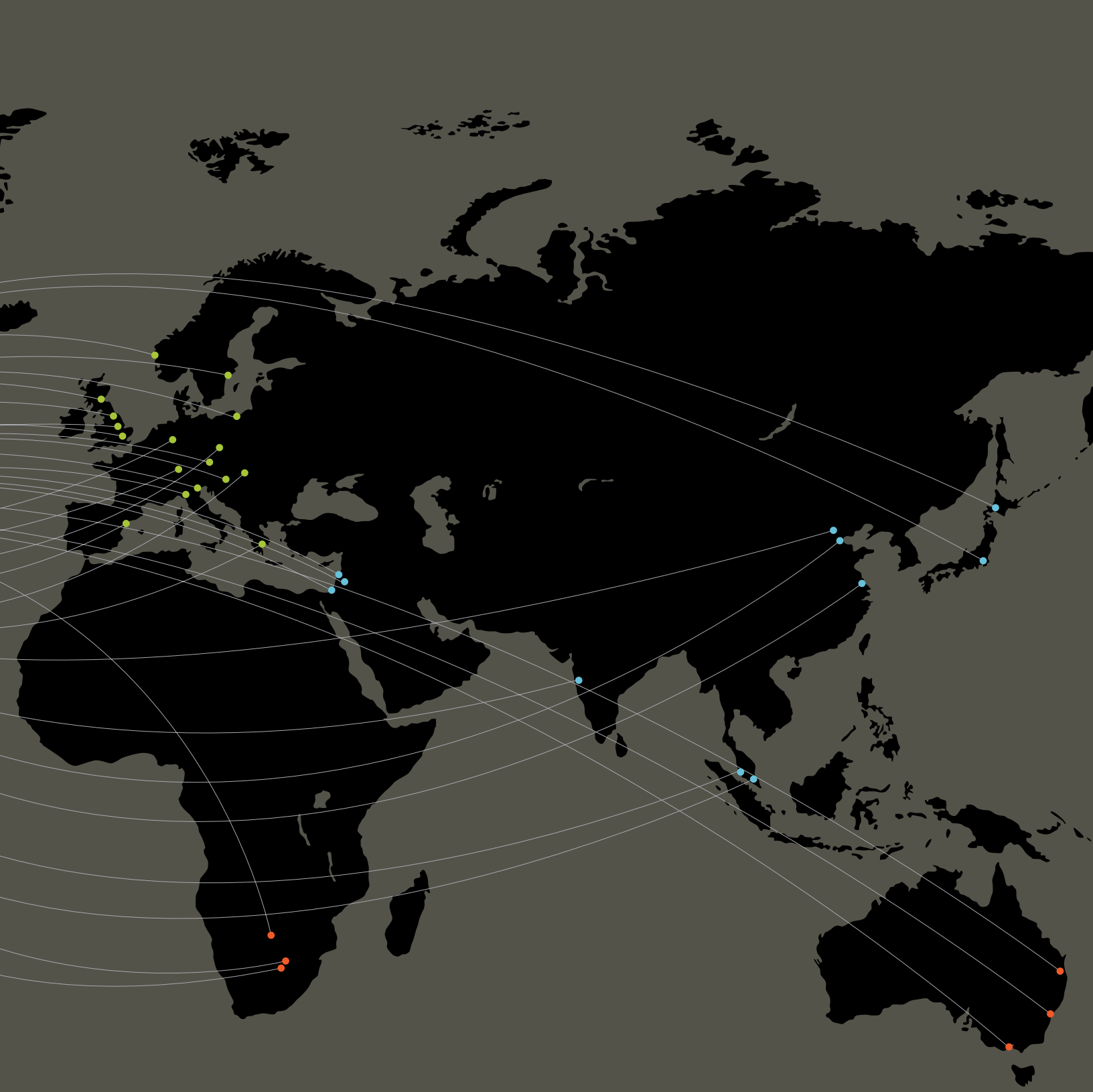
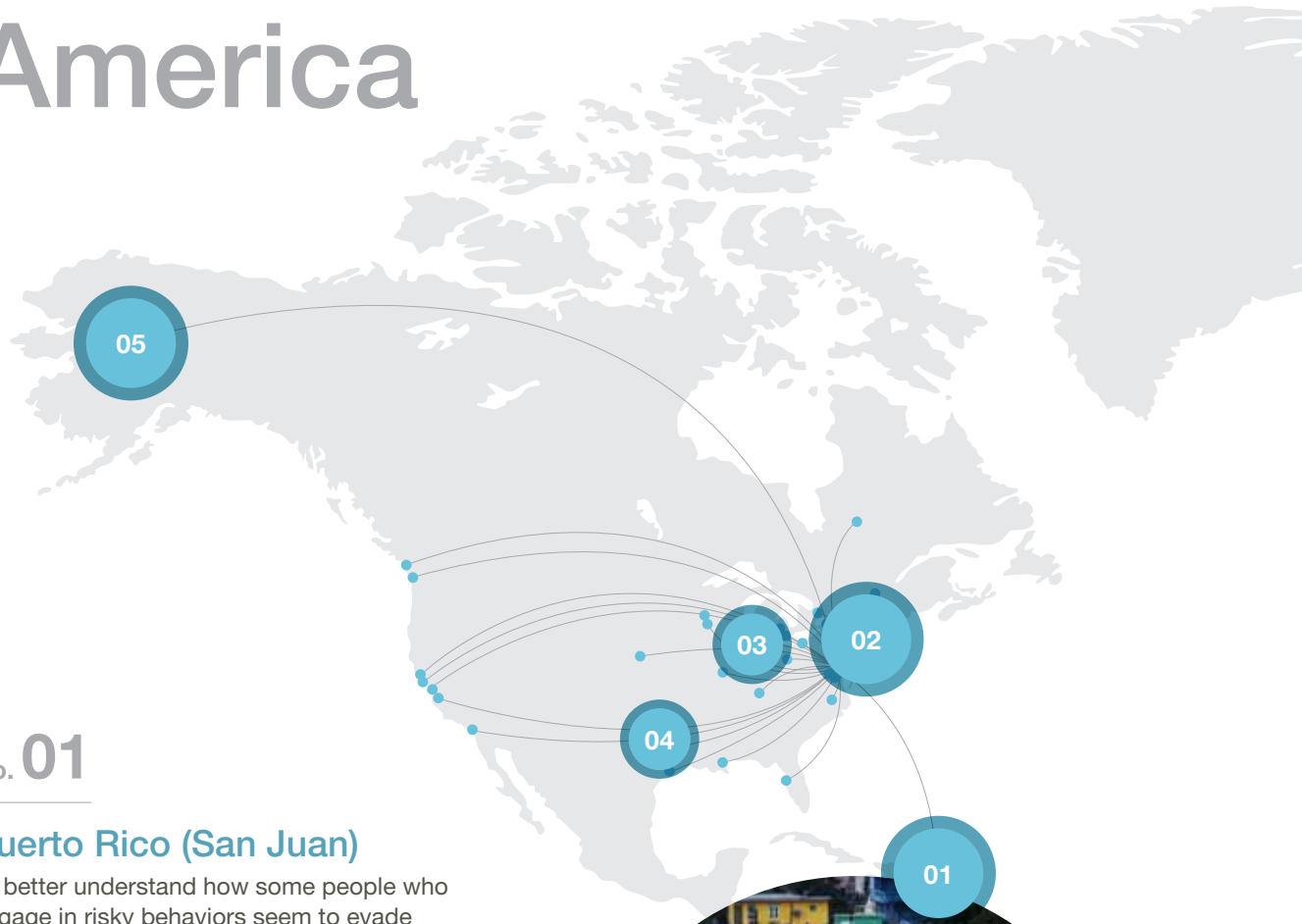
Science Without Borders

