CHANGING THE WORLD

THE WISTAR INSTITUTE

ANNUAL REPORT 2013

Never doubt that a small group of thoughtful, committed people can change the world. Indeed, it is the only thing that ever has.

MARGARET MEAD (attributed)

LOOKING BACK ON 2013, I could not be prouder of The Wistar Institute. These past twelve months we achieved major milestones that both acknowledge our leadership in science and are the foundation for our growth.

Our talented scientists won an exceptional number of new and significant grants, outsized in terms of the relatively small size of our Institute. Their work was recognized by a record number of scientific publications in prominent journals.

Wistar's Cancer Center underwent a rigorous review by the National Cancer Institute for renewal as an NCI-designated cancer center, a prestigious designation that is given to only 68 of the approximately 1,500 cancer centers in the United States. We are proud to say that *both* the Wistar Cancer Center *and* its director, Dr. Dario Altieri, received the highest possible rating, summed up by the NCI review team in one word:

EXCEPTIONAL

As I write this, the Robert and Penny Fox Tower nears completion. Our faculty and staff have put up with inconvenience and interruptions to their work over the last three years. They will soon be able to take full advantage of the new facilities and resources that the Tower will provide.

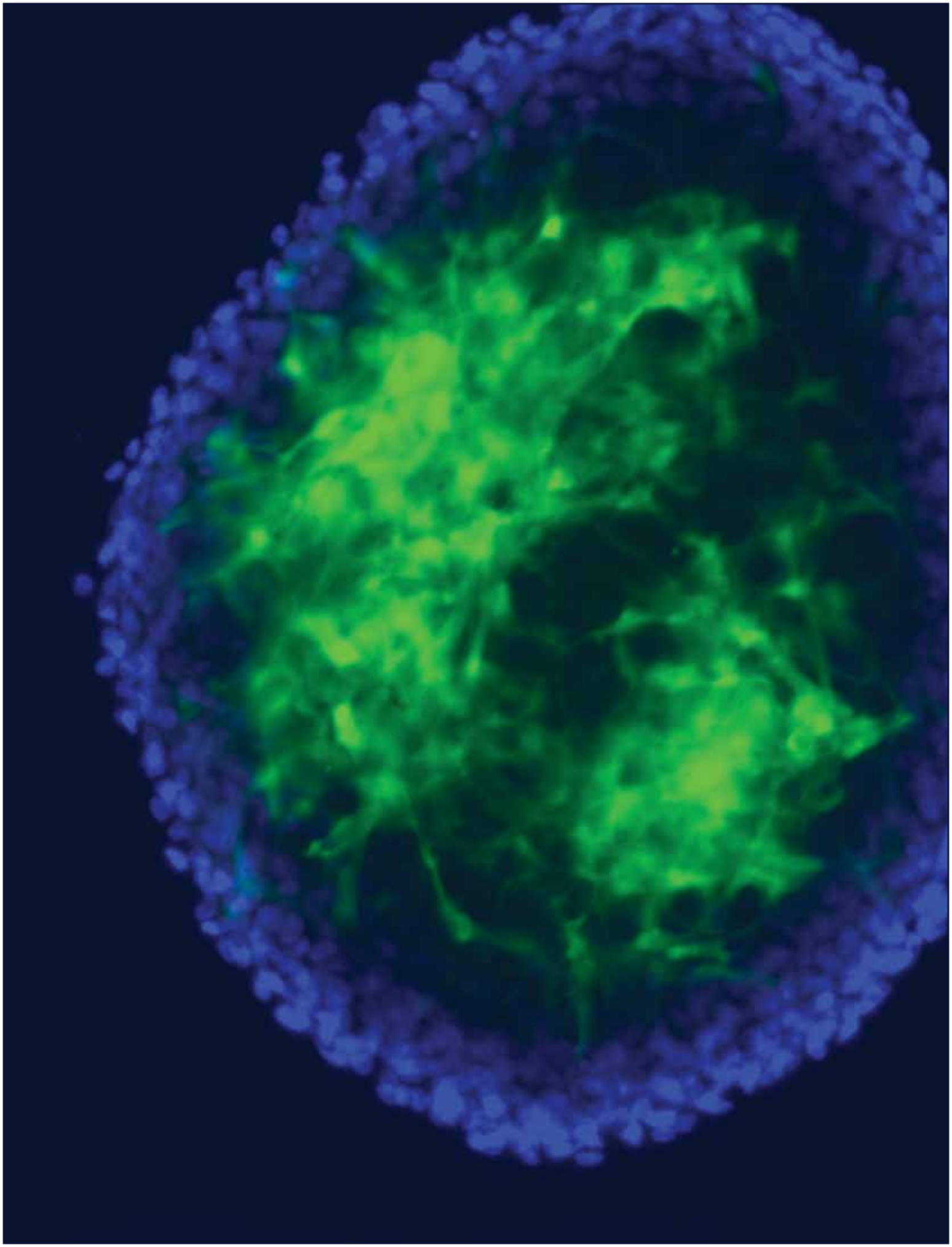
Even when the last new window goes into place and the last construction worker leaves the site, Wistar will still be building. Our highest priority will be to recruit, retain and support the talented scientists who are the lifeblood of the Institute. Our NCI Cancer Center designation, exceptional rating, and modern new Tower will help us attract the most qualified scientists to build our community of researchers who work on the frontiers of knowledge.

We are building Wistar. We are changing the world.

We could not do this without your support. I believe we scientists, staff and supporters share a common conviction: Scientific knowledge can save lives.

Indeed, it is the only thing that ever has.

RUSSEL E. KAUFMAN, M.D.
President and CEO



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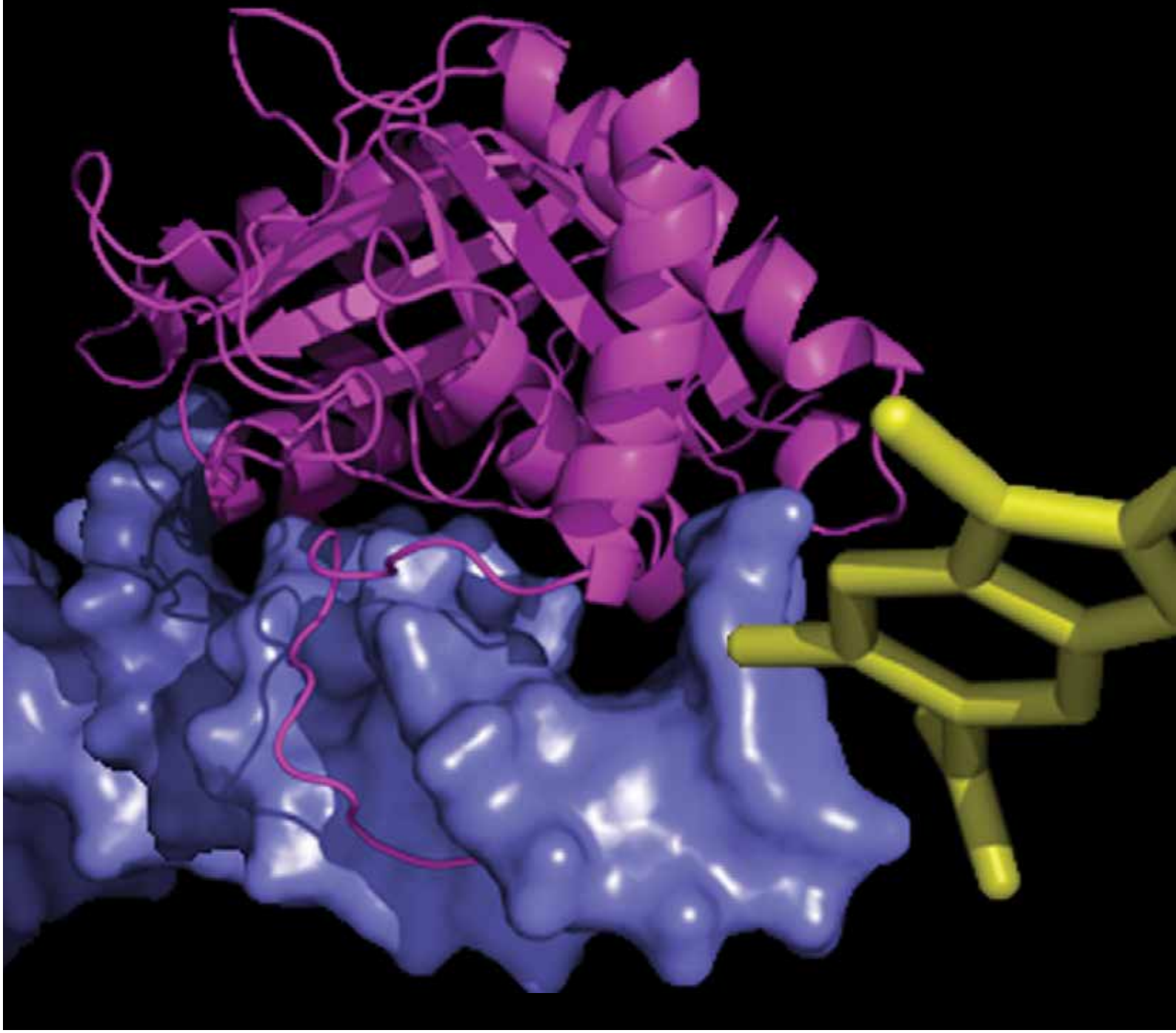
TRANSLATIONAL RESEARCH

