease, as evidenced by a greater percentage of patients having received three or more prior therapies and longer time since initial diagnosis. The company plans to fully analyze the data from this study in order to inform the ongoing development of IPI-504.

"While this outcome is disappointing, we continue to believe in the therapeutic potential of Hsp90 inhibition, and are committed to the development of both IPI-504 and our oral Hsp90 inhibitor, IPI-493," said Julian Adams, president of research and development and chief scientific officer. "We have now fully enrolled and look forward to sharing at ASCO data from our ongoing trial of IPI-504 in non-small cell lung cancer."

The RING trial will not enroll any new patients, and patients currently enrolled in the study will no longer receive IPI-504. Infinity is notifying all participating clinical trial sites and regulatory agencies of its decision.

Infinity plans to continue investigation of IPI-504, an inhibitor of heat shock protein 90 (Hsp90), in other cancers, including in the ongoing Phase 2 portion of a trial in patients with non-small cell lung cancer, a Phase 2 trial in combination with Herceptin (trastuzumab) in patients with HER2-positive metastatic breast cancer, and a Phase 1b trial in combination with Taxotere (docetaxel) in patients with advanced solid tumors. Infinity, in collaboration with appropriate outside parties, will determine what changes, if any, may be needed or desired to maintain patient safety and optimize the development of IPI-504 in these and future studies.

University of Miami Miller School of Medicine and **Heat Biologics Inc**. announced today that the University's Institutional Review Board has approved an expansion and acceleration of the Phase I clinical trial of a novel vaccine to treat non-small cell l ung cancer underway at the University's Sylvester Comprehensive Cancer Center. Heat Biologics holds the exclusive license to develop and commercialize the GP96-Ig cell-based vaccine technology.

As part of an academic study, the University had been enrolling patients in the clinical trial on a limited basis to satisfy the IRB of its safety. The IRB's approval means enrollment can now be expanded to accommodate simultaneous administration of the vaccine on three dosage schedules: twice a week, weekly and bi-weekly. Twelve patients will be enrolled in each group at a rate of three patients every four weeks.

If successful, GP96-Ig is expected to fill a substantial need in the treatment of NSCLC, which accounts for 85 percent of all lung cancers and has a five-year survival rate of just 15 percent. For NSCLC patients, treatment options are often limited.

"There are more than 200,000 new lung cancers patients in America every year, and close to 160,000 will die every year due to a lack of effective therapy for this lethal disease," said lead investigator Luis E. Raez, M.D., associate professor of medicine and co-leader of the Lung Cancer Site Disease Group at Sylvester. "Chemotherapy is largely palliative and new therapy approaches are urgently needed for this disease."

Unlike conventional vaccines, which are used to prevent infectious diseases, the GP96-Ig vaccine stimulates the immune system to fight the disease once

it is diagnosed. The treatment was developed by Eckhard Podack, Sylvester Distinguished Professor of Medicine and chairman of the UM Department of Microbiology and Immunology, who genetically engineered the gp-96 heat shock protein to be secreted by NSCLC cells, triggering an attack response from the body's immune system.

"The heat shock vaccine technology has achieved extraordinary cytotoxic immune responses in large animal models, contributing to our confidence in this vaccine approach for cancer," said Podack. "While the current clinical trial is focused on testing the therapeutic effects of the GP96-Ig vaccine on lung cancer, if successful the underlying technology can be used for many different applications."

Adds Jeffrey Wolf, CEO, Heat Biologics: "The impact the GP96-Ig vaccine will have on the lives of NSCLC patients is significant, but it is just the beginning. The potential this vaccine holds as a technology platform across which treatments for other cancers, as well as viral and other inflammatory and infectious diseases, can be delivered is staggering."