The Global Impact of The Wistar Institute

While relatively small with 30 research labs, The Wistar Institute makes a tremendous impact around the world. Indeed, through its scientific advances which have changed the way researchers everywhere conduct their science — to medical advances such as the vaccines against German measles, rabies and rotavirus that have saved countless lives — few organizations of this size can claim a similar impact. The men and women of The Wistar Institute build upon this rich legacy of innovation every day, and partner with colleagues across the globe to advance medical science. From cancer genetics to improving HIV/AIDS therapy to vaccine research, Wistar science is a global effort.



North America



No. 01

Puerto Rico (San Juan)

To better understand how some people who engage in risky behaviors seem to evade HIV-1 infection, Luis Montaner, D.V.M., D.Phil. teamed up with colleagues at the University of Puerto Rico and a number of institutions in the U.S. Together, the collaborators are studying the correlation between immune system activity in the blood and gene activity of cervical cells of non-infected sex workers. They found that a number of genes are more active in women who are able to remain infection-free despite repeated exposure to HIV-1. They are currently conducting studies to validate their findings.

No.02

New Hampshire (Hanover)

José Conejo-Garcia, M.D., Ph.D., works closely with Dartmouth College researchers with whom he developed synthetic microRNA molecules that he uses to "reprogram" immune cells to kill cancer cells.

No.03

Indiana (South Bend)

David W. Speicher, Ph.D., lends his expertise to colleagues at the University of Notre Dame to understand the mechanism of human red blood cell infection by the parasite that causes malaria.

No.04

Texas (College Station)

Ramana Davuluri, Ph.D., applies the computing power of Wistar's Center for Systems and Computational Biology in collaboration with colleagues at Texas A&M University to understand the genetic changes that occur in Fetal Alcohol Syndrome.

No.05

Alaska (Fairbanks)

Scientific relationships often arise in the unlikeliest of circumstances. Consider Louise Showe, Ph.D., director of Wistar's Genomics Facility, who briefly turned her attention from cancer research to the genomics of hibernating black bears in 2001. With air travel halted in the tumultuous days following 9/11, Showe's husband and colleague Michael Showe, Ph.D., brought home a University of Alaska, Fairbanks graduate student, who had been stranded in Philadelphia. Ever the curious scientist, Showe took the opportunity to apply her Wistar genomics work to help the student and researchers in Alaska gain insights into gene expression — a measure of gene activity — in American black bears.

Showe's lab created a black bear-specific array of gene probes that allowed them to compare differences in gene activity between black bears active in the summer and bears in hibernation. Each year since 2008, a collaborator from Alaska spends two weeks working at Wistar on samples they have collected over the past year.

"These studies show that modulation of gene expression during winter hibernation represents a molecular mechanism of adaptation to extreme environments," explained Showe. "It provides insight into the processes that allow these bears to reduce muscle atrophy and preserve bone mass and structure throughout hibernation."

• For a full list of our collaborations, visit www.wistar.org/globalreach

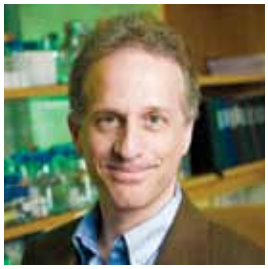
Europe Africa

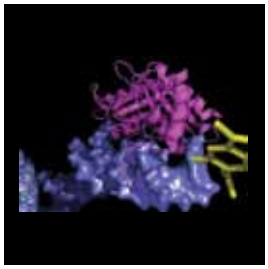
No.06

United Kingdom (London)

Paul M. Lieberman, Ph.D., has undertaken a historic, groundbreaking project that may change the way doctors treat a variety of human cancers. Historic, because Lieberman is the first research scientist in the United States to receive a Seeding Drug Discovery Award from Wellcome Trust, a United Kingdom-based charity.

Groundbreaking, because the award will support the development of what may be the first drug to treat Epstein-Barr virus (EBV)-related cancers by attacking the virus while it remains dormant within a person's cells.





The project is a three-year, multi-stage effort where funding is based on the achievement of defined research milestones, outlined by Lieberman and Troy Messick, Ph.D., a staff scientist in the Lieberman laboratory and co-leader on the project. If successful at each milestone, the laboratory will receive up to $4.7 million in support of its efforts.

With funds from Wellcome Trust, Wistar researchers will further optimize their selected small molecule inhibitors, with the aim of developing at least one into a viable drug candidate. This drug candidate could then be tested in clinical trials to determine its safety and effectiveness for humans.

No.07

Spain (Barcelona)

Ramin Shiekhattar, Ph.D., forged strong ties to the European research community as a faculty professor at the Center for Genomic Regulation in Barcelona, Spain. Their joint efforts in understanding the role of RNA in gene regulation continue today.

