Exceptional SCIENCE

2018 ANNUAL REPORT

THE WISTAR INSTITUTE

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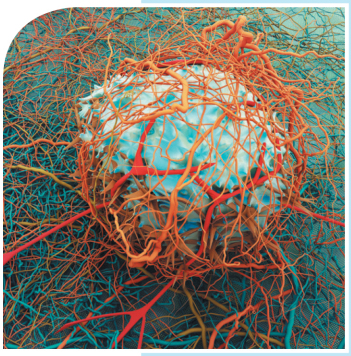


Dario C. Altieri, M.D.
President & CEO
Director, The Wistar Institute Cancer Center
Robert & Penny Fox Distinguished Professor

Expanding on Exceptional Science

This Annual Report caps another exceptional year of accomplishments for Wistar. Our list of achievements and testimonials of national and international distinction is long, and some of those milestones are reviewed here.

You will read about the breadth of our groundbreaking accomplishments in cancer and vaccine research; the renewal of our National Cancer Institute (NCI) Cancer Center Support Grant with an exceptional rating, the highest possible ranking received by Wistar for the second time in a row; and the impact of our science in the community, whether it is education and training of the next generation of scientists or the creation of a life science hub in Philadelphia. And all of this against the backdrop of a financially strong Institute, prepared and eager to make the long-range investments to bring to Wistar not just the best scientists, but the best people to fulfill our mission in research and innovation.

But, of course, this is not the whole story behind last year. The whole story for us may be less tangible – perhaps even more important than our steady success in federal funding, top-tier scientific publications, collaborative spirit, or groundbreaking entrepreneurship. Ours is a story of culture, of reputation and of impact. It is who we are, what we bring to the table and the values that we stand for that make Wistar not only an important presence but a much-needed presence providing exceptional science.

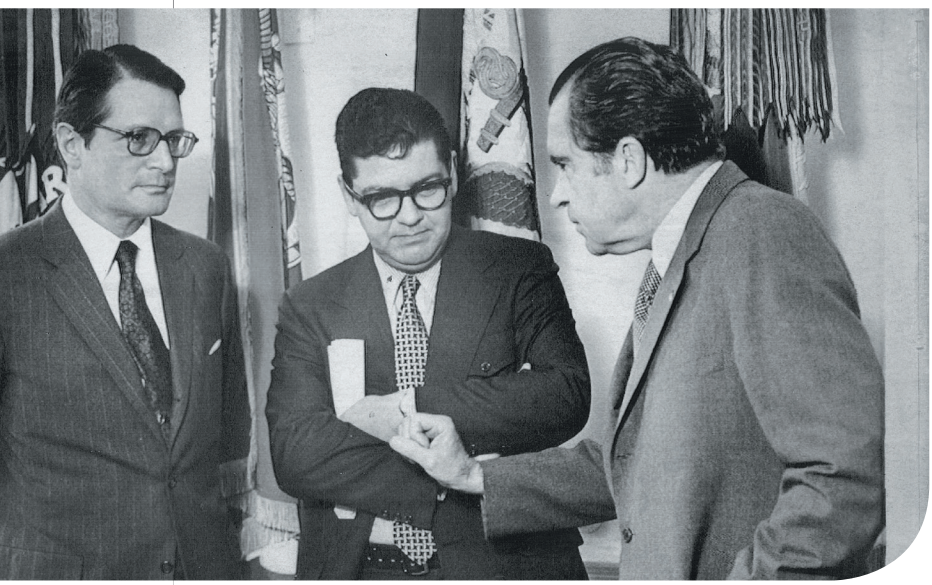
In a time where science is often ignored or belittled, where vaccines that save lives are met with skepticism and even successful medicines are seen as conspiracies, Wistar stands firm for the values and the spirit of research. We stand firm in our quest to address problems, find answers and work hard for solutions that are unbiased, trustworthy and stand the test of time. We stand for a world where research and education conquer diseases and better people's lives.

