

 THE WISTAR INSTITUTE

ANNUAL REPORT

2004

TODAY'S DISCOVERIES

TOMORROW'S CURES

NATIONAL  
CANCER  
INSTITUTE

The Wistar Institute is a National Cancer Institute-designated Cancer Center



# PROGRESS MEANS NEVER STANDING STILL

It's true in science and in every field of worthwhile human endeavor. One discovery lays the foundation for another. One advance leads to previously unimagined questions. The talented researchers at The Wistar Institute follow where their science leads, their restless curiosity always driving them forward.

Like its scientists, The Wistar Institute as an organization is looking ahead. Wistar has a long and distinguished record of achievement since its founding in 1892, but the Institute will never rest on its past accomplishments. Today, Wistar has a bold vision for its future, the result of a comprehensive strategic planning process that identified emerging scientific opportunities with great potential to benefit global public health. The Institute will build on its heritage of excellence in cancer and vaccine research and develop initiatives in new research fields that promise to transform the way doctors diagnose and treat disease. It will also recruit gifted researchers to continue Wistar's rich tradition of creative science in the service of human health.

This report provides a glimpse of the exciting changes underway at Wistar as it embarks on a period of ambitious growth and renewal.

## CONTENTS

2	.....	Message from the President
4	.....	The Strategic Plan
6	.....	Systems Biology
8	.....	Vaccine Development
10	.....	New Recruits
14	.....	2004 Scientific Highlights
16	.....	In the Community
18	.....	2004 Scientific Staff
20	.....	Message from the Chair
21	.....	Membership of the Board of Managers
22	.....	Cumulative Giving
24	.....	Annual Giving
28	.....	Honor and Memorial Gifts
31	.....	Retirements: Clayton Buck, Ph.D., and Leonard Warren, M.D., Ph.D.
32	.....	Financials and Year in Review



## MESSAGE FROM THE PRESIDENT

The past year has been an exciting one for Wistar. Our scientists continue to publish their findings in top-tier journals, an indication of the outstanding quality of their research. Several talented new researchers, some of whom you will meet within these pages, joined our scientific faculty. Ongoing renovations to our facility will ensure that our faculty and staff have an environment of the highest caliber in which to do their work.

The year closed with a significant milestone for the Institute: the approval by the Board of Managers in December 2004 of Wistar's new Strategic Plan. This document outlines the Institute's ambitious goals for the future. We envision the creation of entirely new research initiatives and the expansion of existing ones, significant growth in the size of our faculty, and a comprehensive renewal of our facility, including laboratories, meeting spaces, and administrative offices.

Our Strategic Plan is the result of an intensive process involving Wistar faculty, administration, and staff, a Strategic Planning Committee composed of members of our Board of Managers, and external scientific advisors.

Throughout this process, our guiding principle was that the Strategic Plan must be science-driven, positioning Wistar to build upon its existing strengths and to take advantage of emerging scientific opportunities. Working together, we evaluated which research fields show the greatest promise for advancing both public health and biomedical science.

In this report you will read about our plans for new scientific initiatives, including research in stem cell biology and chemical biology. You will also learn about Wistar's research in two critical areas, systems biology and vaccine development, both of which are targeted for expansion in the Strategic Plan.

Scientists in Wistar's Systems Biology Division have contributed important data to the Human Genome Project about the ends of chromosomes, which are involved both in normal human aging and in cancer development. They are also working to create a blood test for lung cancer, which would enable doctors to diagnose the disease at an early, more treatable stage.

Wistar has long been renowned for its vaccine research, including the development of the rabies and rubella vaccines used throughout the world. Today, the Institute has scientists developing new vaccines for HIV, influenza, HPV (which causes cervical cancer), and colon cancer, to name just a few examples.

Eight new scientists have joined the Institute in the past two years, and recruitment will continue over the next several years. These additions to our faculty will enable Wistar to expand its research capabilities into new areas. It will also offer current Institute scientists new opportunities for collaborations. This report introduces four of the talented scientists who have chosen Wistar as the place to establish their laboratories.



When I arrived at Wistar in 2002, I joined an organization with a track record of scientific excellence and a talented faculty. I was excited by the possibilities I saw for making a great institution even better. For two years before I became president of Wistar, Clayton Buck, Ph.D., did an exemplary job of leading the Institute as its acting director. His assistance was invaluable to me when I began as president and ensured a smooth transition that enabled me to launch our strategic planning efforts. Clayton retired from Wistar at the end of 2004, and I would like to thank Clayton publicly for his outstanding service to the Institute over a thirty-year career as both a scientist and an administrator.

In closing, I would like to acknowledge the members of our Strategic Planning Committee, chaired by Brian Dovey, for their guidance throughout this process. Brian has recently agreed to serve as chair of Wistar's Board of Managers, and we're excited to have his wise counsel as we enter a period of institutional renewal. He succeeds Kevin Tucker, who provided outstanding leadership as chair of Wistar's Board from 1998 through the beginning of 2005. During Kevin's tenure as Board chair, the Institute saw increases in its funding and hired many gifted scientists, to name just a few indicators of our continuing success. Wistar also received major gifts to establish two endowed chairs under Kevin's leadership: the Herbert Kean, M.D., Family Professorship and the Robert and Penny Fox Distinguished Professorship. These generous gifts from our philanthropic partners make possible the vital research that goes on in Wistar labs.

We remain ever grateful to those who share our mission to create a healthier future for all of us through basic biomedical research.

## Research Programs and Faculty

### GENE EXPRESSION AND REGULATION

Shelley L. Berger, Ph.D.  
Susan Janicki, Ph.D.  
Paul M. Lieberman, Ph.D.  
Ronen Marmorstein, Ph.D.  
Gerd G. Maul, Ph.D.  
Steven B. McMahon, Ph.D.  
Kazuko Nishikura, Ph.D.  
Frank J. Rauscher III, Ph.D.<sup>1</sup>  
Ramin Shiekhattar, Ph.D.<sup>4</sup>  
Jumin Zhou, Ph.D.

### IMMUNOLOGY

Roger M. Burnett, Ph.D.  
Andrew J. Caton, Ph.D.  
Jan Erikson, Ph.D.  
Hildegund C.J. Ertl, M.D.<sup>1</sup>  
Walter Gerhard, M.D.  
Luis J. Montaner, D.V.M., D.Phil.  
Laszlo Otvos Jr., Ph.D.  
Ellen Puré, Ph.D.  
Wolfgang Weninger, M.D.  
E. John Wherry, Ph.D.

### MOLECULAR AND CELLULAR ONCOGENESIS

*Cancer Biology Division*  
Anthony J. Capobianco, Ph.D.  
Nadia Dahmane, Ph.D.  
Thanos Halazonetis, D.D.S., Ph.D.  
Dorothee Herlyn, D.V.M., D.Sc.  
Meenhard Herlyn, D.V.M.<sup>2</sup>  
Russel E. Kaufman, M.D.  
Joseph Kissil, Ph.D.  
Ellen Puré, Ph.D.<sup>4</sup>  
Ramin Shiekhattar, Ph.D.

*Systems Biology Division*  
Ellen Heber-Katz, Ph.D.  
Qihong Huang, M.D., Ph.D.  
Carlo Maley, Ph.D.  
Harold C. Riethman, Ph.D.  
Louise C. Showe, Ph.D.  
David W. Speicher, Ph.D.<sup>3</sup>

<sup>1</sup> Program leader

<sup>2</sup> Program leader and division leader

<sup>3</sup> Program co-leader and division leader

<sup>4</sup> Secondary appointment

### OUTSTANDING RESEARCH PROGRAMS

The Institute's laboratories are organized into three research programs, each of which includes scientists who have received international recognition for their work as well as talented junior faculty who represent the future of Wistar. These programs are: Gene Expression and Regulation; Immunology; and Molecular and Cellular Oncogenesis (with two divisions, Systems Biology and Cancer Biology).

To enhance and extend the excellence of these three research programs, as well as to prepare for the future retirements of current faculty, Wistar will make targeted recruitments of new scientists working in areas that complement existing research efforts. The Institute will also purchase new equipment to ensure that its researchers have access to state-of-the-art technology.



### STAKING A LEADERSHIP POSITION

The Strategic Plan has targeted two existing areas of research at Wistar for significant expansion: systems biology and vaccine research. Both of these research fields have tremendous potential to benefit public health, and the Institute has distinguished scientists working in these areas. Expanding Wistar's systems biology and vaccine research efforts will enable the Institute to stake a leadership position in these fields.

#### *Systems Biology*

Systems biology encompasses a range of approaches that allow scientists to study broad patterns of gene and protein activity. These investigations can identify complexes of biomarkers for cancer and other diseases, which may lead to new treatments and better diagnostics. The National Institutes of Health has made systems biology one of its key research priorities, given the field's promise for creating important public health advances.

Wistar has an outstanding group of researchers in its Systems Biology Division working to understand how specific molecular events are systemically involved in cancer development and progression. Recruitment will enable Wistar to extend its systems biology efforts and position the Institute to be an international leader in this field. This report provides highlights of Wistar's current systems biology research on page 6.

