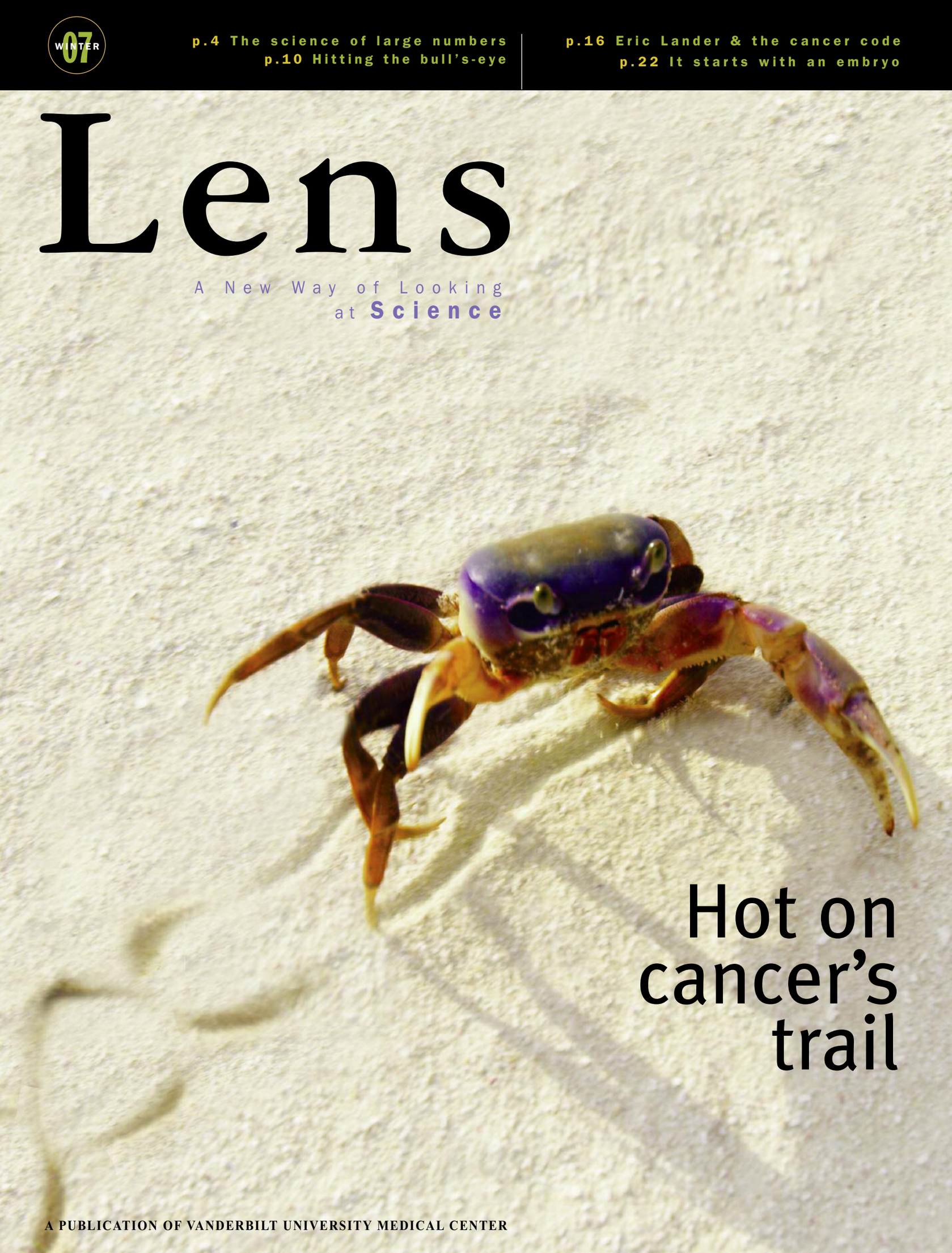
WINTER 07

Lens

A New Way of Looking at **Science**



Hot on cancer's trail

A PUBLICATION OF VANDERBILT UNIVERSITY MEDICAL CENTER

Lens –
A New Way of Looking
at **Science**

WINTER 2007

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Cover: Cancer the crab scuttles across the beach, leaving behind a double-helical trail. Photo illustration by Dominic Doyle. Photo credit: Science Faction/Getty Images.

It is only the vision that can be new;
but that is enough.

– EUDORA WELTY

Lens **is published three times a year by Vanderbilt University Medical Center in cooperation with the VUMC Office of News and Public Affairs and the Office of Research. Lens® is a registered mark of Vanderbilt University.**

Our goal: to explore the frontiers of biomedical research, and the social and ethical dimensions of the revolution that is occurring in our understanding of health and disease. Through our Lens, we hope to provide for our readers – scientists and those who watch science alike – different perspectives on the course of discovery, and a greater appreciation of the technological, economic, political and social forces that guide it.

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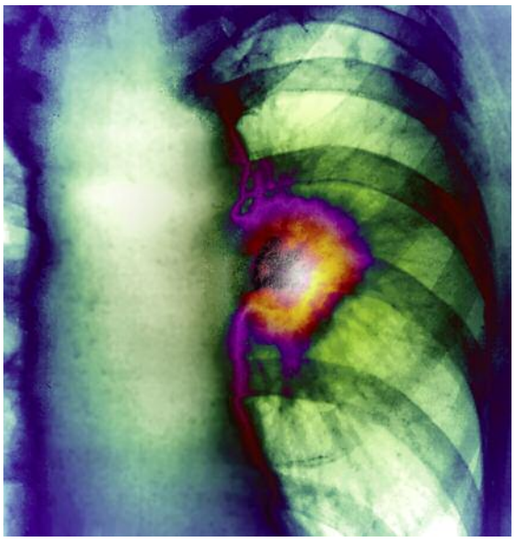

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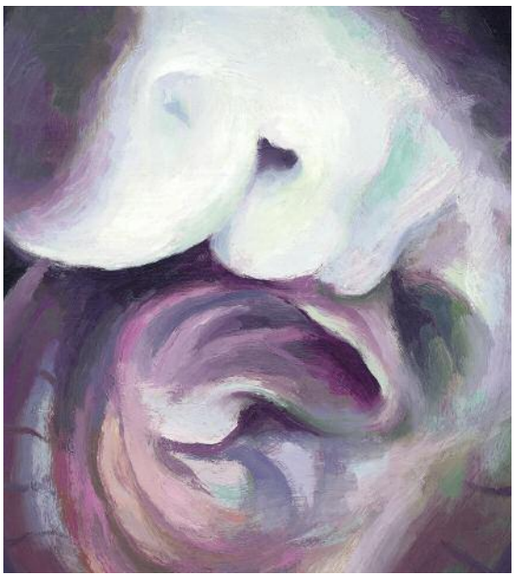

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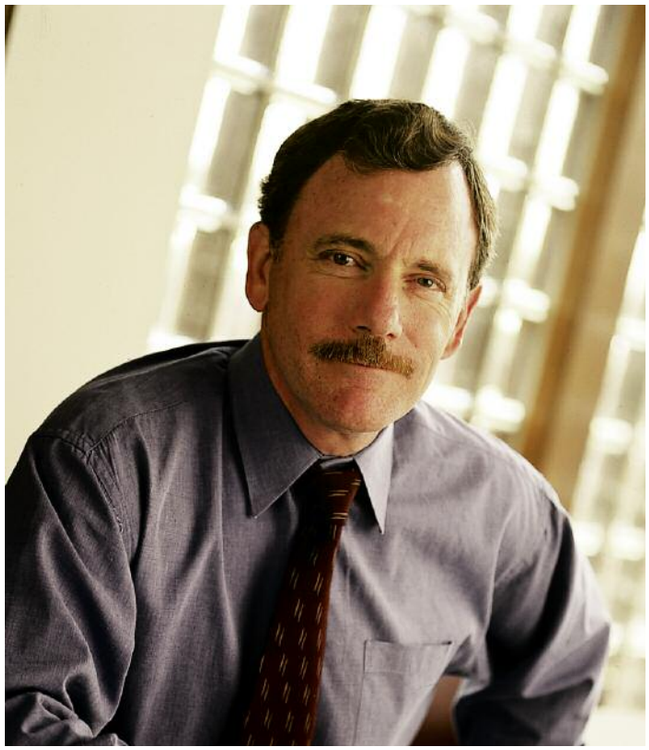


Symphony of knowledge

Science closes in on cancer

By Bill Snyder

The crab on the cover of this issue of *Lens* magazine represents all that is old and new about cancer, the nation's second leading cause of death after heart disease.

Old, because cancer goes back to the dinosaurs; evidence of malignancies has been found in fossils dating back 80 million years.

New, because fields as disparate as genomics and embryology are providing new hope that a war declared 36 years ago by President Richard Nixon one day will be won.

In this issue, Eric Lander, Ph.D., a driving force behind the Human Genome Project, predicts that cancer patients soon will be able to have complete genomic workups to determine exactly what subtype of the disease they have, and which treatments are most likely to work.

The sequencing of the 20,000 or so genes that make up the human being already has improved our understanding of the genetic "switches" that turn on tumors. One benefit: discovery of new compounds that can switch off malignant growth without harming normal cells.

Also on the horizon: screening blood tests that harness the power of proteomic "fingerprints" to detect early cancer, even before symptoms occur.

This issue of *Lens* focuses on the spectrum of research – from basic laboratory studies to clinical trials of new drugs – undertaken by scientists at Vanderbilt University Medical Center, the Vanderbilt-Ingram Cancer Center and colleagues from Boston to Shanghai.

The story would not be complete, however, without mentioning epidemiology, that non-flashy field of medical research that is crucial to understanding what causes disease and how to prevent it.

By recording the incidence of lung cancer among Americans over time and correlating the numbers with smoking rates, researchers were able to establish conclusively the role that cigarettes play in the disease.

Cohort studies, which track the development of disease in large groups over several decades, also may help solve the riddle of cancer disparities – why cancer incidence and death rates are disproportionately high, for example, among African-Americans.

"It's where research always starts," says Jane Weeks, M.D., chief of Population Sciences at Boston's Dana-Farber Cancer Institute. "It generates hypotheses. It generates ideas."

Charting cancer in cohorts, uncovering proteomic fingerprints, discovering clues to cancer in the development of an embryo – all avenues are important.

"By pulling all of this information together into a symphony of knowledge, we will be able to exponentially expand the rate of effective cancer treatment over the next 10 or 20 years," predicts Raymond DuBois, M.D., Ph.D., director of the Vanderbilt-Ingram Cancer Center, who later this year will become provost and executive vice president of academic affairs at the University of Texas M.D. Anderson Cancer Center in Houston.

Continued support of cancer research is crucial, he adds. So is nurturing the next generation of scientists.

"What makes me most impatient and most frustrated is when I hear young people's proposals being criticized for being too ambitious," says Lander, who directs a genomic research powerhouse, the Broad Institute of MIT and Harvard.

"There's nothing wrong with young people being too ambitious. They should be too ambitious … the desire to try to do something important is a great fuel; it's a great resource."

This, incidentally, is the raison d'être for *Lens* magazine – to explore, to explain, to inspire … to follow, if you like, the double helical trail left in the sand by an ancient animal. **LENS**

High-tech surveillance

The power of proteomics

BY BILL SNYDER

Will fingerprinting cancer lead to its arrest?

That's the hope of proteomics, the science of proteins.

Researchers are trying to identify patterns of proteins in blood and tissue samples that reflect the presence of diseases like cancer in the body. These patterns, often called "molecular fingerprints," could serve as biomarkers for early detection.

"We believe that the future of medicine is actually going to depend very heavily on the ability to discover and validate biomarkers in proteomics," Anna D. Barker, Ph.D., deputy director of the National Cancer Institute (NCI), said during a news conference last fall.

By improving early detection, biomarkers could increase the chances for successful treatment and survival, noted Nobel laureate Leland Hartwell, Ph.D., president and director of the Fred Hutchinson Cancer Research Center in Seattle.

In addition, "they will be useful for managing the cancer process at all stages, from risk assessment to early detection to prognosis to therapeutic response and disease recurrence," he said.

Currently, however, there is a lack of standardization of techniques used to analyze proteins. As a result, "the overall reliability of the approach is not currently sufficient to apply it directly to clinical research," says Daniel C. Liebler, Ph.D., director of the Proteomics Laboratory in the Vanderbilt Mass Spectrometry Research Center.

Liebler is heading up one of five teams across the country to standardize proteomic technologies and move them forward. The project, part of the NCI's Clinical Proteomics Technologies Initiative, was announced during last fall's news conference.

Richard Caprioli, Ph.D., co-director of the Vanderbilt team, directs the Mass Spectrometry Research Center and has helped pioneer the technology used to identify and analyze protein biomarkers in tissue samples.

Gordon B. Mills, M.D., Ph.D., director of the Kleberg Center for Molecular Markers at the University of Texas M. D. Anderson Cancer Center, is collaborating with the Vanderbilt researchers.

"A lot of the differences between proteins in disease states and normal health are not differences in the amounts of the proteins themselves, but in the modified forms of proteins that are present," explains Liebler. Abnormal genes, for example, may encode abnormal proteins, which in turn, trigger a cascade of events leading to cancer.

"Proteins are commonly dressed up in many different kinds of modifications that control their activity and function," he says. "And so the problem is not so much in identifying the proteins but it's frisking them, being able to detect differences in modified protein forms."

Vanderbilt's approach to frisking is called "shotgun proteomics," in which proteins from a biological sample are cut into small pieces called peptides, analyzed using mass spectrometry techniques, and then put back together.

"Everybody has their own way of doing shotgun analysis," says Liebler, adding that his team's goal is to standardize the technology.

The standardization effort mirrors approaches being developed for early detection of colorectal cancer in the Jim Ayers Institute for Precancer Detection and Diagnosis. Liebler also directs this institute, part of the Vanderbilt-Ingram Cancer Center.

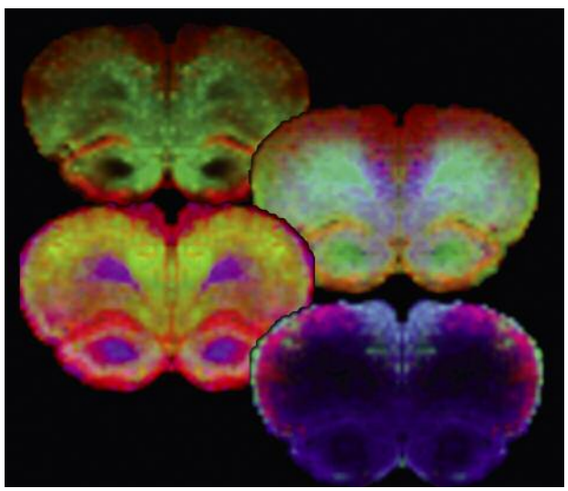
Other Vanderbilt researchers have found proteomic "signatures" that potentially may improve the early diagnosis and treatment of lung cancer, and they are scanning protein profiles found in the blood of African-American and Caucasian women for clues to why African-Americans die more frequently from breast cancer.

Proteomics "is an incredibly promising field," said Barker, "but until we get some standardization here, it's just not going to move forward.

"If we can move this field forward, we believe we can actually diagnose cancer very early," she added. "If we diagnose it very early, we can start to really reduce the burden of this disease and ultimately, potentially, make it history." **LENS**

To learn more about Vanderbilt's proteomics program, go to: www.mc.vanderbilt.edu/msrc.

For more on the federal initiative, visit http://proteomics.cancer.gov.



A montage of molecular images glows with a spectrum of peptides and proteins, their colors assigned to different molecular weights, in sections of a rat brain. Images like these, which were produced by MALDI imaging mass spectrometry, can reveal the distribution of individual proteins in cells and tissues.

Image courtesy of Malin Andersson, Ph.D., research fellow in the Vanderbilt Mass Spectrometry Research Center

Pictured here: Wei Zheng (left) and Xiao Ou Shu, a husband-and-wife research team at Vanderbilt University Medical Center, seem to stroll through a Shanghai market in this photo illustration. Two cohort studies they direct in China's largest city are providing clues to cancer and other diseases.

