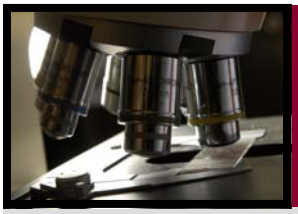

University of Chicago Cancer Research Center

In the News: Our Members in the Media

The University of Chicago Cancer Research Center (UCCRC) publishes this newsletter periodically to provide its members, University of Chicago Cancer Research Foundation members, and other associates with informative articles or press releases regarding cancer and research by our members. If you wish to include a media story in the next issue, please e-mail us at pbutera@medicine.bsd.uchicago.edu.

FEBRUARY 6, 2009

Roadkill Study Could Speed Detection of Kidney Cancer

UCMC Newsroom
January 22, 2009

Large-scale data mining of gene networks in fruit flies has led researchers to a sensitive and specific diagnostic biomarker for human renal cell carcinoma, the most common type of kidney cancer. In the journal *Science*, published early online January 22, a team based at the University of Chicago shows that the biomarker known as SPOP is produced by 99 percent of clear cell renal cell carcinomas but not by normal kidney tissue.

Physicians could use SPOP levels to confirm or rule out a diagnosis of renal cell carcinoma (RCC). It could also help them determine the original source of cancers that have spread to other organs from an unknown primary tumor.

"This could serve as a diagnostic tool, lead us to new drug targets and potentially help us detect kidney cancers sooner," said study-director Kevin White, PhD, Professor of Human Genetics, Ecology, and Evolution, and Director of the Institute for Genomics and Systems Biology at the University of Chicago. "It also confirms our strategy of using genomics and systems-level analysis of model organisms such as fruit flies to identify factors that play crucial roles in human disease."

The study began with the fly genome. White and colleagues, who study gene regulation--how genes or entire networks of genes get turned on or off--wanted to measure the downstream effects of two key genes, known as *Eve* and *Ftz*, that control early steps in the development of flies, beginning just after the eggs are laid.

Because *Eve* and *Ftz* regulate the activity of other genes, and many of those genes control the activity of additional genes, both had a large impact. *Eve* influences the expression of 1,074 different genes and *Ftx* impacts 1,310 genes.

When they narrowed their search to genes directly impacted, the total fell to 235 genes. About 20 percent of those target genes regulate transcription, the activation of other genes, and 40 percent controlled developmental processes.

Kevin White, PhD

About 150 of those target genes have human equivalents. When the researchers ranked those 150 genes according to their impact in flies, the top candidate was a gene known as *CG9924*, or *Roadkill*, the central player in a major hub of networked genes and a crucial component in the development of the nervous system. SPOP, the human equivalent, is about 80 percent identical to *Roadkill*.

Looking closer, they determined that SPOP appeared to play a role not just in development but also in human cancers. It interacts with cell signaling pathways--JNK and RAS--that frequently go awry in multiple human cancers.

At this point, the researchers shifted their focus from fly genetics to human cancer. When they screened hundreds of tissue samples from 18 different tumor types, acquired from patients having surgery, they found that 85 percent of renal cell carcinomas produced high amounts of SPOP, while normal kidney tissue was uniformly negative.

When they looked at 300 renal cell cancer samples, 77 percent were positive for SPOP. All normal kidney samples were negative.

About 75 percent of all renal cell cancers are clear cell RCC. The researchers found that 99 percent of the clear cell RCC samples showed evidence of elevated SPOP. The SPOP test even revealed that a few tumors had originally been misdiagnosed as clear cell RCC. Those turned out to be other types of kidney cancer when examined more closely by pathologists.

"These results indicate that SPOP is a highly sensitive and specific diagnostic biomarker for clear cell RCC," the authors conclude, "and can help distinguish histological subtypes of RCC."

It could also be used to help identify the primary tumor in metastatic cancers, important in treatment decisions.

The W.M. Keck Foundation, the Arnold and Mabel Beckman Foundation, and the Searle Funds at the Chicago Community Trust funded the study.

THE UNIVERSITY OF CHICAGO
CANCER RESEARCH CENTER

Link Between Sexual Activity and Increased Risk of Cancer Open to Question

Medill Reports
January 29, 2009

The results of a recent study that suggests frequent sex and masturbation increase the risk of prostate cancer for men in their 20s and 30s are raising questions and concerns.