FROM PROMISE TO PRACTICE—
WISTAR TRANSFORMS CANCER MEDICINE
THROUGH SCIENCE



"The era of personalized medicine is here. We need to leverage what we learn from 'genomic medicine' to individualize therapy for every cancer patient," said, Dario C. Altieri, M.D., Robert and Penny Fox Distinguished Professor and director of Wistar's Cancer Center. "Our goal is to bring the right drug to the right patient at the right time."

Altieri and his colleagues at The Wistar Institute are working to bridge the gap between promising discoveries in the lab and effective, potentially life-saving therapies in the clinic.

"It's our duty to develop translational research programs with the potential for direct clinical impacts," Altieri said. "What we lack is a full spectrum of new drugs that affect all the molecular targets in cancer that are currently being identified."

In the past, Wistar scientists typically handed off early-stage discoveries to drug companies for further development. Under their license from Wistar, the companies would conduct both preclinical and clinical testing, and advance the most promising drug candidates to market.

Today, that process is no longer so simple. A 2012 analysis published in *Forbes* magazine estimated that it costs nearly $5 billion to bring a new drug into the market. New, innovative drugs of the sort that Altieri believes will change the landscape of cancer medicine are difficult investments for drug companies to undertake.

Under Altieri's leadership, Wistar has sought a new path for translational medicine, one in which Wistar scientists, whether individual laboratories or entire programs, join forces to deliver mature technologies ready for clinical trial.

OPPOSITE: THE VIRAL EBNA1 PROTEIN (PINK) LATCHES ONTO EPSTEIN-BARR VIRUS (EBV) DNA (PURPLE). AN INHIBITOR (YELLOW) PREVENTS EBNA1 FROM BINDING TO DNA AND BLOCKS THE SPREAD OF EBV-ASSOCIATED TUMORS.

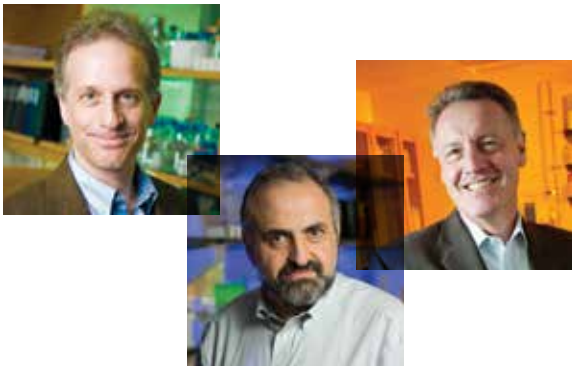
PROMISING APPROACHES

A NEW DRUG FOR PROSTATE CANCER

Altieri's own efforts, a decade-long quest to exploit a fatal flaw in all tumors, received a boost in 2013 from a $1.5 million grant from the U.S. Department of Defense (DOD). This grant, from the DOD's Congressionally Directed Medical Research Program, supports preclinical research on Gamitrinib, a drug developed in the Altieri laboratory. The DOD funds will further the drug's development so that it can enter clinical testing in patients who have advanced and metastatic prostate cancer.

Gamitrinib targets a molecule (HSP90) known to accumulate in large quantities in the mitochondria of cancer cells. Mitochondria are organelles—structures within a cell—that help generate energy for the cell and keep them alive. When in mitochondria, HSP90 functions as a master regulator of multiple functions that are essential for tumor cells to thrive. While mitochondria control energy production, they also control the inherent self-destruct mechanism within cells, a process called programmed cell death or apoptosis.

This is the cellular Achilles' heel that Altieri hopes to exploit with Gamitrinib. The Altieri laboratory designed Gamitrinib to specifically target cancer cells and selectively *disable* their mitochondria, prompting these cells to die. In mice, Gamitrinib also has been shown to enhance the activity of other targeted cancer therapies.



PAUL LIEBERMAN, PH.D
DMITRY GABRILOVICH, M.D., PH.D
DARIO C. ALTIERI, M.D.

The three-year DOD grant supports the cost of generating the data necessary to initiate clinical trials in humans and the development of a biomarker (a unique biological signature) that will enable evaluation of the effectiveness of Gamitrinib in patients.

The goal is to file an Investigational New Drug (IND) application with the U.S. Food and Drug Administration. Through the support of the DOD, Wistar will contract with third-party research organizations to conduct pharmacological studies to demonstrate the drug's effectiveness and safety, the important first step in developing a new therapy.

WELLCOME TRUST MAKES A WELCOME INVESTMENT IN WISTAR

Visionary grant funding is moving a different promising candidate drug toward an IND application in the laboratory of Paul Lieberman, Ph.D., professor and leader of the Cancer Center's Gene Expression and Regulation program. The laboratory is the first in the United States to receive a *Seeding Drug Discovery Award* from Wellcome Trust, a charity based in the United Kingdom.

Lieberman's goal is to create the first-ever therapy for cancers caused by Epstein-Barr virus (EBV), a ubiquitous virus that is responsible for a staggering 400,000 cancer-related deaths each year.

Wellcome Trust's $4.7 million, three-year grant is structured around a newer concept in helping scientists create the new medicines of tomorrow: The researchers must achieve a predetermined set of milestones in order to receive the next portion of funding.

Over the last two years, Lieberman and his team have achieved every goal set for the project. They are now poised to seek additional funding to conduct the studies that will lead to Wistar's application to the FDA for IND status.

A PIONEERING PROGRAM IN TUMOR IMMUNOLOGY

In 2013, Wistar recruited internationally recognized immunologist Dmitry Gabrilovich, M.D., Ph.D., to lead a cutting-edge program of the Cancer Center in Translational Tumor Immunology. (Please see "Exceptional Results," page 18.)

"We have come to understand that the immune system is a critical element of tumor progression," said Gabrilovich, who was named the Christopher M. Davis Professor at the Institute. "Our goal is to make the immune system an active focus of cancer research. We want to convert cancer into a manageable, chronic disease and give patients a better quality of life."

Gabrilovich is developing a dual program: the first, to consider how to stimulate immune response and change the microenvironment (cells and tissues) that gives rise to tumors; the second, to combine immunotherapy with other therapies to create more effective treatment strategies.

"Immunotherapy is a complex area of biomedical research that requires a multifaceted approach to the study of science and disease," said Gabrilovich.