Photo illustration by Dean Dixon
Shanghai photo by Getty Images

THE SCIENCE OF LARGE NUMBERS

COHORT STUDIES SHED LIGHT ON CANCER

By Stephen Doster

Every year, 50 modern-day gumshoes fan out across Shanghai, China, hot on the trail of some of the worst miscreants that afflict the human race.

Armed with survey forms, they question the inhabitants of thousands of homes. Their goal: to find out why some people develop cancer and other diseases, and others don't.

Begun a decade ago by researchers now at Vanderbilt University Medical Center (VUMC), the Shanghai Women's Health Study has yielded important clues to the mysterious connections between environment, genetics and disease.

For example:

- Women who have never smoked but whose husbands are heavy smokers are at greatly increased risk of dying from stroke.
- High intake of soy foods lowers blood pressure and decreases the risk of both coronary heart disease and bone fractures.

"Sometimes the associations between lifestyle and disease are so striking it surprises us," says Wei Zheng, M.D., Ph.D., who directs the Shanghai study with his wife and colleague, Xiao Ou Shu, M.D., Ph.D. "We are conducting additional studies to get more definitive answers."

The Shanghai investigation is known as an epidemiological "cohort" study. It is designed to track the development of disease in a large group of people over an extended period of time – usually decades.

Cohort studies can help reveal the impact that diet, exercise and other lifestyle factors can have on health and longevity. More recently, they've been used to explore the disproportional impact of disease on different ethnic groups.

An example is the landmark Southern Community Cohort Study, which will attempt to explain why African-Americans are more likely than other groups to develop and die from cancer.

The study is a collaboration of the Vanderbilt-Ingram Cancer Center, Meharry Medical College and the International Epidemiology Institute (IEI), a biomedical research firm based in Rockville, Md.

Since the study was launched four years ago, nearly 63,000 adults ages 40 to 79 have been enrolled through community health centers in 12 Southeastern states, including Tennessee. The goal is to recruit 90,000 participants.

"Historically, the home of the African-American population in the United States has been in the South," explains William Blot, Ph.D., IEI chief executive officer and the study's principal investigator. "There had never been an investigation in the South on this order of magnitude.

"When you start getting up in numbers of people with a particular type of cancer that approaches 1,000, that gives you pretty good power to start looking at environmental and genetic factors," says Blot, who also is a professor of Medicine at Vanderbilt.

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Focus on the good

Zheng got the idea for the Shanghai Women's Health Study in the early 1990s while working at the University of Minnesota.

He and his wife met at Shanghai Medical University, where they both earned medical degrees and master's degrees in public health before coming to the United States in 1989 and 1990 for Ph.D. training at Johns Hopkins University and Columbia University in New York, respectively.

"I was involved in the Iowa Women's Health Study and wrote a paper focusing on tea consumption and cancer risk. Most studies look at what is bad about diet. I thought, 'We need to focus on what is good about diets to help protect against cancer.'"

Zheng presented a paper at an annual meeting of cancer research where he noticed tremendous interest in research focusing on protective foods – not just tea, but soy foods, fruits and vegetables.

"I thought, 'We have done all these things to identify risk factors. How about identifying protective factors?' So I came home and developed the proposal to focus on dietary protective factors, and the NIH funded it right away."

So far the study has recruited approximately 75,000 women between the ages of 40 and 70 in seven typical communities in Shanghai.

"With an epidemiological study, we want to recruit a large number of participants in order to have an adequate power to evaluate study hypotheses," he says. "In other words, the more participants we have, the more confidence we have about our research findings."

While working with her husband on this study, Shu realized that more could be gained than simply studying women. In 2001, she launched the Shanghai Men's Health Study. To date, 60,000 men have been enrolled, half of whom are married to participants in the women's cohort.

"First, we did a small pilot study and discovered that the husbands' and wives' dietary habits are very different, although they share the same living environment,"

AN ENDURING LEGACY

One of the exciting potentials of cohort studies is that the collected data can be used by other researchers to address questions that are important to their areas of interest – for years to come.

"Junior faculty, post-doctoral fellows and senior investigators are using our resources in other studies – genetics, nutrition," notes Vanderbilt's Wei Zheng, M.D., Ph.D., MPH, who directs the Shanghai Women's Health Study. "So the cohort studies create opportunities for other research."

Harvard's Walter Willett, M.D., MPH, Dr.P.H., who launched the second Nurses' Health Study in 1989, echoes that sentiment. "We started mostly with a focus on cancer and heart disease, but now we're looking at virtually every major condition, including psychological effects, kidney stones – you name it."

For example, the study has found that a diet high in sugar-sweetened and diet soft drinks, refined grains and processed meat can raise the risk of developing type 2 diabetes, and that obesity and weight gain increase the risk of kidney stone formation.

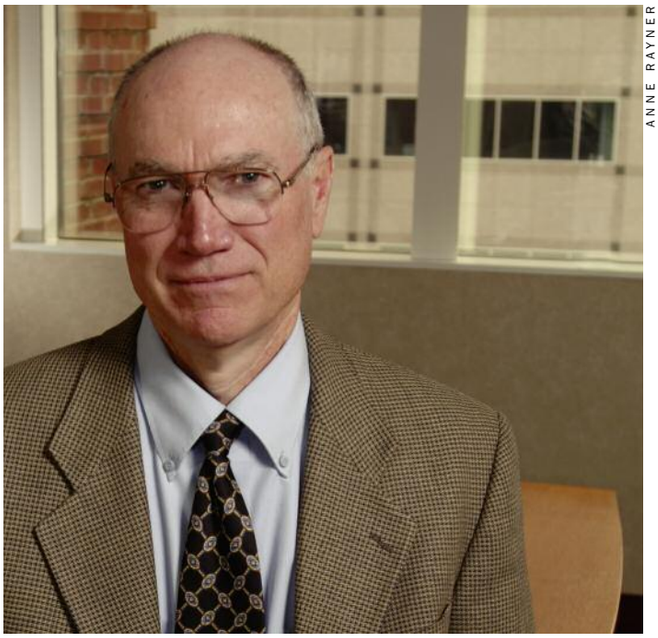
Emily Beauregard sees the potential for a psychological study based on a trend she noticed last year while enrolling people into the Southern Community Cohort Study at the Family Health Centers' Portland Clinic in Louisville, Ky.

"Most of our patients' (annual) household income is less than $15,000," she says. Many "have been diagnosed with depression ... Education, housing, emotional health – everything plays into your well-being."

– STEPHEN DOSTER

"When you start getting up in numbers of people with a particular type of cancer that approaches 1,000, that gives you pretty good power to start looking at environmental and genetic factors."

William Blot, Ph.D.,
Principal investigator,
Southern Community Cohort Study



ANNE RAYNER

Shu says. "For instance, men like to eat more meat compared to the women."

Most women in China also work outside of the home. "So there is an opportunity to look at environmental and occupational factors as well."

One goal of the Shanghai cohort studies is to determine whether differences in traditional Asian and Western diets account for widely varying incidences of different cancers among residents of China and the United States.

Researchers know that Asia and the United States have quite different cancer spectra. In China and Japan, stomach cancer used to be the No. 1 culprit followed by cancer of the esophagus; whereas in the United States, lung, colon and breast cancers dominate.

However, the cancer spectrum in some parts of China, such as Shanghai, is starting to more closely resemble that of the United States. For people who move from China to the United States, the risk of stomach and esophageal cancers decreases while the risk of lung, colon, and breast cancers dramatically increases.

The million-dollar question, of course, is "Why?"

One hypothesis is that lifestyle factors – including diet – account for these differences.

The Shanghai studies were designed to test the hypothesis that the traditional Asian diet, which includes soy foods, bok choy (Chinese cabbage), white radish, ginger root, tea and ginseng, may reduce the risk of diseases including some cancers.

To find out, the Shanghai studies rely on trained interviewers who go door-to-door. Because most Shanghai residents live in apartment towers, dozens of study participants can be found in one building. The interviews are later transferred from paper to an electronic form for data analysis.

"In-person interviews improve the quality of the data," Zheng explains, "particularly across a large population with diverse educational and income backgrounds. If you asked someone to fill out a form, you may get different quantities and quality of responses. In-person interviews minimize the differences.

"Secondly, the response rate is high with in-person interviews. We have a 93 percent response rate. Mailed surveys typically get a 25 percent to 40 percent response."

A higher response rate makes it easier to generalize findings across a population, he adds.

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Empower the people

The Southern Community Cohort Study takes a different tack. Its researchers rely on community health centers to enroll study participants, most of whom are lower income.

Betty Scott, an interviewer at the West End Medical Centers in Atlanta, has enrolled over 2,600 people into the study. Her interest in the project is more than academic.

"I have a history of cancer in my family," she explains, having lost her father, a brother and a sister to cancer. Three other brothers have been diagnosed with cancer.

"Of course, I want to know what is causing so much disease," Scott says. "We all have theories, but until research proves what is causing cancer, we will never know the answers."

"A lot of folks in our area have been affected by cancer," adds Emily Beauregard, who enrolled about 90 people a month last year at the Family Health Centers' Portland Clinic in Louisville, Ky.

"There's not a lot one person can do to stop disease or make someone who has cancer better," says Beauregard, who is currently enrolled in a master's degree program in public health. "But if you can participate in something that may in the long run halt or decrease the rates of cancer, people feel that is empowering to be able to do something about it."

Both studies track participants by name, address, social security number, and in Shanghai, by citizenship IDs. The researchers regularly monitor government registries in China and the United States that track disease and deaths reported by health officials. Participants are also contacted periodically to update their disease and exposure information.

Biological samples – urine, blood, cheek cells (for DNA) – are sent to VUMC, where they are stored in freezers for future analysis.

"We get boxes from up to 30 different centers every day," Blot says. "The blood is separated into 14 different tubes and stored in a freezer bank."

Once the data and biological specimens have been collected, the real detective work begins.

"We will do that through a 'case-control' study," he says. "… We will identify everybody, say 500 people … who (have) developed lung cancer, and get their blood

specimens. Then we choose a control group of 500 or 1,000 people (without cancer) who are the same age, sex, race, etc., and pull their blood specimens.

"Then we look for differences between the cases versus the controls. Meanwhile, we have all this background information on everybody, their smoking history and other factors.

"If the cause of a disease in this lower income population proves to be genetic, we should be able to apply our findings to higher income and higher education populations. Even environmental associations seen in the study population may apply more broadly, but we will examine these closely before making any extrapolations to other segments of society."

Typically, during the first five years of an epidemiological study, most of the effort is devoted to recruiting study participants and collecting survey data and biological samples. The value of the cohort study increases as it is followed over the years and cohort members begin to develop different diseases.

The Shanghai Women's Study has already begun to shed light on a number of areas.

Among the findings: "Women who are non-smokers but who are exposed to the cigarette smoking of their husbands have an increased risk of dying of stroke," Zheng says. "We also learned that soy food intake reduces the risk of fractures, hypertension, coronary heart disease and diabetes."

Simply adopting Asian eating habits may not yield the same benefits in the United States, Shu cautions.

"Even though lots of people in the South eat rice and greens, as do people in Shanghai, the specific type of vegetables and the way the food is prepared is very different," she says.

In addition, "the ways soy foods are consumed in the U.S. are quite different from how they are consumed in China," Shu adds. "For example, many soy products in the U.S. contain a large amount of sugar, while most soy products are consumed in China without the addition of any sugar."

As for the Shanghai Men's Study, which recently completed recruitment, Shu notes that the smoking rate in this cohort is high – 67 percent.

"We found that smokers have a lower body-mass index than their non-smoking counterparts," she says, "but more centralized obesity or beer belly, meaning they gain more weight around their torso. This can more be harmful to health than less centralized obesity and may increase the risk of cardiovascular disease and cancer."

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Conflicting results

Cohort studies can yield conflicting results. For example, a 2003 study of California residents that found no relationship between environmental tobacco smoke and tobacco-related deaths contrasts sharply with a more recent finding from the Shanghai Women's Health Study, which linked secondhand smoke to an increased incidence of cardiovascular disease, stroke and lung cancer.

While conflicting results can sometimes delay effective prevention and treatment strategies, they can also lead to new insights, says Walter Willett, M.D., MPH, Dr.P.H., professor of Epidemiology and Nutrition at the Harvard School of Public Health who launched the second Nurses' Health Study in 1989.

"Efforts to understand the differences (between studies) can result in new knowledge," Willett explains. "Sometimes the questions being asked are really different questions."

Margaret Hargreaves, Ph.D., co-principal investigator of the Southern Community Cohort Study and professor of Internal Medicine at Meharry, is all too familiar with conflicting study results.

"One reason you may see conflicting findings from studies is that people may not

WHAT'S CATERPILLAR GOT TO DO WITH IT?

The role of the private sector in cancer research

Cohort studies are important research investments, says Harvard epidemiologist Walter Willett, M.D., MPH, Dr.P.H.

"They're necessarily long-term investments, too, and as such, they are particularly vulnerable to cutbacks in research funding," he says.

"If you have a project in the lab and it goes a year without funding, you can just start up again," Willett says. "But when you have dozens of people employed, and you have to maintain active intervention with your participants, you can't just start and stop without very serious damage."

That's a major concern, considering the recent drop in federal funding for medical research, adds William Blot, Ph.D., principal investigator of the Southern Community Cohort Study.

"The percentage of grant applications that are funded has been cut in half," Blot says. "It used to be that the top 20 percent of grant applications were funded. Last year it was only the top 11 percent, and this year the National Cancer Institute's budget has already been cut by $40 million."

As a result, the private sector is becoming an increasingly important source of support.

Three years ago, for example, Caterpillar Inc. pledged $1 million to the Southern Community Cohort Study. The Susan G. Komen Breast Cancer Foundation is another major supporter.

Kent Adams, president of Caterpillar Financial Services Corp., says Caterpillar officials were impressed with the scope of the project.

"As we investigated over time," he says, "it became clear that the people behind the Southern Community Cohort Study really had an extraordinary vision of what this work could do. We feel that the study and our participation are an endeavor to ensure that the burden of cancer is reduced for everybody regardless of race or circumstance."

Wendy Mason, director of project management for the Komen Foundation, said the foundation is supporting the cohort study because of its potential to reduce breast cancer disparities.

"Ultimately, … projects (like this) will shed light on factors that influence breast cancer risk, which we hope will lead to a better understanding of the differences in mortality between Caucasian and African-American women," Mason says.

In corporate America, Adams says, "there is a trend towards a greater emphasis on philanthropy as a demonstration of overall social responsibility."

"Non-profits (also) are working really hard to raise dollars that they can contribute to medical research," Mason adds, "because it's something that affects all of us."

– STEPHEN DOSTER

DEAN DIXON

have large enough samples when they do their research," she notes. "That's why we're going for large numbers of enrollees."

Hargreaves recalls that for a long time researchers thought obesity was closely associated with breast cancer. "Then somebody came out and said no it wasn't, based on their findings. Now, there's another wave of studies saying that maybe it is," she says.

"What that means is that you just have to keep doing different studies, studying different kinds of people and gathering more specific information and making sure you see as large a number of people as you can."

Pooling results from cohort studies that involve different population groups also can yield valuable insights.

Researchers at the University of Texas M.D. Anderson Cancer Center in Houston, for example, are planning to compare findings from their Mexican-American Health Study with those from a Native American cohort study in South Dakota.

"We're enrolling families, ages 5 to over 90," says Melissa Bondy, Ph.D., professor of Epidemiology and principal investigator of the Mexican-American Health Study. "The onset of breast cancer occurs at much younger ages in Mexican-American women than in white or African-American women. And there is a high rate of diabetes in the population.

"The rate of smoking among Mexican-American women is very low, but we're seeing it in girls," Bondy says. "We're seeing kids as young as 11 and 12 years old already experimenting with smoking tobacco."