"There is a lot of folklore with prostate cancer risks," said Dr. Rick Kittles, PhD, at the University of Chicago Division of Biological Sciences Department of Medicine. "This study is going to confuse people," he said, referring to a recent prostate cancer study involving more than 800 men in Great Britain.

The research article, "Sexual activity and prostate cancer risk in men diagnosed at a younger age," was published in the January issue of BJU International and funded by a grant from the Prostate Cancer Research Foundation and Cancer Research UK.

The study findings are not definitive, according to Kittles. He said the researchers were comparing apples to oranges. "I don't see their conclusions in this data set, and some of their analyses are problematic," Kittles said. "Throughout the article, there are several generalizations without the support of data. They are coming up with risk odds ratios and risk ratios that the data doesn't really support."

The study concluded that the risk of prostate cancer rises with the frequency of sexual activity for men in their 20s and 30s but did not give specific benchmark figures for frequency. Kittles said he felt the authors did offer a helpful context for the research by including a literature review of previous studies and weaving in their own findings.

The researchers listed three characteristics that differentiated their study from previous prostate cancer research. It looked at early onset prostate cancer by including young men in their 20s and the frequency of sexual activity including masturbation. It then compared findings between age groups ranging from 20 to 50 years old.

The study included 431 men with prostate cancer (the case group) and 409 men without (the control group) who filled out a questionnaire the researchers mailed to them. Seventy-three percent of the case group and 74.1 percent of the control group responded. The questions asked for estimates of frequency of intercourse and masturbation during the participants' 20s, 30s, 40s and 50s, as applicable. The questions also asked subjects to indicate the number of their sexual partners over time; types of partners; age of first intercourse and masturbation; and any history of sexually transmitted diseases.

Rick Kittles, PhD

Kittles said follow-up studies would be needed to explore the study results. The authors of the study could not be reached for comment.

Cozy House of Blues Setting Fit For Kings

Chicago Tribune
Januray 26, 2009

Midway through Kings of Leon's set at sold-out House of Blues, singer Caleb Followill paused to address the crowd, noting, "On the road there are a lot of nights where you get up [onstage] and you're just going through the motions." Thankfully, this wasn't one of those nights.

Whether it was the cozier theater setting (consider that the group headlines Madison Square Garden later this week), or the meaningful cause behind the concert (a portion of the proceeds will benefit University of Chicago Comer Children's Hospital, which specializes in the research and treatment of pediatric cancer), the band came out swinging for the better part of 90 minutes. Brothers Caleb, Nathan and Jared Followill, along with first cousin Matthew Followill, opened with a churlish "Closer" before launching into the feedback-drenched "Crawl." "Four Kicks" sounded even more ferocious than its recorded version, Jared revving his six-string like an outsize monster truck.

Openers the Whigs sounded gleefully unencumbered by such responsibility. Animated frontman Parker Gispert, who wielded his guitar as though he were reeling in a prize catch, led the youthful trio through an excellent 35-minute set heavy on shaggy rockers.

EDITOR'S NOTES:

This issue of "In the News" highlights the important contributions our members are making in all phases of cancer research and outreach.

In the article on page 1, Kevin White, PhD, discusses how new discoveries involving the biomarker SPOP could lead to new drug targets, and enable clinicians to more effectively detect kidney cancer.

On page 2, Rick Kittles, PhD, is quoted in an article about a recent study that suggests frequent sex increases the risk of prostate cancer for men in their 20's and 30's.

On pages 3-4, Mark Lingen, DDS, PhD, is quoted in an article about the accuracy of a screening test for oral cancer.

New Oral Cancer Tests: Crucial or Wasteful?

The New York Times
February 2, 2009

Though relatively rare, it is one of the easiest cancers to spot and diagnose. And if treated early, it is usually curable. So why do experts find oral cancer so vexing?

Despite the many advances against cancer in recent decades, the statistics on this particular form of cancer remain discouraging: more than 60 percent of cases are diagnosed in the late stages, and the five-year survival rate is a disappointing 59 percent. Moreover, oral cancer is increasing in people traditionally at low risk, a phenomenon partly attributed to the rise of the cancer-causing human papillomavirus, or HPV, which can be transmitted through oral sex.