"Our goal is to make the immune system an active focus of cancer research. We want to convert cancer into a manageable, chronic disease and give patients a better quality of life."

"We're building our team with accomplished scientists investigating different aspects of the regulation of the immune system," Gabrilovich said. Over the next two years, he plans to recruit four new team members with the aim of assembling a world-class interdisciplinary team.

TOWARD A WISTAR DRUG PIPELINE

How do you create a new drug for therapy? As Lieberman and Altieri have shown, you start with a target, usually a protein. Then, you aim for that target with a small molecule inhibitor or engineered antibody—a molecule that will bind to and abrogate the functions of the target. Fortunately, Wistar scientists excel at finding targets.

The Center for Chemical Biology and Translational Medicine, directed by Lieberman, was created to help Wistar scientists turn their research discoveries into potential therapies.

The Center leverages the advanced technologies of Wistar's Molecular Screening Facility to identify promising molecular compounds that can bind to—and inhibit—targets of interest.

Once Wistar investigators identify molecular compounds that are possible drug candidates, the Center works closely with medicinal chemists at partnering institutions, such as the Moulder Center for Drug Discovery Research of Temple University's School of Pharmacy, to "humanize" these molecular compounds, that is, make them suitable for use as clinical drugs.

KNOWLEDGE IN THE SERVICE OF NOVEL THERAPIES

The Wistar Institute was built on the promise of basic research. Wistar provides a creative and stimulating environment in which scientists are free to pursue essential, high-risk high-reward science that can elucidate the basic mechanisms of human biology. Their discoveries have led to tests and treatments that change patients' lives, among them: identifying gene mutations that contribute to breast cancer, new vaccines, a diagnostic test for lung cancer, and potential drugs to treat melanoma.

Through translational research, Wistar scientists are exploring and identifying the targets and pathways that can lead to novel, more effective, more accessible, and more affordable treatments for cancer and other diseases.

"It is a new day across the Institute," said Altieri. "We have the tools, we have the talent, and we have the model we need to translate science into new drugs. We have cured enough mice: now it is the time to start curing people."

THE TOWER OF INNOVATION

Silicon Valley is the classic example. Cambridge, Massachusetts is another. Even University City in Philadelphia can be considered what historian Margaret O'Mara, Ph.D., called a "City of Knowledge."

A City of Knowledge is a place where the excitement for science and research is in the air and in the blood. It's a community where the culture supports and encourages risk-takers, techno-pioneers, and innovators.

Wistar's President and CEO, Russel E. Kaufman, M.D., considers Wistar to be a self-contained "City of Knowledge" with the new Robert and Penny Fox Tower as its central, unifying hub.

"Wistar is a destination for great minds to come together to do great things," said Kaufman. "Our new Tower's design reflects and encourages team science, collaboration that crosses the boundaries of disciplines. It is a purpose-built tower of innovation."

The Robert and Penny Fox Tower formally opens in September of 2014.

WISTAR'S NEW ROBERT AND PENNY FOX TOWER IS A SELF-CONTAINED CITY OF KNOWLEDGE.

ON INFRASTRUCTURE: "The new Tower provided an opportunity to unify the infrastructure across the Institute—heating, cooling, electricity, and data. It is engineered and built to meet the full spectrum of our scientists' needs."

ON THE UNIFYING NATURE OF THE TOWER: "The Tower is a hub for the entire Institute. It now links the West Building with the historic East Building. Core teams of scientists will work together in this hub with easy access to colleagues and related facilities located in the East and West Buildings."

ON NEW MEETING SPACES:
"Groundbreaking ideas often emerge from chance encounters that occur *outside* the laboratory. We hope the Robert and Penny Fox Tower will function as a scientific 'matchmaker.' Its comfortable formal and informal meeting places are designed to encourage these meetings and boundary-crossing ideas."

groundbreaking ideas

REMOVING THE BARRIERS TO

collaboration

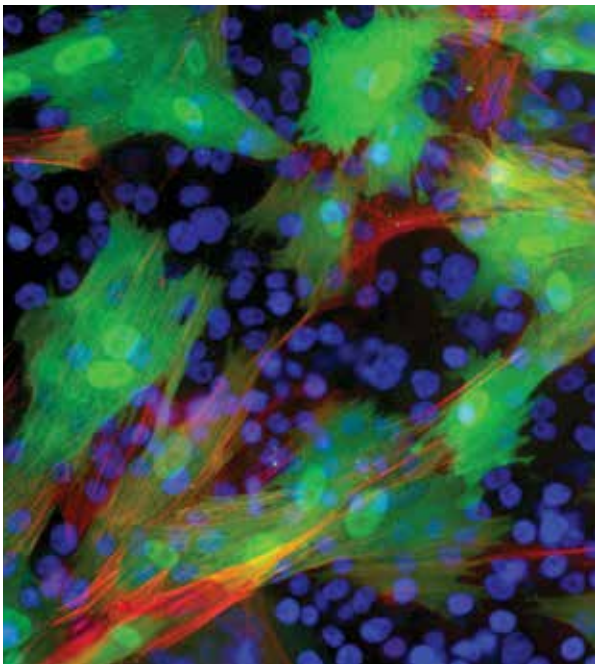
ON NEW PUBLIC SPACES: "The Wistar Institute has a new front door, a welcoming space on Spruce Street that announces our presence to the world. Visitors will be greeted with both objects from our past and our ideas about the future. The public spaces are areas for lectures, demonstrations, and activities that make Wistar's science immediate and relevant to the community."

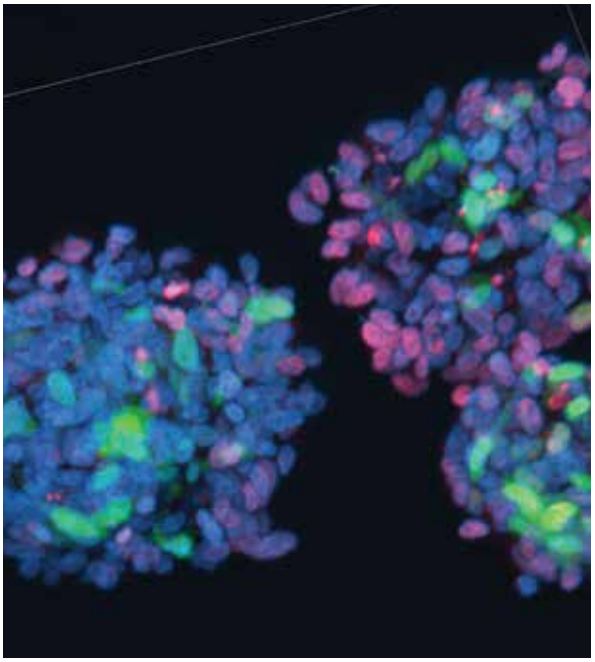
ON LABORATORY SPACES: "These are advanced laboratories designed for team science. We will bring four professors and their scientific staff together in one open space. We remove the barriers to collaboration by bringing teams to one area where it is easy to share ideas, collectively solve problems, and collaborate on projects."

ON THE NEW AUDITORIUM: "The high-tech Caplan Auditorium more than doubles the capacity of our previous largest meeting room. This sophisticated venue for scientific lectures and public events is going to be a real jewel of the Institute."

WISTAR RESEARCH IN REVIEW

THE TOP SCIENCE STORIES OF 2013





Melanoma is an aggressive, deadly form of skin cancer. While smaller melanoma tumors can usually be successfully treated with surgery, there are limited options for patients with metastatic melanoma, where the skin cancer has spread to other organs.

In advanced metastatic melanoma, while drugs can initially succeed in targeting tumors, these tumors inevitably become drug resistant and return, more aggressive than before.

The following scientists are making progress in tackling this difficult issue.

Diabetes Therapy May Treat Melanoma

MEENHARD HERLYN, D.V.M., D.SC.