#### *Vaccine Research*

Wistar has long been renowned for its vaccine research, including the development of the rubella and rabies vaccines used throughout the world. Recruitment of scientists working in vaccine research will enable the Institute to create a dedicated Vaccine Center.

The Vaccine Center will draw on Wistar's strong scientific underpinnings in fundamental aspects of cellular immunology and will build the Institute's translational efforts by emphasizing new approaches to cancer vaccines and the development of new vaccine platforms targeting infectious diseases such as HIV, influenza, and HPV (cervical cancer), as well as emerging diseases and agents that could be used in bioterrorism. Read more about Wistar's current vaccine research efforts on page 8.

## NEW RESEARCH INITIATIVES

The Institute will create two new research initiatives—stem cell biology and chemical biology. Both of these research fields hold strong promise to lead to new treatments for disease and to advance biomedical science, and they build on existing Wistar strengths.

### *Stem Cell Biology*

Stem cells have emerged as a crucial area of investigation for biomedical scientists because of their great potential both as therapeutics and as research tools that can help researchers understand cancer and other serious diseases. Wistar is well positioned to be a leader in stem-cell research, given its long-standing strengths in genetics, gene expression and regulation, and cancer biology.

Although federal funding for research using human embryonic stem cells is limited at present, the future for funding of stem cell research by federal and private agencies appears very promising. Regardless of how the federal government's position on human embryonic stem cells unfolds, stem cells are also found in many adult tissues, and research using these adult stem cells will not be limited by ethical considerations. Also, stem cells from mice can be used to study embryonic development, to establish mouse models of human disease, and as experimental systems for in vitro genetic studies; these types of investigations should attract strong interest from funding agencies.

### *Chemical Biology*

Chemical biology is an emerging research field that aims to advance drug discovery. Research in chemical biology focuses especially on the design of small molecules as laboratory probes, which can be used to study biological processes involved in cancer and other diseases. These molecules may also be candidates for new therapeutic agents. In cancer research, scientists can screen chemical libraries to identify or design possible inhibitors for cancer-causing proteins or activators for tumor suppressor proteins. An initiative in chemical biology will extend the capabilities of many research areas in which Wistar already excels, such as structural biology, genomics, and proteomics.

To establish a strong program in chemical biology, the Institute will need not only to recruit investigators but also to establish a new drug screening core facility. These resources will make Wistar an attractive partner for collaborations both with clinical investigators and pharmaceutical companies.

## *The Strategic Planning Committee*

### CHAIR

Brian Dovey

### MEMBERS

Robert Barchi, M.D., Ph.D.

Ian J. Berg

Ira Brind

Harold M. Davis

Robert A. Fox

Richard M. Horowitz

Albert Ominsky, Esq.

Seymour S. Preston, III

Edward Sickles

Daniel H. Wheeler

## RECRUITING GIFTED SCIENTISTS

To implement Wistar's ambitious scientific goals, the Strategic Planning Committee has recommended that the Institute expand its faculty to 42 principal investigators. The Institute projects that it will reach this target by adding 2-3 new investigators per year through 2012. Read more about some of Wistar's new recruits beginning on page 10.

## ENHANCING THE FACILITY

Wistar must provide a superior scientific environment to its researchers in order to recruit and retain talented investigators. To ensure that both existing faculty and new recruits have laboratory space of the highest caliber, the Institute will renovate and expand its current facility in University City. The Institute has initiated a facilities planning process that will include a comprehensive review of the Institute's building and infrastructure, supporting mechanical systems, and possibilities for expansion.

Biomedical scientists are increasingly taking a holistic approach to studying disease. Rather than studying a single gene or set of proteins, they are examining how complex webs of genes and proteins drive cellular behavior in health and disease. With this knowledge, researchers can identify targets for treatment in cancer and other diseases, more accurately predict therapeutic outcomes, and achieve earlier diagnoses. Wistar researchers have been among those developing the tools needed to push the field of systems biology forward, and the new Strategic Plan calls for expanding the Institute's efforts in this important area of discovery.

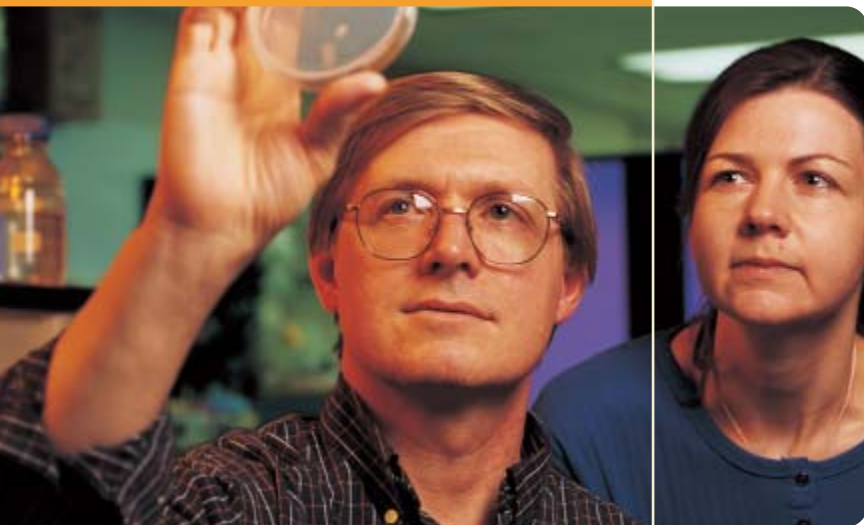
#### GENES, CANCER, AGING, AND THE COMPUTER ERA

Analyzing the daunting quantities of information flowing from the Human Genome Project and other systems biology efforts presents researchers with a challenge. To make sense of the data, scientists in the new field of bioinformatics are creating computer tools to help with the process. Harold C. Riethman, Ph.D., is one of the scientists both generating the data and developing the computing strategies needed to manage the information.

In October, the final draft of the human genome sequence was published in *Nature*. Riethman, one of the authors of the study, made critical contributions to the project, sequencing the regions at the tips of the chromosomes called telomeres. The Riethman laboratory cloned the DNA of telomeres along with large pieces of adjacent subtelomeric DNA.

Telomeres contain clues about how the body ages and are also implicated in the development of cancer. These regions are vital for cell division and the faithful passage of a DNA copy from a parent cell to its progeny. With every cell division, the telomeres become shorter until eventually the cell can no longer divide. This limit on cellular lifespan is believed to play an important role in determining human lifespan and how individuals age. Telomere length depends both upon traits inherited from parents and upon environmental influences—for example, several studies have shown that identical twins have more similar telomere lengths than unrelated individuals, and a recent study has shown that stress increases the rate at which telomeres are lost. Lost or destabilized telomeres may also play a role in the formation of cancer.

Working with the telomere data from his experiments, Riethman has developed a number of valuable bioinformatics tools, using techniques from applied mathematics, computer science, and statistics. For example, the lengthy stretches of duplicated DNA that characterize the telomeres make these regions complicated to analyze. Riethman's laboratory has developed computational methods to align very similar sequences in order to pinpoint their differences and better understand how they work.



Harold C. Riethman, Ph.D., with Sheila Paul



Ramin Shiekhhattar, Ph.D.

## EARLY DETECTION OF A TOP KILLER

In March, a multi-institutional research collaborative led by Wistar's David W. Speicher, Ph.D., and including Louise C. Showe, Ph.D., was awarded \$3.4 million by the Commonwealth of Pennsylvania to pursue development of an early detection blood test for lung cancer.

The need for such a test is great. Lung cancer kills more Americans by far than any other form of cancer, according to statistics compiled by the American Cancer Society. As with most cancers, treatment for lung cancer is much more effective when the cancer is detected at an early stage.

The team will use a systems-biology approach—including proteomics and genomics applications developed in their laboratories—to find proteins and genes in the blood that indicate the presence of early lung cancer. They will then develop blood tests based on this information that could aid thousands by detecting their cancers at an earlier stage than is currently possible.

The aim of proteomics is to catalogue the full complement of proteins in a given tissue or blood sample. In contributing to the development of a lung-cancer test, Speicher will analyze the full set of proteins in blood samples from patients with lung cancer. He will then compare them to the proteins in the blood of healthy individuals. Proteins that appear only in the patient samples but not in the normal ones become potential biomarkers for lung cancer, pending further validation.

Similarly, Showe will use DNA microarrays in her genomics studies of blood samples from lung cancer patients. DNA microarrays enable researchers to assess the activity of several thousand genes at once in a blood or tissue sample. By comparing the genes active in the samples from patients to the active genes in normal samples, Showe hopes to identify those genes that are active only in early-stage lung cancer. As with the proteins that appear only when lung cancer is present in the body, the genes activated in patients become possible biomarkers for that cancer.



## USING THE KNOWN TO HOOK THE UNKNOWN

With innovative biochemical techniques developed in his laboratory, Ramin Shiekhhattar, Ph.D., can take known proteins and use them to open windows into complex biological systems. As with proteomics and genomics, his approach discovers sometimes surprising biological connections.