This is the story behind the exceptional successes showcased in our 2018 Annual Report. ■

46 Years & Counting

Leading The Charge In Cancer Research

Renewal of the Cancer Center Support Grant (CCSG) marks 46 years of continuous support and recognition from the National Cancer Institute (NCI) of Wistar science and its contributions to the fight against cancer.



(L-R) Elliot Richardson, Education and Welfare Secretary, Frank J. Rauscher Jr., Ph.D., National Cancer Institute Director and President Richard Nixon

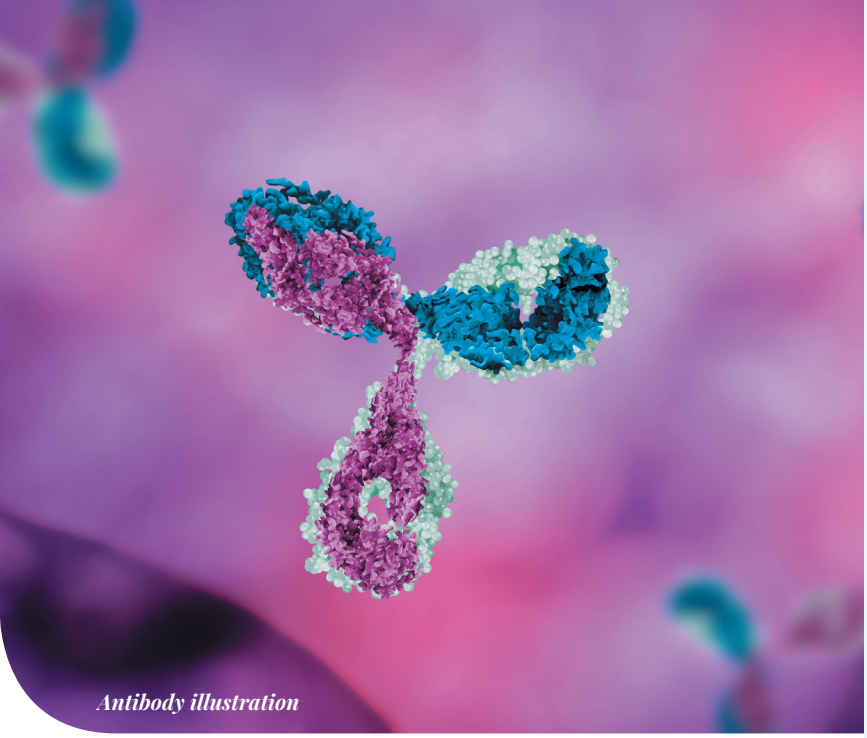
The Wistar Institute received designation as an NCI Cancer Center in 1972. At that time, cancer had become the second leading cause of death in the country, and President Nixon had declared a "war on cancer" and signed the National Cancer Act of 1971. As part of this endeavor, the federal government provided funding to basic and translational research programs present on the territory through the designation of NCI Cancer Centers. Developing and translating scientific knowledge from promising laboratory discoveries into new treatments, these NCI-designated cancer centers rapidly became the backbone of the NCI's efforts for studying and controlling cancer.

With its leading-edge research and an international pool of top biologists on its faculty, Wistar entered the program at its onset. With support from a $3M NCI grant and an additional $1.5M raised by the Institute to build a new Cancer Research Building, Wistar made another piece of history — becoming the first NCI-designated cancer center solely devoted to basic research. The Wistar Institute Cancer Center has been at the forefront of the field for 46 years, investigating the underlying causes of cancer while working to translate fundamental discoveries into cures.

A LOOK BACK

Under the scientific leadership of Wistar director Hilary Koprowski, M.D., research at Wistar's Cancer Center focused on the genetic alterations that take cells on a path of malignant transformation and the connection between viral infections and cancer, advancing new technologies for research and therapy.

46 Years & C



Antibody illustration

Wistar researchers characterized some of the first chromosomal translocations, or genetic abnormalities caused by rearrangement of parts between chromosomes, responsible for lymphoma and leukemia. They also described how these rearrangements could break or alter the DNA sequence of oncogenes, leading to cancer.