No.08

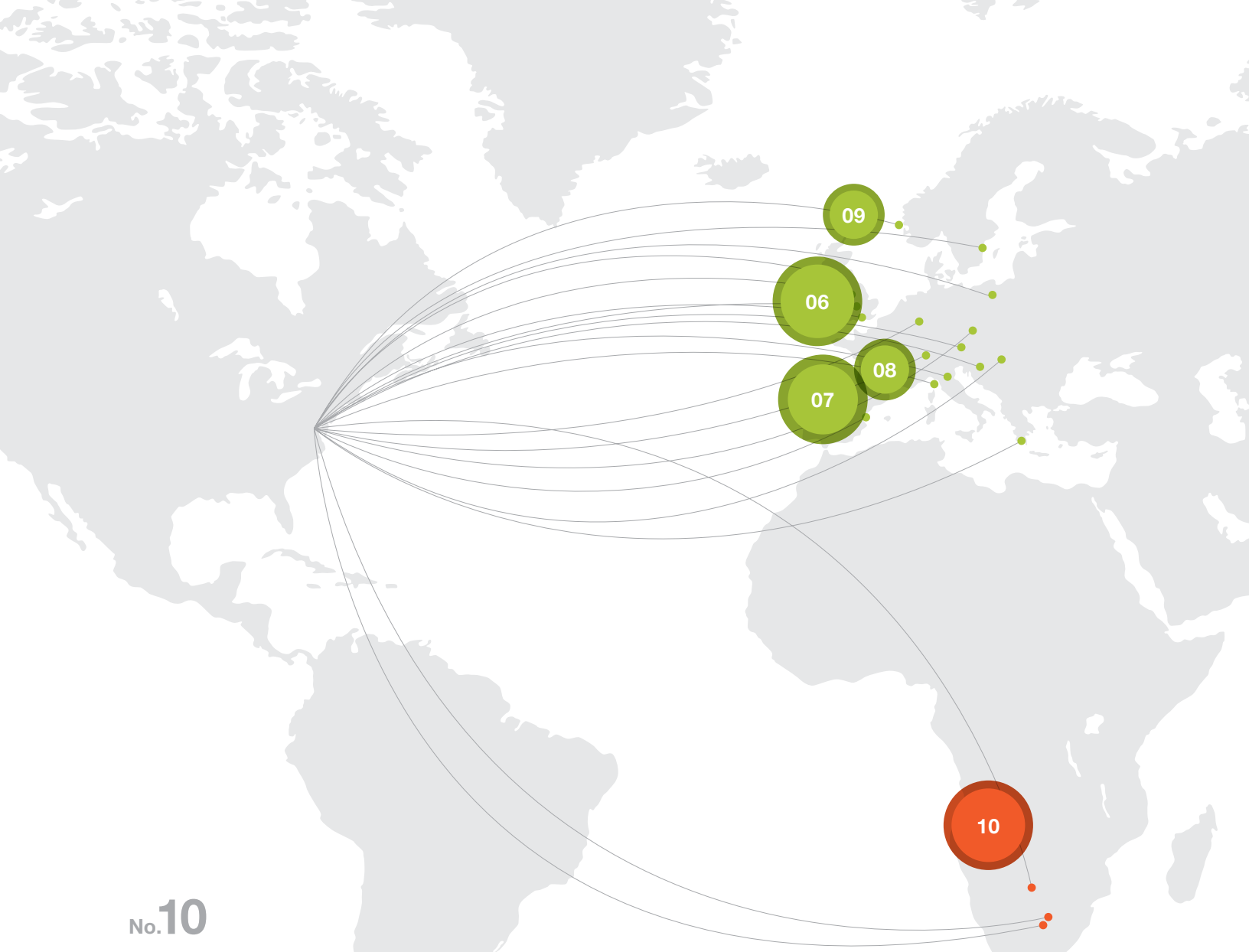
Italy (Milan)

Wistar Cancer Center Director Dario C. Altieri, M.D., studies the role of "polarity proteins" in cancer metastasis with University of Milan researchers.

No.09

Norway (Bergan)

Norwegian researchers working with Ronen Marmorstein, Ph.D., are helping to determine the molecular structure and behavior of an emerging family of protein-tagging enzymes.



No.10

South Africa (Johannesburg)

To better understand how HIV-positive infants respond to antiretroviral therapy (ART), Luis Montaner, D.V.M., D.Phil., participates in the Comprehensive International Programme for Research on AIDS in South Africa.

For his part of the study, Montaner and his colleagues examined data from 377 infants who were HIV-positive at birth. They found that early ART treatment was associated with a reduced infant mortality of 76 percent and slowed the progression of the virus by 75 percent. “Infants have this natural immune response at birth, and coupled with the HIV treatments, those babies do better,” Montaner said.

Recently, Montaner devised a novel statistical method with Yale University that will better allow the analysis of data with missing time-points, such as datasets on newborns.

For a full list of our collaborations, visit www.wistar.org/globalreach

South America
Australia
Asia

No.11

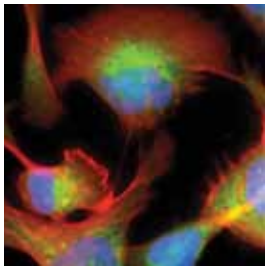
Brazil (São Paolo)

The laboratory of Hildegund C.J. Ertl, M.D., has worked extensively with researchers at the University of São Paolo to develop a DNA vaccine that will attack tumors caused by human papillomavirus (HPV).

No.12

Australia (Brisbane)

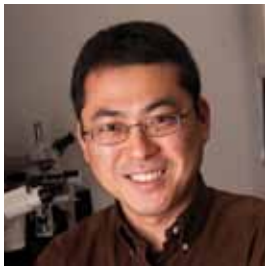
Scientists in The Wistar Institute Melanoma Research Center work with researchers in sun-drenched Australia to study the genetic processes that underlie skin cancer.



No.13

Japan (Tokyo)

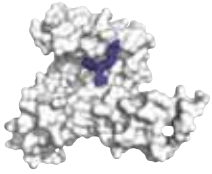
Ken-ichi Noma, Ph.D., collaborates with colleagues at Japan Women's University to use electron microscopy in developing the 3-D structure of the yeast genome at various stages in the life cycle.