For example, beginning with the BRCA1 protein—mutations of which have been linked to an increased risk of breast and ovarian cancer—Shiekhhattar was able to identify a larger protein complex that contains BRCA1 and of number of other proteins. The power of his method becomes clear in the questions that come quickly to mind. What are the other proteins associating with BRCA1? Are any of them linked to elevated risk of cancer when mutated? What is the biological role of the larger complex? One other protein found in the complex was BRCA2, also known to increase risk of the same cancers when mutated, but not previously directly connected with BRCA1. Two additional proteins in the complex may also play a role in breast and ovarian cancers and invite further study.

In November, Shiekhhattar reported in the journal *Nature* that he had tracked a known protein called Drosha to discover its role in a small complex responsible for creating tiny bits of short-lived genetic material called microRNAs. These microRNAs have attracted enormous interest from scientists since their discovery in humans only a few years ago. Viewed most broadly, they appear to play significant roles in controlling gene expression and development in many different settings.

The complex identified by Shiekhhattar, dubbed the microprocessor complex, contains another protein, in addition to Drosha, that has been linked to DiGeorge syndrome, the most common disorder of genetic deletion in humans. In DiGeorge syndrome patients, a swath of DNA containing multiple genes is missing, and many are born with heart defects, immune deficiencies, and developmental and behavioral problems. Intriguingly, one in four also goes on to develop schizophrenia, a disorder for which causative genes have yet to be identified.

Vaccines may have done more to promote public health than antibiotics, surgery, or any other advance in medicine. With their ability to marshal the weapons of the immune system against specific pathogens, vaccines have brought many dangerous diseases under control and offer enormous promise for improving public health in the future. The Wistar Institute's legacy in vaccine development is well known—the standard protections against both rabies and rubella are Wistar vaccines, for example. The Institute's new Strategic Plan outlines plans for Wistar to enhance and expand its longstanding vaccine development efforts to confront both infectious diseases and cancer.

Hildegund C.J. Ertl, M.D. (right), with Nia Tatsis, Ph.D.



## *Rubella Eradicated in the U.S.*

On March 21, 2005, Centers for Disease Control head Dr. Julie Gerberding held a news conference in Atlanta to declare that the viral disease rubella had been eliminated in the United States. She credited the vaccine against rubella developed at The Wistar Institute by Stanley Plotkin, M.D., in the 1960s.

Plotkin began work on the vaccine after a pandemic of rubella swept across Europe and the U.S. in 1963 and 1964, leaving in its wake about 12,000 infants born deaf or deaf and blind. In 1969, the vaccine developed by Plotkin and his co-workers was introduced for use by physicians, signaling the beginning of the end for the virus in the U.S.

Public health officials note that work remains to be done, however. Some 100,000 infants around the world each year are born with birth defects traceable to maternal rubella infections.

## BEYOND THE ANNUAL FLU SHOT

Globally, the influenza virus, or flu, is thought to cause between three and five million cases of severe illness and between 250,000 and 500,000 deaths annually, according to the World Health Organization. New strains of the virus emerge each year, so that the U.S. Centers for Disease Control and other public health services must produce and distribute a new vaccine each year, using methods developed decades ago. And people seeking to avoid a flu infection must arrange to receive an annual flu shot; there is no vaccine available that offers multi-year or lifelong protection, as is the case for many other infectious diseases.

At Wistar, Walter Gerhard, M.D., is developing a new kind of flu vaccine, one that would not need to be given annually nor even as a shot. The current flu vaccine prepared by health officials each year targets two large molecules on the outside of the flu virus. These molecules mutate each year to generate new flu strains, which is the reason a new vaccine is needed each year. Gerhard's vaccine, however, would take aim at a third and much smaller molecule on the flu virus that does not change each year. Because his vaccine targets an unchanging part of the virus, it may provide lasting protection from the flu without the need for an annual shot. In fact, the researchers are designing their experimental vaccine as a nasal spray, so it may not involve a shot at all.

Early results from laboratory tests are promising: Mice given the vaccine generated a powerful antibody response to the vaccine, according to Gerhard. Efforts are under way to move the new vaccine toward clinical testing as soon as possible.

## CONFRONTING THE CHALLENGE OF HIV

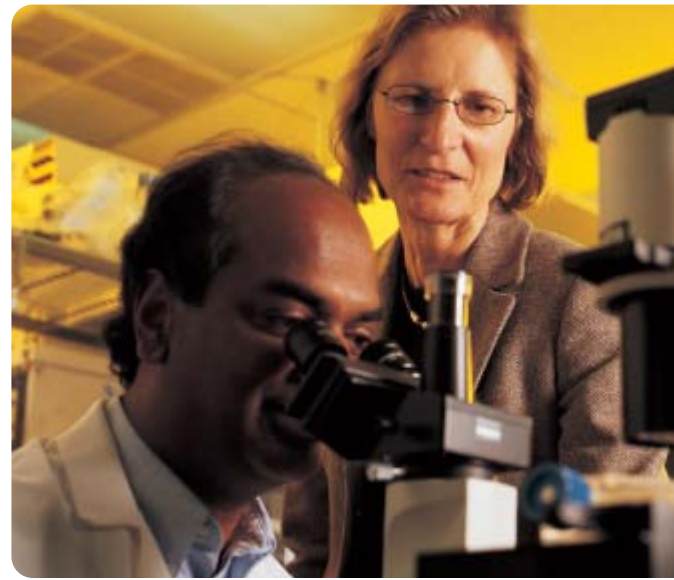
As the number of people living with HIV worldwide nears 40 million, the need for an effective vaccine has become greater than ever.

In July 2004, a Wistar-led team of researchers reported success in monkeys of an innovative triple-vaccine strategy aimed at creating an effective HIV vaccine regimen. In a test of the new approach, the scientists attempted to maximize the immune response to a specific HIV gene with a series of three different vaccines and succeeded in dramatically stimulating a certain class of immune cells that many scientists believe will be an important key to creating an effective HIV vaccine. The novel vaccine regimen induced unprecedented levels of these immune cells in the monkeys, according to Hildegund C.J. Ertl, M.D., who headed the effort.

Many current experimental vaccines employ human adenoviruses engineered to include elements from disease-causing agents. Adenoviruses, a cause of the common cold, are relatively easy to manipulate in the laboratory and readily enter a wide variety of cells, including important cells of the immune system, to stimulate a vigorous, long-lasting immune response. An unaddressed problem with this approach, however, is that many people are exposed to adenoviruses in childhood and carry antibodies against the viruses that would interfere with the effectiveness of any vaccine based on them.

To circumvent this potential difficulty, Ertl and her colleagues have developed a series of vaccines based on chimpanzee adenovirus strains that possess the immunological strengths of human adenoviruses without their drawbacks. In their 2004 study, the scientists created three vaccines, each with a different adenovirus strain as a backbone but all containing the same HIV gene. Two of the vaccines were based on chimpanzee adenoviruses, and the third was based on a human adenovirus. The three vaccines, when given in sequence, built on each other to generate an ever stronger immune response to a repeating element in the vaccines—the HIV gene.

For eventual clinical use, vaccines incorporating additional viral elements would be needed to elicit a sufficiently broad immune system response. Still, the study suggests that a coordinated series of vaccines might be the key to effective protection against HIV. Other efforts in the Ertl laboratory include developing an improved vaccine against rabies and creating a vaccine designed to prevent HPV (cervical cancer).



Dorothee Herlyn, D.V.M., D.Sc.

## DEVELOPING A COLON CANCER VACCINE

Dorothee Herlyn, D.V.M., D.Sc., is working to develop a vaccine against colorectal cancer. Her idea is to create a therapeutic vaccine to treat patients with this cancer, rather than a vaccine to prevent the cancer. Such a therapeutic vaccine would train the immune system to see cancer cells as the threat they are and attack them, much as it does infectious entities. After identifying a number of markers on the surface of the cancer cells that distinguish them from normal cells, Herlyn began to design vaccines that would target those markers.

Recent observations from Herlyn's laboratory, however, suggest that the immune systems of many cancer patients already generate cells capable of specifically attacking tumors, but that the cells rarely seem to do so. What prevents these cells from taking action? Apparently, the immune cells with the potential to attack cancer—called cytolytic, or killer, T cells—are prevented from acting by a newly identified class of immune cells called regulatory T cells.

Previous research has focused on finding ways to stimulate the killer T cells to act, but her research suggests that drugs that inactivate the regulatory T cells might be more effective in freeing the killer T cells to attack. If true, this approach would likely advance many other experimental cancer vaccines in development. In the Herlyn laboratory alone, for example, vaccines are under development against melanoma, breast cancer, and brain tumors.



## NEW RECRUITS

### E. JOHN WHERRY, PH.D.

The immune system contains a reservoir of T cells, generated during development, that stands poised to respond to infection or to stimulation by vaccination. Often a very small number of these T cells are specific for, say, a particular virus. When these T cells recognize the virus, they become activated, dramatically change their pattern of gene expression, and expand greatly in number in order to kill off the virus.