Wistar scientists were among the first to pioneer monoclonal antibody technology, the first immunotherapy to be applied to cancer research. The Institute became a center of expertise in their production, quickly generating a large panel of antibodies for research and therapeutic purposes. The first clinical trial testing a monoclonal antibody for gastrointestinal cancer was conducted using a Wistar-generated antibody, and the first U.S. patent for monoclonal antibody technology was granted to Wistar. Monoclonal antibodies brought a revolution in tumor immunology and provided the basis for most of today's targeted therapies and immunotherapies.

Armed with a deeper understanding of the role of genetic alterations in cancer and with the ability to study and manipulate protein function with new technologies such as monoclonal antibodies, the field of cancer research moved to studying gene networks and signaling pathways. These pathways act in a highly orchestrated fashion so that

WISTAR CANCER CENTER

DIRECTORS

Dario C. Altieri, M.D. (2010 to present)

Altieri is Wistar's current Cancer Center director and was appointed president and CEO in 2015. Altieri expanded the strategic planning and faculty and administrative leadership recruitment efforts. He realigned the scientific vision of the Cancer Center, reestablished the Vaccine & Immunotherapy Center, and diversified funding sources to support the Institute. Since 2010, he has led an active research lab at Wistar that focuses on the role of mitochondria in cancer metastasis.

Russel E. Kaufman, M.D. (2002 to 2010)

Appointed Wistar president and CEO until his retirement in 2015 and director of the Cancer Center until 2010, Kaufman embarked on strategic planning, faculty recruitment and a $35 million capital campaign that resulted in the opening of the transformational Robert and Penny Fox Research Tower.

Clayton Buck, Ph.D. (2000 to 2002)

A Wistar scientist since 1975, Buck took on the role of acting director and CEO following Rovera's retirement from Wistar. His steady leadership and guiding hand were instrumental in ensuring a smooth transition for the Institute.

Giovanni Rovera, M.D. (1991 to 2000)

Rovera's long-standing commitment to cancer research led him to recruit a talented group of young cancer investigators with expertise in genetics, structural biology, biology and immunology. The Institute's basic science programs were restructured to align with new research directions and faculty expertise.

Hilary Koprowski, M.D. (1972 to 1991)

During his tenure as the first Cancer Center director, Koprowski led the Institute through an unprecedented era of international attention and scientific discovery. His work on viruses and vaccine research evolved into fundamental cancer research that led to Wistar's Cancer Center designation.

NCI Cancer Center

A Cancer Center Designated by the National Cancer Institute

Clayton Buck, Ph.D., Cancer Center director from 2000 to 2002, in the lab.

changes in the function of one protein can affect a cascade of downstream events and drive tumor formation and spread. Wistar scientists focused specifically on signaling pathways in breast cancer and melanoma.

One of the historic strengths of Wistar's Cancer Center is structural biology — the study of the three-dimensional shape and structure of proteins, which informs how they function and interact with one another and with DNA. This type of investigation has led to important advancements such as describing the physical structure of the enzyme that protects chromosome ends, called telomerase, and the creation of small chemical molecules that can fit into the functional pockets of target proteins and block their function.

The completion of the Human Genome Project in 2003 opened the post-genomic era. Scientists started to explore the concept that gene activity and function are not solely determined by the DNA sequence. It was revealed that an additional important layer of regulation exists and orchestrates the dynamic interaction between genes and external stimuli. Wistar embraced this nascent field of study, called epigenetics and genome regulation, launching a new gene regulation research program. Wistar scientists contributed critical discoveries, unveiling the role of new proteins and RNA in the regulation of gene expression.

WISTAR CANCER CENTER

1979

First U.S. patent to use monoclonal antibodies for cancer therapy granted to Wistar.

1985

Carlo Croce, M.D., discovers *BCL2*, a gene implicated in lymphoma and a host of other cancers. Croce also showed that chromosomal translocations contribute to both cancer initiation and progression.