Now some dentists — whose visual examinations have long been a first line of defense against oral cancer — are using screening devices that they say may help identify cancers and premalignant lesions.

But these new tests have set off a debate over cost and effectiveness. Experts are divided on whether they will reduce mortality from oral cancer or simply lead to a wave of expensive and unnecessary biopsies.

An estimated 35,300 Americans learned they had oral cancer last year, and about 7,600 died from the disease. For survivors, oral cancer can be painful and disfiguring, and can destroy the ability to taste and enjoy food. Smokers and heavy drinkers are considered at highest risk for the disease, but 25 percent of those who receive a diagnosis are neither. Still, the lifetime risk of oral cancer — about 1 in 99 — is very low compared with breast and prostate cancer.

Because the disease is often diagnosed late, many experts believe that screening can reduce mortality. This has not been proved, partly because there is a dearth of research on oral cancer.

Indeed, no one knows for sure whether even a visual examination in the dentist's office saves lives, though most oral cancer experts believe it does. That hypothesis is based on the proven benefits of early detection of other cancers and the better survival rates in cases that are detected early — about 80 percent five years after diagnosis.

"We know in every cancer where we've seen a reduction in the death rate — cervical, skin, breast — that what has brought the death rate down is early detection," said Brian Hill, an oral cancer survivor from Laguna Niguel, California, and a Founder of the Oral Cancer Foundation, a nonprofit group.

One large study from India, where oral cancer rates are much higher than in the United States, found that when high-risk subjects had a visual exam, it reduced the mortality rate by 34 percent compared with control subjects who were not screened. But some experts say this research cannot be applied to the general population or to Americans.

The American Cancer Society and the American Dental Association recommend a regular visual exam. But even though it is generally covered by insurance, not all dentists perform it. "Studies show that most dentists don't leave dental school feeling comfortable doing it," said Dr. Michael A. Siegel, a Professor and the Chairman of Diagnostic Sciences at Nova Southeastern University College of Dental Medicine in Fort Lauderdale, Florida.

Now medical companies are marketing several new screening tests and devices to dentists, saying they will vastly improve early detection of oral cancer. The devices, which can cost several thousand dollars, use rinses, dyes and different types of lights to detect abnormal cells.

Some experts say the new technology will lead to earlier detection, if only by encouraging dentists to do a screening exam. "The tests change the paradigm by which they practice," Dr. Siegel said. "Simply because it's new, they say, 'I'm going to use it.' "

They can also charge for the test, and some insurers have started covering it. "We're advocates of using these devices because there are some things your eye might miss," Mr. Hill said. Yet no extensive studies of the general population show that these devices are any better than the naked eye for screening, and they have not been shown to reduce mortality.

Mark Lingen, PhD, DDS

"There's no evidence for their use by front-line screeners, no evidence," said Dr. A. Ross Kerr, an Assistant Professor at the New York University College of Dentistry.

In small studies, the devices successfully detected potentially malignant lesions that experienced specialists missed with the naked eye. For example, in one group of subjects a scanning system called the VELscope identified all of the cases of moderate to severe dysplasia, or potentially precancerous cells, compared with just 68 percent for a visual exam, said the study's author, Dr. Edmond Truelove, a Professor and the Chairman of Oral Medicine at the University of Washington. (Dr. Truelove does not receive financing from LED Dental, the company in British Columbia that makes the VELscope.)

Another study of 688 high-risk patients examined by experienced specialists found that when only a visual exam was performed, the specialist requested a biopsy of 12 of the 30 lesions that turned out to be cancerous. Of those who also used toluidine blue, a dye that is a component of a test called ViziLite Plus, 29 of the 30 lesions would have been biopsied, said the study's author, Dr. Joel Epstein, a

Continued on next page

New Oral Cancer Tests: Crucial or Wasteful?

Continued from p. 3

Professor of Oral Medicine at the University of Illinois, Chicago.

But he added, "What we don't know is what happens if we use the same technique in a low-risk population by people with less experience." (Dr. Epstein said that in the past he had received compensation from Zila Pharmaceuticals, which makes ViziLite, and is currently receiving financing from the company for a small study.)