But in chronic infections, something goes wrong; the immune system fails to eliminate the pathogen completely. Often the immune system does mount a response, but one that is insufficient to clear the infection.

Assistant professor E. John Wherry, Ph.D., who recently joined Wistar's Immunology Program from Emory University, studies the interplay between chronic viral infection and T cell response in order to understand how control of the virus might be enhanced.



Once the T cells that have become activated and have expanded in number—called effector T cells—have killed off the virus, the majority of them die off. But about five to 10 percent remain and continue to differentiate. Their gene expression patterns change, and they acquire the capacity to self-renew and maintain themselves as a stable population of cells for decades. These are called memory T cells, and they respond much faster to infections than T cells that have never before confronted the virus.

In chronic infections, the initial T cell response may begin normally, but sometime during the infection, defects arise in the ability of T cells to perform their normal antiviral functions. They have diminished capability to create antiviral proteins, and they don't undergo rapid and robust proliferation.

Using mouse cells, Wherry has taken dysfunctional T cells and studied their gene expression patterns, comparing them to well-functioning effector T cells and memory T cells. "We were looking to see whether there are genes that define a protective memory cell that are absent during chronic infection," Wherry says. His group found that there were hundreds of genes with different expression patterns during chronic infection versus acute infection.

For some of the dysfunctional T cells, there were inhibitory factors affecting them. The observation has important implications for developing therapeutics, Wherry says, because it suggests that, if the negative signals could be alleviated, at least some antiviral function might be restored to the cells.

In shedding light on how T cells work and sometimes fail to work optimally, Wherry's research may also contribute insights that could improve vaccine design.



#### WOLFGANG WENINGER, M.D.

On a laptop video screen, assistant professor Wolfgang Weninger, M.D., can view real time movies of cells circulating throughout the blood stream. New technology is enabling scientists like Weninger to study important biological processes without interrupting them, a major advance from still-life microscopic images or other single-moment data captures.

In these real-time movies, Weninger can observe white blood cells patrolling the circulatory system, alert to assaults on the body, whether by infection or injury. When these cells receive a biochemical distress call from the surrounding tissues, they slow down and begin to roll along the blood vessel walls. Then they come to a stop, sticking to the vessel wall and slowly passing through it to investigate the trouble beyond. The process, including its underlying biochemistry, is known as the white blood cell adhesion cascade.

“White blood cells are constantly checking to see if anything is going on in the body that shouldn’t be,” says Weninger, who has joined Wistar’s Immunology Program. “It’s called immunosurveillance, and we’re trying hard to understand which molecules regulate the process.”

When, for example, an influenza virus attacks the respiratory tract, various elements of the immune system—specific subsets of T cells, particularly—are quick to arrive on the scene.

“We are trying to dissect all the different steps a T cell takes in order to migrate from the inside of a blood vessel to the outside, into the particular tissue where that T cell type is needed,” Weninger says.

As a postdoctoral fellow at the CBR Institute for Biomedical Research/Harvard Medical School, Weninger helped apply or develop specialized tools to answer these questions. The first was intravital microscopy, which uses a fluorescence microscope to create videos of cells circulating in the bloodstream. The other was a strain of mouse developed by Weninger in which T cells fluoresce green, making it possible to track them with intravital microscopy. Using these tools, he has conducted a number of studies that contribute significantly to scientists’ understanding of the biochemical steps of the adhesion cascade.

More recently, Weninger has begun to explore a new technology that would permit him to follow the T cells after they leave the circulation and pass into the tissues. It is there that the T cells make contact with tumor cells, virus-infected cells, or other cells of interest. Multiphoton microscopy, as the new technology is termed, uses extremely short pulses of infrared laser light to penetrate into tissues to reveal more about the interactions of T cells with these other cells.



### NADIA DAHMANE, PH.D.

In recent years, scientists have increasingly looked to the earliest days of life for clues about how cancer develops and spreads. Following conception, an orchestrated series of biological signals guides the development of the embryo as its cells divide and begin to specialize, forming tissues and organs. But researchers have discovered that many of the genes and biological pathways involved in normal embryo development also play a role in cancer. By studying development, scientists hope to understand better how cancer arises.

Assistant professor Nadia Dahmane, Ph.D., takes such an approach in her research centering around the nervous system. Her work offers insights both into normal nervous system development and brain tumor formation. Dahmane has joined Wistar's Albert R. Taxin Brain Tumor Research Center and the Molecular and Cellular Oncogenesis Program.

In normal development, primitive cells begin to specialize, dividing rapidly and traveling to their proper position in the body in order to form tissues and organs. Cancer cells also divide rapidly and, in the case of metastasis, travel through the body inappropriately, which has caused scientists to speculate that cancer cells may in effect revert to a more primitive state.

As a postdoctoral fellow at New York University's Skirball Institute, Dahmane began studies of a signaling pathway that plays a major role in embryonic development, including of the central nervous system. Signaling pathways are chains of instructional messages that control biological processes.

Dahmane has focused on a signaling pathway involving a gene called Sonic hedgehog and a family of proteins called GLI that mediate this pathway. With colleagues at NYU, she looked at samples from patients with basal cell carcinoma, a type of skin cancer. They found that in all the patients, the Sonic hedgehog pathway was activated, suggesting that it is involved in tumor formation and maintenance.

"In normal development, it is known that Sonic hedgehog acts on the growth of hair follicles," Dahmane says. "And basal cell carcinomas are thought to be hair follicle tumors. They appear to use the Sonic hedgehog pathway to proliferate."

Later, Dahmane and her colleagues explored the role of the Sonic hedgehog pathway in brain development and how it might be implicated in medulloblastoma, a pediatric brain cancer. Their work suggests that the Sonic hedgehog pathway modulates normal brain growth controlling the proliferation of precursor cells, and that this pathway somehow becomes deregulated in brain tumor formation. The research suggests that the Sonic hedgehog-GLI pathway may become a useful target for new brain cancer therapies as scientists learn more about its function. At Wistar, Dahmane is continuing her studies of the Sonic hedgehog pathway's role in brain development and its implications for understanding brain cancer.

### JOSEPH KISSIL, PH.D.

Cells in the body communicate constantly with each other to control vital biological processes. Any breakdown in these communications can lead to disease conditions, including cancer.

Messages are sent between cells in the form of small signaling molecules broadcast by the sending cell and received by receptor molecules on the target cell's surface. Once received at the cell surface, these biochemical communications trigger cascades of further messages within the cell. These cascades may be linear pathways of signaling molecules or, more often, branching networks, complex webs of information and instruction. Scientists refer to the biochemical chatter between pathways as crosstalk.

Assistant professor Joseph Kissil, Ph.D., is investigating some of these signaling networks that relay information from the surrounding environment into the cell. Kissil, a new recruit to the Molecular and Cellular Oncogenesis Program, is also a member of the Albert R. Taxin Brain Tumor Research Center.

To understand the activity of a signaling molecule, many researchers will introduce large quantities of the molecule into a living system, either directly or through stimulating overproduction of the molecule, and then analyze the effects. Kissil believes that while these approaches have been instrumental in elucidating many aspects of signaling pathways, the use of a "brute force" approach might obscure their finer details.

"Within the cell are elaborate networks of signaling pathways with lots of crosstalk among them," Kissil says. "It's all very finely tuned, and when you introduce in a single component in vastly exaggerated quantities, you throw the whole system out of balance."

Instead, his strategy is to develop ways to study signaling molecules under more normal circumstances, whether in whole animals, cell cultures, or at the biochemical level. Just prior to coming to Wistar, Kissil was a postdoctoral fellow at the Massachusetts Institute of Technology, where he worked on a mouse model for lung cancer that closely recapitulates the human disease. At Wistar, he plans to work with this model to explore the signaling pathways that appear to be pivotal in the genesis of the disease when disturbed.

Another disease Kissil is investigating is neurofibromatosis type 2, or NF2, a relatively rare disease linked to the development of tumors of the schwann cells of the eighth cranial nerve. These tumors develop around the auditory nerve and can have a serious impact on the brain.

Both diseases involve common disrupted signaling pathways. Kissil's aim is to elucidate how the molecules that make up these pathways communicate with each other to discover where they go wrong in disease and identify potential targets for therapies.



## 2004 SCIENTIFIC HIGHLIGHTS

In May, professor **Ronen Marmorstein, Ph.D.**, reported new findings about a family of enzymes called sirtuins, which are known to play critical roles in aging, metabolism, and gene expression. Previous studies by other researchers have suggested that low-calorie diets that extend life boost sirtuin activity dramatically, hinting at a link between metabolism and aging through sirtuins. These enzymes also promote genomic stability, which often goes awry in cancer and particularly as one ages. Marmorstein's group offered structural insights into sirtuins, which could inform drug discovery centered around boosting sirtuin activity. The research was published in *Proceedings of the National Academy of Sciences*.