Heat Biologics also holds the exclusive license to a second treatment developed by Podack, tumor necrosis factor receptor 25 (TNFR25) agonists and antagonists. TNFR25 agonists have the ability to block the production of regulatory T cells, allowing the immune system to work uninhibited. By applying this therapy in conjunction with GP96-Ig, anti-tumor treatment can be much more effective. TNFR25 antagonists work as anti-inflammatory agents, easing the symptoms of asthma and several other auto-immune diseases.

"It is gratifying to see this important technology advance. We are hopeful that the results continue to be favorable. Podack's discovery has the potential to help a large number of patients. He is a first rate scientist who has pursued an erudite line of scientific investigation. I am cheering for his success and the success of the technology," said Bart Chernow, professor of medicine and Vice Provost for Technology Advancement at the University of Miami.

Drug Approvals & Applications:

Firm Plans Phase III Trial Of OGX-011 In Prostate Cancer

(Continued from page 1)

that FDA has confirmed are appropriate for marketing approval, and both endpoints for which we have had success in our phase II clinical trials. Based on the recent survival benefit of combining OGX-011 with first-line docetaxel chemotherapy, we have initiated discussions with FDA for evaluating the overall survival benefit in first-line CRPC, instead of second-line CRPC."

The phase III trial evaluating durable pain palliation has been designed in collaboration with internationally recognized experts in the treatment of patients with CRPC (previously referred to as hormone-refractory prostate cancer) including Dr. Tomasz Beer at the University of Oregon and Sebastian Hotte at Juravinski Cancer Centre, in Hamilton, Ontario, Canada. This will be a randomized, controlled, international trial in approximately 300 men with metastatic CRPC who responded to first-line docetaxel therapy, but subsequently have progression of disease, including prostate cancer-related pain, and are able to receive docetaxel retreatment as second-line chemotherapy.

Patients will be randomized to receive treatment with either OGX-011 and docetaxel/prednisone or docetaxel/prednisone alone. The primary endpoint of the trial will be to determine whether a greater proportion of patients in the arm treated with OGX-011 and docetaxel/prednisone experiences durable pain palliation as compared to patients in the arm treated with docetaxel/prednisone alone. It is expected that approximately 50 clinical sites in the United States and Canada will participate in this trial.

OGX-011 is designed to inhibit the production of clusterin, a protein that is associated with cancer treatment resistance and is currently being evaluated in prostate, lung and breast cancer.

Deals & Collaborations:

Groups Plan Research Project In Ovarian Cancer Genomics

The **National Functional Genomics Center**, funded through an assistance agreement that is awarded and administered by the U.S. Army Medical Research & Materiel Command (USAMRMC) and the Telemedicine & Advanced Technology Research Center, will be conducting a multi-institutional collaborative project in ovarian cancer.

For the first phase of the project, the group will use a biologically-driven approach to characterize gene expression and oncogene activation of copy number and point mutations in preclinical models by profiling ovarian cancer cells and ovarian cancer stem cells. The consortium will also characterize platinum resistance and the interaction between ovarian cancer cells and the immune environment.

The participants who will be sharing data include

Jack Pledger and Johnathan Lancaster (Moffitt Cancer Center); Max S. Wicha and Weiping Zou (University of Michigan Comprehensive Cancer Center and Medical School); Stephen P. Ethier (Barbara Ann Karmanos Cancer Institute); Ryan Miller and Chaoying Yin (The University of North Carolina at Chapel Hill); Mark D. Carlson and Tracy Christianson (Southeast Nebraska Cancer Center); and Tak Sugimura (Hawaii Institute for Molecular Sciences).

The NFGC was established to bridge the gap between pure science and patient care and is accelerating applied, translational research by bringing together partners from government, industry, and academia. The NFGC is using this network to develop strategic alliances that will produce benefits that directly apply to the future military healthcare effectiveness and efficiencies. NFGC research is discovering molecular signatures of cancer that will allow military and civilian personnel anywhere in the world to be quickly and accurately diagnosed and treated based on each individual's genetic profile.