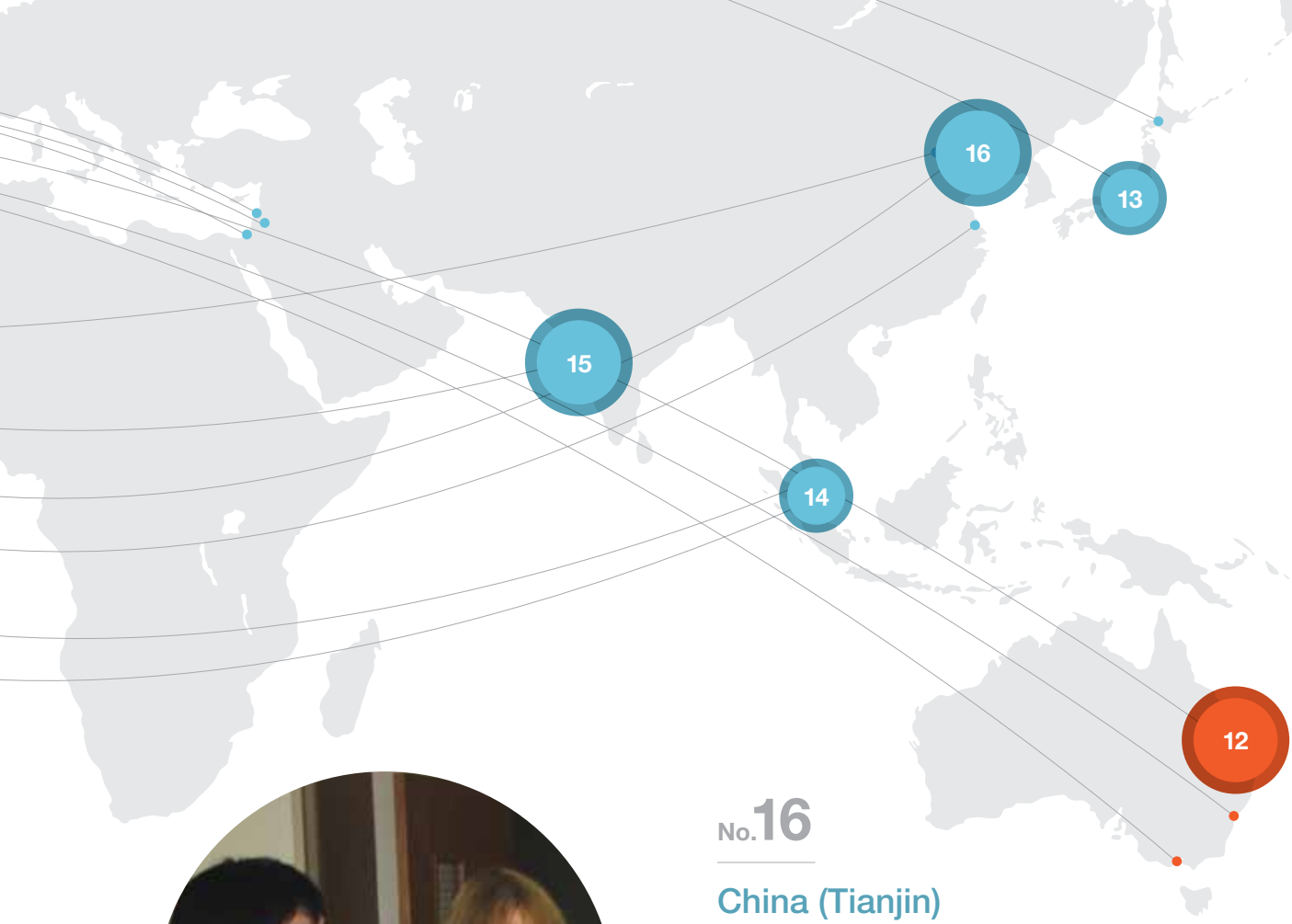


No.14

Singapore

Frank Rauscher, III, Ph.D., collaborates with researchers at the National University of Singapore and the Max Planck Institute in Germany to create a new small molecule inhibitor drug that could prevent two crucial proteins from binding and, thus, may eliminate the metastatic growth of cancers.





No.15

India (Pune)

Rabies remains a devastating killer in India, where roughly 36 percent of the world's deaths from rabies occur each year, according to the World Health Organization. The vast majority of victims are children. Because of this urgent humanitarian need, the Serum Institute of India has developed a rabies vaccine based on Wistar's rabies virus strain, to prevent and treat rabies in rural India.

No.16

China (Tianjin)

In May 2012, The Wistar Institute signed an agreement that will allow the large-scale production of the first therapeutic HPV cancer vaccine. The vaccine, created through the efforts of Wistar's Vaccine Center and its director, Hildegund C.J. Ertl, M.D., may vastly improve the prognosis for the majority of women diagnosed with cervical cancer.

The agreement allows Tianjin Bioroc Pharmaceutical & Biotech Co., Ltd., to license and develop the Wistar HPV vaccine — the next step in bringing the vaccine to the public. Bioroc is closely affiliated with Tianjin Medical University Cancer Institute and Hospital (TMUCIH), where clinical trials for the new vaccine will take place.

For over 50 years, TMUCIH has been the premier cancer hospital in China, and is in the process of building the largest state-of-the-art cancer hospital in all of Asia. This agreement with Bioroc would enable Wistar's vaccine to reach what is possibly the biggest single pool of cancer patients on the planet.

"An advantage of conducting clinical trials in China, especially at TMUCIH, is that, if we do pursue licensing in the United States, we can present an attractive set of clinical data from China," Ertl said.

For a full list of our collaborations, visit www.wistar.org/globalreach

Philadelphia Region

Closer to home, The Wistar Institute has a strong presence in the Greater Philadelphia region's thriving life sciences sector. Here is a sampling of the regional partnerships formed by the Institute and its scientists.

Allentown

Melanoma biologist Ashani Weeraratna, Ph.D., partners with Lehigh Valley Health Network to obtain new specimens of melanoma cells and plan clinical trials of potential new therapies for patients.

Newark, Delaware

Wistar's ovarian cancer researchers receive much-needed tissue samples for study through a partnership with The Helen F. Graham Cancer Center of Christiana Care Health System.

University of Pennsylvania

Among the many partnerships between Penn and Wistar, José Conejo-Garcia, M.D., Ph.D., works with Penn's Julia Tchou, M.D., Ph.D., to develop a means of manipulating the immune system to create a breast cancer treatment for minority women.

Drexel University

Drexel researchers work with Ellen Heber-Katz, Ph.D., to undertand the mysteries of tissue regeneration in mice.

Temple University

Wistar's partnership with Temple's Moulder Center for Drug Discovery Research is designed to accelerate the translation of basic research into new drug therapies for cancer and other diseases.

University of the Sciences

In 2012, Wistar and the University of the Sciences launched a combined Ph.D. program in Cancer Biology to train the next generation of cancer researchers.

Thomas Jefferson University

Ramana Davuluri, Ph.D., of Wistar's Center for Systems and Computational Biology assists Jefferson researchers with bioinformatics support in oncogene research.

Fox Chase Cancer Center

Frank Rauscher, III, Ph.D., teams with Fox Chase mesothelioma researchers to better understand the underlying genetics of the disease.