First discovered twenty years ago, the cancer gene MYC is the most overexpressed oncogene in human cancers. MYC mutations are associated with a wide range of cancers, including breast, colon, ovarian, and prostate cancers, as well as melanoma. Recent studies have determined that the protein product of MYC, which is known as a transcription factor, binds to about 15 percent of all genes. Scientists had long believed that when MYC binds to a target gene, it turns that gene on, or activates it. Surprisingly, new work by assistant professor **Steven B. McMahon, Ph.D.**, and others demonstrates that MYC often binds to genes without activating them. In an article published in *Nature Reviews Cancer* in July, McMahon's research team offered a reanalysis of several previous studies of MYC's binding to target genes. The discovery that MYC binds to so many genes without necessarily activating them raises many new questions for cancer researchers. Does MYC have other functions besides activating genes? Are there other unknown factors that play a role in whether MYC activates a gene? The research was done in collaboration with the laboratory of associate professor **Louise C. Showe, Ph.D.**



Roger M. Burnett, Ph.D.

Peter Olson

Robert H. Clink



Thanos D. Halazonetis, D.D.S., Ph.D.

Scientists estimate that at least half of all human cancers involve mutations in the tumor suppressor gene p53. Wistar associate professor (now professor) **Thanos D. Halazonetis, D.D.S., Ph.D.**, published important new findings about the workings of p53 in a pair of papers in 2004. In the course of performing its normal duties, p53 binds to DNA. Halazonetis reported new information about how this binding occurs in the journal *Structure* in July. Then, in November, the Halazonetis laboratory detailed the initial sensor in the p53 tumor-suppressing pathway. Radiation, toxic chemicals, and other environmental factors can cause DNA breaks in cells. These breaks in the DNA must be repaired promptly—otherwise, cancer may result. When these breaks cannot be repaired, p53 provides vital back-up protection, triggering cells with fatally damaged DNA to self-destruct so that they cannot cause cancer. But scientists had not known how p53 is alerted to the presence of DNA breaks in the first place. Halazonetis identified a sensor protein that detects DNA breaks and triggers the p53 cell death program. The research was published in *Nature*.

A study by assistant professor **Jumin Zhou, Ph.D.**, that was published in October called into question some long-held notions about how genetic information is passed on from one organism to its offspring. Scientists have long believed that only information in the DNA is heritable, but Zhou's work in fruit flies suggests that this is not the full story. Instructions that control gene activity and are recorded solely in the molecular packaging of the DNA can also be passed to an organism's offspring, according to Zhou's findings. The research was published in *Genes & Development*.

Wistar professor **Roger M. Burnett, Ph.D.**, with colleagues at the University of Helsinki, has discovered structural similarities among viruses that infect hosts from all three domains of life. These similarities suggest that the viruses, despite their genomic differences and differences in hosts, may have evolved from a common ancestor billions of years ago. The three domains of life are eukarya (animals, plants, and other higher order organisms), bacteria, and archaea (microorganisms that differ from bacteria and are commonly found in extreme environments like geysers and alkaline, acidic, or salty waters). While viral lineage is in itself of interest to scientists, research in this area could help inform anti-viral drug discovery. Structural similarities in viruses may point to sites of enzymatic activity that could be targeted with drugs. The research was published in *Molecular Cell* in December.

## TRAINING PROGRAM

**K**asirajan Ayyanathan, Ph.D., a staff scientist in the laboratory of professor **Frank J. Rauscher III, Ph.D.**, won the 2004 Ching Jer Chern Memorial Award, given annually for the best scientific publication by a postdoctoral fellow in the previous year. The winning paper, on epigenetic gene silencing, was published in August 2003 in *Genes & Development*. The award honors the memory of Dr. Chern, a Wistar scientist. Ayyanathan presented his award-winning work on June 18 at a special lecture and reception attended by Mrs. June Chern, wife of the late Dr. Chern.

**Marc Holbert**, a predoctoral trainee in the laboratory of professor **Ronen Marmorstein, Ph.D.**, received the 2004 Dr. Monica H.M. Shander Fellowship in October. The award honors annually a predoctoral trainee who displays excellence in the laboratory and diligence in scholastics. The fellowship was created by Dr. Shander's parents, Mr. and Mrs. Charles Shander, and former Institute director Hilary Koprowski, M.D.

## SPECIAL LECTURES

**W**istar hosted a special research symposium on chromatin regulation of gene expression and epigenetics on May 25. The symposium featured leading scientists from across the nation and overseas. It was given in honor of **Shelley L. Berger, Ph.D.**, to celebrate her appointment as the Hilary Koprowski Professor at Wistar. The session chairs were Wistar associate professor **Ramin Shiekhatter, Ph.D.**, and professor **Ronen Marmorstein, Ph.D.** Guest speakers were: C. David Allis, Ph.D., Rockefeller University; Tony Kouzarides, Ph.D., Wellcome Trust/Cancer Research, University of Cambridge; Mary Ann Osley, Ph.D., University of New Mexico Health Sciences Center; Lorraine Pillus, Ph.D., University of California, San Diego; Danny Reinberg, Ph.D., University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School; Robert Roeder, Ph.D., Rockefeller University; Jerry L. Workman, Ph.D., Stowers Institute for Medical Research; and Richard A. Young, Ph.D., of the Whitehead Institute, the Broad Institute, and the Massachusetts Institute of Technology. Sponsors included Beckman Coulter, Inc., Denville Scientific Products, GlaxoSmithKline, Invitrogen, Open Biosystems, Perkin Elmer Life and Analytical Sciences, and Upstate Cell Signaling Solutions.



Luis J. Montaner, D.V.M., D.Phil., and Paul E. Farmer, M.D.

Stephen Buratowski, Ph.D., of Harvard Medical School, gave the 2004 **George Khoury Memorial Lecture** on September 21. The event was sponsored by The Hassel Foundation. Buratowski's talk was titled, "Connecting Transcription with Chromatin and mRNA Processing." The annual lecture brings a leading scientist to Wistar to honor the memory of George Khoury, M.D., former head of the Laboratory of Molecular Virology at the National Cancer Institute and trustee of The Hassel Foundation.

Renowned physician and anthropologist Paul E. Farmer, M.D., Ph.D., of Harvard Medical School and Brigham and Women's Hospital, gave the 2004 **Jonathan Lax Memorial Lecture** on November 5. Farmer delivered a pair of lectures, one in the afternoon and an evening lecture at the Doubletree Hotel in Center City in the evening. Farmer spoke about his efforts to treat HIV/AIDS among poor communities in Haiti. He has won many prestigious awards for his work, including the MacArthur Foundation's "genius" award. The Lax lecture, co-sponsored by Philadelphia FIGHT, honors the memory of Jonathan Lax, an activist and former president of FIGHT's board of directors who died of AIDS in 1996. Associate professor **Luis J. Montaner, D.V.M., D.Phil.**, organizes the annual lecture.

Jay Berzofsky, M.D., Ph.D., of the National Cancer Institute, was the speaker at the 2004 **Tadeusz J. Wiktor Memorial Lecture** on November 17. The title of Berzofsky's talk was "The Role of Cytokines and Co-stimulatory Molecules in Regulating Vaccine-Induced Cytotoxic T Lymphocyte Memory and Avidity." The annual lecture was founded by The Wistar Institute in memory of Tadeusz J. Wiktor, former head of Wistar's rabies unit.

# IN THE COMMUNITY

Wistar initiated a new science journalism award in 2004 to recognize outstanding reporting on the biomedical sciences. The joint winners of the inaugural award were Sue Goetinck Ambrose, of *The Dallas Morning News*, and W. Wayt Gibbs, of *Scientific American*. The co-winners shared a cash prize of \$5,000 and were honored at a ceremony on June 4. A day-long professional seminar for journalists on vaccine research was held at the Institute in conjunction with the awards presentation.

The new Wistar Institute Science Journalism Award recognizes biomedical research as a key force for change in the world today, with important economic and social implications for the future. Intelligent, perceptive journalism written in broadly accessible language plays a primary role in communicating progress in biomedicine to the public, which both supports and is the beneficiary of basic biomedical research. For these reasons, journalistic excellence in this area is of the highest importance and deserves to be honored.

Ambrose and Wayt were recognized for stories about epigenetics, an emerging and still not widely understood field of genetic research.

An independent committee of accomplished science and medical reporters judged the entries. The six judges were: Deborah Blum (co-chair), professor of journalism, University of Wisconsin-Madison, and 1992 Pulitzer Prize winner; Joe Palca (co-chair), senior science correspondent, National Public Radio; Robert Bazell, chief science correspondent, NBC News; Carol Ezzell Webb, freelance journalist and contributing editor for *Scientific American*; Usha Lee McFarling, science writer, *Los Angeles Times*; and Charles Petit, senior writer, *U.S. News & World Report*.

The Institute launched a new authors series in 2004 in order to introduce a wider audience to Wistar and its research mission. The program brings to Wistar authors of science and medical books geared to a general-interest audience.

The 2004 Authors Series debuted in February, with John M. Barry speaking at Wistar about his book, *The Great Influenza: The Epic Story of the Deadliest Plague in History*. The Institute's Joseph N. Grossman Auditorium held a capacity crowd for the event. Barry also discussed his work earlier in the day on WHYY-FM's "Radio Times."