The mission of the NFGC is to validate the concept that molecular signatures in tumors predict cancer risk, diagnosis, prognosis, and response to therapy, as well as to identify new molecular targets for the development of more effective cancer prevention and personalized therapeutic care.

Clarient Inc. (NASDAQ: CLRT) of Aliso Viejo, Calif., said it has been granted an exclusive intellectual property license from the **Indiana University Research and Technology Corp**. for the rights to commercialize the FOXA1 biomarker, which predicts the likelihood of recurrence and long-term, disease-free breast cancer survival.

The licensing of this intellectual property further strengthens Clarient's deep menu of molecular tests for breast cancer and will complement the Clarient Insight Dx Breast Cancer Profile, which is expected to be released soon.

The FOXA1 marker, also known as forkhead box A1, is a gene known to cause breast cancer. Recent data presented at the 2009 USCAP (United States and Canadian Academy of Pathology) meeting demonstrated that the expression of FOXA1, now known to be an estrogen receptor associated transcription factor, correlated with Oncotype Dx when performed in patient samples from Indiana University.

In this clinical study of 79 ER-positive, node-negative breast cancer patients, researchers found that FOXA1 expression identified the same low risk, ER-positive, node-negative patients who can be spared toxic chemotherapy (P=0.002). Researchers concluded Oncotype Dx and the FOXA1 marker can potentially be used interchangeably if further validation studies confirm the findings.

Clarient CEO Ron Andrews noted that FOXA1 has shown it can predict risk of cancer recurrence in ER-positive, node-negative breast cancer patients. "Licensing FOXA1 and better understanding what advantages it might have over competitive tests will help put this marker on a rapid commercial track and support our mission to determine the most effective and reliable ways to evaluate breast cancer recurrence in women with early stage disease. Clearly, this marker is a tremendous addition to Clarient's rich menu in breast cancer," Andrews said. "It is also a significant new addition to our Clarient Insight Dx program, which aims to provide pathologists and oncologists with a panel of assays that help deliver personalized medicine in the community setting. Our dedication to translating cancer discovery and information into enhanced patient care is evidenced by our ability to license such coveted IP from prestigious institutions."

Gen-Probe Inc. (NASDAQ: GPRO) of San Diego and **DiagnoCure Inc**. (TSX: CUR) of Quebec City said they have signed an amendment to their 2003 license agreement, establishing new FDA submission milestones and key distribution arrangements to leverage the full market potential of the PCA3-based test for prostate cancer in the United States, Europe and around the world.

As part of the amendment, Gen-Probe will acquire 4.9 million shares of newly issued DiagnoCure convertible preferred stock for US$5.0 million (C$6.1 million), representing a premium of 19.8% over the average market price of the common shares of DiagnoCure during the 20 trading days from yesterday, subject to DiagnoCure securing the required regulatory approvals from the Toronto Stock Exchange. These convertible preferred shares are non-voting, and may be exchanged for common shares on a one-for-one basis. DiagnoCure has the option to redeem the preferred shares or to require their conversion into common shares in certain circumstances. As part of its investment in DiagnoCure, Gen-Probe will receive a liquidation preference in certain cases and a security interest in some intellectual property. This subscription will take place on or around May 7th 2009 and will be completed pursuant to a statutory prospectus and registration exemptions.

The new milestones for an FDA submission of a

PCA3 test can be fulfilled by Gen-Probe with its current end-point TMA assay or its investigational, real-time TMA assay. As part of the contract amendment, Gen-Probe will make annual payments of US$500,000 to DiagnoCure until specific milestones are met. Half the amounts paid will be applied against future royalties payable to DiagnoCure.

Also, in an effort to maximize the global reach for the PCA3 prostate cancer test, DiagnoCure and Gen-Probe have agreed on terms to develop key distributor relationships in countries where it is commercially more effective to do so, such as in Japan, Asia, Israel, South Africa and others.

InteRNA Technologies B.V. and **Radboud University Nijmegen Medical Centre** of The Netherlands entered into a research agreement to develop microRNA (miRNA)-based therapeutics for prostate cancer.