While the goal of this study is to identify risk factors associated with disease patterns within Mexican and Mexican-American populations, "comparisons across groups with ethnic and cultural differences may help explain determinants of the differences in disease rates across these groups," Blot points out.

Blot hopes eventually the studies will identify certain subsets of people who are more likely than others, because of their genes, to respond to lifestyle and environmental exposures that put them at an increased risk.

"If you know that some people have an increased risk, then we can advise them to avoid certain exposures," he says. "You could advise those at high risk to be under increased surveillance for early detection of a cancer. For, even if you can't prevent the cancer, at least you may be able to catch it early when the disease is more amenable to successful treatment." **LENS**

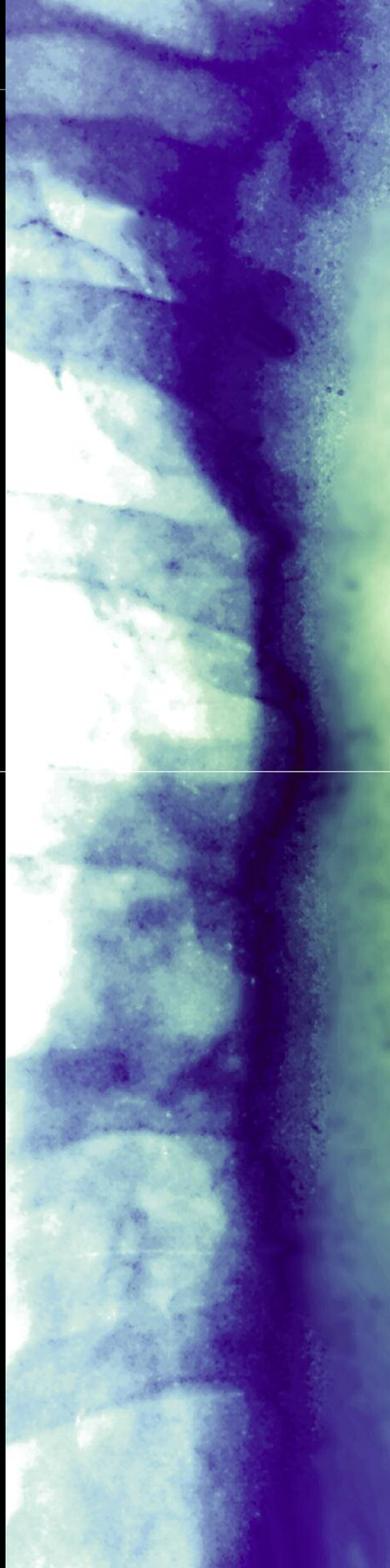
> "....you just have to keep doing different studies, studying different kinds of people and gathering more specific information and making sure you see as large a number of people as you can."
>
> **Margaret Hargreaves, Ph.D.,**
> **professor of Internal Medicine, Meharry Medical College**

Pictured with her at the Matthew Walker Community Health Center in Nashville are (from left) technical assistant Lawana McKissack and health educator/coordinator Tamara Currin.

BY LEIGH MACMILLAN

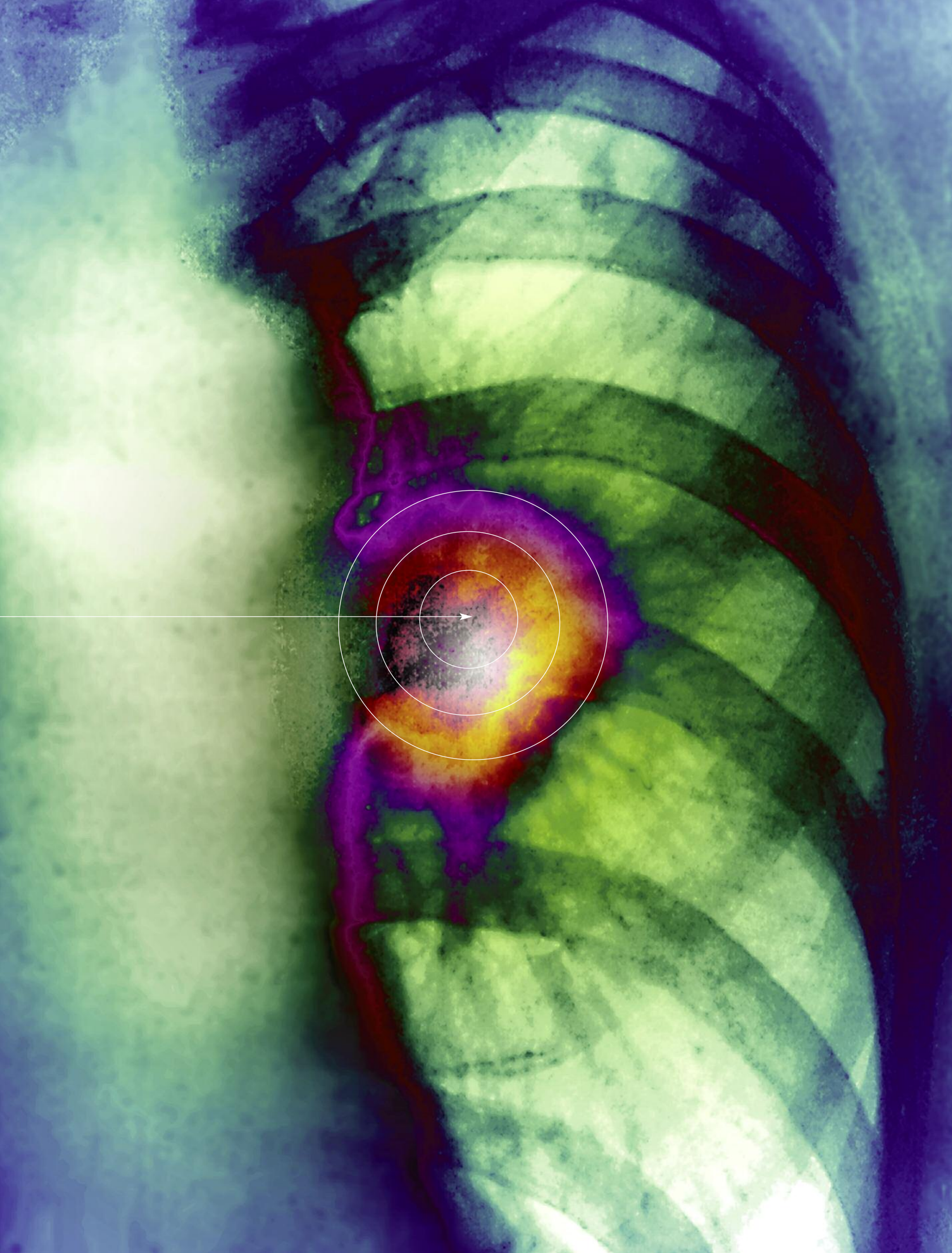
HITTING THE BULL'S-EYE

TARGETED CANCER THERAPIES BEGIN MAKING THEIR MARK



Pictured here: Colorized X-ray of a lung tumor.

Zephyr/Photo Researchers, Inc.



Alan Sandler, M.D., pulls up a slide on his computer screen that shows – in schematic fashion – the signaling pathways inside a malignant cell. At a glance, it looks hopelessly complicated. White arrows indicate the chain of communication between proteins; the arrows point here and there, crisscrossing the cell like strands of spaghetti left on a plate. "I'll give you a minute to jot this down," Sandler quips, adding that this line draws chuckles when he uses it during lung cancer seminars.

The image is actually an oversimplification of the molecules and pathways that "drive" the cancer cell and which are targets for the newest generation of anti-cancer drugs. Seventeen blue boxes on the slide list 29 different "targeted therapies" that are already approved or still in development, and where in the cell they act.

"The explosion of new drugs that are out there to study in cancer is astonishing," says Sandler, associate professor of Medicine and medical director of the Thoracic Oncology program at the Vanderbilt-Ingram Cancer Center. He recalls that in 1992, when he finished his fellowship, it was common not to even give chemotherapy to patients with metastatic non-small cell lung cancer because the benefit was still questionable.

Today, chemotherapy and targeted agents are extending life and offering hope to these very same patients.

"These are really exciting times in cancer therapy, especially for lung cancer," says David Carbone, M.D., Ph.D., Harold L. Moses Professor of Cancer Research at Vanderbilt-Ingram. "Ten years ago we had extremely limited options." Today, some of the new targeted therapies are "nearly miraculously effective."

Carbone cites the effects of the drug imatinib (Gleevec) in patients with chronic myelogenous leukemia and gastrointestinal stromal tumors, and the drug erlotinib (Tarceva) in select lung cancer patients. "It's like a Lazarus response," he says.

But as the number of new drugs climbs, so do the challenges in designing clinical trials to test the new therapies, selecting the patients who will most benefit from them, managing the costs of these drugs – thousands of dollars per month – and moving forward to develop drugs aimed at different targets in the cancer cell.

A RARE LEUKEMIA'S LESSON

The concept of a "magic bullet" to treat disease dates to the late 19th century.

"THESE ARE REALLY EXCITING TIMES IN CANCER THERAPY, ESPECIALLY FOR LUNG CANCER. TEN YEARS AGO, WE HAD VERY LIMITED OPTIONS."

Nobel laureate Paul Ehrlich, M.D., coined the term in reference to compounds that would seek out and destroy pathogenic microbes without harming the patient.

Targeted cancer therapies are envisioned as the "magic bullets" of cancer treatment. Ideally, they affect proteins and signaling pathways unique to malignant cells and leave normal cells alone.

While that ideal has not yet been achieved, the contrast to traditional chemotherapy is obvious.

"Chemotherapy drugs control the growth of cancer cells, but they do so in a way that's kind of like using a hammer to kill a housefly on a table. If you bang the table hard enough, you destroy the fly and the table too," says David Johnson, M.D., deputy director of Vanderbilt-Ingram and past president of the American Society of Clinical Oncology.

Likewise, surgery and radiation therapy can cause "tremendous collateral damage," although recent technological advances have dramatically improved both of these approaches, he says.

Among the first of the new targeted therapies was Gleevec, whose behind-the-scenes development was described in the book *Magic Cancer Bullet* by Daniel Vasella, M.D., chairman and chief executive officer of the pharmaceutical company Novartis.

Gleevec bounded onto the world stage in 2001, with accelerated approval from the Food and Drug Administration for the treatment of chronic myelogenous leukemia (CML).

The abnormality that causes CML – the so-called Philadelphia chromosome (named for the city in which it was discovered) – was first described in 1960. It results from a translocation, a rearrangement that fuses two genes from different chromosomes together. This in turn produces an abnormal protein, a tyrosine kinase receptor called bcr-abl, which drives cells to become leukemic. Drugs like Gleevec can inhibit the activity of the aberrant receptor, and thus block cancerous growth.

"Imatinib surprised everyone," says Mace Rothenberg, M.D., Ingram Professor of Cancer Research at Vanderbilt-Ingram. "Even the sponsor was surprised at how effective that drug was in causing complete hematologic and cytologic remissions, remissions where the Philadelphia chromosome disappeared.

"And this was done by a single pill whose main side effects were skin rash, some weight gain and some edema. This was remarkable."

In the last five years, investigators have discovered how some patients develop resistance to imatinib, by acquiring additional mutations in the bcr-abl receptor that hinder Gleevec binding. A newly approved drug called dasatinib (Sprycel) is able to bind to the mutated bcr-abl, overcoming resistance to Gleevec in patients with such mutations.

"Suddenly we have two highly effective therapies for CML," Rothenberg says. "This is like the grand slam home run."

But CML appears to be a simple cancer, primarily driven by one genetic mutation, he adds.

"What we're coming to realize is that the majority of cancers, especially solid tumors, tend to be polygenetic in origin," he says. "It's more than just a single dysregulated pathway, and so blocking a single pathway isn't really sufficient in the majority of cases to cause true tumor regression."

SIGNATURE RESPONSE

The more specific a targeted therapy is – in terms of its target – the more restricted is the patient population that benefits, Carbone says.

"The reality is that lung cancer is probably 10, 15, 20 different diseases, driven by different molecular mechanisms and combinations that we're just beginning to understand," he says. "If we could find what subpopulations of tumors are driven by particular pathways, then we could find drugs to target those pathways and they'd be very effective in that subpopulation."

Carbone's laboratory was the first to identify a mutation in the epidermal growth factor receptor (EGFR) that predicts which lung tumors will respond to drugs such as gefitinib (Iressa) and

erlotinib (Tarceva). In a manner similar to Gleevec, these drugs bind to and inhibit the receptor's abnormal tyrosine kinase domain.

"We noted very early on at Vanderbilt that some lung cancer patients had a great response, but most patients didn't," Carbone says. The EGFR mutation that his group found in a patient's tumor is found in about 10 percent of the U.S. patient population, and is "probably the best predictor of clinical response to these drugs."

But the single mutation identifies only the "fantastic responders," Carbone says. "Most studies are showing that there's a much bigger set of lung cancer patients who will benefit from these drugs."

Through the National Cancer Institute's Strategic Partnering to Evaluate Cancer Signatures (SPECS) program, Carbone and his colleagues are searching for the "molecular signatures" that will predict which lung cancer patients will benefit from Tarceva.

They have found eight proteins in the blood that together "really seem to identify patients who will live longer when they are treated with erlotinib," Carbone says. He presented the findings last June at the American Society of Clinical Oncology meeting in Atlanta.

These kinds of molecular signatures or "profiles" will be key to successfully using targeted therapies and moving them to earlier stages of treatment.

Clinical trials of new drugs start in the sickest patients – those with metastatic disease for which there is no known effective therapy. These patients have already endured the standard therapies, and the probability of *anything* working at that point is probably remote, Johnson says.

Unless the drug is tested first in patients in whom it is most likely to work.

This is what happened with the targeted therapy trastuzumab (Herceptin), which is directed against the HER-2 protein (a receptor similar to the EGFR). Herceptin first proved itself in clinical trials in the sickest patients whose tumors had high expression of HER-2.

It is now used as an adjuvant therapy – a treatment given usually after the main treatment, to boost its effectiveness – in breast cancer. Herceptin may never have reached that stage if patients in the early trials had not been "selected" for high expression levels of HER-2 in their tumors.

"If those initial trials had not been limited to patients with high HER-2 levels, it would have threatened the development of a drug that we know works as long as it is used against the right cancers," says Carlos Arteaga, M.D., Vice Chancellor's Professor of Breast Cancer Research at

One arrow's not enough

Think of targeted therapies as poison arrows piercing Achilles' heel.

There's validity to the idea that the new drugs "take advantage of our improved knowledge of the biology of cancer to exploit weaknesses in its defenses," says David Johnson, M.D., a lung cancer specialist at Vanderbilt-Ingram Cancer Center.

"But it's incredibly simplistic to assume that every cancer will have only one such vulnerability. Most cancers are far, far, far more complex than that and will likely require not just one arrow into the heel of Achilles, but multiple arrows."

Alan Sandler, M.D., of Vanderbilt-Ingram, and Roy Herbst M.D., Ph.D., of the University of Texas M.D. Anderson Cancer Center in Houston, are taking just such an approach. They are studying the impact of two targeted agents, bevacizumab (Avastin), which blocks blood vessel formation, and erlotinib (Tarceva), which inhibits the epidermal growth factor receptor, in treating non-small cell lung cancer.

The early results, reported last June at the American Society of Clinical Oncology meeting, suggest that the combination of the two targeted agents is nearly as effective in improving progression-free survival as Avastin combined with standard chemotherapy.

The median time to progression, the point at which half of the lung tumors began to grow again after treatment, was 4.4 months for Avastin plus Tarceva, compared to 4.8 months for Avastin plus chemotherapy, and 3.0 months for patients in the chemotherapy plus placebo group.