Philadelphia FIGHT

Luis Montaner, D.V.M., D.Phil., conducts HIV/AIDS patient trials in coordination with FIGHT's clinics, and the University of Pennsylvania and Drexel University.

Children's Hospital of Philadelphia

David W. Speicher, Ph.D., works with CHOP researchers to study the differences in the red blood cell proteome in several diseases that cause severe anemia.

PERSONALIZED MEDICINE:
HAS THE FUTURE ARRIVED?

By Greg Lester

"Personalized medicine"—the concept of using genetic information to tailor medical care to each patient's specific needs—is usually thought of as a future possibility. But that possibility is becoming a reality at Fox Chase, where researchers and physicians have played a lead role in a scientific breakthrough that has improved the treatment of patients with colorectal cancer. Their achievement is helping to save lives—and changing the face of cancer medicine.

For years, the phrase "personalized medicine" has represented little more than a pipe dream of a time when a simple blood test could direct an entire course of treatment. A blood scan for genes, proteins, and other molecules could determine the specific nature of a person's cancer, for example, and allow physicians to select the therapy that would work best for that patient. Someday, its proponents claim, such personalized care will lead to earlier and more successful treatment of cancer and other diseases.

In the case of colorectal cancer, that day may already be here, thanks to groundbreaking research by Fox Chase scientists and physicians.

Neal J. Meropol, director of the Gastrointestinal Cancer Program and the Gastrointestinal Tumor Risk Assessment Program, has pioneered personalized medicine as part of his everyday practice in the treatment of metastatic colorectal cancer, a disease that claims nearly 50,000 lives each year in the United States.

"The first crack you take at metastatic colorectal cancer provides the best chance of beating the disease," Meropol says. "Right now, we have an arsenal of drugs to choose from—including traditional chemotherapies and targeted pharmaceuticals—but you need to pick the right one or combination as early as possible to get the most benefit for the patient."

Until very recently, there was no reliable means of determining which therapeutic weapon would provide the best first option for a given patient. Just five years ago, speaking at the annual meeting of the American Association for Cancer Research, Meropol posed the question: Could a patient's unique biology—or even the biology of a tumor itself—dictate how his or her cancer should be treated? The answer was critical to the viability of a new drug for metastatic colorectal cancer called cetuximab, known by the trade name Erbitux. The treatment had shown tremendous promise in clinical trials—but only for a select few. Cetuximab was a potential boon for patient care, Meropol knew, but how

could physicians identify those for whom it would work best?

Just a few years later, Meropol answered his own question. In 2007, the clinical researcher and his Fox Chase colleagues, along with collaborators from around the country, published a study in *Journal of Clinical Oncology* demonstrating that patients with a mutation in a gene known as K-RAS are less likely to respond to cetuximab. Meropol also co-authored a later study showing that the K-RAS mutation also predicts response to a related drug, panitumumab—known as Vectibix—which works in much the same way as cetuximab.

Today, Fox Chase patients with metastatic colorectal cancer are routinely screened for the K-RAS mutation. The research finding has been "wholly integrated into patient care at Fox Chase," Meropol says. "In fact, I'd say that it is now inappropriate to prescribe cetuximab or panitumumab without first testing for K-RAS mutations. Period."

UNDERSTANDING A DISEASE

Both cetuximab and panitumumab were designed with a single goal in mind—to block a cell-surface receptor called epidermal growth factor receptor, or EGFR, which is an important driver of cancer growth. The drugs consist of antibodies that bind to and inactivate EGFR.

In nature, antibodies tag specific foreign particles in the body, such as viruses or bacteria, for destruction by the immune system. Laboratory researchers can manufacture antibodies designed to bind to a specific target—in this case, EGFR. (These "monoclonal antibodies," as they are known, are the source of the "mab" suffix in the names of the drugs.)

EGFR plays a central role in cell biology: It serves as an "on switch" on the surface of many cells that tells the cell to divide. In the case of certain colorectal and head and neck cancers, the EGFR switch is continually on, leading to the out-of-control cell growth that is the hallmark of cancer. In theory, anti-EGFR antibodies should block the on switch, preventing chemical signals from reaching EGFR and, therefore, preventing the cell from multiplying.

For patients who benefit from cetuximab and panitumumab, this is indeed what the drugs do, and quite effectively. In 2004, the Food and Drug Administration approved cetuximab for the treatment of patients with colorectal cancers whose tumors tested positive for EGFR. However, that test proved ineffective: For most patients with the receptor, cetuximab had little or no effect, and some patients who failed the test still responded to cetuximab. Apparently, simply testing for EGFR was not enough.

> "NOW MORE THAN EVER, industry and academia must identify, recognize, and pursue shared goals regarding the clinical development of personalized treatments."

Cancer medicine had a good drug at its disposal, Meropol recalls, but the science was not yet clear on who should receive that drug. To help identify the right patients, Meropol turned to colleague Andrew K. Godwin, director of Fox Chase's Clinical Molecular Genetics Laboratory, a facility uniquely suited to surveying the genes of patients who were cetuximab-indifferent.

Godwin established the laboratory to analyze mutations of the BRCA1 and BRCA2 genes involved in hereditary forms of breast and ovarian cancer, and the facility now performs that type of analysis on a wide variety of human genes. For their 2007 study with Meropol, Godwin and his team studied tumor biopsies taken from 110 patients with metastatic colorectal cancer before they were given cetuximab. Scanning the biopsies for genes and mutations that might explain why patients responded differently to the drug, they found that patients without the K-RAS mutation were much more likely to respond to treatment: Cetuximab checked tumor growth in nearly half of those patients, as opposed to only 10 percent of patients with the mutant gene.

K-RAS is a member of a gene family well known to cancer researchers. The proteins these genes produce are part of the chain of molecules that communicates signals from outside the cell—from EGFR on the cell surface, for example—

A FOX CHASE FIRST

In 1974, Fox Chase Cancer Center became one of the first institutions to receive the National Cancer Institute's elite designation of comprehensive cancer center—a status that recognizes excellence in both research and clinical care.

to the nucleus, which contains the cell's genetic information. The overall chain, or pathway, has evolved to allow factors outside the cell to dictate which proteins the cell should make and when.

In the case of some colorectal cancers, the researchers found that the mutation in the K-RAS gene somehow activates growth signals, regardless of whether EGFR is present. "Although we don't fully understand all of the factors that contribute to this disease," Godwin says, "it is apparent from our studies that a significant number of colon tumors are being driven by mutated K-RAS."