Author Stephen S. Hall visited Wistar in May to discuss *Merchants of Immortality: Chasing the Dream of Human Life Extension*, a book that details the efforts of scientists and entrepreneurs who are working to extend the human life span. And journalist Maryn McKenna spoke in November about her book, *Beating Back the Devil: On the Front Lines with the Disease Detectives of the Epidemic Intelligence Service*, which explores the elite unit at the Centers for Disease Control that investigates outbreaks worldwide.

Talks are followed by a reception and book signing in Wistar's atrium. The Joseph Fox Bookshop, an independent bookseller located in Center City, provides books for sale at the events.

Author John M. Barry





Wistar's Elizabeth O'Brien, Esq., with Ronald B. Herberman, M.D., of the University of Pittsburgh (left), and Brad Clemensen, who received the Pennsylvania Cancer Alliance award on behalf of Rep. John P. Murtha.

A group of Wistar scientists and administrators visited Harrisburg, Pa., on January 26 and 27 with colleagues from across the state representing the Pennsylvania Cancer Alliance, a coalition of the Commonwealth's leading cancer centers. Organized by The Wistar Institute and Fox Chase Cancer Center in 1998, the Pennsylvania Cancer Alliance works on collaborative projects to fight cancer through basic research, clinical investigations, and prevention studies.

Alliance members visited with members of the Pennsylvania legislature to update them on how funds from the Master Tobacco Settlement are being used to support vital cancer research projects. They emphasized the importance of this funding in fostering collaborations and in supporting early-stage research projects with the potential to lead to advances in cancer detection and treatment.

On the evening of January 26, the Alliance held a reception at the Whitaker Center honoring U.S. Representative John P. Murtha for his longstanding support of cancer research funding while serving Pennsylvania's 12th District in Congress.

Representing Wistar were president and CEO Russel E. Kaufman, M.D.; Elizabeth O'Brien, Esq., who manages Wistar's government relations efforts as vice president of legal and external affairs; Louise C. Showe, Ph.D., an associate professor working on a lung-cancer project supported by funding from the Commonwealth; and Franklin Hoke, director of public relations.

Wistar again played host to Nikon's Small World Competition, a traveling show of 20 prize-winning scientific images. The annual competition honors excellence in photomicrography—photography taken through the microscope. The winning images were on display in the Institute's atrium in November and December. The exhibition kicked off November 12 with an opening night party sponsored by Optical Apparatus Company, a scientific instruments dealer in Pennsylvania. James Hayden, manager of Wistar's microscopy facility, coordinated the exhibition. Hayden is a past Small World winner and judge.

In July, the Food and Drug Administration approved a new imaging agent called NeutroSpec™ that can detect appendicitis more rapidly and accurately than was previously possible. The agent, also likely to be used to diagnose other hidden infections, such as bone infections, post-surgical abscesses, or even inhalation anthrax, is based on an antibody discovered at Wistar in 1978.

Developed further by Palatin Technologies Inc. with assistance from Thomas Jefferson University, NeutroSpec™ will be marketed by Mallinckrodt Imaging, a unit of Tyco Healthcare.

The Wistar antibody, labeled with a radioactive tracer molecule to create NeutroSpec™, binds selectively to neutrophils, a type of white blood cell that travels through the body to sites of infection. When injected into the blood, NeutroSpec™ locates and binds to neutrophils battling an infection, allowing physicians to visualize the infection with a gamma camera, a common piece of equipment in hospital nuclear medicine departments.

The FDA approved NeutroSpec™ for use in patients five years of age and older with equivocal symptoms of appendicitis. It is estimated that about half of the 700,000 patients in the United States with suspected appendicitis each year lack distinctive symptoms, such as pain and tenderness in the right lower abdomen, fever, nausea, and an elevated white blood cell count.

NeutroSpec™ enables physicians to diagnose appendicitis rapidly in cases without straightforward symptoms, eliminating the delays and risks associated with current diagnostic capabilities, including unnecessary surgeries. In Phase III clinical studies of NeutroSpec™, ninety percent of appendicitis cases were diagnosed within an hour.

The antibody was discovered by then Wistar scientists Barbara Knowles, Ph.D., and Davor Solter, M.D., Ph.D. Today, Knowles is with The Jackson Laboratory in Bar Harbor, ME, and Solter with the Max Planck Institute for Immunobiology in Freiburg, Germany.

"It's wonderful to be part of something that can be used to help patients in everyday medicine," Knowles told *The Philadelphia Inquirer* in July.

**PRESIDENT AND CEO**

Russel E. Kaufman, M.D.

**PROFESSOR AND VICE PRESIDENT  
FOR ACADEMIC AFFAIRS**

Clayton A. Buck, Ph.D.

**PROFESSOR AND DEPUTY  
DIRECTOR OF THE  
CANCER CENTER**

Frank J. Rauscher III, Ph.D.

**PROFESSOR AND ASSOCIATE  
DIRECTOR OF TRAINING  
PROGRAMS**

Ellen Puré, Ph.D.

**HILARY KOPROWSKI PROFESSOR**

Shelley L. Berger, Ph.D.

**PROFESSORS**

Roger M. Burnett, Ph.D.  
Andrew J. Caton, Ph.D.  
Jan Erikson, Ph.D.  
Hildegund C.J. Ertl, M.D.  
Walter Gerhard, M.D.  
Ellen Heber-Katz, Ph.D.  
Dorothee Herlyn, D.V.M., D.Sc.  
Meenhard Herlyn, D.V.M.  
Elliot M. Levine, Ph.D.  
Ronen Marmorstein, Ph.D.  
Gerd G. Maul, Ph.D.  
Kazuko Nishikura, Ph.D.  
David W. Speicher, Ph.D.

**ASSOCIATE PROFESSORS**

Anthony J. Capobianco, Ph.D.  
Thanos D. Halazonetis, D.D.S., Ph.D.\*  
Paul M. Lieberman, Ph.D.  
Luis J. Montaner, D.V.M., D.Phil.  
Laszlo Otvos Jr., Ph.D.  
Harold C. Riethman, Ph.D.  
Ramin Shiekhattar, Ph.D.  
Louise C. Showe, Ph.D.

**ASSISTANT PROFESSORS**

Nadia Dahmane, Ph.D.  
Joseph L. Kissil, Ph.D.  
Steven B. McMahon, Ph.D.  
Wolfgang Weninger, M.D.  
Jumin Zhou, Ph.D.

**CORE DIRECTORS**

John Rux, Ph.D.  
William H. Wunner, Ph.D.

**SENIOR SCIENTISTS**

Klara Berensci, M.D.  
Jihed Chehimi, Ph.D.  
Emmanuel Faust, Ph.D.  
William Fredericks, Ph.D.  
Steven Kazianis, Ph.D.  
Zhao-Jun Liu, Ph.D.  
Michael Showe, Ph.D.  
Rajasekharan Somasundaran, Ph.D.  
Rolf Swoboda, Ph.D.  
Zhi Quan Xiang, Ph.D.

**STAFF SCIENTISTS**

Naiyer Azam, Ph.D.  
Livio Azzoni, M.D., Ph.D.  
Lois Cavanagh, Ph.D.  
Lise Clark, D.V.M., Ph.D.  
Dong Fang, Ph.D.  
Amuthan Govindasamy, Ph.D.  
Michele Jacob, Ph.D.  
Dimitri Negorev, Ph.D.  
Emmanouil Pappasavvas, Ph.D.  
Hongzhuang Peng, Ph.D.  
Eleni Stavridi, Ph.D.  
Hsin-Yao Tang, Ph.D.  
Qiyi Tang, Ph.D.  
Qingde Wang, M.D., Ph.D.  
Kehao Zhao, Ph.D.

**ASSOCIATE STAFF SCIENTISTS**

Celia Chang, Ph.D.  
JingQi Feng, Ph.D.  
Santosh Hodawakekar, Ph.D.  
Thanuja Krishnamoorthy, Ph.D.  
Easwari Kumaraswamy, Ph.D.

**INSTITUTE PROFESSOR**

Leonard Warren, M.D., Ph.D.

**CASPAR WISTAR SCHOLAR**

David Kritchevsky, Ph.D.

**PROFESSOR LAUREATE**

Hilary Koprowski, M.D.

**EMERITUS PROFESSORS**

Vincent Cristofalo, Ph.D.  
Stanley Plotkin, M.D.  
Robert Roosa, Ph.D.  
Zofia Wroblewska, M.D.