Under the research collaboration with professor Jack Schalken (Laboratory of Experimental Urology), InteRNA's unique lentiviral-based miRNA overexpression library will be applied in multi-parametric, high-throughput functional screening assays to identify the biological role of individual miRNAs and novel therapeutic targets in prostate cancer.

Pharmacyclics Inc. (NASDAQ: PCYC) of Sunnyvale, Calif., entered into a global strategic alliance with **Servier**, a French independent pharmaceutical company.

The alliance will focus on the research, development, and commercialization of Pharmacyclics' PCI-24781, an orally active, novel, small molecule inhibitor of Pan HDAC enzymes, that is currently in Phase I/II clinical trials in the United States and being developed for the treatment of solid tumors and hematologic malignancies. Pharmacyclics expects that this alliance will enable it to aggressively pursue its goal of developing and commercializing its innovative anti-cancer Pan HDAC inhibitor agents.

"This alliance with Servier allows us to accelerate our productive discovery efforts, to expand our clinical development capabilities and potentially commercialize our unique and differentiated Pan HDAC inhibitor product outside of the United States in rapid fashion," said Robert Duggan, chairman and CEO of Pharmacyclics. "We are honored to be partnering with the Servier Company, they are incredibly professional in all aspects of their business dealings. Their success and advancement of human healthcare is respected around the world."

Under the agreement, Servier acquired the exclusive right to develop and commercialize the Pan HDAC inhibitor product worldwide except for the United States and will pay a royalty to Pharmacyclics on sales outside of the United States. Pharmacyclics will continue to own all rights within the United States. Pharmacyclics will receive from Servier upfront payments totaling $11 Million on signing the contract and an additional guaranteed $4 Million for research collaboration over a 24 month period, paid in equal increments every 6 months with the initial payment due October 1, 2009. Servier will pay for all development costs outside the United States. In addition Pharmacyclics will receive $24.5 Million based on the achievement of certain milestones up to and including commercialization.

HDAC inhibitors are a class of compounds that inhibit histone deacetylation, a process that regulates gene expression. PCI-24781 is an oral compound currently in multiple Phase I clinical trials in solid tumors and hematological malignancies. PCI-24781 is in a Phase I clinical study in patients with advanced solid tumors and in a Phase I/II clinical study in patients with Non-Hodgkins lymphomas.

In another development, Pharmacyclics said it has begun treating patients in a Phase 1 dose-escalation study to evaluate the safety and tolerability of PCI-32765, an orally available, selective inhibitor of Bruton's tyrosine kinase, or Btk, as a potential treatment for patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. This is the first Btk selective inhibitor to be tested in humans, and is Pharmacyclics' fourth product in clinical development.

Bruton's tyrosine kinase is the gene that is disrupted in the human disease X-linked agammaglobulenemia (XLA). Patients with XLA are devoid of mature B-lymphocytes and immunoglobulins in the bloodstream, but are otherwise healthy. XLA thus provides strong clinical rationale for development of a novel therapeutic drug targeting Btk for safe inhibition of B-cell mediated diseases.

In preclinical studies, PCI-32765 has the remarkable ability to selectively inhibit human B-cell activation without effecting T cells. Strong preclinical validation of Btk as a target in lymphoma was generated using PCI-32765 in a mouse model of B-cell receptor-driven lymphoma and in spontaneous B-cell lymphoma in companion canines. These studies will be reported in presentations at the 2009 AACR annual meeting in Denver, Colorado (see below). Unlike anti-CD20

protein therapies, treatment with PCI-32765 in animal models is not myeloablative, which could result in prolonged and dangerous immunosuppression for the patient.

Santaris Pharma of Copenhagen announced the completion of the delivery of six cancer target drug candidates to collaboration **Enzon Pharmaceuticals**.

All six drug candidates have been designed, synthesized and selected in collaboration with Enzon, within 24 months of commencing the collaboration.