The laboratory of Meenhard Herlyn, D.V.M., D.Sc., has discovered a promising new approach that may be an effective strategy for keeping tumors at bay.

"Our findings suggest that a simple strategy to kill metastatic melanoma, regardless of cell type within the tumor, is to combine anticancer drugs with a diabetes drug," said Herlyn, Caspar Wistar Professor in Melanoma Research, director of Wistar's Melanoma Research Center, and professor in the Molecular and Cellular Oncogenesis program of Wistar's Cancer Center.

Their studies examined the results of combining standard therapies, such as the chemotherapy cisplatin or a drug called vemurafenib that targets a common melanoma mutation, with phenformin, a diabetes drug that has been available for decades.

"The diabetes drug puts the brakes on the cells that would otherwise repopulate the tumor, thus allowing the anticancer drug to be more effective."

ALTIERI: The recent studies by the Herlyn lab provide a rational foundation to repurpose a drug used in the treatment of diabetes to tackle

IN 2013, WISTAR RESEARCHERS COLLECTIVELY PUBLISHED APPROXIMATELY 153 SCIENTIFIC STUDIES IN MANY OF THE WORLD'S TOP-TIER JOURNALS.

WISTAR'S CHIEF SCIENTIFIC OFFICER AND CANCER CENTER DIRECTOR, DARIO C. ALTIERI, M.D., OFFERS SOME OF THE HIGHLIGHTS OF 2013 IN MELANOMA.

the aberrant metabolism of advanced melanoma. It is the innovative and multidisciplinary nature of the Melanoma Research Center (MRC) that makes possible these advances. The MRC explores all possible routes to combat melanoma to expand our future arsenal in the treatment of advanced disease.

Roesch, Alexander, et al. "Overcoming intrinsic multidrug resistance in melanoma by blocking the mitochondrial respiratory chain of slow-cycling JARID1B(high) cells," *Cancer Cell*, June 10, 2013.

This research is supported by: the National Institutes of Health and the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation.

WHILE MELANOMA ACCOUNTS FOR

ONLY 2%

OF ALL SKIN CANCERS, IT CAUSES ABOUT

75%

OF SKIN CANCER DEATHS.

Finding a Marker for Drug-Resistant Melanoma

ASHANI WEERARATNA, PH.D.

The laboratory of Wistar's Ashani Weeraratna, Ph.D., has found a clue to personalizing treatment. Weeraratna, assistant professor in the Wistar Cancer Center's Tumor Microenvironment and Metastasis program and member of Wistar's Melanoma Research Center, is pursuing new insights into what might drive metastasis in patients with melanoma.

The Weeraratna lab has found that different protein receptors on the outside of tumor cells can alter its phenotype, or outward physical appearance. In one type of highly invasive melanoma, the cells appear to have large amounts of a specific receptor, called Wnt5A; the researchers found that this type of tumor may not respond as well when treated with the anti-melanoma drug vemurafenib. However, people whose tumors had lower levels of Wnt5A responded better to the drug.

"By using Wnt5A as a biomarker [a biological marker detectable in the bloodstream], we could determine which patients are likely to respond better to therapy with vemurafenib and help prolong that response," Weeraratna said.

ALTIERI: While there has been enormous effort to understand the genetic makeup of tumors and identify "actionable" driver mutations, it is ultimately a better understanding of the biology of tumor cells that will guide treatment decisions. Weeraratna's work may be ideally positioned to inform critical therapeutic decision-making for patients with metastatic melanoma.

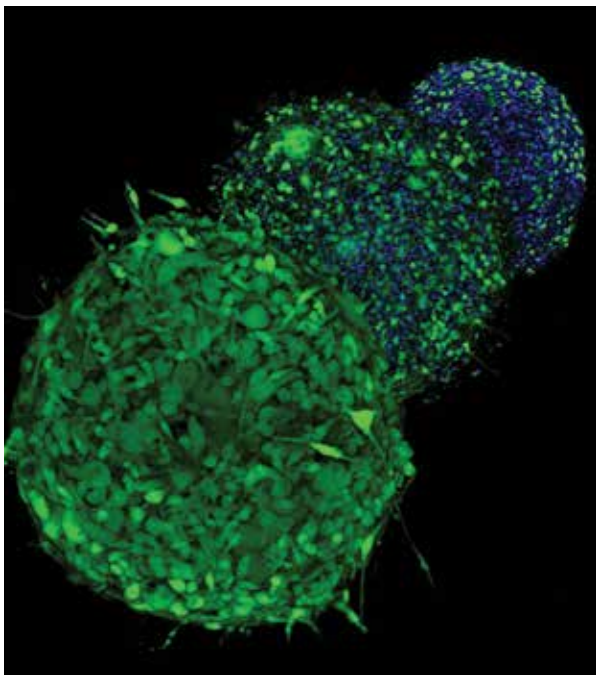
O'Connell, Michael P., et al. "Hypoxia induces phenotypic plasticity and therapy resistance in melanoma via the tyrosine kinase receptors ROR1 and ROR2," *Cancer Discovery*, December 2013.

This research is supported by: the National Institute on Aging Intramural Research Program, the PA Department of Health Commonwealth Universal Research Enhancement (CURE) Program, and the Joanna M. Nicolay Foundation.

Cutting Off All Escape for Melanoma Cells

JESSIE VILLANUEVA, PH.D.

A powerful combination of drugs (known as BRAF and MEK inhibitors) has shown great effectiveness in treating advanced cases of melanoma. The problem is that patients inevitably develop a resistance to the treatment.



In 2013, a team of Wistar researchers reported on research that helps to unravel how drug resistance occurs in combination therapy, describing how melanoma tumors evolve to evade the effects of these drugs.

"Combining BRAF and MEK inhibitors was conceived as a one-two punch against what is called the MAP kinase pathway," said Jessie Villanueva, Ph.D., assistant professor of the Wistar Cancer Center's Molecular and Cellular Oncogenesis program and member of Wistar's Melanoma Research Center. "While this therapy is considered successful in the clinic, some tumors do not respond and others develop resistance, which underscores the need for new therapeutic strategies."

Villanueva and her colleagues demonstrated that resistant melanomas acquired a mutation in the MEK2 gene and multiple copies of the mutant BRAF oncogene, simultaneously decreasing the sensitivity to both drug targets.

"Melanoma tumors are particularly adept at rewiring themselves so that anticancer drugs lose their effectiveness, and we must continue to outthink the disease in order to block off all points at which it can evade therapy," Villanueva said.

AN ESTIMATED

9,710

PEOPLE ARE EXPECTED TO DIE OF MELANOMA IN 2014.*

**American Cancer Society*

ALTIERI: Over the last few years, we have developed effective targeted therapies that spare normal tissues while killing the tumor cells. However, the biggest problem that we face is that clinical gains for our patients are short-lived, and almost invariably followed by the emergence of a drug-resistant relapsed tumor.

Only the kind of in-depth understanding of biology that comes from studies like Villanueva's will enable us to get ahead of this problem and create lasting therapies for our patients.

Villanueva, Jessie, et al. "Concurrent MEK2 mutation and BRAF amplification confer resistance to BRAF and MEK inhibitors in melanoma," *Cell Reports*, September 26, 2013.

This research is supported by: the National Cancer Institute, the PA Department of Health Commonwealth Universal Research Enhancement (CURE) Program, The V Foundation for Cancer Research, the Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, and research funds from GlaxoSmithKline.

Shutting Down DNA Construction

RUGANG ZHANG, PH.D.

A living cell is like a construction site—an organized flurry of building, changing and recycling. New cells are built as they replicate a copy of their DNA and divide. Cancer cells, however, are greedy for resources, and their growth can be checked by the available amount of DNA building blocks, called nucleotides. According to Rugang Zhang, Ph.D., when cells lack nucleotides, they temporarily shut down in a process called "senescence," where the cell remains alive yet cannot reproduce.