\* Promoted to professor on January 1, 2005



#### ADJUNCT PROFESSORS

Steven M. Albelda, M.D.  
*University of Pennsylvania*

Richard Assoian, Ph.D.  
*University of Pennsylvania*

Garret M. Brodeur, M.D.  
*Children's Hospital of Philadelphia*

H. Fred Clark, D.V.M., Ph.D.  
*Children's Hospital of Philadelphia*

Peter J. Curtis, Ph.D.  
*Thomas Jefferson University*

David E. Elder, M.B., Ch.B.  
*University of Pennsylvania*

Beverly S. Emanuel, M.D.  
*Children's Hospital of Philadelphia*

Nigel W. Fraser, Ph.D.  
*University of Pennsylvania*

Mark I. Greene, M.D., Ph.D.  
*University of Pennsylvania*

Dupont Guerry, M.D.  
*University of Pennsylvania*

Katherine A. High, M.D.  
*Children's Hospital of Philadelphia*

Ruth Muschel, M.D., Ph.D.  
*University of Pennsylvania*

Paul A. Offit, M.D.  
*Children's Hospital of Philadelphia*

Reynold Panettieri, M.D.  
*University of Pennsylvania*

George C. Prendergast, Ph.D.  
*Lankenau Institute for Medical Research*

Thomas D. Stamato, Ph.D.  
*Lankenau Institute for Medical Research*

Barbara L. Weber, M.D.  
*University of Pennsylvania*

John H. Wolfe, V.M.D., Ph.D.  
*University of Pennsylvania*

#### ADJUNCT ASSOCIATE PROFESSORS

Frederic G. Barr, M.D., Ph.D.  
*University of Pennsylvania*

Horace M. DeLisser, M.D.  
*University of Pennsylvania*

Dennis E. Discher, Ph.D.  
*University of Pennsylvania*

Wafik S. El-Deiry, M.D., Ph.D.  
*University of Pennsylvania*

Jonathan A. Epstein, M.D.  
*University of Pennsylvania*

Ann Jeglum, V.M.D.  
*Veterinary Oncology Services and  
Research Center*

#### ADJUNCT ASSISTANT PROFESSORS

Aili L. Lazaar, M.D.  
*University of Pennsylvania*

Mark S. Lechner, Ph.D.  
*Drexel University*

Ali Shokoufandeh, Ph.D.  
*Drexel University*

David A. Tuveson, M.D., Ph.D.  
*University of Pennsylvania*

Omaida C. Velazquez, M.D.  
*University of Pennsylvania*

#### EXTERNAL SCIENTIFIC ADVISORY COMMITTEE

##### MEMBERS

C. David Allis, Ph.D.  
*The Rockefeller University*

Claudio Basilico, M.D.  
*New York University Medical Center*

Olivera J. Finn, Ph.D.  
*University of Pittsburgh*

James N. Ihle, Ph.D.  
*St. Jude Children's Research Hospital*

Antonio Lanzavecchia, M.D.  
*Institute for Research in Biomedicine*

Peter E. Lipsky, M.D.  
*National Institute of Musculoskeletal and Skin  
Diseases*

Scott W. Lowe, Ph.D.  
*Cold Spring Harbor Laboratory*

Joseph S. Pagano, M.D.  
*University of North Carolina Comprehensive  
Cancer Center*

Hidde Ploegh, Ph.D.  
*Harvard Medical School*

Sidney Strickland, Ph.D.  
*The Rockefeller University*

Richard A. Young, Ph.D.  
*Whitehead Institute for Biomedical Research  
Massachusetts Institute of Technology*

Edward Ziff, Ph.D.  
*Howard Hughes Medical Institute  
New York University Medical Center*

In February 2005, I stepped down as Chair of The Wistar Institute's Board of Managers. My resignation was effective upon the election of new Board Chair Brian Dovey at the April 2005 meeting of the Board. Hal Davis continues in his role as Vice Chair of the Board.

My tenure as Board Chair, which began in May 1998, has been a source of great satisfaction for me, with the Institute's capacities in genetics and cancer research steadily increasing over that period. I am particularly proud of the successful recruitment in June 2002 of Wistar President and CEO Russel E. Kaufman, M.D., ensuring vital leadership for Wistar in the coming years.

As many of you know, the Board approved at its December 2004 meeting an ambitious new Strategic Plan for Wistar that refocuses Wistar's scientific goals to build on existing strengths and move into several areas of emerging research opportunity. The plan also envisions nothing less than a complete renewal of the Institute's facilities in support of the scientific goals spelled out in its pages. Brian oversaw development of the new Strategic Plan, working closely with Dr. Kaufman. Brian's extensive experience and knowledge in the fields of medical research and technology transfer helped him to guide the planning process with a sure hand. Those abilities will also make his leadership invaluable to the future growth of the Institute. Hal's expertise in real estate and construction will be a great asset to Dr. Kaufman as he rebuilds the infrastructure of the Institute.

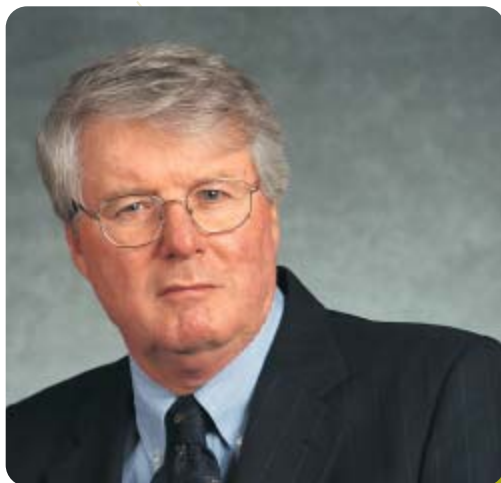
Wistar has entered a period of profound change and is moving forward quickly. The catalyst for this change has been Dr. Kaufman. Under his guidance, Wistar has recruited a number of talented new young scientists to join the creative and productive researchers already on board, and more are expected to join the faculty this year. Any visitor to the Institute today can hardly fail to notice the construction and renewal under way throughout the facility.

The Wistar Institute has a history of remarkable accomplishment. In early 2005, for example, the Centers for Disease Control declared rubella, a disease responsible for a range of damaging birth defects, to be eradicated in the United States, thanks to a vaccine developed at Wistar by Dr. Stanley Plotkin. In July 2004, the Food and Drug Administration approved a new imaging agent for detecting certain difficult-to-diagnose cases of appendicitis quickly and accurately. That agent, NeutroSpec™, is based on a monoclonal antibody discovered at Wistar.

Still, it is the future that we focus on today. Under Brian's leadership and that of Dr. Kaufman, with the steadfast support of the Institute's faculty, staff, friends, and supporters, it is clear that Wistar's greatest days are yet to come.

**Kevin M. Tucker**

Chair, Board of Managers





## 2004 Board of Managers

### OFFICERS

**Kevin M. Tucker**  
Chair  
**Harold M. Davis**  
Vice Chair  
**Brian H. Dovey**  
Vice Chair  
**Doris Taxin**  
Secretary  
**Ian J. Berg**  
Treasurer

### MEMBERS

**D. James Baker, Ph.D.**  
President & CEO  
Academy of Natural Sciences  
**Robert Barchi, M.D., Ph.D.**  
President  
Thomas Jefferson University  
**Vincent G. Bell, Jr.**  
President  
Verus Corporation  
**Ian J. Berg**  
Managing Director  
Eastern Technology Fund  
**Robert S. Blank**  
Partner  
Whitcom Partners  
**Ira Brind**  
President  
Brind Investment, Inc.  
**Harold M. Davis**  
Chairman  
Realen Properties  
**Peter C. Doherty, Ph.D.**  
Chairman, Department of Immunology  
St. Jude Children's Research Hospital

**Brian H. Dovey**  
General Partner  
Domain Associates  
**Robert A. Fox**  
Chairman and C.E.O.  
R.A.F. Industries, Inc.  
**Roger S. Hillas**  
**Richard M. Horowitz**  
President  
R.A.F. Industries, Inc.  
**James N. Ihle, Ph.D.**  
Chairman, Department of Biochemistry  
St. Jude Children's Research Hospital  
Howard Hughes Investigator  
Howard Hughes Medical Institute  
**Herbert Kean, M.D.**  
**Hilary Koprowski, M.D.**  
Director  
Biotechnology Foundation Laboratories  
and Center for Neurovirology  
Thomas Jefferson University  
Professor Laureate  
The Wistar Institute  
**Ira M. Lubert**  
Managing Director  
Quaker BioVentures, Inc.  
**Faye S. Olivieri**  
President  
Agenda, Inc.  
**Albert Ominsky, Esq.**  
Ominsky & Ominsky, P.C.  
**Ruth Patrick, Ph.D.**  
Francis Boyer Chair  
The Academy of Natural Sciences  
**Seymour S. Preston III**  
The Millrace Group  
**Helen P. Pudlin, Esq.**  
Senior Vice President & General Counsel  
The PNC Financial Services Group  
**Samuel V. Rhoads**  
Senior Vice President  
Philadelphia Industrial Development Corporation

**Robert H. Rock**  
President  
MLR Holdings LLC  
**Gerald B. Rorer**  
**Adele K. Schaeffer**  
**Paul J. Schmitt**  
Managing Director  
Pennsylvania Early Stage Partners  
**Ernest R. (Roy) Shapiro**  
**Edward Sickles**  
**Arthur L. Stokes, M.D.**  
Chief Medical Officer  
Senzo Research Corporation  
**Susan Sullivan**  
**Doris Taxin**  
**Kevin M. Tucker**  
**David V. Wachs**  
**Daniel H. Wheeler**  
Deputy Secretary for Property Management  
Department of General Services

### EMERITUS BOARD MEMBERS

**Jean Bellet Green**  
**Harris N. Hollin**  
President  
Conquer Fragile X Foundation  
**Isadore M. Scott**  
**Howard S. Turner, Ph.D.**

# RETIREMENTS

## CLAYTON A. BUCK, PH.D.

Clayton A. Buck, Ph.D., professor and vice president for academic affairs at Wistar, retired in December 2004. Buck had an extraordinary career as both a scientist and administrator at Wistar. He has been appointed emeritus professor.