A NEW PARADIGM FOR CANCER MEDICINE

K-RAS mutations allow physicians to identify the subset of patients who won't benefit from EGFR inhibitors like cetuximab and panitumumab. They do not indicate for certain which of the remaining patients will benefit, but excluding the patients who shouldn't have the treatment is a big first step in personalizing colorectal cancer treatment, Meropol says. It also represents a new way of thinking about drug development.

"Now that we're shifting the personalized medicine paradigm into practice, we'll need to think about what targeted therapies mean for the future," he says. "Overall, this is a great thing for patients. They benefit from more effective treatment with fewer side effects."

The implications of the paradigm shift for the pharmaceutical industry remain unclear, since personalized medicine essentially narrows a given drug's potential market. How that might affect drug pricing and the enormous cost of drug research has yet to be determined.

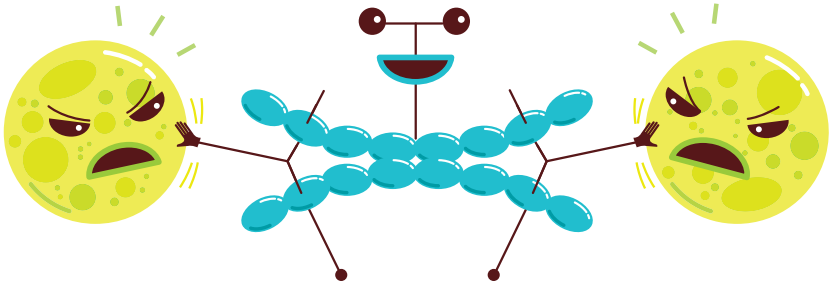
"Now more than ever, industry and academia must identify, recognize, and pursue shared goals regarding the clinical development of personalized treatments," Meropol notes. "Personalized medicine is here, but this is still just the beginning." ■

Headcase Design

Novel Molecule Could Slow Cancer's Spread, Boost Treatment

A molecule created at Fox Chase may provide a means of slowing cancer's spread and delivering more aggressive drugs directly to cancer cells. Nicknamed "ALM," the small molecule has been shown to halt the growth of breast cancer cells in laboratory tests.

ALM resembles an antibody—a protein that attacks and neutralizes foreign invaders such as viruses or bacteria. However, unlike naturally occurring antibodies, which bind to only one target at a time, ALM attaches to two targets simultaneously: the signaling proteins ErbB2 and ErbB3, found on the surface of many cancer cells, including head and neck cancer and drug-resistant breast cancer. When connected, the proteins can transmit messages into the cell nucleus that promote cancerous growth.



"In essence, ALM can get between ErbB2 and ErbB3 and hold them apart at arm's length, much like you would if you were separating two fighting children."

"In essence, ALM can get between ErbB2 and ErbB3 and hold them apart at arm's length, much like you would if you were separating two fighting children," says molecular biologist Matthew Robinson, lead author of a study published in November in *British Journal of Cancer*.

ALM was developed over many years at Fox Chase in the laboratory of Greg Adams, in collaboration with former Fox Chase oncologist Louis Weiner. The investigators created the molecule by linking the active anti-ErbB2 portion from one antibody with the anti-ErbB3 portion of another.

While ALM can stop cancer cells from growing and possibly even metastasizing, it has only a modest ability to kill the cells. The molecule might be best suited not as a weapon but as a delivery system, Robinson says, in that the small amino acid chain that links its two active areas could serve as a "trailer hitch" for stronger, more effective cancer-killing drugs.

"Since ALM is so specific for its target—and since its target is found in great numbers only on cancer cells—it could be used to 'tow' what would otherwise be toxic therapeutics directly to cancer cells without harming nearby healthy cells," Robinson says. "We are currently investigating how best to tether these other molecules to ALM in order to target metastatic breast cancer and related diseases."

Robinson and his colleagues believe that ALM might also provide a means for diagnosing cancer. By connecting it to a "marker" molecule, ALM could be used to detect early-stage cancers or determine the extent of a cancer's spread. The researchers are investigating ALM's diagnostic and therapeutic potential.

The study was funded by grants from the National Cancer Institute, U.S. Army Medical Research and Materiel Command, the American Cancer Society, the Bernard A. and Rebecca S. Bernard Foundation, and the Pennsylvania Department of Health.

Study Suggests Opportunity for Early Intervention in Cancer

A recent Fox Chase study suggests an avenue for identifying those at risk of developing cancer—and stopping the disease before it starts.

People receive one copy of each gene from each parent. More than 30 years ago, Fox Chase researcher Alfred Knudson Jr. revolutionized the field of cancer genetics by showing that, to develop cancer, a person must sustain "hits" to both copies of cancer-inhibiting genes called tumor-suppressor genes. These "hits" can be inherited or environmental: For example, a person might inherit one hit in the form of a nonfunctional gene. The remaining normal copy of the gene would protect against cancer—unless that gene, too, developed a mutation—a second hit—through exposure to carcinogens or some other factor. Knudson's theory is often called the "two-hit hypothesis."

Now Knudson and his colleagues offer evidence that a single inherited mutation—a "one-hit event"—is enough to change cells in detectable ways, providing an opportunity to prevent or delay the cancer. The researchers studied patients with an inherited disorder called familial adenomatous polyposis, or FAP, which predisposes them to colon cancer. FAP patients carry mutations in one copy of their adenomatous polyposis coli, or APC, tumor-suppressor gene, which prevents colon cells from growing out of control and becoming cancerous.

The researchers found that the cells of people with an inherited mutant APC gene look different from normal cells. In particular, the altered proteome—the sum total of proteins a cell creates from its DNA—of mutant APC carriers offers an indication of the cell's predisposition toward cancer.

"While these cells are just one hit away from becoming cancerous, their altered patterns of protein production may represent new biomarkers of cancer and novel targets for preventive and therapeutic drugs—a chance to strike at cancer before a second hit can happen," says molecular biologist Anthony Yeung, lead author of the paper.

While the scientists used colon cancer as a model, the findings may be applicable to other forms of cancer. Through genetic testing, it could be possible to identify those who are at risk of developing cancer because they carry an inherited mutation, Yeung says. These individuals could then take steps to reduce their risk of sustaining a second hit that would lead to cancer, whether through preventive drug therapy or by changing risky behaviors such as smoking or excessive tanning.

The findings were published in September in the journal *Cancer Research.*

Yeung and his colleagues are searching for biomarkers that could indicate a patient's risk for FAP and perhaps describe how close that patient's colon cells are to becoming cancerous. The researchers also seek to extend their studies to patients at risk for hereditary non-polyposis colon cancer.