The study comes on the heels of a multi-center clinical trial led by Sandler that demonstrated that adding Avastin to the chemotherapy drugs paclitaxel (Taxol) and carboplatin in patients with advanced, non-squamous, non-small cell lung cancer improved median survival from 10.3 to 12.3 months. Additional data and analysis from that trial have been published in the *New England Journal of Medicine*.

"Two months may not sound like a lot," Sandler says, "but that's actually the first time in the front-line setting of non-small cell lung cancer that we've ever seen a targeted therapy improve survival, and it's the first time in 10-plus years that we've seen any agent show an additional survival advantage in this cancer."

Based on the work led by Sandler, Avastin was recently approved for use in advanced lung cancer. It's now time to study the drug in earlier stage disease, Sandler says, and to continue testing rational combinations of targeted therapies. To do that, "we're going to have to do a better job of enrolling patients in clinical trials," he adds.

"The cure for cancer could be sitting on a shelf somewhere, but if we can't study it, we're never going to know."

– LEIGH MACMILLAN

ANNE RAYNER

Alan Sandler, M.D.

THE NEXT TARGETED THERAPIES

WE'RE HITTING A PLATEAU and facing a gap of several years before the next targeted therapies emerge from pre-clinical and early stage clinical trials, says Mace Rothenberg, M.D., director of the Phase I Drug Development Program at Vanderbilt-Ingram.

"So far we've seen agents directed mainly at two molecular targets – the epidermal growth factor receptor and vascular endothelial growth factor," Rothenberg says. "We're now seeing the benefits of those drugs in many common cancers, and we're beginning to understand how best to utilize them. But we have to find new targets in order to make the next leap forward in our treatment."

He describes the new targets being explored in the Phase I program – proteins like transforming growth factor-beta, insulin-like growth factor receptor 1, src kinase, and toll-like receptor 9.

"From a clinical and translational perspective, these are both the best of times and perhaps the most challenging of times," Rothenberg says. "It's great to have these newer agents that are going to be novel and may allow us to make substantial progress in cancers where we haven't made much progress – like pancreatic cancer.

"But at the same time, they're being developed in a much more crowded field. It now becomes a challenge to rationally develop combinations that make both biological sense and have the best chances of making an impact on a therapeutic level."

Investigators will need to rely on "more robust animal models of human cancer," Rothenberg says, some of which are being developed at Vanderbilt, and on careful testing in patients.

"It's exciting to be at a place like Vanderbilt where there's an open dialogue between the clinicians and the basic scientists who have studied these agents in a pre-clinical setting," he says. "They are able to guide our decisions about what to look for in the tumor tissue and how to measure it.

"And ultimately we rely on cancer patients, who have been very willing to play an active role in our research. They want to help us understand the drugs, the cancer, and the biology better, even when it doesn't directly benefit them."

– LEIGH MACMILLAN

A QUIVER OF CANCER FIGHTERS

DRUG	APPROVED IN	FOR TREATMENT OF	BY TARGETING
Avastin	2004	colorectal cancer	VEGF*
	2006	lung cancer	VEGF
Erbitux	2004	colorectal cancer	EGFR
	2006	head and neck cancer	EGFR
Gleevec	2001	CML	bcr-abl
	2002	GIST*	c-kit*, PDGFR*
Herceptin	1998	breast cancer	HER-2
Iressa	2003	lung cancer	EGFR
Nexavar	2005	kidney cancer	Raf kinase*
Sprycel	2006	CML	bcr-abl
Sutent	2006	kidney cancer, GIST	VEGF receptor, PDGFR, c-kit
Tarceva	2004	lung cancer	EGFR

* VEGF – vascular endothelial growth factor; GIST – gastrointestinal stromal tumor; c-kit, Raf kinase – proteins linked to cancer growth; PDGFR – platelet-derived growth factor receptor.

Vanderbilt. "Herceptin alters the natural history of women with breast cancer over-expressing the HER-2 protein (by increasing their chances for survival)."

ARE THEY WORTH IT?

Targeted therapies come at a cost.

"The presumption is that targeted therapies will only cause good things to happen and not bad things. Sadly, that is not the case," Johnson says. He cites studies showing that long-term use of both Gleevec and Herceptin can cause heart failure.

And then there's the financial cost – up to $10,000 per month for the newest drugs.

"There's no rhyme or reason for the cost of cancer drugs in this country," Johnson says. "And what's interesting is that the drug gets the blame for being 'ineffective' because it only offers a two-week survival advantage. I'm not praising the drug for giving you two weeks of survival, but each of us knows that used in a more appropriate way, we can get these huge benefits that were seen with Herceptin."

The trouble, Johnson says, is the hype about the promise of these new drugs, which when apparently not met, creates disappointment and cynicism.

Carbone takes issue with the idea perpetuated in the lay press that the effectiveness of targeted drugs can be fully assessed by measures of median survival.

"It's extremely misleading to say that a drug only gives you a six-week survival difference, without any additional explanation," Carbone says.

Survival curves report a population average. About half of the patients will get no benefit at all and half will have "some benefit that's very real: the tumor shrinks by a measurable amount, the patients feel better, and they live longer," he says. About a quarter of the patients will have major shrinkage of the tumor, and in about 5 percent, the tumor will virtually disappear.

"For that 5 or 25 percent of patients, that's a heck of a lot more benefit than a six-week survival difference tells you about," Carbone says.

"The future is extraordinarily bright," adds Johnson, "if we can stay focused on the real ultimate object of our research and that's the human being – your sister, your husband, your mother, your child. That's the target." **LENS**

Turning genes on to turn cancer off

Last year, the drug decitabine (Dacogen) joined its sister molecule azacytidine (Vidaza) as an approved treatment for myelodysplastic syndromes – diseases of the blood-forming cells of the bone marrow that can progress to leukemias.

What's interesting about these two drugs is how they work: they both "turn on" genes that have been aberrantly silenced in cancer cells, putting them in a new class of drugs called "epigenetic therapies."

"Epigenetics" refers to the control of gene expression by mechanisms "in addition to" (from the Greek epi) the DNA sequence.

In general, chemical "tags," added like bracelet charms to DNA or to histone proteins around which DNA winds in the nucleus, regulate whether genes are expressed (turned on) or silenced (turned off). These epigenetic tags are influenced by the environment – hormone levels, diet, drugs – and can be passed to daughter cells during cell division.

They are key to cell identity – a stem cell does not turn on the same genes as a mature brain cell, for example – and they change with time. A study published in 2005 by Manel Esteller, M.D., Ph.D., and colleagues at the Spanish National Cancer Center in Madrid showed that identical twins who share the same genome are "epigenetically indistinguishable" in their early years. But as they age, their epigenetic tags diverge, potentially explaining differences in disease susceptibility.

Epigenetic changes are increasingly being linked to cancer.

"Almost all cancers that have been studied have an epigenetic component to them," says Peter Jones, Ph.D., director of the University of Southern California/Norris Comprehensive Cancer Center in Los Angeles.

The best-characterized epigenetic change in cancer is the "hypermethylation" of promoter regions – the addition of many chemical "methyl" groups to the areas of DNA that control gene expression.

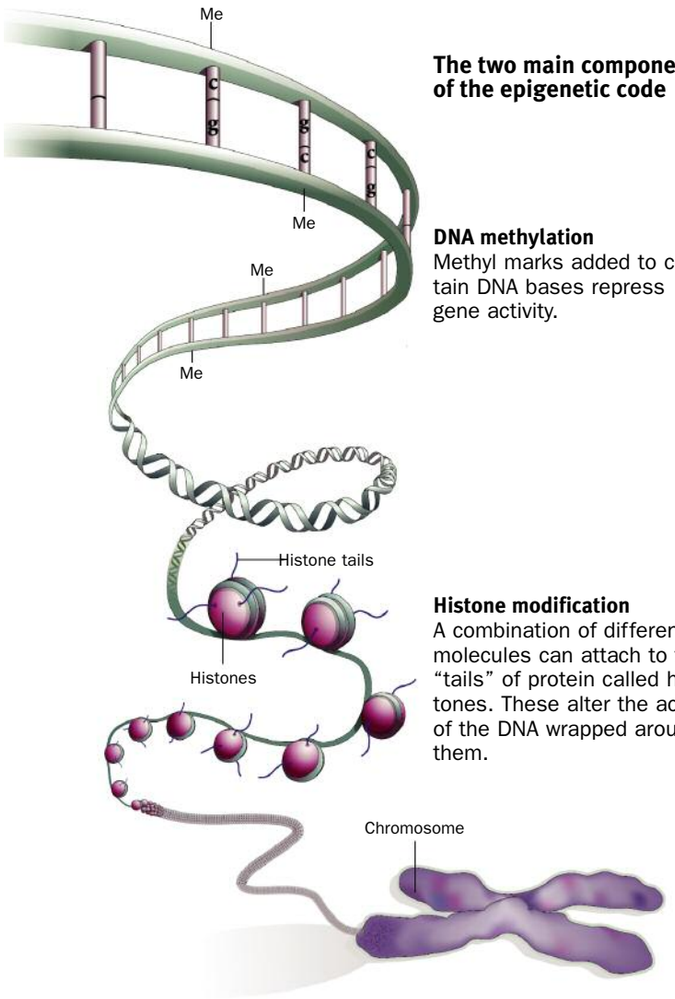
Hypermethylation inappropriately silences genes, particularly so-called tumor suppressor genes that normally put the brakes on uncontrolled cell growth. Mutations in the DNA sequence of such genes cause inherited forms of cancer. And now we know that silencing of the same genes by hypermethylation can also cause sporadic forms of cancer, Jones says.

The good news, he adds, is that an epigenetic modification like hypermethylation is "a treatable defect." That's where the drugs Vidaza and Dacogen come in, reversing the hypermethylation and turning silenced genes back on.

Jones demonstrated this mechanism in 1980. He and colleagues had shown first that Vidaza and related drugs could turn on genes, and later that they did so by inhibiting DNA methylation.

"When those two processes were tied together, it gave people a tool to really start looking at the relationship between gene expression and DNA methylation," Jones says.

Vidaza and Dacogen are now joined by a lengthy list of DNA methylation inhibitors and chromatin-modifying drugs that are in preclinical and clinical testing. Chromatin is the DNA-histone protein complex.



The two main components of the epigenetic code

DNA methylation
Methyl marks added to certain DNA bases repress gene activity.

Histone modification
A combination of different molecules can attach to the "tails" of protein called histones. These alter the activity of the DNA wrapped around them.

"We're just beginning this era of epigenetic drugs," Jones says.

DNA methylation and other epigenetic "biomarkers" may also be useful for early cancer detection, diagnosis and prognosis.

Wael El-Rifai, M.D., Ph.D., and colleagues at the Vanderbilt-Ingram Cancer Center have noted DNA hypermethylation of several genes in Barrett's esophagus – a change in the cells lining the esophagus that can progress to esophageal adenocarcinoma. The frequency of hypermethylation increases as the cells progress from Barrett's esophagus to dysplasia (pre-cancerous condition) to adenocarcinoma.

"Promoter DNA hypermethylation is an early change in tumorigenesis, and it's a progressive one," says El-Rifai, professor of Surgery and Cancer Biology.

It's now time, Jones and other contend, to engage in a Human Epigenome Project, an effort to identify and understand all of the chemical tags that coordinate expression of genes.

"It's critically important that we understand the human epigenome: it's at the heart of what stem cells are, it's an essential component of aging, and it's of major importance in human diseases, particularly cancer," Jones says. "We're going ahead full speed."

– LEIGH MACMILLAN

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Photo by Jared Leeds

THE GREAT AMPLIFIER

ERIC LANDER'S AUDACIOUS THINKING MAY HELP CRACK THE CODE OF CANCER

Eric Lander, Ph.D., strides down a sun-drenched hallway to yet another research meeting in the genome center he directs, his face beaming with purpose and excitement. His bear-like handshake radiates strength; his patience is easily taxed by the pedestrian and the hesitant. But he is anything but intimidating. On the contrary, his sparkling blue eyes and easy smile convey a warmth and vitality that are often described as infectious. A driving force behind the sequencing of the human genome, Lander is now tackling the "cancer genome." He and his colleagues around the country are out to redefine tumors by the genetic changes that trigger their malignant growth, rather than by where in the body they strike.

BY BILL SNYDER

Within 15 years, he predicts,

"every patient in the clinic (will) have a complete genomic workup … for a couple of hundred dollars per patient." Their doctors will be able to determine the precise genetic characteristics of their illnesses, and therefore which treatments are most likely to be successful.

"I don't want to pretend that having such a comprehensive description of human disease automatically gives us therapies," says Lander, the dynamic founding director of the Broad Institute of the Massachusetts Institute of Technology (MIT) and Harvard University. "There's still a tremendous amount of work.

"But I can't imagine how we're ever going to make therapies for these diseases without actually knowing what's wrong."

In 2005 a panel led by Lander and Nobel laureate Leland Hartwell, Ph.D., president and director of the Fred Hutchinson Cancer Research Center in Seattle, proposed a 10-year, $1.5 billion effort, called The Cancer Genome Atlas project, to identify the major mutations in human cancer. A three-year, $100 million pilot to test the project's feasibility is currently under way.

While federal health officials hail the initiative as the beginning of a new era in cancer diagnosis and treatment, others complain that it will divert limited research funds from equally important cancer projects (*See "Bonanza or boondoggle?" on page 21*).

Those who know Lander, however, are hesitant to doubt him.

"People will say, 'Oh well, Eric says this is going to happen, but you know … (it) doesn't,'" says Oxford University geneticist Kay Davies, D.Phil., who has made key contributions to understanding Duchenne muscular dystrophy. "But then three years later, it does happen."

"I've worked with a lot of smart people, but we're talking about a difference in kind," adds Fintan Steele, Ph.D., director of Scientific Education and Public Communications at the Broad *(pronounced "Brode")* Institute. "He's a force of nature."

Tom Sawyer approach

Lander, who turns 50 this year, is perhaps the world's best known mathematician-turned-geneticist.

The former Rhodes Scholar and MacArthur Fellow established and directed one of the five centers primarily responsible for completing the Human Genome Project.

While hundreds of scientists contributed to this landmark achievement, "he certainly was one of the leaders in … starting to turn out the sequence on a large scale," says Philip Green, Ph.D., professor of Genome Sciences at the University of Washington in Seattle, who worked with Lander in the late 1980s.

"That took a lot of organizational skill and fairly aggressive approaches," Green continued, "to really acquire the resources and motivate the people in his group to get going on that."

"You know Tom Sawyer getting everybody together to paint the fence? That's Eric," says Lander's younger brother Arthur, laughing. "He can get groups of people to do enormous amounts of work and thank him for it."

The ability to inspire others actually may be Lander's greatest talent, and his most enduring legacy.

Eight hundred scientists actively contribute to the Broad Institute's projects, of which the cancer genome is one of a dozen. When they congregate for coffee, they're more likely to discuss a colleague's latest paper in *Nature Genetics* than the sports pages of the *Boston Globe*.

"This is the truly important work for our generation in science," enthuses Mark Daly, Ph.D., an assistant professor of Medicine at Harvard Medical School who has worked with Lander since he was a freshman at MIT 20 years ago. "We have an unswerving belief that this is the work that is going to make a difference in medicine in the future."

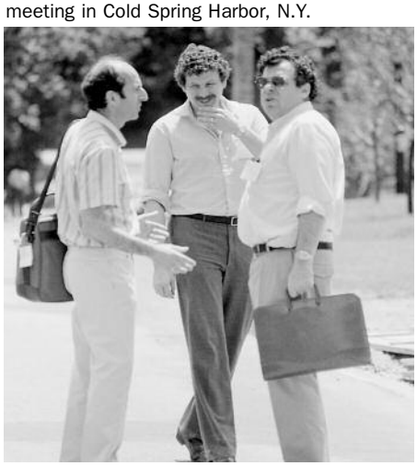
Lander's "big science" approach to cancer has its share of critics, among them Nobel laureate Sydney Brenner, D.Phil.