"Oncogene-induced senescence is an automatic mechanism that arrests the growth of normal cells when an activated oncogene [or cancer-causing gene] threatens to turn these cells cancerous," said Zhang, associate professor in the Wistar Cancer Center's Gene Expression and Regulation program. "We identified how an oncogene can set senescence into motion by suppressing RRM2, an enzyme necessary for producing nucleotides."

Since cells that lacked nucleotides became senescent, the researchers wondered what would happen if they resupplied the cell with nucleotides—in essence, providing eager workers more bricks. They found that, even in cells with an inactive RRM2 gene, the cell rapidly resumed growing and dividing. Such an event in moles, for example, could be a cause of melanoma, so the Zhang laboratory collaborated with the Wistar Melanoma Research Center in order to study oncogene-induced senescence in tissue samples of human moles.

"Moles are probably the most visible example of the effect of oncogene-induced senescence in human cells," said Katherine M. Aird, Ph.D., lead author of the study and post-doctoral fellow in the Zhang laboratory. "The cells within a mole may have arrested growth, but they are still alive, and may regain activity, even turning cancerous. That is why your dermatologist might tell you to keep an eye on a seemingly benign mole, as changes in its size, color or shape could indicate that it is no longer benign."

According to Zhang, if you could stabilize senescence, perhaps by targeting RRM2, it could put the brakes on even drug-resistant cells.

ALTIERI: One of Wistar's strengths is the ability to bring together scientists with different backgrounds and expertise to solve a fundamental biological problem. Zhang's collaboration with Melanoma Research Center researchers is an example of our team science approach, and of how we bring the knowledge gained to bear for the benefit of our patients. These specific studies provide us with critically new insights into the mechanisms that may promote or suppress the conversion of an otherwise benign mole into a malignant melanoma.

Aird, Katherine M., et al. "Suppression of nucleotide metabolism underlies the establishment and maintenance of oncogene-induced senescence," *Cell Reports*, April 25, 2013.

This research is supported by: the National Cancer Institute, the Department of Defense Ovarian Cancer Academy Award, and the Liz Tilberis Award from the Ovarian Cancer Research Fund.

Substantial Funding for Tomorrow's Melanoma Research

Wistar's Melanoma Research Center has established an impressive track record of trailblazing research on targeted therapies in melanoma. In 2013, that success was recognized by the National Cancer Institute with the award of a $12.5 million program project grant (PO1). An application for another highly prestigious grant, a $12.5 million NCI SPORE (Specialized Program of Research Excellence) grant, received favorable reviews and is expected to be funded in April, 2014.

The P01 grant will fund a team of scientists from Wistar and the University of Pennsylvania to study the intractable problem of melanoma drug resistance.

"This grant enables scientists from different backgrounds—tumor biology, structural biology, chemistry, pathology, oncology, and biostatistics—to pool our talents and tackle melanoma from different vantage points," said Meenhard Herlyn, D.V.M., D.Sc., director of Wistar's Melanoma Research Center.

Meanwhile, the SPORE grant will improve the understanding and treatment of metastatic melanoma and other skin cancers, with the overall objective of turning fundamental research discoveries into new therapeutics.

ALTIERI: The ability of the Wistar Melanoma Research Center (MRC) to attract grants such as these is a testament to the strengths of our research teams.

The SPORE grant, in particular, is not only highly prestigious but more importantly a testament to the scientific innovation, creativity, and rigorousness of our team science. With the participation of Dmitry Gabrilovich, M.D., Ph.D., in a SPORE with his former colleagues at the Moffit Cancer Center, Wistar will hold the absolutely unique distinction of participating in two melanoma SPORE grants. The MRC continues to serve as a model for team science within the Institute.