1989

Giorgio Trinchieri, M.D., discovers IL-12, a cell-signaling molecule essential for regulating the body's response to infection and cancer, which has applications in combination with cancer immunotherapy to boost the immune response.

Kazuko Nishikura, Ph.D., discovers RNA editing, a mechanism of RNA regulation, and characterizes a family of enzymes called ADAR, involved in this process. These discoveries contributed to opening an entirely new field of investigation on RNA.

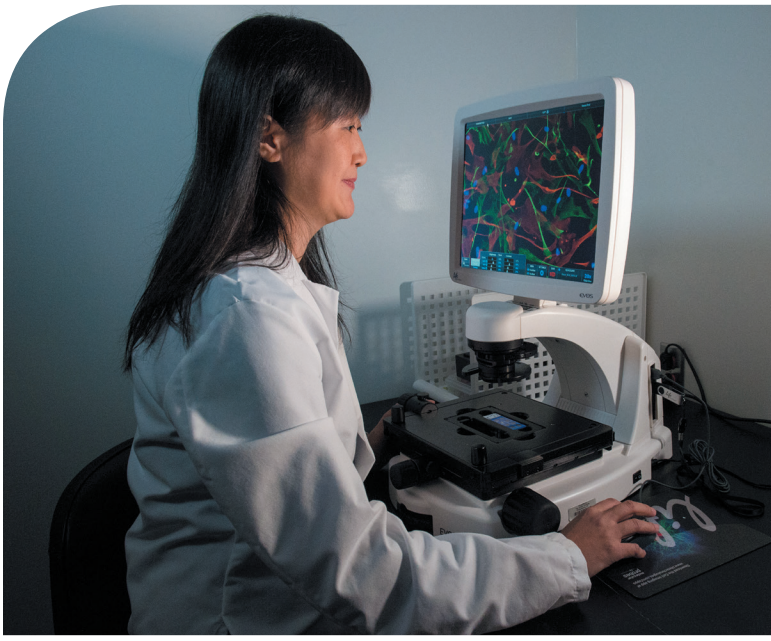
THE CANCER CENTER TODAY

In recent years, Wistar has brought onboard a group of both early career and distinguished scientists to strengthen and expand its programs in the fields of tumor immunology and immunotherapy, cancer cell metabolism and plasticity, tumor microenvironment and cancer genomics.

Wistar cancer scientists work cooperatively and share their diverse array of skills to meet new scientific challenges. They are furthering our understanding of how tumor cells interact with and adapt to the surrounding environment to grow and spread; the intricate role of our immune system in fighting and sometimes cooperating with the cancer; and how altered gene regulation can lead to cancer and affect patient response to therapy. Basic discoveries in these areas are informing the Cancer Center's translational efforts for the early development of novel immunotherapies, targeted therapies and biomarkers, thanks to a newly added medicinal chemistry expertise and a vibrant network of collaborations with academic institutions and the biotech industry. Some molecules are currently moving to the clinical phase of development.

The NCI CCSG provides funding for eight of Wistar's Shared Resources — state-of-the-art facilities that contribute technological and professional expertise to support and potentiate the work of Wistar scientists and external users.

Qing Chen, M.D., Ph.D., looking at neurons to study their interaction with breast tumor cells that metastasize to the brain.



Wistar's application for renewal of the NCI CCSG was rated as "exceptional" in 2018 for the second review cycle in a row, showcasing the strength of Wistar science and ensuring future support of its research programs. ■

Scientific Achievements & Discoveries

1990

Meenhard Herlyn, D.V.M., D.Sc., develops a three-dimensional human skin reconstruct model that is instrumental in the study of melanoma biology and resistance to therapy, and is used in melanoma research labs around the world.