Santaris Pharma and Enzon Pharmaceuticals signed their agreement in 2006.

As part of the agreement Santaris Pharma retains the lucrative commercial rights to the drugs within Europe. The agreement included two LNA based RNA inhibitors at the pre-clinical stage, EZN2968 against HIF-1Î±, and EZN3042 against Survivin, both of which are currently in Phase I studies conducted by Enzon, and the development of six additional cancer target drugs selected by Enzon which are in various stages of preclinical development.

ImQuest BioSciences and **Arisyn Therapeutics** announced that they have entered into a strategic drug development partnership to provide support necessary to develop Arisyn's portfolio of novel inhibitors for the treatment of infectious disease and cancer.

Arisyn has recently announced its acquisition of a series of inhibitors with demonstrated preclinical efficacy against HIV, HCV, HTLV-I, influenza virus, herpes viruses and cancer. These inhibitors were originally discovered and developed by The Proctor & Gamble Co. Lead molecules from the portfolio have already been evaluated in Phase 1 human clinical trials for the treatment of HIV and cancer, and an IND-application has been prepared for submission to the FDA to initiate trials for HCV therapy.

"The Arisyn compounds represent an entirely new treatment paradigm by effectively suppressing the ability of the HIV or HCV-infected cells to act as the factories of progeny virus production," stated Robert Buckheit, Jr., Director of Research and Development for Arisyn and President and Chief Scientific Officer of ImQuest BioSciences. "The compounds have proven efficacy and safety in preclinical studies and their successful development will be of immense benefit to the millions of individuals living with HIV and HCV infection."

ImQuest BioSciences, a Contract Research service provider specializing in the discovery and development of anti-infective and anti-cancer agents, will provide all required support to initiate human clinical trials with lead products ATI-0312 for HIV and ATI-0810 for HCV and will initiate mechanistic studies to define the unique virus transcription inhibitory mechanism of action of the class of inhibitors. ImQuest will also lead Arisyn's efforts to develop next generation inhibitors from structure activity relationship studies and target-based drug design programs.

Oncology Management:

Pharmatech Oncology Opens Data Management Unit

Pharmatech Oncology Inc., a Denver-based research management organization, announced the launch of the data management business unit to the bioscience and pharmaceutical industries.

The Pharmatech Oncology Data Management business unit is branded as C(3)DM (Customized, Consistent, and Clinical Data Management). The Data Management business unit maintains and processes data for a broad range of clinical trials in various therapeutic areas, not only in the fields of oncology and hematology.

In managing clinical data projects, the C(3)DM business unit has built a solid data system platform focused around the EDC (electronic data capture) solution TrialMaster from OmniComm Systems Inc.

The platform is designed to be customized to incorporate all of the clinical data aspects involved in each individual clinical trial.

"The Data Management team has worked extremely hard over the last few months to develop a fully-integrated solution for data capture and patient accrual for a lymphoma trial. Our unique platform gives clients access to a wide-range of capabilities by having their data managed through a trusted and reliable source, while also having our clinical sites trained by the creators of the system," said Jason Lones, clinical data manager.

The data management business unit focuses on customized data capture solutions for any clinical development marketplace. Data integrity throughout the data management process is assured by following FDA regulations, adhering to industry standard GCPs, and maintaining 21CFR Part 11 compliance.

The University of California, Los Angeles, has selected the services of Velos and its product, Velos eResearch, the clinical research management system is being implemented at UCLA's Jonsson Comprehensive

Cancer Center and an affiliated clinical research network, Translational Oncology Research International.

Plans are in place to deploy the system in non-cancer studies being conducted in the David Geffen School of Medicine at UCLA. A UCLA selection committee chose Velos eResearch because the system offered the best core functionality for managing clinical trials and it was the most adaptable and user-friendly for tracking patients.