ABOUT

76,100

NEW MELANOMAS WILL BE DIAGNOSED IN 2014.*

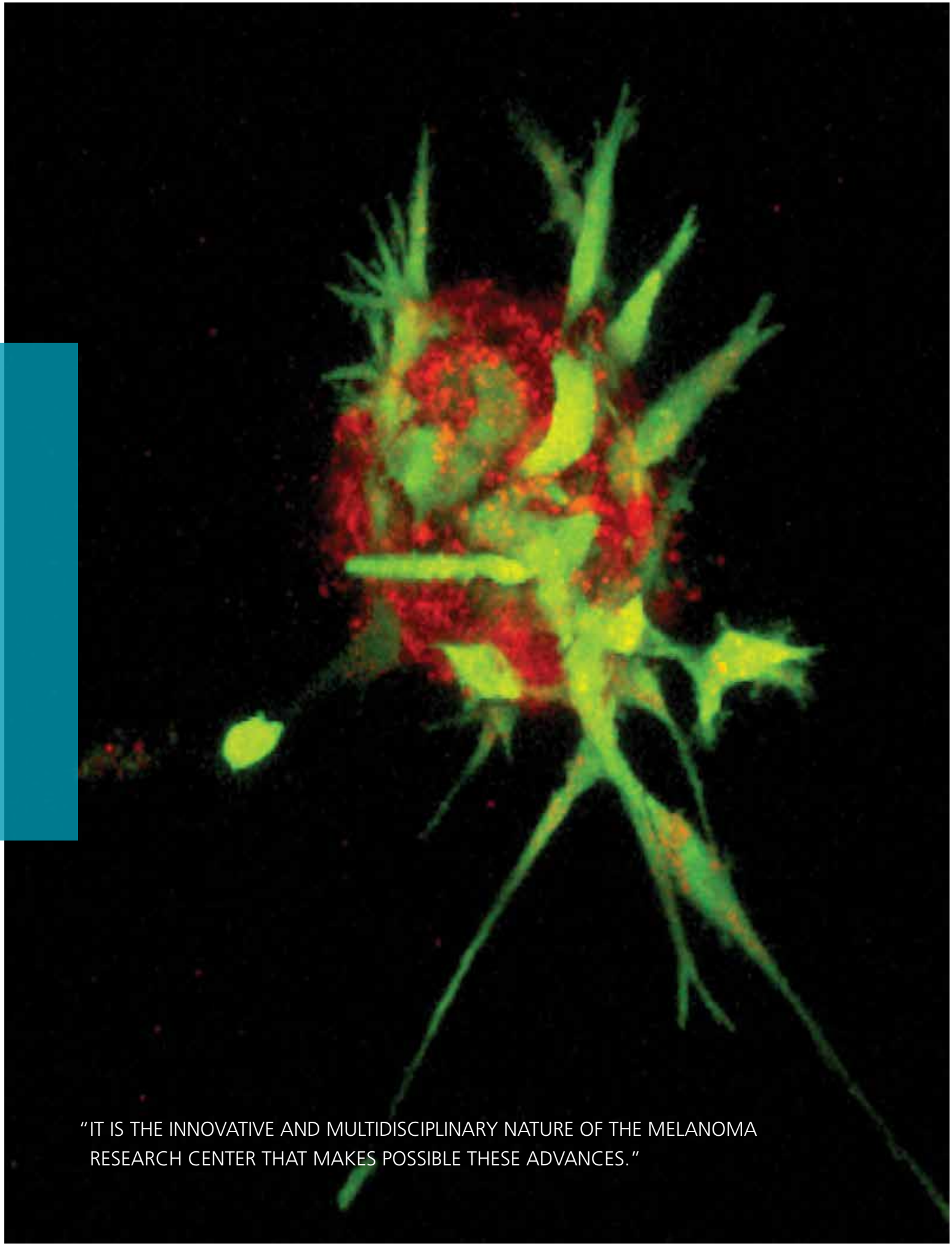
**American Cancer Society*

ABOUT MELANOMA

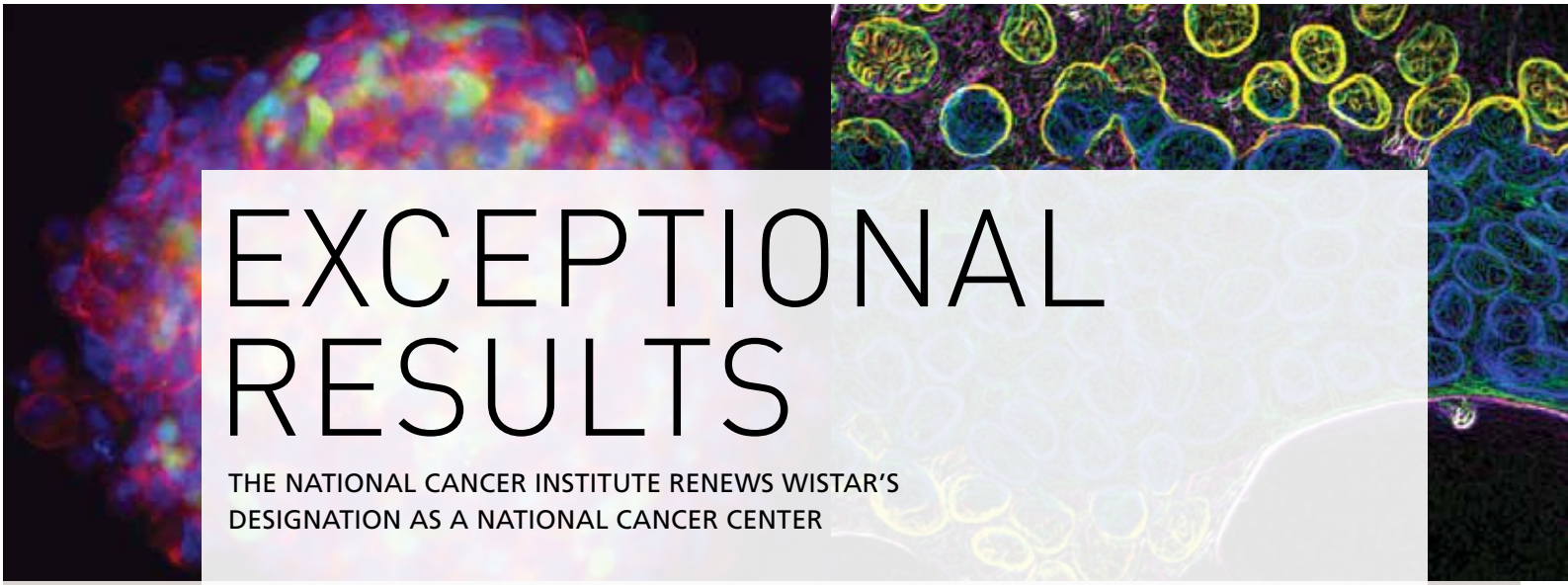
Melanoma begins as a malignant tumor of melanocytes—the cells that produce the pigment responsible for skin color. If caught early, it may be treated through surgery. Advanced, late-stage melanoma is considered incurable.

Recent advances in targeted drug therapies for melanoma offer hope for sufferers, but the effects of these drugs are temporary, as tumors quickly find ways to become resistant. Researchers at Wistar's Melanoma Research Center lead the field in discovering new means to combat drug resistance in melanoma and developing new targets for the next generation of melanoma drugs.

OPPOSITE: A TIME-LAPSE COMPOSITE IMAGE OF THE THREE-DIMENSIONAL GROWTH OF A MELANOMA TUMOR.



"IT IS THE INNOVATIVE AND MULTIDISCIPLINARY NATURE OF THE MELANOMA RESEARCH CENTER THAT MAKES POSSIBLE THESE ADVANCES."



EXCEPTIONAL RESULTS

THE NATIONAL CANCER INSTITUTE RENEWS WISTAR'S DESIGNATION AS A NATIONAL CANCER CENTER

After an extensive review, the National Cancer Institute rated The Wistar Institute Cancer Center—and its Director—as "EXCEPTIONAL" and recommended renewal for Wistar's Support Grant with an award of $14.9 million over the next five years.

In 1972, Wistar became the first NCI-designated cancer center in the city of Philadelphia and the first in the nation solely devoted to fundamental research in the biology of cancer.

Although many institutions call themselves "cancer centers," only 68 nationally are so designated by the National Cancer Institute. This designation clearly distinguishes The Wistar Institute Cancer Center.

"This Support Grant represents who we are as an institution, and we take immense pride in our NCI designation," said Dario C. Altieri, M.D., director of Wistar's Cancer Center. "The recent renewal is a testament to the excellence of our science, our culture of collaboration and sharing, and the success of our researchers in pushing the boundaries of discovery and knowledge in cancer biology and cancer therapy."

The NCI designation affirms Wistar's contributions to cancer research and recognizes its strengths, including a culture of collaboration, the success of Wistar researchers in generating new knowledge in cancer biology, and the development of novel therapeutics for a variety of cancers.

Wistar's commitment to collaboration across disciplines and in partnership with other institutions played a significant role in securing renewed status as an NCI Cancer Center. NCI reviewers cited Wistar's powerful connections to The Helen F. Graham Cancer Center in Delaware, the Moulder Center for Drug Discovery at Temple University, and the Community College of Philadelphia, among others, as evidence that Wistar is truly a collaborative hub of excellence and innovation.

Wistar's investment in facilities to support accomplished and innovative researchers with sophisticated resources and opportunities was also key to the Support Grant renewal. The new Robert and Penny Fox Tower, a research facility with 89,700 square feet of new space, will help ensure the Institute's place at the forefront of cancer research.

"The Support Grant is a potent driver of research at Wistar, and our NCI designation is highly valued in the research community," said Wistar President and CEO, Russel E. Kaufman, M.D. "'Exceptional' is the highest rating the review panel could give, and I can't think of a better way to describe the efforts of Dr. Altieri and all of our faculty."

YULIA NEFEDOVA, M.D., PH.D.
DMITRY GABRILOVICH, M.D., PH.D.

POWERFUL—AND PERSONAL—

PARTNERSHIPS

The Wistar Institute has been home to many scientists whose partnerships are both professional and personal. One prominent example is Meenhard Herlyn, D.V.M., D.Sc., and Dorothee Herlyn, D.V.M., D.Sc., who pioneered monoclonal antibodies (immune system proteins) and melanoma research at Wistar. Another is Jan Erikson, Ph.D., and Andrew Caton, Ph.D., both immunologists specializing in diseases such as lupus and rheumatoid arthritis.

Wistar's newest "power couple" is Dmitry I. Gabrilovich, M.D., Ph.D., Christopher M. Davis Professor and the founding leader of the Wistar Cancer Center's new Translational Tumor and Immunology program, and Yulia Nefedova, M.D, Ph.D., assistant professor in the Tumor Microenvironment and Metastasis program.

The pair was recruited in 2013 from the H. Lee Moffitt Cancer Center and Research Institute in Tampa, Florida. Their appointments were made possible, in part, by a grant from The Pew Charitable Trusts.

Gabrilovich's work focuses on the methods that tumors use to suppress the immune system, and on the development of new, effective vaccines to kill tumors.

In particular, the Gabrilovich laboratory studies how tumors interact with dendritic cells, which are crucial to the immune system's ability to detect foreign invaders or diseased cells, like tumors. Normally, dendritic cells alert the immune system to the presence of tumors and elicit an anti-tumor response. Tumors, however, can emit chemical signals that alter this protective behavior. Gabrilovich investigates the nature of these signals and how they affect dendritic cells, in order to develop new therapeutic strategies that counteract these signals.

Gabrilovich also has a long track record of translational development—collaborating with physicians on clinical trials that serve to apply scientific findings to patient medicine. His efforts toward curing cancer also include pre-clinical development of a vaccine that targets tumors that exhibit survivin, a protein that allows cells to evade the natural cellular mechanisms that control cancerous growth.