Funding for the study was provided through the National Cancer Institute, the Fannie E. Rippel Foundation, The Shöller Foundation, the Commonwealth Universal Research Enhancement Program of the Pennsylvania Department of Health, the Pew Charitable Trusts, the Kresge Foundation, and private philanthropy.

Clinical Trial Investigates Use of Ultrasound to Relieve Pain from Bone Cancer

Fox Chase researchers are exploring a new method of alleviating the intense pain that can be caused by cancer that has spread to the bone.

While medications, radiation therapy, and surgery are sometimes effective in reducing pain from bone cancer, Fox Chase researchers are investigating a new approach to alleviating the discomfort. It's called MRI-guided focused ultrasound, and the Center is participating in an international study to see if the method can safely and effectively reduce the pain associated with bone metastases when other treatments don't help. Fox Chase is the only hospital in the region studying the technology for this use.

"This isn't a regular ultrasound device you might see at your doctor's office; it is much more powerful and can be targeted to a small area," explains radiation oncologist Gary Freedman, one of the lead investigators in the study. "However, like a common ultrasound, this technique also does not involve additional radiation to the body."

Also known as high-intensity focused ultrasound, or HIFU, the technique has been approved for treating uterine fibroids. It works by focusing high-frequency sound waves to heat a small area, much like using a magnifying glass to burn a hole in a piece of paper. Unlike light, the ultrasound passes through the skin into the body, where it can be directed to a particular spot.

For this clinical trial, physicians are using MRI to guide them to the area in the bone to which the cancer has spread. With the ultrasound, the physicians can then destroy the nerves that supply sensation to the bone, alleviating pain. The MRI allows physicians to monitor and continuously adjust the treatment.

"We're cautiously optimistic about this approach, but we won't know how useful it will be until the trial is complete," Freedman notes. "In time, we also hope that this technology can lead to new techniques to treat tumors in the liver, breast, and prostate."

One in Four College-age Adults Suffer from 'Tanorexia'

A survey conducted by Fox Chase researchers reveals that more than a quarter of college-age adults report symptoms of tanning dependence—a craving for the sun (or tanning booths) that holds many similarities to drug or alcohol addiction. The study, published in the September/October issue of *American Journal of Health Behavior*, also found that those with tanning dependence are more likely to be thin and smoke cigarettes, suggesting possible links among risky behaviors in young adults.

"Adolescents and young adults tend to put themselves at risk for skin cancer by exposing themselves to high levels of ultraviolet radiation," says Carolyn Heckman, the behavioral scientist who led the study.

"By understanding some possible reasons why, we hope to develop innovative interventions to help prevent these risky behaviors."

There is some evidence that UV tanning dependence may have biological underpinnings similar to those of other addictions.

Skin cancer is the most common form of cancer, according to the American Cancer Society. The disease accounts for half of all human cancers, with more than a million new cases diagnosed each year in the United States. It is reported that up to 90 percent of skin cancers are associated with ultraviolet radiation.

Heckman and her colleagues recruited 400 students and other volunteers at Virginia Commonwealth University in Richmond during the spring semester of 2006. Participants were queried about their level of intentional and incidental sun exposure, tanning booth use, and chemical sunless tanner use. The survey also asked about health-related factors such as body mass index, smoking, and exercise.

"The media and lay public may know tanning dependence as 'tanorexia,' alluding to similarities to both substance addictions and body image disorders like anorexia," Heckman notes. "There is some evidence that UV tanning dependence may have biological underpinnings similar to those of other addictions, such as the production of endorphins that produces the 'runner's high.' "

The researchers classified 27 percent of those surveyed as "tanning dependent." Sun tanning appeared to be more closely related to tanning dependence than indoor tanning, though use of indoor tanning during warm weather also signaled dependence.

The study was funded by the National Cancer Institute.

Breast Cancer Survivors Regain Normal Quality of Life, Study Shows

Women with breast cancer who undergo breast-conserving lumpectomies and radiation report being able to resume a normal quality of life within three to 15 years after treatment, according to a survey conducted by Fox Chase physicians. In fact, 10 years after treatment, these cancer survivors report a very high quality of life compared to the general female population of the United States.

"Treatments for breast cancer may decrease quality of life temporarily, but this is evidence that survivors on average will return to a normal quality of life," says radiation oncologist Gary Freedman, who led the study. Freedman presented his findings in September at the annual meeting of the American Society for Therapeutic Radiology and Oncology.

The survey included 1,050 women with early-stage breast cancer treated with breast-conserving surgery and radiation, with or without chemotherapy and hormone therapy. During routine follow-up visits, the women were asked to complete a brief, standardized questionnaire on health issues including mobility, self-care, anxiety/depression, pain or discomfort, and ability to perform usual activities.

The researchers compiled scores based on a scale of 0 to 1, with 1 being the most positive. Ten years after treatment, the average score for breast cancer survivors ages 18 to 44 was .96, compared to .91 for women of the same age in the general U.S. population. Survivors ages 45 to 64 scored .93, compared to .84 for the general population; and those over 64 scored .76, compared to .81 for the general population.

Molecular Discovery Could Turn Tables on Drug-resistant Cancer

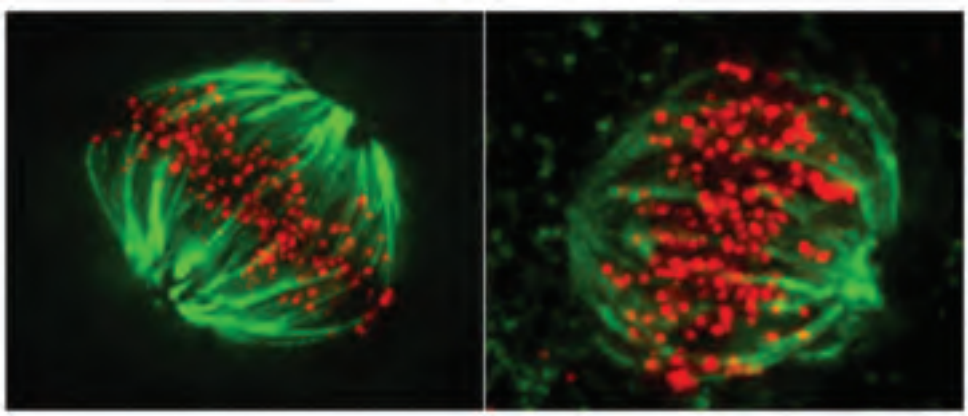
Fox Chase researchers have identified a potential means of turning a cancer cell's chief strength—the ability to rapidly evolve past the reach of therapies—into a weakness that can be exploited to stop cancer's growth.