Buck arrived at Wistar in 1975 as a professor. His research focused on cell-cell and cell-matrix adhesion receptors in cancer and cardiovascular development. From 1992-99, he was editor-in-chief of the journal *Cell Adhesions and Communication*. In addition to his appointment at Wistar, Buck was also an adjunct professor at the University of Pennsylvania in biology, pediatric cardiology, and pediatrics in medicine. He is an author of more than 115 scientific publications.

During the 1990s, Buck devoted an increasing amount of his time to leadership positions at Wistar. From 1990-92 he was director of scientific development, followed by positions as deputy director of the Institute from 1992-99 and chief administrative officer from 1999-2000.

In 2000, Buck became acting director and CEO of the Institute, a position he held until the appointment of Russel E. Kaufman, M.D., in 2002. During his tenure as acting head of Wistar, the Institute's per-investigator levels of federal funding grew substantially, and major new efforts were initiated in functional genomics, proteomics, and bioinformatics. From 2002-2004, Buck served as vice president for academic affairs.

Buck was honored for his outstanding contributions to Wistar at a reception in March 2005, which was attended by his family, friends, and colleagues.

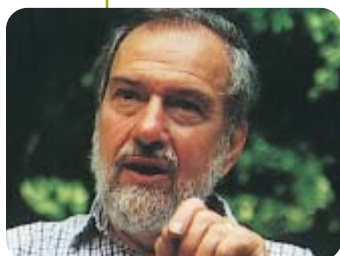
## LEONARD WARREN, M.D., PH.D.

Leonard Warren, M.D., Ph.D., retired from Wistar as Institute Professor in December 2004. He was honored in January 2005 with the title of emeritus professor at a dinner celebrating his distinguished career as a scientist, scholar, and author.

Like his colleague Clayton Buck, Warren joined Wistar as professor in 1975. His research interests included studies of glycoproteins, the biochemistry of surface membranes of normal and malignant animal cells, and secretory processes in normal and malignant cells, including cells from patients with hereditary diseases. He also held positions as professor of anatomy at the University of Pennsylvania and a research professorship with the American Cancer Society, among others.

More recently, Warren turned to writing science biographies. His first book, *Joseph Leidy: The Last Man Who Knew Everything*, provides a detailed account of a leading nineteenth-century scientist who, despite being considered the founder of vertebrate paleontology and the father of parasitology, is little known today. The book, published in 1998, was winner of the Athenaeum Literary Award. Since then, Warren has also published books about Adele Marion Field, a nineteenth-century scientist, social activist, and missionary, and Constantine Samuel Rafinesque, a nineteenth-century naturalist noted both for his accomplishments and his profoundly difficult personality.

He is completing work on his fourth book, on geologist William Maclure, who was president and a major benefactor of Philadelphia's Academy of Natural Sciences. Warren spends his summers writing at the Marine Biological Laboratory in Woods Hole, Massachusetts.



# THE YEAR IN REVIEW

## FINANCIALS

### SOURCES OF FUNDS

Federal grant funding	\$28,793,000	66%
Foundation and other private research funding	\$5,387,000	12%
State funding	\$2,720,000	6%
Corporate-sponsored research	\$154,000	<1%
Unrestricted contributions	\$1,564,000	4%
Technology transfer	\$1,823,000	4%
Total return on invested funds	\$3,300,000	8%

**Total** **\$43,741,000**

### STAFF

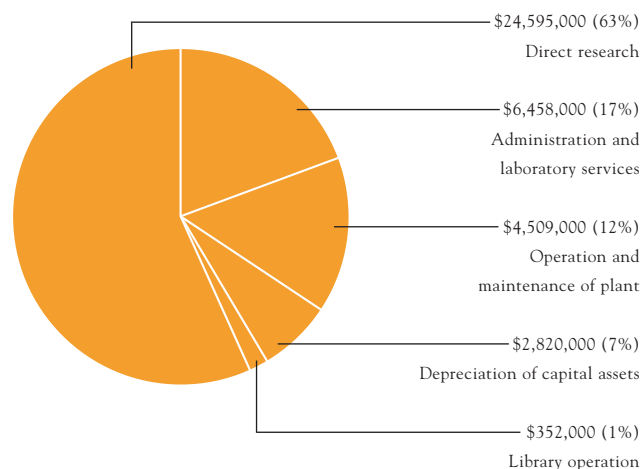
Total employees	346
Number of laboratories	33
Number of postdoctoral fellows	82
Number of predoctoral fellows	36
Number of visiting scientists	18
Number of countries of origin represented	30

(Algeria, Argentina, Australia, Austria, Brazil, Canada, China, Ethiopia, France, Ireland, Germany, Ghana, Greece, Hungary, India, Iran, Israel, Italy, Japan, Korea, Poland, Romania, Russia, Singapore, Trinidad, Turkey, Ukraine, United Kingdom, United States, Vietnam)

### USES OF FUNDS

Direct research	\$24,595,000	63%
Administration and laboratory services	\$6,458,000	17%
Operation and maintenance of plant	\$4,509,000	12%
Library operation	\$352,000	1%
Depreciation of capital assets	\$2,820,000	7%

**Total** **\$38,734,000** 100%



### U.S. PATENTS ISSUED IN 2004

Method of Preventing Cancer Recurrence, Alessandra Cesano, Giovanni Rovera, Daniela Santoli, U.S. Patent No. 6,716,425.

Peptides and Peptidomimetics with Structural Similarity to Human p53 that Activate p53 Function, Thanos Halazonetis, Wolfgang Hartwig, U.S. Patent No. 6,784,157.

Method of Modifying Cytotoxic Cells and Uses Thereof, Alessandra Cesano, Giovanni Rovera, Daniela Santoli, U.S. Patent No. 6,828,147.

Bridging Integrator-2 (BIN2) Nucleic Acid Molecules and Proteins and Uses Therefor, Kai Ge, George Prendergast, U.S. Patent No. 6,831,063.

### CENTERS

Cancer Center  
Robert A. Fox Structural Biology Center  
Albert R. Taxin Brain Tumor Research Center

### FACILITIES

Animal Facility  
Bioinformatics Facility  
Flow Cytometry Facility  
Genomics Facility  
Histotechnology Facility  
Hybridoma Facility  
Library and Wistar Archives  
Microscopy Facility  
Mouse Genetics Facility  
Protein Expression Facility  
Proteomics Facility  
Research Communications Facility  
Research Supply Facility

## ADMINISTRATION

*Russel E. Kaufman, M.D.*  
President and CEO

*Larry A. Keinath, C.P.A.*  
Vice President, Finance and Administration

*Elizabeth O'Brien, Esq.*  
Vice President, Legal and External Affairs

*Ellen Puré, Ph.D.*  
Professor and Associate Vice President  
of Academic Affairs

*Frank J. Rauscher III, Ph.D.*  
Professor and Deputy Director of The Wistar  
Institute Cancer Center  
Associate Director of Research Programs

*Peter Corrado*  
Director of Institutional Development

*Denise DiFrancesco*  
Animal Facility Director

*Franklin Hoke*  
Director of Public Relations

*Elliot Levine, Ph.D.*  
Director of Research Compliance and  
Resources

*Nina Long, M.L.S.*  
Director of Library Services, Archivist, and  
Curator of The Wistar Museum Collections

*Ronen Marmorstein, Ph.D.*  
Director of Training

*Meryle J. Melnicoff, Ph.D.*  
Director of Business Development

*Jo-Ann Mendel*  
Director of Human Resources

*Ray Preis*  
Director of Information Systems

*Berenice Saxon*  
Director of Research Services

*Kenneth J. Sulkowski*  
Director of Facilities Planning

*William H. Wunner, Ph.D.*  
Director of Outreach and Technology  
Training Programs



# THE WISTAR INSTITUTE

TODAY'S DISCOVERIES – TOMORROW'S CURES

3601 Spruce Street  
Philadelphia, PA 19104-4268  
(215) 898-3700  
[www.wistar.org](http://www.wistar.org)

The Wistar Institute's 2004 Annual Report was produced by the Office of Public Relations.

Franklin Hoke, Director of Public Relations  
Marion Wyce, Public Relations Associate  
Design: SK Designworks  
Principal photographer: Addison Geary  
Accent imagery: Peter Olson

The Wistar Institute is an equal opportunity/affirmative action employer. It is the policy of The Wistar Institute to provide equal employment opportunities to all individuals regardless of race, color, creed, religion, national origin, ancestry, sex, age, veteran status, disability, sexual orientation, or gender identity for all terms and conditions of employment.