Nefedova explores the molecular mechanisms that enable tumor cells to interact with their micro-environment, the cells and tissues in which a tumor cell exists (such as the surrounding blood vessels, immune cells, and signaling molecules). She has focused on the molecular signals that drive multiple myeloma, a cancer of the plasma cells that affects 22,000 new patients annually and which accounts for 10,000 deaths every year. Nefedova has demonstrated how proteins along one such pathway of molecular signals, called the "Notch" pathway, enable myeloma cells to resist chemotherapy.

Wistar is proud to have recruited this talented pair to the Institute and to support their groundbreaking research.

TOTAL NUMBER OF EMPLOYEES:
377

NUMBER OF POST-DOCTORAL FELLOWS:
62

NUMBER OF VISITING SCIENTISTS:
9

NUMBER OF PRE-DOCTORAL FELLOWS:
41

NUMBER OF LABORATORIES:
30

NUMBER OF COUNTRIES* OF ORIGIN REPRESENTED:
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PATENTS ISSUED

U.S. PATENT NO. 8,476,458
Methods and Compositions for Modulating P300/CBP Activity
Filed: 06/19/2008
Issued: 07/2/2013
Inventors: Ronen Marmorstein, Xin Liu, Philip A. Cole, Ling Wang, Erin M. Bowers, David J. Meyers, Chandrani Mukherjee

U.S. PATENT NO. 8,377,992
TRBD-Binding Effectors and Methods for Using the Same to Modulate Telomerase Activity
Filed: 02/08/2010
Issued: 02/19/2013
Inventor: Emmanuel Skordalakes

U.S. PATENT NO. 8,374,838
Method for Identifying a Compound that Modulates Telomerase Activity
Filed: 10/21/2008
Issued: 02/12/2013
Inventor: Emmanuel Skordalakes

U.S. PATENT NO. 8,518,940
FP-Pocket-Binding Effectors and Methods for Using the Same to Modulate Telomerase Activity
Filed: 02/08/2010
Issued: 08/27/2013
Inventor: Emmanuel Skordalakes

U.S. PATENT NO. 8,476,420
Method for Diagnosing Lung Cancers Using Gene Expression Profiles in Peripheral Blood Mononuclear Cells
Filed: 12/05/2008
Issued: 07/2/2013
Inventors: Louise C. Showe, Michael K. Showe, Malik M. Yousef, Steven M. Albelda, Anil Vachani, Andrei V. Kossenkov

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The Center for Chemical Biology and Translational Medicine
The Center for Systems and Computational Biology
The Robert A. Fox Structural Biology Center
The Wistar Institute Cancer Center
The Wistar Institute Melanoma Research Center
The Wistar Institute Vaccine Center

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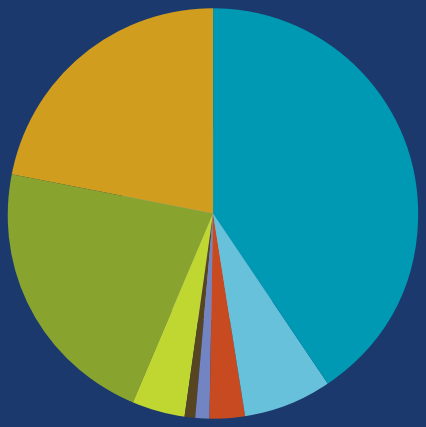
Histotechnology Facility
Imaging Facility
Molecular Screening Facility
Protein Expression Facility
Proteomics Facility
Translational Research Management Facility

SOURCES OF FUNDS

Federal grant funding	$ 30,523,000	41%
Foundation and other private funding	5,760,000	7%
State funding	1,979,000	2%
Corporate-sponsored research	427,000	1%
Unrestricted contributions	558,000	1%
Capital campaign contributions	2,735,000	4%
Technology transfer	16,328,000	22%
Investment and other gains	16,692,000	22%
	$ 75,002,000	**100%**



USES OF FUNDS

Direct research	$ 32,576,000	56%
General and administrative	11,611,000	20%
Operation and maintenance of plant	8,088,000	14%
Depreciation/disposal of capital assets	5,526,000	10%
	$ 57,801,000	**100%**
Change in net assets	$ 17,201,000	

TEAM SCIENCE—TEAM SUCCESS

The past year has been one of great productivity and achievement, continuing our success and setting the stage for an expansion as we open the new Robert and Penny Fox Tower in September.

Not only did Wistar achieve successful renewal of its status as an official Cancer Center by the National Cancer Institute (NCI), but it was also awarded the highest possible rating, "exceptional," of both the Cancer Center and its director, Dario C. Altieri, M.D.

The director of Wistar's Melanoma Research Center, Meenhard Herlyn, D.V.M, D.Sc., led successful efforts that won two NCI programmatic grants. One was a prestigious SPORE (Specialized Programs of Research Excellence) grant to support interdisciplinary translational cancer research.

Louise C. Showe, Ph.D., began clinical trials of the world's first blood test designed to detect lung cancer at an early stage in people who are at an increased risk for the disease. These are some of the hardest-to-treat, least understood cancers. Having an early detection method can make a difference in the outcome.

Paul Lieberman, Ph.D., made remarkable progress on a new therapy to target cancers caused by the Epstein-Barr virus, and Maureen Murphy, Ph.D., developed a new intervention to block a protein (HSP70) that may contribute to multiple types of cancer.

These are a just a few illustrations of the significant work of our scientists. Recruitment of top scientific talent remains the Institute's priority. We highlight one such newly recruited top husband-wife team in this report: Dmitry Gabrilovich, M.D., Ph.D., Christopher M. Davis Professor, and Yulia Nefedova, M.D., Ph.D., assistant professor in the Wistar Cancer Center's Tumor Microenvironment and Metastasis program.

Our scientists will soon be housed in expanded facilities thanks to the new Fox Tower. As the Fox Tower opens, our capital campaign, *Building Wistar, Changing the World*, will move toward its close. Although we are nearing our fundraising goal, we are not there yet. We look forward to focusing on building the future programs that will be housed in our new facilities, and we need your continued financial support to finish the campaign.

Wistar's accomplishments would not be possible without the support of philanthropists who share our mission, recognize the Institute's unique strengths, and are committed to being leaders in improving scientific knowledge and human health.

With gratitude and optimism, we move forward into a new era of innovation and achievement.

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2013 WISTAR GALA

On Saturday, October 26, 2013, Wistar honored Stanley A. Plotkin, M.D., and Brian H. Dovey for their significant impact on biomedical research.

Plotkin was bestowed the inaugural Caspar Wistar Medal of Achievement for his contributions to global health. Dovey was presented with The Wistar Award, established in 1994, for embodying the compassion, commitment, and vision demonstrated by the Institute's founding members.

This event raised more than $300,000 for the *Building Wistar, Changing the World* capital campaign that supports the completion of the Robert and Penny Fox Tower.

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The Robert and Penny Fox Tower Naming Celebration took place on a future laboratory floor of the tower at The Wistar Institute. The reception and ceremony to honor Robert and Penny Fox brought together supporters of the *Building Wistar, Changing the World* campaign.

IN HONOR OF...