The cancer center tracks everything from simple studies to very complex, multi-arm clinical trials that require very detailed patient information, Ryba said. The system will also be used to track studies within the TORI network, a large group of participating research sites and medical practices stretching throughout the country, as well as some international sites.

Implementation of Velos eResearch at the cancer center began through interviews with experts in clinical trials and stakeholders at the institution. It was determined that the system would first be deployed to tackle the most important business process needs of leadership and staff.

The National Comprehensive Cancer Network has updated the NCCN Clinical Practice Guidelines in Oncology(TM) for Kidney Cancer to reflect the recent FDA approval of Afinitor (everolimus), sponsored by Novartis, for advanced renal cell carcinoma in patients whose disease has progressed after treatment with kinase inhibitors such as sunitinib (Sutent(R), Pfizer Inc.) and sorafenib (Nexavar(R), Bayer HealthCare).

The FDA approval is based on recent results of a clinical trial which showed that the growth or spread of tumors was delayed in patients who were being treated with everolimus and that the treatment improved median progression-free survival to 4.9 months compared to 1.9 months in patients who did not receive the treatment.

Based on this trial data, the NCCN Guidelines Panel for Kidney Cancer has added everolimus as a category 1 option for patients with metastatic renal cell carcinoma following failure of tyrosine kinase therapy.

Everolimus targets a protein known as mTOR, which affects tumor cell division, angiogenesis, and cell metabolism. The mTOR pathway integrates signals from nutrients and growth factors and is considered to be a major regulator of cell growth and angiogenesis. By inhibiting the mTOR pathway, everolimus has the potential to block renal cell cancer growth.

PGxHealth, a division of **Clinical Data, Inc**. (NASDAQ: CLDA), announced it has begun a broad research collaboration with the **University of Pittsburgh** to discover and further validate the application of genetic variants in FCGR (Fc gamma receptor) genes, including FCGR3A, for predicting response to monoclonal antibodies (mAbs) in cancer treatment.

The strategic collaboration aims to conduct a series of clinical programs to evaluate the response to mAb-based therapies, such as Erbitux (cetuximab), Rituxan (rituximab) and Herceptin (trastuzumab) and potentially other mAbs of the IgG1 subclass in treating a variety of cancers. The collaboration builds upon the large and growing body of evidence demonstrating the contribution of genetic variants in the FCGR family to mAb response in cancer treatment.

It also expands PGxHealth's own FCGR program, which includes collaborations with other prominent researchers at leading institutions, and its own PGxPredict:RITUXIMAB test for a gene variant used to determine response to rituximab monotherapy in follicular non-Hodgkin's lymphoma. Fc gamma receptors are antibody receptors found on immune-regulatory white blood cells, such as T-cells.

The initial research program is between PGxHealth and the University of Pittsburgh. Robert Ferris, Associate Professor and Chief, Division of Head and Neck Surgery at the University of Pittsburgh Cancer Institute, will lead studies focusing on Erbitux in the treatment of head and neck cancer. PGxHealth and UPCI plan to expand the scope of their research in the near term to include other cancers and treatments. The research may also extend to other disease areas where mAb therapies are important, such as rheumatoid arthritis.

"UPCI is one of the leading research institutions in the country and this collaboration represents a significant step forward in our goal to expand our Fc gamma program in oncology," said Marcia Lewis, Vice President, Biomarker Development at PGxHealth. "We intend to expand the scope of our research with UPCI to include response to other mAb-based therapies, such as Rituxan (rituximab) and Herceptin (trastuzumab) and mAbs of the IgG1 subclass, in treating a variety of cancers and other diseases where mAb therapies are used, such as rheumatoid arthritis."

FCGR3A, a gene that encodes an Fc gamma receptor, binds both natural and therapeutic IgG1 antibodies. The FCGR3A receptor transmits signals from the membrane into the cell via tyrosine kinase activity. This signaling pathway is important in regulating antibody-dependent cellular cytotoxicity, a mechanism important to the efficacy of many mAb therapies.

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