Even though he was an early proponent of what would become the Human Genome Project, Brenner worries that

Eric Lander (third from left) poses with other members of the Stuyvesant High School math team in 1974. To Lander's right are Jesse Deutsch and teacher Irene Finkel; to his left are Francis Barany, Kelly Pan and Paul Zeitz.

Photo by James Hamilton

Lander (center) chats with David Botstein, Ph.D., (right) and Marc Fellous, M.D., Ph.D., of INSERM, the National Institute of Health and Medical Research in Paris, during a 1986 meeting in Cold Spring Harbor, N.Y.



Lander listens intently to Oxford University's Kay Davies, D.Phil., during the 1986 symposium, which debated the feasibility of sequencing the human genome.

Middle and right photos courtesy of the Cold Spring Harbor Laboratory Archives

investment in expensive technology is now driving the research agenda, rather than the other way 'round.

During a lecture at Vanderbilt University last fall, the Oxford-trained geneticist joked that he would like to buy Lander's gene sequencers "and throw them into the sea. That would be the inverse of the Boston Tea Party."

Yet for Lander, big science is not about the machines.

"It's about taking on the responsibility of creating datasets of tools, and then putting them in the hands of thousands of young scientists who make them 50 times more efficient," he says.

"So it's always 'big science' in the service of the individual investigator. That was what the Human Genome Project was about … And that's what the projects going on here on inherited genetic variation of disease, on cancer, on evolution, on infectious disease – all of them share that role.

"We're playing a great amplifier … We're trying to empower a generation of remarkable scientists who really want to take on the important problems in disease."

Productive collisions

Empowering remarkable people has been a hallmark of Lander's life, at least as far back as high school.

Lander and his brother – now chair of the Department of Developmental and Cell Biology at the University of California, Irvine – grew up in the Flatlands section of Brooklyn.

Their parents were lawyers, but their father, Harold, became disabled from multiple sclerosis and died when Eric was 11 and Arthur was 10. Pitching in to help with housework and home repairs, the boys early on developed a strong sense of initiative.

Their mother, Rhoda, who died two years ago, told the *Boston Globe Magazine* in 1999 that she was mystified by her sons' achievements. "They did their thing, and then I paid the bills," she said.

Pursuing an early interest in mathematics, Eric enrolled in Stuyvesant, one of New York's premier math and science high schools, and became a leader of Stuyvesant's celebrated math team.

At age 17, he won the Westinghouse Science Talent Search prize for a paper on "quasi-perfect" numbers, but he was much more than a math whiz, recalls former math teammate Kelly Pan.

"Eric has what is probably unusual in the field of math, a very outgoing personality," says Pan, who went on to earn an MBA and who now runs an investment management firm, Pantheon Capital Management, in Manhattan. "He reaches out to people and is always very willing to share what he knows."

In 1974, Lander enrolled at Princeton University, where he earned his bachelor's degree in math with highest honors. He also met his future wife, Lori, in a constitutional law class their sophomore year. Married since 1981, the Landers have three children: Jessica, 19, Daniel, 15, and David, 12.

Lander describes his life as if he were an atomic particle, bouncing randomly into key people. Not knowing what he wanted to do after earning his doctorate in mathematics from Oxford, he went to Boston, he says, "because the probability of productive collisions was higher."

He joined the faculty of the Harvard Business School, where he taught courses in business management and negotiation. Meanwhile his brother, who at the time was earning his M.D. and Ph.D. degrees at the University of California, San Francisco (UCSF), urged him to switch to the life sciences.

"Even in high school, he'd had an affinity for genetics," Arthur Lander recalls. "Lots of mathematicians like genetics. It really fits with the mathematical view of the world."

Lander took a few courses, and learned fruit fly genetics at Harvard. He also worked with MIT biologist Robert Horvitz, Ph.D., who would share the 2002 Nobel Prize with Brenner and John Sulston, Ph.D., for their ground-breaking studies of organ development and programmed cell death in the round worm, *C. elegans.*

Then in 1985, in one of those productive collisions, Lander bumped into MIT geneticist David Botstein, Ph.D.

Up to the task

Five years earlier, in a pivotal paper, Botstein and his colleagues Ronald Davis,

How to crack the cancer code

In 2003, 13 years and $2.6 billion after it started, the Human Genome Project completed the sequence of nearly all of the 2.9 billion letters of genetic code that make up the human being.

Now researchers are tackling what may be an even more ambitious challenge – developing an "atlas" that describes the genetic characteristics of the more than 200 different types of cancer.

Last fall the National Cancer Institute and the National Human Genome Research Institute announced that lung, brain (glioblastoma) and ovarian cancers will be studied during a three-year pilot to determine the feasibility of a full-scale Cancer Genome Atlas project.

Patients will be asked to donate a small portion of tumor tissue that has been removed as part of their treatment. The biospecimens will be processed at a central facility, and distributed to cancer genome characterization centers, which will determine which genes are selectively turned on or off in the tumors.

Genome sequencing centers will conduct further investigations, looking for changes in the DNA sequence that may be associated with specific cancer types. This information will be entered into public databases so that researchers ultimately can use it to improve cancer diagnosis, treatment and prevention.

The attempt to redefine cancer by its genetic code has been made possible by phenomenal technological advances during the past two decades.

In the mid-1980s, a scientist could spend a day determining the sequence of 50 to 100 nucleotide bases, the four "letters" (adenine, guanine, cytosine and thymine) that make up the DNA code, at a cost of $10 per base.

The current generation of sequencing machines can sequence 1 million bases a day for about 50 cents a base. A new generation of machines – now being tested – may increase the output to 500 million bases a day at a cost that is 100 times lower.

The machines are not cheap, however. Both the current and new machines cost about $300,000 each.

To succeed, The Cancer Genome Atlas project must push the technology even further so that researchers can decipher the complex genetic and molecular interactions that underlie malignant growth, and at a reasonable cost.

– BILL SNYDER

For more information, go to http://cancergenome.nih.gov.

"And he's here (in the lab) with all of these young, very bright people … who don't want to go home they're so excited … We're blown away."

Ph.D., of Stanford and Mark Skolnick, Ph.D., and Ray White, Ph.D., of the University of Utah had proposed a method to map the entire human genome using restriction fragment length polymorphisms or RFLPs.

RFLPs are pieces of DNA that have been sliced apart by restriction enzymes. In 1978, researchers at UCSF discovered that one of the restriction fragments from patients with sickle-cell anemia differed in length from normal fragments from people without the disease.

Botstein and his colleagues reasoned there were many such genetic differences between individuals. Most were probably innocuous, but theoretically they could be used as markers to create a map of the entire human genome.

Mathematical methods available at the time, however, were not up to the task of unraveling the intricate web of genetic interactions that contribute to complex disorders like cancer or diabetes.

"It became clear that what was needed was somebody to think about this problem who had mathematical tools beyond what I knew," says Botstein, now director of Princeton's Lewis-Sigler Institute for Integrative Genomics.

So he asked around and eventually was directed to Lander. Within a week of their meeting, "we had a lot of stuff worked out," Botstein recalls.

Thus began what Lander happily describes as his "chaotic career path."

In 1986, on Botstein's recommendation, Nobel Prize-winning virologist David Baltimore, Ph.D., invited Lander to become a fellow of the Whitehead Institute for Biomedical Research in Cambridge.

"When I met Eric, I knew immediately that he had enormous potential," says Baltimore, the institute's founding director, who went on to become president of the California Institute of Technology (Caltech).

The next year, Lander received a five-year MacArthur Foundation "genius grant" to support his innovative application of statistics to the study of genetics.

Meanwhile, he and Botstein churned out half a dozen papers detailing their methods for mapping complex genetic traits. With the help of Philip Green, who, like Lander, was a mathematician-turned-molecular biologist, they put those methods to work at a Massachusetts biotechnology company called Collaborative Research Inc.

"What the company was trying to do was to identify lots of these RFLP markers and then determine where they were on the chromosomes by finding their locations relative to each other," Green recalls. This approach was called genetic linkage mapping.

At the time, researchers could map only three or four markers at a time. Green and Lander met frequently to discuss ways to construct maps with many more markers, and independently developed software programs to implement their ideas.

In 1987, the team, led by Collaborative Research senior researcher Helen Donis-Keller, Ph.D., published the first genetic linkage map of the human genome.

"He certainly is competitive," Green says his former collaborator. "That can create a tension because you're both collaborating and competing in a sense at the same time, trying to come up with ideas first. But overall, you get past that, and I actually think competition really drives science."

In 1990, the National Institutes of Health (NIH) and Department of Energy (DOE) officially launched an ambitious international effort – dubbed the Human Genome Project – to determine the sequence of every human gene.

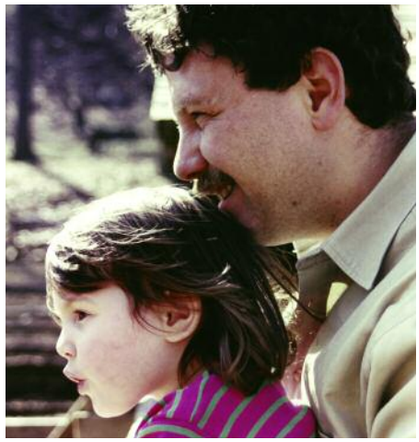
That year Lander, a recipient of one of the project's first grants, founded the Whitehead Institute/MIT Center for Genome Research to exploit recent advances.

Among them: automated DNA sequencing machines, and "shotgun" sequencing, in which randomly sliced up fragments of DNA are cloned and sequenced, and – with the help of powerful computer programs – pieced back together in proper order.

Others were racing to embrace the new technology. In 1998, former NIH scientist Craig Venter, Ph.D., shocked the scientific world when he announced that his new company, Celera, would sequence the human genome by 2001 – several years earlier than the target date set by the Human Genome Project.

Urged by Lander, among others, the public effort reorganized its priorities to produce a rough draft sequence first and a final finished product later.

Lander's center became the largest of the project's top five gene-sequencing operations. The others were Washington



Eric Lander shows photos he's taken of Masai children during a trip to Kenya (at left); he and Daniel prepare to feast on chili crabs in Singapore (below left); and he shares a quiet moment with Jessica, now 19 (below).

Photos courtesy of the Lander family

University in St. Louis, Baylor College of Medicine in Houston, the DOE Joint Genome Institute and the Wellcome Trust Sanger Institute near Cambridge, England.

In June 2000, the race ended in a "tie:" Celera and the Human Genome Project jointly announced working drafts of the human genome sequence. The public genome project went on to complete a final sequence three years later.

Blown away

In October 2001, Lander and his colleagues were filling in the gaps in the sequence when Eli Broad called him up, and asked if he and his wife Edythe could visit his lab during a visit to Cambridge.

Broad, founder of two Fortune 500 companies and a Caltech trustee, previously had been introduced to Lander by Baltimore. Through their foundations, Broad and his wife had made major contributions to the arts and education, and recently had begun to support medical research.

"This was Saturday," Broad recalls. "So my wife and I go to see his lab and we're blown away by 140,000 square feet of robotics and computers working 24 hours a day decoding the human genome.

"And (Lander's) here with all these young very bright people from Harvard Medical School and MIT who don't want to go home they're so excited."

Asked what he wanted to do once the sequence was completed, Lander said he'd like to apply the new knowledge to help patients. "That whole notion appealed to me," says Broad, who began talking to officials at Harvard and MIT.

In June 2003, Broad and his wife announced a $100 million gift to establish the institute that bears their name. Eighteen months later, they doubled their philanthropy to $200 million.

Within their sparkling labs near the MIT campus, institute researchers are applying genomic tools to better understand a wide range of ailments, from malaria and tuberculosis to psychiatric disorders, diabetes – and cancer.

Cancer lends itself to genomic investigations because it's a genomic disease, Lander explains.

"We're not talking about common, pre-existing genetic variations," he said. "We're talking about new mutations that arise in each tumor.

"So once you have a sequence of the human genome, you can then ask, 'How does (this tumor) differ amongst 400 lung cancers?' And in each case you are comparing it to the normal genome that the person started with.

"There's background noise; there are (random) changes that occur. But … if you see a gene mutated 10 percent of the time, that's no accident," Lander says. "It must be playing an important, causal role. So by simply collecting enough data, the genome should be willing to tell us which genes matter."

Lander shrugs off criticism that The Cancer Genome Atlas project is too expensive or simply can't be done. The proposed cost would be less than 3 percent of the National Cancer Institute's budget, he notes. And, the technological hurdles will be overcome. The important thing is to nurture visions of what might be.

"What's the biggest product of this place? It's scores of people who have come out of the genome center and the Broad Institute who … (are) willing to work together, to do the heavy lifting necessary to change the world," Lander says.

"It's faith, a confidence that the way to change the world is to get information and tools into the hands of as many people as rapidly as possible." **LENS**

Bonanza or boondoggle?

Can the sequence of the human genome be used to find genes that cause cancer?

A study published last fall in the journal *Science* suggests that it can.

Researchers at Johns Hopkins University in Baltimore, compared the protein-coding regions of genes in 22 samples of breast and colorectal cancer to the corresponding "normal" sequences. After eliminating errors and normal variations, the study yielded 189 candidate cancer genes, most of which had never been seen in tumors before.

Francis Collins, M.D., Ph.D., director of the National Human Genome Research Institute, called the study "a big shot in the arm" for The Cancer Genome Atlas project.

Not so fast, say other scientists who believe the sequencing project is misdirected, premature and too expensive.

Jonathan King, Ph.D., professor of Molecular Biology at MIT and a founder of the Council of Responsible Genetics, worries that the emphasis on genetics has overshadowed prevention.

"I'm not arguing against getting all of the information we can about the nature of tumors," King says. "But the information collection should not take the form that obscures the basic fact: most human cancers are caused by carcinogens that act on you in your lifetime.

"Recognition that carcinogens damage the genes in tumor cells opens the avenue to prevention as a major anti-cancer strategy," he says. "At the present time, however, research in this area is totally inadequate and woefully underfunded, and has almost disappeared."

Margaret Spitz, M.D., professor and chair of Epidemiology at the University of Texas M.D. Anderson Cancer Center in Houston, disagrees.

"Most of the really important environmental causes of cancer have been identified," says Spitz, who serves on the National Cancer Institute's Board of Scientific Advisors and who was a member of the working group that recommended The Cancer Genome Atlas project.

"But the epidemiologic focus should now be on studying these exposures in the context of the genetic background of the subjects," she says. "There are good epidemiologic studies ongoing. Of course, we should fund more, but we don't have unlimited resources."

That's worth emphasizing, particularly since the technology required by The Cancer Genome Atlas project hasn't been developed yet.

"There's no way they can afford even for over a billion dollars to screen all the genes in all the tumors they want," says Mark Skolnick, Ph.D., whose team at the University of Utah and Myriad Genetics cloned and developed diagnostic tests for the breast and ovarian cancer genes BRCA1 and BRCA2.

"But they know the cost of sequencing went down a thousandfold during the time of the Human Genome Project, and they expect it to go down a thousandfold again," Skolnick says. "… So they're going to push the frontier."

– BILL SNYDER

in the BEGINNING

What developmental biology can teach about cancer

BY MELISSA MARINO

IT COULD BE NATURE'S CRUELEST JOKE – the molecules that give us shape at the beginning of our life also can lead to the end of it. ¶ The genes and proteins that help sculpt a single cell, the fertilized egg, into a complex multicellular organism are also responsible for the birth of many cancers. ¶ This link between embryogenesis and tumorigenesis has been suspected for more than a century, but only within the last 20 years have the striking molecular similarities between these two monumental events come into focus.