In a study published in October in *The Journal of Cell Biology*, Timothy J. Yen demonstrated how the BubR1 protein controls the sorting of chromosomes in dividing cells. In normal cells, BubR1 evenly sorts the cell's duplicated DNA, in the form of chromosomes, into each new "daughter" cell. When cancer cells divide, however, this process can go wrong and one daughter cell can inherit more—or less—than its fair share of chromosomes, which may confer drug resistance and other cancer-related behaviors on the new cell.

In effect, cancer cells accelerate their own evolution by creating new combinations of genes. Certain combinations prove fatal to daughter cells, but other combinations allow the new cells to survive. As long as the genetic alterations are made on a relatively small scale, cells within the tumor will continually evolve so that they can adapt to a changing environment, Yen says.

"Improper chromosomal segregation is a hallmark of cancer—it scrambles chromosomes and shuffles the genetic deck in a way that helps some cancer cells to evade destruction," he explains. "This shuffling can, in effect, push a cancer cell to evolve in a way that allows it to survive drug or radiation therapy."

By altering BubR1 in the laboratory, Yen and his colleagues were able to mimic the improper genetic sorting seen in cancer cells. This ability may provide an opportunity to turn the tables on cancer cells by causing more genetic disarray than even they can handle. Inhibiting the protein could increase the effectiveness of drugs that operate by disrupting cancer cells' DNA replication or preventing their division, thus stopping the cells' growth or destroying them altogether.



The protein BubR1 controls the sorting of chromosomes in dividing cells. At left, during normal cell division, microtubules (shown as green lines) connect to chromosomes at the spots designated in red and pull them apart. At right, when BubR1 is mutated, the microtubules attach to chromosomes poorly.

By altering BubR1 in the laboratory, Yen and his colleagues were able to mimic the improper genetic sorting seen in cancer cells.

The research was supported by grants from the Leukemia & Lymphoma Society, National Institutes of Health, the Commonwealth of Pennsylvania, and private philanthropy.

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A CONVERSATION WITH BARUCH S. BLUMBERG

'Fishing Expedition' Led to Nobel Prize

Paul Cohen

By Greg Lester

Fox Chase's Baruch S. Blumberg was awarded the Nobel Prize in medicine in 1976 for his work in discovering the hepatitis B virus, the leading cause of liver cancer. He subsequently invented a vaccine against the disease—effectively, the first cancer vaccine—that has become one of the most widely used in the world, with billions of doses administered. Here, Blumberg describes the path that led to his groundbreaking discovery.

***Q** You were trained as a physician. How did you make the jump to research?*

A Even before entering medical school, I had a strong inclination, based in large part on my father's suggestion, that I would enter research. In 1955, after four years of medical training at Bellevue Hospital and the Presbyterian Hospital of Columbia University, I decided to get into laboratory work. I went to Balliol College at the University of Oxford to earn a doctorate in biochemistry. That was where I became interested in inherited biochemical variation.

My colleagues and I began taking field trips and doing studies on human blood specimens. This was before we had the tools to study genes—well before the Human Genome Project—so we studied blood serum proteins, looking for small differences and determining which were genetically influenced. We were getting an idea of the distribution of these traits among different populations and how the environment of each might have had an effect. Over the years, we crossed the globe. One year we'd visit a remote Arctic village, the next Africa or an island in the Pacific.

Q ***Why were you interested in these genetic variations?***

A I was always interested in why some people get sick and others don't. It is a basic question in medicine—perhaps *the* basic question. As a physician, you see someone lying in bed and think, "Why is he or she there and I'm not, even though we've had the same kind of exposure?"

The plan was to look at each inherited difference in a protein, then figure out which disease it was related to. Sometimes such things are prejoratively called "fishing expeditions," but that's exactly what we wanted to do. We were trained medically and in laboratory research; in the field, we became more familiar with the background disease patterns.

Q ***You came to Fox Chase in 1964. What drew you here?***

A The approach here was to do basic science—to understand cells and genetics at a basic scientific level. I thought that was the way to go forward in understanding the basis of disease, and I still do. Our study of genetic variation was a basic science question, with the expectation that applications would come in time.

Q ***Did you set out to find hepatitis B?***

A We did not, but you can't say that it was accidental, either. We didn't know what we would find, but we knew we'd find something. Very often, when people tell the story, they recast it as if finding hepatitis B was the original intention. That wasn't our story.

Q ***How did the hepatitis discovery come about?***

A We began to look for proteins that differed from each other in an antigenic sense, or how they elicited an immune response. The notion was that, if someone received many blood transfusions, they would be exposed to variants of proteins they hadn't inherited. If those transfused proteins were antigenic, you'd find an antibody in the patient. We would then use that antibody to look for the antigen in the blood of people we'd sampled. Nobody had thought of using that technique, as far as we knew.

We found, in a hemophilia patient, an antibody against what we would later learn was the surface antigen of hepatitis B virus. We found the antigen in a number of samples we collected, including that of an Australian, so we called it the Australia antigen and, for half a year or so, we didn't know what it was.

Q ***Did you have any idea that it was hepatitis B?***

A Even early on, we had some idea it was hepatitis. We knew that people who had transfusions got hepatitis, so we had an inkling.

Within a short time, a few episodes increased our suspicions. For example, we were studying Down syndrome patients, who had a prevalence of hepatitis B, and found that many also had the Australia antigen. That led to our first publication identifying hepatitis B in 1967. In 1969, Fox Chase filed the patent for the vaccine, with Irving Millman and me as co-inventors; it was granted a few years later. The vaccine was made by extracting the antigen from the blood of carriers and treating it to kill any live viruses. Nobody has made a vaccine like that before or since.

"We didn't know what we'd find, but we knew we'd find something."

Q ***Did you know you were making a cancer vaccine?***

A We suspected, but there wasn't sufficient supporting data. There had been studies in West Africa, primarily, linking liver cancer to underlying liver disease—cirrhosis—that was thought to be caused by hepatitis. We also published studies in the '60s linking liver cancer and the Australia antigen, but they were not conclusive.

Q ***Have you thought about how many lives your research has saved?***

A People have made calculations, and the numbers are in the millions. Of course, the impact is hard to appreciate. One of the problems with preventative medicine is that, if it works, nothing happens. ■