The screening tests can cost the patient $35 to $65, though some dentists do not charge extra for it. And the tests have a high false-positive rate that may lead to unnecessary biopsies. If a suspicious lesion is detected, dentists typically ask the patient to return in two weeks to see if it has improved. If not, the patient may be given a biopsy or referred to a specialist.

Some dentists are telling their patients that because of the rise of oral cancers linked to HPV, every adult, not just the traditionally high-risk groups, should be screened with these devices.

Yet oral cancers associated with the papillomavirus are still rare, and they typically occur near the base of the tonsils and the back of the tongue, where they are very difficult to see at the earliest stages, even with the use of these devices, said Dr. Maura L. Gillison, a Professor of Medicine at Ohio State who is a leading expert on oral HPV.

Dr. Mark Lingen, an Associate Professor of Pathology at the University of Chicago Medical Center, agreed. "If you can't get back there to see it," he asked, "how is that device going to help you?"

But Dr. Epstein says the devices may help. "If you're someone with a high risk of HPV exposure, meaning that you've had oral sex with multiple partners, you need to be examined carefully," he said. "Higher-risk people could maybe benefit from some of these adjuncts."

Dr. Truelove, who did the VELscope study, said he would not recommend expensive screening for normal individuals, but he added, "On the other hand, a low-cost test, say $5, that enhances a clinician's ability to detect something they might otherwise miss is potentially useful, particularly in people who have some increased risk of the disorder."

Researchers are working on the holy grail of oral cancer screening: a test that can analyze saliva for early gene changes that could lead to the disease.

Most experts agree that everyone should have an annual visual exam. A dentist or trained hygienist should examine the cheeks, the gums, the floor of the mouth, the area behind the teeth, the palate and the tonsil area, pulling the tongue forward — often to the point of gagging. The dentist should also feel the lymph nodes of the neck, sometimes the first visible sign of oral cancer.

"The emphasis should also be placed on educating physicians about oral cancer," said Dr. Kerr, of N.Y.U. Only 60 percent of adults see a dentist at least once a year, he continued, adding, "The 40 percent who never go to the dentist are likely to have the highest risk factors.

"When I teach my students," he said, "I say at the end of the day, all you need is to have one patient with an early cancer that you picked up and you will do this for the rest of your career."

ASCO Releases It's First Provisional Clinical Opinion (PCO)

ASCO.org
February 2009

Patients with metastatic colorectal cancer who are candidates for anti-EGFR therapy should have their tumors tested for *KRAS* gene mutations, according to ASCO's first Provisional Clinical Opinion (PCO).

If a patient has a mutated form of the *KRAS* gene, the Society recommends *against* the use of anti-EGFR antibody therapy, based on recent studies indicating this treatment is only effective in patients with the normal (wild-type) form of the *KRAS* gene. It is estimated that 40 percent of patients with colon cancer have the *KRAS* mutation.

"Personalized medicine is the next frontier in cancer care," said Richard L. Schilsky, MD, a Professor of Medicine at the University of Chicago, and the ASCO President. "Using *KRAS* testing to guide colorectal cancer treatment is a prime example of where cancer care is heading."

"Basing cancer treatment on the unique genetic characteristics of the tumor or the individual with cancer will improve patient outcomes and help avoid unnecessary costs and side effects for patients who are unlikely to benefit," Dr. Schilsky added.

PCOs are intended to offer timely preliminary clinical direction to oncologists following the publication or presentation of potentially practice-changing data from major studies. ASCO's PCO on *KRAS* gene testing was given prior to the January 15-17, 2009 Gastrointestinal Cancers Symposium in San Francisco, California. The Symposium was co-sponsored by ASCO, the American Gastroenterological Association (AGA), the American Society for Radiation Oncology (ASTRO), and the Society of Surgical Oncology (SSO).

Among the 500 presentations was an important economic and scientific study that discussed the possibility of more than half a billion dollars in savings for the United States healthcare system. The study showed that routine testing for *KRAS* gene mutations in patients with metastatic colorectal cancer could save the U.S. health system up to $604 million per year by identifying who would benefit from the drug cetuximab.

Information on the PCO is currently available on ASCO.org and the entire report will be published in the next issue of the Journal of Clinical Oncology (**JCO**).