2000s

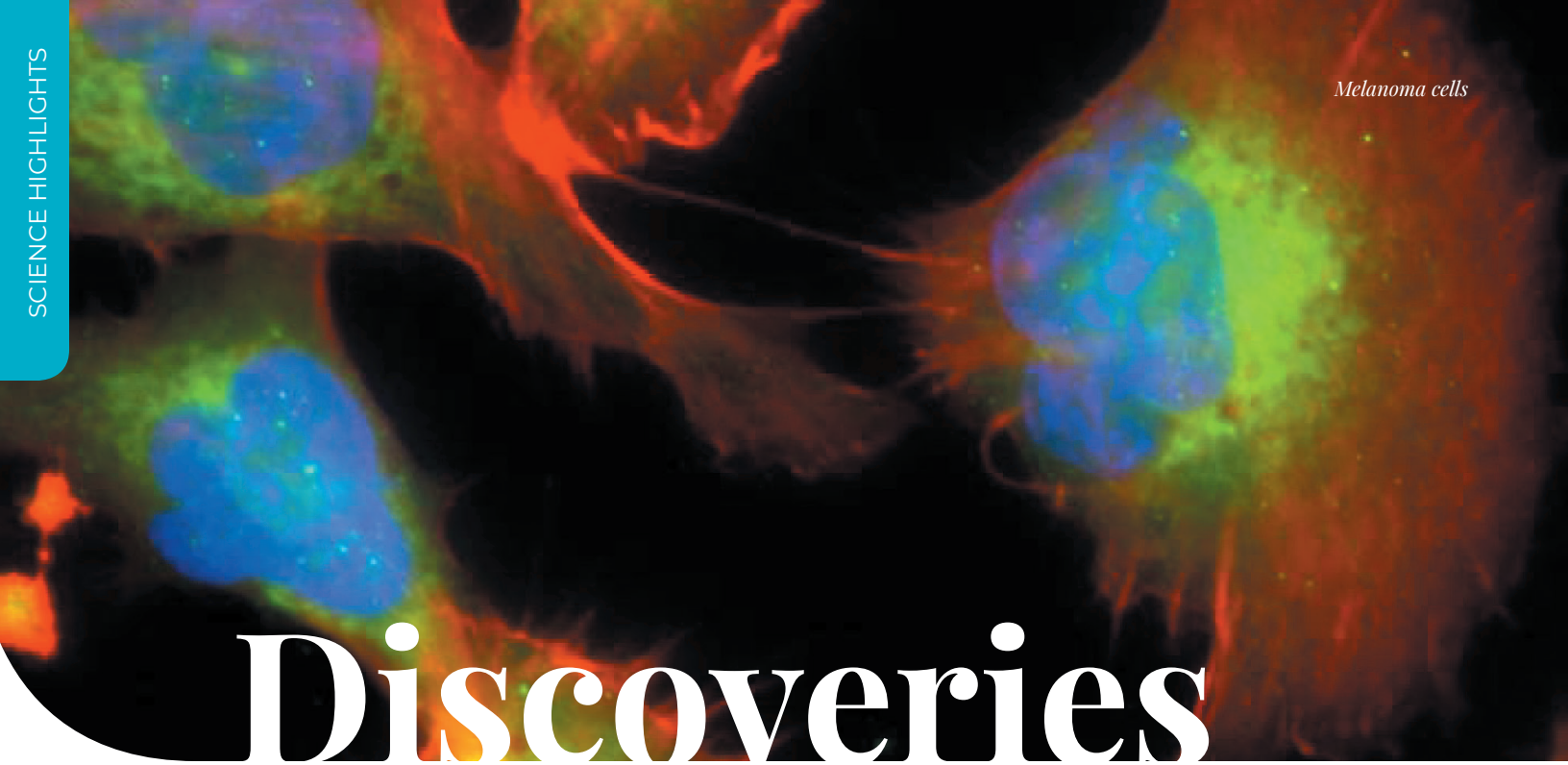
Wistar scientists make seminal discoveries in the field of epigenetics and RNA transcription, describing how different non-protein-coding RNA species including microRNAs (miRNA) and long noncoding RNAs (lncRNA) regulate gene expression.