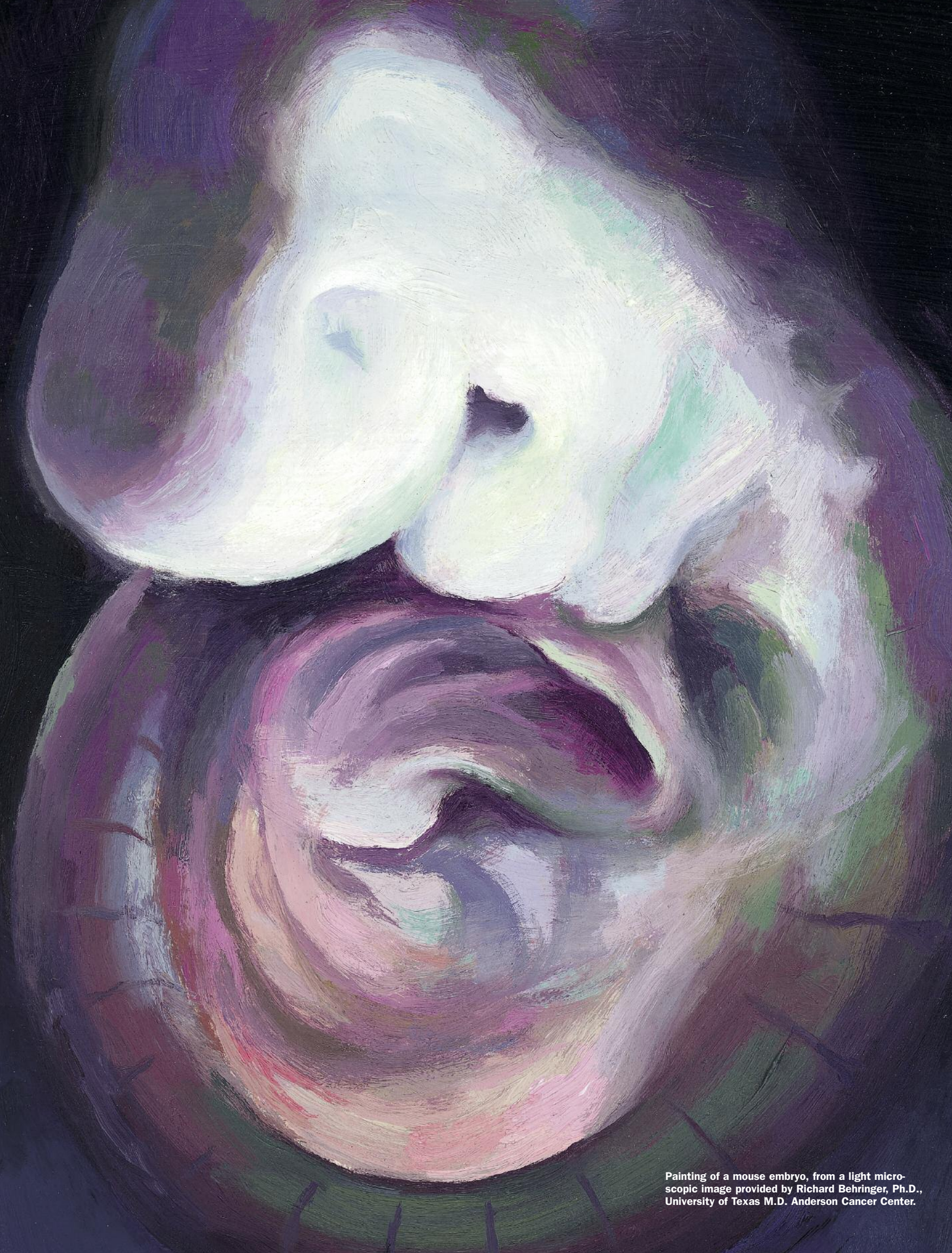
Illustration by Allen Garns

"These developmental molecules that cell biologists know and love – our favorite proteins that operate in the early embryo – are the same molecules that seem to go haywire in cancer," says Jason Jessen, Ph.D., assistant professor of Medicine and Cancer Biology at Vanderbilt University Medical Center.

The rapid and exponential cell division, differentiation and cell movements that characterize embryonic development bear a close resemblance to those involved in tumor initiation and metastasis.

"It does make sense because in the developing embryo, so many things are happening: cell migration, cell specification, cells interacting with each other," Jessen says. "So, if those proteins get activated in an adult cell, it's no wonder it can have dire consequences."

Definitive links between the two processes have been a long time coming, mostly because of the academic divide between the separate cultures of developmental biology and cancer research. Now that divide is beginning to close.



Painting of a mouse embryo, from a light microscopic image provided by Richard Behringer, Ph.D., University of Texas M.D. Anderson Cancer Center.

One of the first links between cancer and embryogenesis was made in the early 1980s.

Roel Nusse, Ph.D., and Harold Varmus, M.D., identified a cancer-causing "oncogene," which they called int-1, in a mouse model of breast cancer. When int-1 is activated or turned on by the "integration" (thus its name) of a mouse mammary tumor virus into its DNA, a tumor forms.

Around the same time, Christiane Nusslein-Volhard, Ph.D., and Eric Weischaus, Ph.D., who were studying development of the fruit fly, *Drosophila*, found that a gene they called wingless was involved in setting up the polarity of the embryo. When the protein encoded by the gene is defective, the fly fails to develop proper body segment boundaries – and wings.

Nusse and colleagues soon determined that the two seemingly unrelated genes were homologs – genes similar in structure, function and evolutionary origin, and found throughout the animal kingdom. So the names (int-1 and wingless) were combined, and Wnt was born.

"I can imagine that they were thinking: 'What in the world is this cancer protein doing in a Drosophila embryo?'" says Jessen. "It's a classic example of the two worlds coming together."

Wnt is probably best known for its involvement in one of the earliest aspects of development, the formation of the primary body axis.

"You have a ball of cells, and somehow this signal tells the ball of cells which parts form the head and which form the tail," says Ethan Lee, M.D., Ph.D., assistant professor of Cell and Developmental Biology at Vanderbilt who studies the Wnt pathway in frog (*Xenopus*) embryos.

In 1989, Andrew McMahon, Ph.D., and Randall Moon, Ph.D., demonstrated that injection of the int-1 (Wnt-1) gene into Xenopus embryos induced the formation of a secondary axis, resulting in a two-headed tadpole.

"This was critical because it was the first biological assay for int/Wnt-1, and it linked a proto-oncogene to a developmental process," Lee says.

This multipart pathway has a number of other developmental roles in patterning the brain, heart and limbs and possibly in stem cell differentiation. Additionally, mutations that activate the Wnt pathway have been linked to cancers of the colon, skin, blood, liver and several other tissues.

One of the strongest links between Wnt and cancer was revealed with the discovery that mutations in the APC (adenomatous polyposis coli) gene – a component of the Wnt pathway – were required for the initiation of colon tumors.

Researchers have already identified more than a dozen Wnt ligands (proteins that bind Wnt receptors and initiate signaling), and new components of the pathway are being cloned and added to the already complicated system at a rapid pace.

"It really looks like a mess," Lee says. "I would say we are basically 'stamp collecting' right now, putting together a picture that is very complex."

Finding the switch

To make sense of the overwhelming data on this pathway, Lee and colleagues developed a mathematical model to examine how the pathway is regulated. They found that a protein called axin may be the limiting factor.

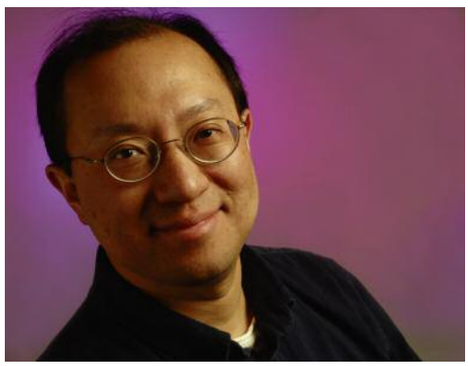
"Based on the model, we can propose that controlling axin levels and its turnover is the major way by which the pathway can be regulated," Lee says. "Perhaps that is the way the pathway can be turned on or off.

"Interestingly, the genes that this pathway turns on are classic examples of proto-oncogenes," he says. Researchers believe that if they could find a way to selectively switch the pathway "off," they could halt tumorigenesis.

Toward that goal, Lee and colleagues are taking advantage of high-throughput screening methods and an in vitro model based on extracts of *Xenopus* embryos that Lee developed as a postdoctoral fellow.

"We were able to recapitulate the pathway in a test tube," says Lee. This method provides an efficient tool to screen for molecules that either inhibit or activate the pathway.

"We're now using this assay to do drug screens," Lee says. "The idea is that if any of these molecules work out, they could be



At Vanderbilt University Medical Center, Ethan Lee, M.D., Ph.D., (top) Jason Jessen, Ph.D., (far left) and Michael Cooper, M.D., (left) are studying the striking similarities between the development of an embryo and the growth of a tumor. The two fields "have intersected in a wonderful way," says Cooper.

Photos by Anne Rayner

used as tools to study the pathway – and further down the line, as potential drugs to inhibit the pathway."

Lee is screening the large catalog of small molecules available through the Vanderbilt Institute of Chemical Biology, as well as extracts from medicinal plants and herbs through Harvard University's high-throughput screening facility.

Although currently there are no chemotherapeutic drugs that specifically inhibit the Wnt pathway, pharmaceutical and biotech companies have taken an interest.

"In the future, I think you'll see more companies targeting developmental pathways with the realization that they play a role in cancer," Lee predicts.

Jessen is also attempting to unite the worlds of developmental and cancer biology with the help of a tiny tropical fish.

Zebrafish have a long history in developmental biology research. Their embryos are transparent and develop outside the mother. They also develop rapidly and are inexpensive to maintain, making zebrafish embryos an efficient model for studying genetic and environmental factors that influence early development.

While indispensable for development research, they haven't been widely used in cancer research – yet.

As a postdoctoral fellow in the lab of Vanderbilt developmental biologist Lila Solnica-Krezel, Ph.D., Jessen realized that one of the key developmental events he was studying in zebrafish – gastrulation – might offer some insights into the aspect of cancer that is the most deadly – metastasis.

Cell migration

Gastrulation is a time in early development when an initially amorphous ball of cells begins taking on its adult shape due to rapid and extensive cell movements. Metastasis also is characterized by cell movements – cancer cells break off the primary tumor and spread throughout the body.

"My main interest is trying to understand the fundamental migratory differences between metastatic (invasive) tumor cells and primary (non-invasive) tumors," Jessen says. He is currently searching for molecular signals in the Wnt pathway that might underlie cell motility during both metastasis and zebrafish gastrulation.

A major goal of the Jessen lab is to develop a model of melanoma, a deadly form of skin cancer, by transplanting human melanoma cells into zebrafish embryos. The idea of using the zebrafish

Embryo's cellular 'dance' may choreograph cancer, too

One of the classic examples of aberrant activation of a developmental pathway in cancer is the APC gene, a component of the Wnt signaling pathway.

People with mutations in this gene, named for adenomatous polyposis coli, a pre-cancerous polyp found in the colon, have a high risk of developing colorectal cancer at a young age.

Prostaglandins appear to be involved. Researchers at Vanderbilt University Medical Center and elsewhere have found that drugs like aspirin, which interfere with prostaglandin signaling, can reduce colorectal cancer risk by up to 50 percent.

"We've been on a quest for the last 10 years to understand why such a simple drug leads to such a significant reduction in cancer risk," says Raymond DuBois, M.D., Ph.D., director of the Vanderbilt-Ingram Cancer Center.

Developmental biology may help solve the mystery.

Prostaglandins are hormone-like substances involved in a wide range of physiological functions, including pain, inflammation and, in the case of a particular prostaglandin, PGE_2, colorectal cancer.

Last year, Vanderbilt researchers led by DuBois and Lilianna Solnica-Krezel, Ph.D., professor of Biological Sciences, identified a new role for prostaglandins in early embryogenesis.

They found that prostaglandins help choreograph the intricate cell movements during the gastrulation phase of early embryonic development in zebrafish.

Treating zebrafish embryos with an inhibitor of PGE_2 synthesis slowed down the cell movements of gastrulation.

Blocking one of the prostaglandin receptors, EP4, caused similar abnormalities. The shapes and trajectories of embryonic cells were normal; they simply moved much more slowly.

This suggested that prostaglandin signaling through the EP4 receptor regulates the speed of cell movements during gastrulation.

The results highlight how perturbations in this pathway might influence the spread of cancer as well as development.

"The movements that happen in cancer might be, to some extent, recapitulation or modification of the normal migratory program that happens during normal development," Solnica-Krezel says.

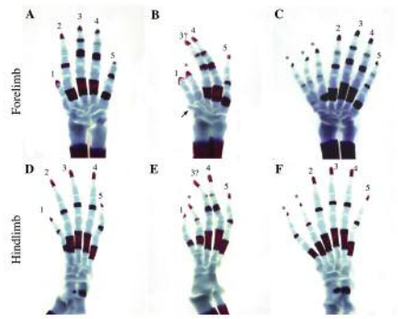
In 2005, researchers at the National Institutes of Health reported a direct link between the Wnt pathway and prostaglandin signaling. PGE_2 increased the transport of Wnt-associated transcription factors into the nucleus of cultured colorectal tumor cells and enhanced proliferation.

"Understanding the role of the newly defined PGE_2- regulated transcription factors and gene products may reveal additional therapeutic targets," DuBois wrote in a commentary on the NIH study.

Together, these two studies show that prostaglandins could regulate two cell activities, cell proliferation and movement, involved in tumor formation and metastasis, respectively.

Their results could help explain how prostaglandins influence the development of colorectal cancer, and provide clues about the chemopreventive effects of non-steroidal anti-inflammatory drugs like aspirin.

– MELISSA MARINO



POINTING THE WAY TO CANCER
Researchers at Vanderbilt University Medical Center have found that attachment of cholesterol to Sonic hedgehog, a mammalian version of the Hedgehog protein, controls finger and toe development in mice. The paws of a normal mouse embryo are shown in panels A and D. Mice lacking cholesterol-modified Sonic hedgehog (panels B and E) have malformed digits, while those expressing half the amount of Sonic hedgehog without cholesterol (panels C and F) develop extra, ectopic digits. In addition to directing development, the Sonic hedgehog pathway – named for the video game character – is also involved in a number of human conditions, including cancer.

Image courtesy of Chin Chiang, Ph.D., associate professor of Cell and Developmental Biology at Vanderbilt. From Yina Li, et. al., *PNAS USA*, April 25, 2006; 103(17):6548-53.

embryo to model a disease that afflicts humans is very exciting, Jessen explains.

"We can manipulate the embryonic environment to determine what kind of environmental cues (such as the Wnt pathway) might influence tumor cell migration."

An added benefit of zebrafish cancer models is the ease and cost-effectiveness of doing in vivo drug screens.

"What's interesting is that fish tumors look very similar to human tumors," Jessen says. "And you can bathe (zebrafish embryos) in chemicals and look for molecules that inhibit or promote growth of the tumor."

Jessen is also combining developmental biology and cancer research through a more traditional approach, using the zebrafish embryo to determine how proteins associated with cancer and metastasis regulate cell migration normally, such as during gastrulation.

"It is important to remember that for the majority of cancer proteins, we know very little about how these proteins function to control basic cellular activities such as motility," Jessen says.

While both cancer and development are exceedingly complex processes, insights about developmental pathways like Wnt are slowly beginning to reveal the genetic underpinnings of tumorigenesis.

"It's so complex that no one lab or company is going to come up with the answer to cancer," says Jessen. "I see myself as trying to fill in some of the key gaps in our knowledge."

Another pathway involved in both embryonic development and cancer is the "Hedgehog" (Hh) pathway. First identified in fruit flies, it is named for the short and prickly appearance of fly embryos that have an abnormal Hh protein due to a genetic mutation.

Like Wnt, Hh is a secreted signaling molecule involved in the patterning of the embryo. Also like Wnt, Hh appears linked to the formation of tumors in those tissues where it is required for development – the cerebellum, foregut, prostate, skin and lung, for example.

In some cases, the Hh protein "may tell some cells to proliferate," says Michael

Pathway to glioma?

The Hedgehog (Hh) signaling pathway plays a critical role in embryonic development and has been linked to a number of different types of cancer.