In honor of Erica Bleznak and Doris Taxin
Dr. and Mrs. Kenneth Scott Resnik

In honor of Peter Bruan's speedy recovery
Dr. Herbert Kean and The Honorable Joyce Kean

In honor of Alan Bruck's birthday
Mr. and Mrs. Bernard Zolot

In honor of Matthew Caplan's Bar Mitzvah
Helen and David Pudlin

In honor of Hal Davis
Mrs. Eleanor Davis

In honor of Mr. and Mrs. Samuel E. Dennis
Mr. and Mrs. Richard L. Weisberg

In honor of Brian Dovey
Mr. and Mrs. Ronald P. Burd
Ms. Maria Colelli
Mr. and Mrs. Frank Fischer
Mrs. Nancy L. Kiss

In honor of our friendship with Paula Dresnin and Albert Ominsky
Mr. and Mrs. Leonard Dubin

In honor of Jacob Farber
Mr. and Mrs. John Eringis

In honor of Bob and Penny Fox
The Honorable and Mrs. Arlin M. Adams
Fred Fox and Jennifer Mendel
Mr. and Mrs. Benjamin Frankel
Doris Taxin and Jack Stievelman
Mr. and Mrs. Raymond H. Welsh

In honor of Bob and Penny Fox Tower Naming
Mr. and Mrs. William A. Albert
Mr. and Mrs. John K. Binswanger
Mr. and Mrs. Robert Gamberg
Mr. and Mrs. Joseph Kestenbaum
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In honor of Elizabeth A. Gillespie
Mr. and Mrs. John Donaldson

In honor of Bruce and Judi Goodman
Mr. and Mrs. Robert Sternberg

In honor of Alexander Wistar Haynes's graduation from Warren Wilson College
Gloria Marin Darthea Sharples, Ph.D.

In honor of Rick Horowitz
DocuBank

In honor of Richard A. Jones
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In honor of Dr. and Mrs. Russel Kaufman
The Honorable and Mrs. Harris N. Hollin

In honor of Russel E. Kaufman
Dr. Harry Rosenthal, in Memory of the Rosenthal-Moellerich-Voehl Families

In honor of Dr. and Mrs. Herbert Kean
Mr. and Mrs. Joseph F. Ladzenski

In honor of Dr. Herbert Kean's contributions to The Wistar Institute
Mr. and Mrs. Donald Kardon

In honor of Matthew Kestenbaum's Bar Mitzvah
Mr. and Mrs. Matthew Loffer

In honor of Stuart Lacheen
Mr. and Mrs. Bernard Zolot

In honor of Mary and Clarence Lemanske
Ms. Marie Webster

In honor of Jen Mendel and Fred Fox
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In honor of Abraham and Andrea Morris
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In honor of Albert Ominsky's 80th birthday
Dr. and Mrs. Alan Dickerman
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Mr. James R. Schaeffer and Ms. Nicole Dresnin
Ms. Merle Wolf

In honor of Shirley and Marty Orliner's birthdays
Mr. and Mrs. Robert Gamberg

In honor of Helen Pudlin
David E. Cohen, M.D. and Cathleen D. Cohen, Ph.D.

In honor of Drs. Roling, Weiss, Halpern and MacFarlane
Ms. Angela Krout

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Mr. and Mrs. Benjamin Frankel
Dr. and Mrs. Richard H. Rothman

In honor of Nicole Dresnin and Jim Schaeffer's wedding
Mr. and Mrs. Benjamin Frankel
Ms. Caryl Levinson
Ms. Bonnie Squires and Mr. Sami Ouahada

In honor of Joan and Bernard Spain's birthdays and their new home
Mr. and Mrs. Leonard Dubin

In honor of Bonnie Squires' birthday
Ms. Paula Dresnin

In honor of Fran Tobin's birthday
Mr. and Mrs. Bernardino D'Antonio

In honor of Donna Webster
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In honor of Richard Weisberg's birthday
Mr. and Mrs. Samuel E. Dennis

In honor of the Wistar Family Fund
Mr. and Mrs. Robert H. Clapham, Sr.

In honor of Dr. Eli Zebooker's 100th birthday
Mr. and Mrs. Robert Gamberg

IN MEMORY OF...

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Mr. and Mrs. Bernard Zolot

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In memory of Christina, sister of Alex Angelides-Cohen
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In memory of Sandy Berkowitz
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In memory of Marshall Bernstein
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In memory of Richard Bockol
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In memory of Erwin Harris
Dr. Herbert Kean and The Honorable Joyce Kean

#GIVING TUESDAY

#Giving Tuesday is a global movement celebrating philanthropy and encouraging giving back to charity during the holiday season. In 2013, The Wistar Institute post-doctoral fellows mobilized around a social media campaign that raised over $7,000 for the postdoctoral research program.

In memory of Eddie Hessler
Mrs. Robert Blumenthal

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Mrs. John Roberts

In memory of Marty Holzman
Ms. Bonnie Squires and Mr. Sami Ouahada

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Mrs. Lillian S. Kosloff

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In memory of Isabel Markovitz
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In memory of Gerald Marks' wife
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Mr. and Mrs. Andrew M. Ominsky

In memory of Noreen O'Neill
Mr. and Mrs. John Victor Gober

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Donna and Lester Weinraub

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Eunice Trevor, Esquire

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In memory of Julia Rousso
Mr. and Mrs. S. Peter Albert
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Albert Ominsky and Paula Dresnin

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Mrs. Lillian S. Kosloff

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In memory of Mary Wexler
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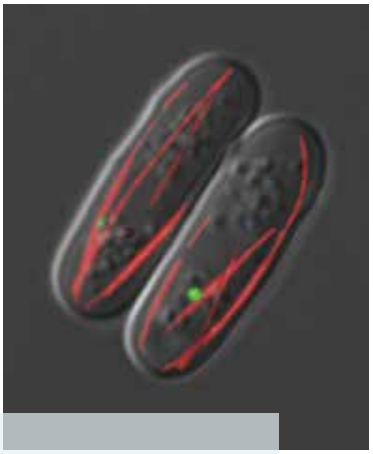
** Deceased*



A SNAPSHOT OF SCIENCE

Ken-ichi Noma, Ph.D., associate professor in the Wistar Cancer Center's Gene Expression and Regulation program, studies how the structure of the genome itself affects how cells "read" genes. Here, using yeast cells as a simpler model for human cells, Noma can visualize how DNA structures called centromeres (green) are moved along microtubules (red) like freight cars on rails.

IN MEMORIAM: HILARY KOPROWSKI, M.D. (1916-2013)

Hilary Koprowski, M.D., was director of The Wistar Institute from 1957 to 1991, a period during which Wistar achieved international prominence for its vaccine research and first earned designation as a National Cancer Institute Cancer Center. At Wistar, Koprowski built a prestigious research faculty by recruiting top biologists from around the world.

A distinguished virologist, Koprowski developed the first polio vaccine, which proved successful in clinical trials in Eastern Europe and the Belgian Congo. During his tenure as director, Wistar scientists developed vaccines against rubella (German measles) and rabies, both of which are in universal use today. His impact on science was demonstrated by his election to the National Academy of Sciences and the American Academy of Arts and Sciences.

WISTAR HERITAGE SOCIETY

The Wistar Heritage Society recognizes the foresight and generosity of the individuals who elect to perpetuate their support of biomedical research by including the Institute in their wills or estate plans. Members as of December 31, 2013 are:

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WISTAR FAMILY GIFTS

The Wistar Institute was founded in 1892 through generous gifts from Isaac Jones Wistar, a prominent Philadelphia lawyer and former Civil War Brigadier General, in honor of his great uncle, Caspar Wistar, M.D., a physician and the author of the first American textbook on anatomy. Isaac Wistar's descendants, as well as those of Dr. Caspar Wistar, continue to support the Institute to this day. The Wistar Institute gratefully acknowledges the following family members who made contributions in 2013:

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Marion and Frederic Ballard
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WISTAR'S MELANOMA AWARENESS DAY, AT CITIZENS BANK PARK

With the generous support of Citizens Bank and Independence Blue Cross, Wistar staffers, scientists, and their families took the opportunity to spread the news about the dangers of melanoma and raise awareness about melanoma prevention.

(L TO R) GARRY MADDOX; IRENE HANNAN, SENIOR VICE PRESIDENT OF CITIZENS BANK; RUSSEL E. KAUFMAN, M.D., WISTAR PRESIDENT AND CEO; CHRIS CASHMAN, EXECUTIVE VICE PRESIDENT AND PRESIDENT OF COMMERCIAL MARKETS AT INDEPENDENCE BLUE CROSS

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1 Departed 2013
2 Secondary appointment
3 Deceased 2013
** Program initiated December, 2013*

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