2008

Emmanuel Skordalakes, Ph.D., decodes the structure of the active portion of telomerase, an enzyme that conserves the ends of chromosomes, a process with great implications for aging and cancer.

2016

Dmitry I. Gabrilovich, M.D., Ph.D., identifies a marker for myeloid-derived suppressor cells (MDSCs), a population of immune cells implicated in tumor resistance to various types of cancer treatment.



Melanoma cells

Discoveries That Make an Impact

Scientists working in Wistar laboratories conducted numerous studies that were published in high-impact research journals in 2018. The work highlighted in these pages provides examples of the vibrant science at the Institute.

WHAT'S NEW IN THE LABS

The Hu Lab:

DISSECTING THE CELLS' RESPONSE TO STRESS AND ITS INFLUENCE ON CANCER

Chih-Chi Andrew Hu, Ph.D., associate professor in the Immunology, Microenvironment & Metastasis Program, studies the mechanisms of B cell development and B cell cancer formation, focusing on the endoplasmic reticulum (ER) stress response and the associated stress signaling molecules.

The ER is the manufacturing and packaging system in the cell, devoted to production, processing and transport of proteins and lipids. In particular, the ER is the site in which proteins are folded and assembled into their proper three-dimensional shape.

Several cellular conditions can impair protein folding, resulting in the accumulation of misfolded proteins. This condition is harmful and triggers the ER stress response, designed to detect and clear the unfolded proteins.

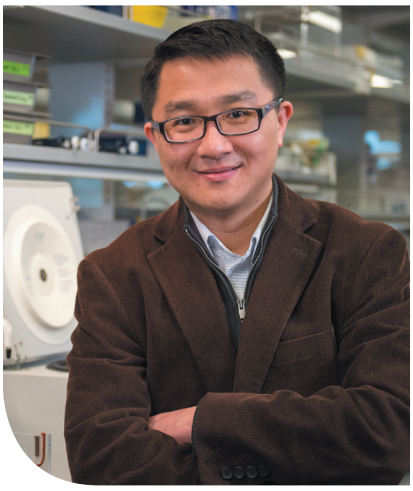
Hu is especially interested in how B-cell cancers employ the ER stress signaling molecules in favor of their survival, spreading and response to therapy. In 2018, his team authored

two studies that shed light on the complexity of the ER functions.

Research published in the ***Journal of Cell Biology*** described how IRE1, a key protein residing in the ER, helps cells respond to stress and its importance in B cells. This protein senses ER stress and responds by triggering two cascades of cellular events. One leads to increased production of factors that resolve the accumulation of misfolded proteins; the other slows down RNA translation to reduce the load of proteins coming into the ER until the crisis is resolved.

IRE1 function is especially critical in B cells since the ER of a B cell plays a central role in the production of antibodies. Because of this research, Hu and colleagues were able to characterize a novel molecular mechanism critical for IRE1 function during production of antibodies in response to immunization.

In the second study, published in ***Cancer Immunology Research***, the Hu lab dissected the tumor suppressive role of B cells in chronic lymphocytic leukemia (CLL), a malignancy characterized by the progressive accumulation of mature B cells. They found that soluble antibodies produced by B cells induce accumulation of myeloid-derived suppressor cells (MDSCs), a population of immune suppressive cells that hinder the antitumor functions of T cells and cause worse outcomes in many cancer types. Since the ER stress response is critical for producton of antibodies in B cells, the lab demonstrated that targeting the IRE1/XBP-1 pathway of the ER stress response can indeed result in decreased numbers of MDSCs. They are currently developing potent small molecule inhibitors against IRE1 to combat cancers associated with high numbers of MDSCs.



Chih-Chi Andrew Hu, Ph.D.