Researchers at Vanderbilt University Medical Center are now examining its role in one of the most fatal types of brain tumors – gliomas.

Gliomas are the most common type of primary brain tumors (meaning they arise in the brain and not from elsewhere in the body). These tumor cells resemble glia – cells in the brain that support and nourish the neurons, and some studies have suggested that an abnormality in the Hh pathway might be involved in their development.

Michael Cooper, M.D., assistant professor of Neurology, has teamed up with Reid Thompson, M.D., director of Neurosurgical Oncology, to examine Hh pathway activity in brain tumor samples stored in a tissue bank that Thompson established.

To date, they have found that the Hh pathway is activated in certain types of gliomas – those of intermediate grades II and III, but not in the most advanced grade IV tumors (known as GBMs, or glioblastoma multiforme). Importantly, they have found that the Hh pathway is activated in what appear to be progenitor or stem cell-like cells.

"Investigators have speculated for some time that grade IV gliomas may be different (than the others)," Cooper says. "This may suggest that not all stem cells – and not all cancer stem cells – would be the same.

"It's a controversial idea," he adds, "but our data suggest that grade IV gliomas may arise from a cell type that's not Hh responsive, where grades II and III gliomas may arise from an Hh-responsive cell type."

While the results suggest that Hh activity might someday be useful in predicting tumor behavior, the role of pathway activation in the tumor is not yet clear.

"It is guilt by association at this point," Cooper says. "We still need to know what the pathway is doing. We think that it may have a role in tumor growth and invasion, but to determine that, we need a good animal model."

While Cooper plans to develop an animal model, a Clinical Scientist Development Award he recently received from the Doris Duke Charitable Foundation will support a prospective clinical study to assess Hh pathway activity in gliomas that have been surgically removed from patients. Those patients will then be followed long-term.

"I'm a clinician, but my research has been at the basic science level," he says. "So this award is taking (the research) to the next level, and it gives me a chance to learn a whole new set of skills."

– MELISSA MARINO

Cooper, M.D., an assistant professor of Neurology at Vanderbilt. In other cases, "it may tell cells to differentiate along a certain lineage … to become a motor neuron," for example.

The exact instruction imparted by the Hh signal depends on what type of cell is receiving the signal and the location of that cell.

"Hh regulates a number of cell types, but most importantly, stem cells or progenitor cells," says Cooper, who is studying the role of Hh in primary brain tumors called gliomas. "We've learned that these pathways regulate not only stem cells in development, but also in tumorigenesis."

Stem cell theory

Most tissues have stem or progenitor cells well into adulthood. When adult tissues like the epithelium require repair or renewal because of an injury or normal cellular turnover, these cells most likely respond by activating or reactivating the developmental pathways that led to that tissue's formation in the first place – pathways like Hh and Wnt.

"Stem cells or progenitor cells can respond to Hh by self-renewing, that is by dividing to form more stem or progenitor cells," Cooper says. "In a setting where mutations can occur and accumulate, the process becomes dysregulated, and the self-renewal process may become turned on in a way that it can't be turned off."

When the pathway can't be turned off, the anomalous cell divisions can lead to tumor formation. This is known as the "stem cell" theory of tumorigenesis. Indeed, the Hh pathway appears to be activated in many cancer types, particularly within cells that have a stem- or progenitor-like appearance.

While a research fellow at Johns Hopkins University, Cooper was examining how compounds known to cause birth defects (teratogens) interfere with Hh signaling. The research unexpectedly pointed toward the Hh pathway as a possible chemotherapeutic target.

Working with Philip Beachy, Ph.D., professor of Molecular Biology and Genetics at Johns Hopkins, Cooper was looking at how the teratogenic compounds jervine and cyclopamine cause a range of birth defects of the face and brain, from mild holoprosencephaly, such as cleft lip, to the most severe and fatal form of holoprosencephaly, cyclopia (development of a single, centrally-positioned eye).

Beachy and colleagues had demonstrated earlier that cholesterol played a critical role in Hh signaling during development; to be active, the Hh protein must be cleaved and one end of the protein modified by cholesterol. If this modification was inhibited, birth defects such as holoprosencephaly resulted.

Cooper suspected that these teratogens, whose chemical structures are similar to the structure of cholesterol, were somehow interfering with cholesterol modification of Hh, thus inhibiting Hh signaling required for development.

"We thought that we had this mechanism all figured out before we'd done a single experiment," Cooper says. "But we were wrong. And it was the most spectacular mistake ever!"

They eventually determined that the compounds inhibited Hh signaling not by interfering with cholesterol modification in the Hh-generating cell, but by inhibiting receiving cells from responding. And because the Hh pathway was known to be activated in a number of cancers, it immediately became clear that these chemicals, which can produce such horrible birth defects, might have some redeeming value in treating cancer.

Since this discovery, Beachy and colleagues have demonstrated the effectiveness of cyclopamine against several tumor types in animal models.

"So far, those tumors types that require Hh signaling for their growth shrink in animals treated with cyclopamine," Cooper says.

Cyclopamine and related compounds are now being investigated as possible chemotherapeutic agents by pharmaceutical companies.

"This has become a spectacular molecule – not only is it interesting as a biological tool, but it may have therapeutic value in treating tumors," says Cooper.

Whether or not the revelation that embryonic development and cancer share fundamental pathways results in new therapeutic treatments for cancer, the traditional "departmental" borders that defined research in years past have been broken down.

"Cancer biology and developmental biology have traditionally been two separate fields," says Cooper, "but now they have intersected in a wonderful way." **LENS**

Signaling cancer

Essential for embryonic development, the Wnt and Hh signaling pathways also are potential targets for new anti-cancer drugs. This illustration shows a very simplified representation of the two pathways, with only a few key components included.

The Wnt protein is thought to exert its effects through a family of transmembrane receptors called "Frizzled." Wnt binding triggers an intracellular signaling cascade that activates ß-catenin. This protein, in turn, enters the nucleus and interacts with transcription factors to regulate gene expression. Frizzled genes were first discovered in the fruit fly, where they control wing hair and bristle patterns.

Hh acts through a separate receptor called "Patched" (Ptc), a cell surface protein called "Smoothened" (Smo), and another intracellular signaling cascade to activate Gli, a gene first identified in malignant glioma. Like ß-catenin, the Gli protein can enter the nucleus to regulate gene expression. The Patched and Smoothened genes are named for their roles in patterning body segments during development.

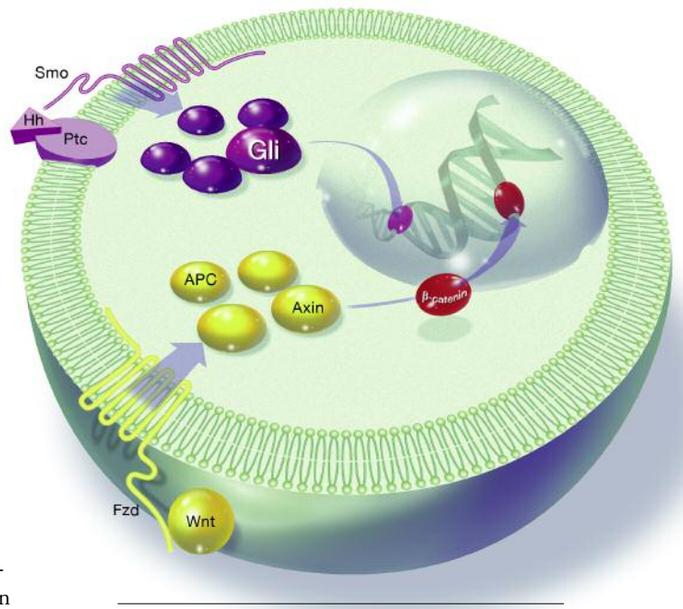


Illustration by Dominic Doyle

Q & A

A PROBLEM OF SOCIAL INJUSTICE

Research alone will not close the cancer gap

Harold Freeman, M.D., and Jane Weeks, M.D., discuss what needs to be done to reduce the disproportionate impact of cancer on racial and ethnic groups, the poor and the elderly.

Freeman is medical director of the Ralph Lauren Center for Cancer Care and Prevention, and professor of clinical surgery at Columbia University in New York City. A leading authority on the link between race, poverty and cancer, Freeman has served as president of the American Cancer Society, chairman of the President's Cancer Panel, and director of the National Cancer Institute's Center to Reduce Cancer Health Disparities.

Weeks is professor of Medicine at Harvard Medical School, professor of Health Policy and Management at the Harvard School of Public Health, and chief of the Division of Population Sciences at the Dana-Farber Cancer Institute. She is a member of the NCI's Board of Scientific Advisors, and directs the Dana-Farber Center for Outcomes and Policy Research, which studies ways to improve the quality of cancer care.

They spoke with *Lens* editor Bill Snyder via conference call.

HAROLD FREEMAN, M.D.

ILLUSTRATIONS BY DAVID JOHNSON

How well are we doing in reducing disparities in cancer incidence and outcomes?

Freeman: We're not addressing it very well … Everyone has made progress as measured by diminishing mortality from cancer in general and (in) specific cancers, but the gap between groups has not closed.

Why aren't we closing the gap?

Weeks: It's possible that patients may be poorly informed about effective treatments and/or are unequipped to deal with the health care system to make sure that they get effective treatments. They may have preferences for treatments that are associated with poorer outcomes.

Physicians caring for minority patients and elderly patients may be unaware of the current evidence, or they may have biases that cause them to selectively give less effective treatments in those settings.

They may also have inadequate evidence to guide the care that they give. This is particularly a problem with the elderly where there have been so few clinical trials in treatment of elderly cancer patients – and I might point out that cancer is largely a disease of the elderly – that we really don't know whether the same treatments that are useful in younger patients are also useful in older patients.

Finally there are potential problems in the structure of the health care system itself. So patients may face difficulty accessing the health care system. They may have difficulties with coordination of care that causes key components of their treatment to be left out. And providers may have inadequate reimbursement to deliver high quality care.

That's a very long list of potential reasons for these disparities and we need to understand which items on that list are in play if we're going to have effective strategies for coping with the problem.

Freeman: I argue that there are three major factors that cause disparities. And they are, first of all, whether or not people have resources, whether it's poverty or lack of insurance …

Second … is what I put in the category of culture, meaning the culture as a determinant of lifestyle, attitude and behavior, values, belief systems, communication systems … how people behave including the culture of the caregivers themselves …

Then there's a third element that overlaps both of those circles which I call social injustice … whether or not people have been treated fairly in the system.

You and colleagues across the country are following hundreds patients with lung and colorectal cancer. How will this help reduce disparities?

Weeks: The goal of the study is to move us from the 'Yes, disparities exist' observation to 'Why are they happening?' because that's really the policy relevant question at this point ...

We're nearing the end of the study and I expect over the next year there will be a flurry of publications that begin to address some of these questions.

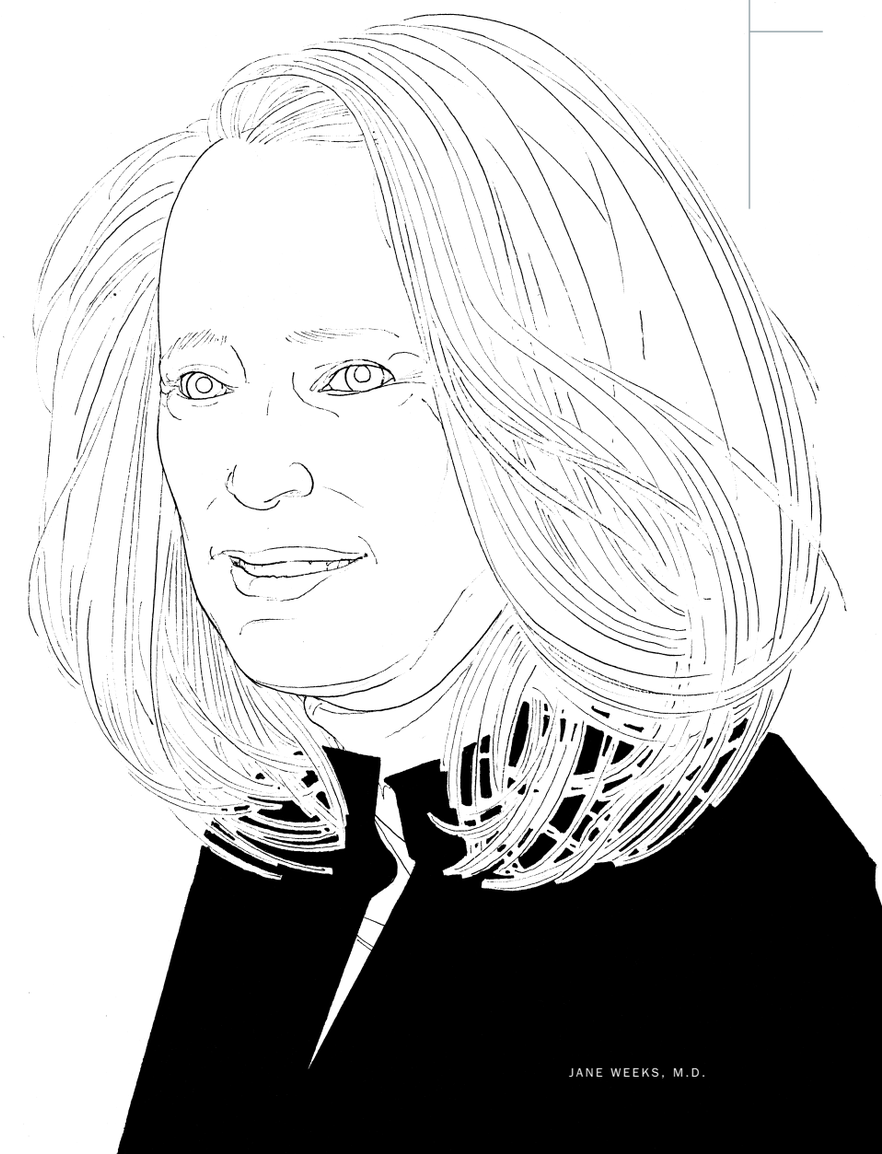
What impact has patient navigation had on cancer disparities?

Freeman: This is a concept that I invented starting in 1990 at the time I was at Harlem Hospital as director of surgery ...

We had published a paper showing that (of breast cancer) patients who came to Harlem Hospital over a 22-year period ending in 1986 … only 39 percent of them were alive at the end of five years, compared to about 70 percent in the country as a whole at that time …

This is a problem throughout the nation related to people who are diagnosed and treated too late … I concluded that barriers to getting through the health care system was a fundamental issue for people who were poor and uninsured, and living in communities such as Harlem.

So we set up a program called patient navigation … (to assure that) when people get a test … they will get rapidly treated.



JANE WEEKS, M.D.

We began to see real dramatic results… In the six-year period ending in 2000, the five-year survival of breast cancer patients at Harlem Hospital was 70 percent, compared to the previous 39 percent.

How important are cohort studies and epidemiological research?

Weeks: I think Dr. Freeman's story about the navigator program, it's a little like penicillin. You know, it's so obviously worked that it's definitely worth pursuing.

But what other things would work? Are there lower cost alternatives that would also work? Do we best put our resources into re-engineering the health care system or providing one-on-one support for individual patients? I think those are the open questions, and the best way to begin to answer those questions is with cohort studies and epidemiology.

It's where research always starts. It generates hypotheses. It generates ideas. Then you can narrow down with a randomized trial of a specific intervention and test to see whether it works. It's very inefficient to do that without first understanding the lay of the land, and that's what the cohort studies and epidemiology do for you.

Isn't it difficult to ensure continued funding for studies that last a long time?

Weeks: I think it is true and there are several reasons for that. One of them is the equity issue.

If you are a congressman and you have great health insurance and disparities are not a part of your life and you're looking at the way the NCI spends research money, you want them to spend every single dime on finding the cure for the cancer that you might get. It's human nature.

And when research funding is ample and there's plenty to go around, it's also great to spend some money on understanding the causes of disparities. But when the budget shrinks, as it is right now, that's the first thing to go.

Are we not investing enough in these kinds of studies?

Weeks: I would say we are absolutely not investing enough.

Freeman: I fully agree with the need to invest more money in these areas … but maybe even an overriding issue is that the problem of disparities finally comes down to delivering what we already know …

There is this huge disconnect between our discovery system and our delivery system … To the extent that we don't connect what we find to helping everyday people, I think it's a moral and ethical dilemma …

The biggest thing we could do to reduce disparities this day and this year would be to apply everything we know, that we believe should be done for people, to all people, irrespective of their race, their ethnicity, their age, their sex or their ability to pay. That I think is the great challenge ...

You cannot solve the disparities problem solely within biomedicine. Something else has to occur … If the problems are occurring in communities, which they are, then we need to bring in the social scientists like sociologists, anthropologists, even the historians to help us to understand what's going on in our communities.

And if the problem is inequity, and at its core I believe it fundamentally is a problem of inequity that drives disparities, we need to consider even the extraordinary possibility that, at its heart, maybe disparities are related to human rights and civil rights.

Won't deciphering the genetics of abnormal growth through The Cancer Genome Atlas project, for example, help reduce disparities by leading to more rational and successful treatments?

Weeks: Obviously it is a critically important challenge in oncology now to move from a one-size fits-all to a more tailored approach to treatment. But my guess is that this movement is going to make care in specialized centers even more important. It's going to make cancer care even more expensive, and, if anything, it's going to widen rather than narrow the pre-existing gaps.

So I think there is a moral imperative to address inequities at the same time that we are pushing forward the science, otherwise the situation will get worse, not better ...

Careful studies have shown that when African-American patients, for example, are treated in the same way as their white counterparts, their outcomes are very similar.

The gaps that we are seeing are not about biology. They're about failure to get what we know works to the patients who need it. And as what we know works changes over time, those disparities are not going to go away. This is not a problem of genetic differences. This is a social problem.

Freeman: The peculiar thing about progress without equity is that the cutting-edge progress tends to widen disparities as opposed to narrowing them. The things that you discover are going to be very costly for an individual patient – to have a genetic profile, for example.

I think we should push forward with this work, and I'm certainly in favor of spending what is necessary to move our understanding of carcinogenesis at the molecular level ahead … But the moral problem is that as we do that we don't seem to be paying attention to applying the technology to all people.

Weeks: I think the message that we need to communicate to our leadership is that, as in all other investment strategies, it's crucial to have a balanced portfolio.

I've found that to be a useful metaphor, actually. It goes back to something that we all understand in our daily lives, which is the importance of pursuing multiple options at the same time.

Even though the science couldn't be more exciting and absolutely should be pursued, it needs to be combined with research that will allow us to … get effective treatment to the patients who are not getting it today.

And one of the appealing things about that is that it has the potential to yield health benefits immediately, as opposed to a long-term benefit which is where the exciting basic science is taking us.

CENTER FOR OUTCOMES AND POLICY RESEARCH

The Center for Outcomes and Policy Research was established in 1995 by its current director, Jane Weeks, M.D., at the Dana-Farber Cancer Institute in Boston.

Among other projects, the center oversees the Cancer Care Outcomes Research and Surveillance Consortium (CanCORS), a five-year study of 10,000 patients with newly diagnosed lung or colorectal cancer.

The study is examining patterns of care, symptom control, health outcomes, costs and other factors with the goal of improving quality of care.

For more information, visit **www.dfhcc.harvard.edu** and search for "outcomes."

Freeman: If you go back to 1971, President Richard Nixon declared a war against cancer … (He) believed that the war would be over in approximately eight years … He likened it to putting a man on the moon.

Well the problem of cancer, first of all, is that it's much more complex. It's not one disease; it's more than 100 diseases …

Also, … the war … was fought as though it were only a research war … (We) put more money into the research community, which was great, but … (paid) no attention to funding access to care, for example. No attention. That got worse over this same period in many ways …

I think that war needs to be fought the way it was declared; it had some good outcomes with respect to research. But at the same time we need to fight a guerrilla war in the neighborhoods of America where people live and too often die … We have to do things for real people who have real problems … At any given time we must apply what we know to all people irrespective of their ability to pay.

The approach to disparities certainly requires the biomedical community to do its part, (to) teach us how to understand how disparities are driven from a biomedical perspective. But it quickly gets outside of that, because people live in communities where they behave in different ways and they have different levels of access.

We have to shift the war into not only biomedical science solutions but also social science solutions as well as equity solutions that have to do with social justice, and even take it into the level of civil and human rights. **LENS**

THE RALPH LAUREN CENTER

The Ralph Lauren Center for Cancer Care and Prevention opened in 2003 in Harlem, on 124th Street between Madison and Park Avenues. It is a partnership between the Memorial Sloan-Kettering Cancer Center and Harlem's North General Hospital. Lauren pledged a $5 million leadership grant from the Polo Ralph Lauren Corp. to open the center, which is focused on developing new models of patient care, research, education and outreach to address the unique needs of its community.

For more information, visit
http://ralphlaurencenter.org

EDGE OF THE WORLD

Lens magazine asked four leading scientists about the ethics of genomics research. Should we direct our own evolution? Are there places we shouldn't go?

1

KAY DAVIES, D.Phil., associate head, Department of Physiology, Anatomy and Genetics at Oxford University, and honorary director of the Medical Research Council's Functional Genetics Unit:

Cloning is one of those places we shouldn't go.

We've also got to be very careful that we don't think that handicap is something that can be totally avoided because it can't. You get mutations coming up in the population. I think the biggest danger is that society starts to reject anyone that's imperfect slightly …

There is a general sense that some sort of imperfection, not having this right or that right, makes you less of a person … I think these people are just as fantastic personalities as those we classify as 'normal' …

You have to remember that even the geniuses in the past have always turned out to be psychologically slightly unusual people. We don't want to have a unified gene pool. We do want interesting personalities to be there, always.

2

PHILIP GREEN, Ph.D., professor of Genome Sciences and adjunct professor of Computer Science and Engineering, University of Washington, Seattle:

I think it's inevitable that at some point in the future we probably are going to wind up changing our own DNA, and that when we get to that point people will be wondering why it took so long to get there …

It's certainly premature to try to attempt that now … But there will be discoveries made involving genes related to intelligence … and then the question comes, is it fair that some people start out with a better genetic complement relating to intelligence than other people do? And I think the answer has got to be no, it's not fair …

It does raise all sorts of ethical issues that have to be worked through … but that's not a reason not to move forward.

3

ERIC LANDER, Ph.D., director of the Broad Institute, professor of Biology at MIT and professor of Systems Biology at Harvard Medical School:

We shouldn't be trying to direct our own evolution, or try to do germline gene therapy because, for starters, we would be utterly incompetent at it.

It is an incredibly complex system involving 20,000 genes that has evolved over 3 billion years, and we've come along in the last five years and we can read the genetic instructions now. How can we possibly have the hubris to say, 'I could do it better'? …

The major risks (to current research) are privacy questions … Can we manage to get the public policy right so that we don't violate privacy? As long as we make sure that the control of genetic information is in the hands of the patient … I have great confidence that people will work out how to use the information for their own good.

4

MARK SKOLNICK, Ph.D., Chief Scientific Officer, Myriad Genetics, Inc., and adjunct professor of Medical Informatics, University of Utah, Salt Lake City:

I personally think that you can't try to regulate advance … Mistakes are made. They've been made in every generation of human's existence, and we've managed to come this far …

Humans will be the first species that directs its own evolution, as well as the evolution of everything else … If abortion is an issue, what will be the issue when we understand how the genome works, and when we're manipulating it in one way or another to cause people to live longer, to cause healthier babies to be born? …

Think of the beginning of the 20th century, when … there was almost no electricity … This next century will be as dramatically different from today as that was. We can't even imagine.

Pictured here: Abbie Foust embraces children from Lwala, a village in Kenya where she conducted a health survey.

Lwala diaries
(a postscript)

Editor's note: The previous issue of Lens chronicled the efforts of Milton Ochieng' – now a third-year medical student at Vanderbilt – to construct the first health clinic in Lwala, his village in Kenya. Last summer, after earning her undergraduate degree from Vanderbilt, Abbie Foust spent 10 weeks in Lwala helping Ochieng' conduct a health survey. Here are excerpts from her e-mail journal, which can be found at www.lwaladiaries.blogspot.com.

May 27 Oyare (good morning)!

I can't believe I've only been here three days. This place is amazingly inspiring, beautiful and heartbreaking at the same time … There is no electricity … and no running water …

I am staying in the home of the Ochieng's … The first day they took me to a very sick woman in the village who was vomiting and weak … The clinic isn't running yet, so there was nothing we could do except massage her back and feet and keep her company ...

June 3 Lwala is quickly becoming my second home … I am now used to showering with one bucket of water and a cup. I am used to having beans at every meal …

I am even becoming accustomed to the extreme poverty that is prevalent in this community – poverty that can be seen in the distended bellies of children (and in) the lack of books and chairs in the local primary school … It doesn't make me any less sad and angry every time I see it, though …

We started the health surveys on Wednesday … Some days we walk over two hours to get to a certain village and go from hut to hut … We interview the mothers; some … as young as 14 ...

You'd be surprised how many mothers say their kids have had convulsions and blood in their stool – both of which are NOT good. I am also learning how many of the children are not vaccinated in this area …

June 19 We had the privilege of speaking to a woman who is openly HIV positive – something that is very rare in Lwala. Even though 30 to 50 percent of the population is infected with HIV, people are incredibly secretive about it ...

This woman, an AIDS widow, had seven children, five of her own and two that she took in from her sister and brother-in-law who both died with AIDS a year ago. She struggled every day to feed her children because she was too weak to work in the farm (just like the rest of the community, she lives on subsistence farming). Often, she relies on neighbors to give her family food …

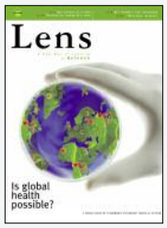
I went over to the 2-year-old boy of the family, who had a clubbed foot and couldn't walk very well, and scooped him up in my arms … He hugged my neck and held onto my hair and nuzzled his face into mine. I tried to set the little boy down … but he wouldn't let go. He wrapped his legs tightly around my waist and hugged harder – and that's when the tears came for both of us …

August 1 About a week ago I visited an orphanage called Sally Orphanage, where 120 AIDS orphans live ... Sally Orphanage is located near the Tanzania border … where HIV rates are as high as 40 percent … The death rate is so high … the government is running out of land in which to bury people … Parts of the village were almost ghost towns. Hut after hut after hut was empty because all their occupants were dead from AIDS …

I met a 17 year old, Emily, who was the eldest of 40 – yes, 40 – AIDS orphans in a single homestead (it's what happens when women are in remote villages, have no access to birth control, and don't have any say in using condoms). Emily was a mother who got pregnant after sleeping with a sugar cane worker in a field who offered her 100 shillings (the equivalent of $1.50). She accepted the offer because she hadn't eaten in three days …

I've experienced some of the hardest moments of my life here. I've seen some of the most devastating sights … followed by some of the most beautiful and inspirational … I have seen incredibly capable, intelligent people in Lwala leading the effort to build the clinic …

I leave Kenya … with the hope that I can encourage others to become equally touched by what's happening in Lwala and around Africa. There's so much good that we … can collectively accomplish … LENS



Global health issue wins international award for best periodical

Lens magazine has won a 2006 Global Media Award for Excellence from the Population Institute for its summer issue on global health.

Editor Bill Snyder accepted the award for Best Periodical during a ceremony Dec. 6 in Washington, D.C.

The Population Institute is an international, non-profit organization that works to achieve "a world population in balance with a healthy global environment."

The annual Global Media Awards are given to recognize "outstanding contributions to greater awareness of population, environment and resource issues."

Other awardees included *USA Today*, Best Major Daily; NOVA's "Rx for Survival," Best TV Documentary; and Al Gore's "An Inconvenient Truth," Best Film Documentary.

Previous winners in the Best Periodical Category have included *Scientific American* and *TIME Magazine*. **LENS**

FEATURED SCIENTISTS NAMED "AMBASSADORS" FOR RESEARCH

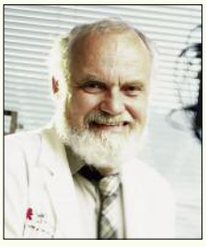
Three scientists featured in the summer 2006 issue of *Lens* magazine have been named to a new national group that aims to increase awareness of – and make the case for greater U.S. investment in – global health research.

James Hildreth, M.D., Ph.D., Sten Vermund, M.D., Ph.D., and Peter Wright, M.D., are among the first 27 "ambassadors" named to the Paul G. Rogers Society for Global Health Research.

The society was launched last summer by Research!America, a non-profit alliance that advocates to make health research a higher national priority. Named for the former Florida congressman and Research!America chair emeritus, the society was established with a $1.2 million grant from the Bill & Melinda Gates Foundation.

As ambassadors, Hildreth, Vermund and Wright will meet with opinion leaders and decision makers, make presentations to non-scientific groups and write newspaper columns about the need for global health research.

Hildreth directs Meharry Medical College's Comprehensive Center for Health Disparities Research in HIV; Vermund directs the Vanderbilt Institute for Global Health; and Wright is chief of the Division of Pediatric Infectious Diseases at Vanderbilt. **LENS**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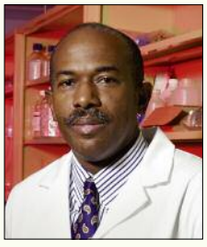
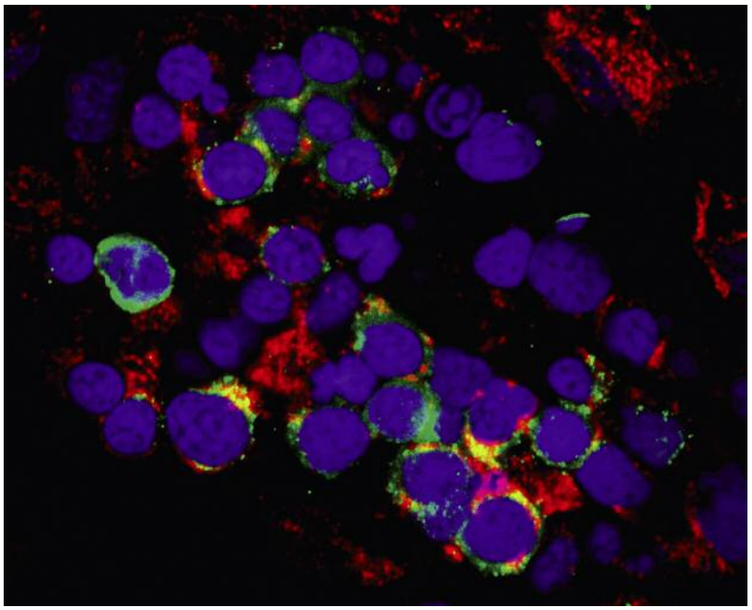
VERMUND


HILDRETH

Confocal microscope image shows muscle cells developing within a cardiac infarct, heart tissue that has died due to lack of oxygen. The image, created by researchers at New York Medical College's Cardiovascular Research Institute in Valhalla, provides visual evidence that ischemic injury can trigger activation of cardiac stem cells, some of which can regenerate damaged heart muscle.

Image courtesy of Jan Kajstura, Ph.D., and Piero Anversa, M.D., Cardiovascular Research Institute, New York Medical College. From Konrad Urbanek, et. al., *PNAS USA*, June 14, 2005; 102(24):8692-7.



IN THE NEXT ISSUE:

Crush of clots
Diabetes increases the risk of heart disease. Vanderbilt researchers are trying to find out why.

Sudden death
Genetic factors contribute to abnormal heart rhythms, a leading killer in the United States.

At the cutting edge
Stem cells and other advances could lead to new ways to heal an injured heart.

Lens

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