The Villanueva Lab:

LOOKING FOR VULNERABILITIES TO BEAT THERAPY-RESISTANT MELANOMA

Jessie Villanueva, Ph.D., assistant professor in the Molecular & Cellular Oncogenesis Program, studies the signaling pathways that become deregulated in melanoma with the goal of iden-

RESEARCH ADVANCEMENTS

AT A GLANCE

AGING AND MELANOMA

Ashani Weeraratna, Ph.D.
Ira Brind Professor,
Co-leader, Immunology, Microenvironment and Metastasis Program

- Changes in the structure of the skin and the lymphatic system that occur with aging create permissive conditions for melanoma to spread and form metastasis. These changes are caused during aging by loss of the HAPLN1 protein, which is part of the extracellular matrix. Published in two back-to-back papers in ***Cancer Discovery***.

ADVANCES IN IMMUNOLOGY

Dmitry I. Gabrilovich, M.D., Ph.D.
Christopher M. Davis Professor,
Leader, Immunology, Microenvironment and Metastasis Program

- When given in combination, a novel inhibitor of the protein CK2 (casein kinase 2) dramatically enhances the antitumor activity of immunotherapy with an immune checkpoint inhibitor. CK2 inhibition blocks the maturation of populations of immune-suppressive cells that are implicated in tumor resistance to various types of cancer treatment, including immune checkpoint inhibitors. Published in ***Cancer Research***.
- Insight into the role of a type of white blood cells called neutrophils in the early stages of tumor progression. When overt metastasis has not yet formed but the conditions for metastatic spread are being created, neutrophils migrate from the bone marrow to distant sites and facilitate tumor cell seeding. Published in ***Nature Immunology***.

RESEARCH ADVANCEMENTS

AT A GLANCE

OVARIAN CANCER THERAPY

Rugang Zhang, Ph.D.
Deputy Director, The Wistar Institute Cancer Center, Co-leader, Gene Expression and Regulation Program

- Novel combination therapy is shown to be effective for ovarian cancers without BRCA1/2 mutations. A small molecule inhibitor of the BET family of proteins expands efficacy of PARP inhibitors, recently approved for the treatment of BRCA-mutant ovarian cancer, to a wider range of ovarian tumors, regardless of the BRCA status. Published in ***Cell Reports.***
- Inhibitors of a protein called EZH2, in clinical development for hematopoietic malignancies, provide an effective strategy to treat a subset of ovarian cancers with elevated expression of the CARM1 oncogene. Published in ***Nature Communications***.
- Identification of a mechanism of resistance to novel EZH2 inhibitor therapy in ovarian cancers with mutations in the ARID1A gene. Study suggests a BCL2 small molecule inhibitor may be used in combination with EZH2 inhibitors to prevent the onset of resistance. Published in ***Nature Communications***.

tifying novel therapeutic targets, especially for difficult-to-treat tumors, such as melanoma with mutations in the NRAS gene, which are present in approximately 30 percent of patients.

NRAS-mutant tumors are highly aggressive and have a poor outcome. The mechanisms driving them are still poorly understood and very limited therapeutic options exist for patients.

Research has shown that targeting NRAS directly is very challenging; hence, the Villanueva lab and colleagues are working to identify and block other proteins on which NRAS-mutant tumors are dependent and that are essential for tumor survival. The lab found two such molecules.

Jessie Villanueva, Ph.D.

They showed that elevated expression of BRD4, a member of the BET family of transcriptional regulators, correlated with poor survival of NRAS-mutant melanoma patients and BRD4 function was required for tumor cell proliferation. In fact, small molecule BET inhibitors decreased viability of NRAS-mutant melanoma cells.

Furthermore, combination of BET inhibitors with MEK inhibitors, which block a fundamental signaling pathway in melanoma, potently slowed down tumor growth and increased survival of mouse models bearing melanoma resistant to several targeted therapies and immunotherapies. These findings, published in ***EMBO Molecular Medicine***, indicate that co-targeting BET and MEK may be a valuable salvage strategy for patients that have failed all available therapies.

According to Villanueva, since BET inhibitors are in advanced clinical trials and MEK inhibitors are FDA-approved for BRAF-mutant melanoma patients, clinical studies of BET and MEK combination therapy could be rapidly implemented.

Another study by Villanueva and colleagues, published in ***Oncogene***, linked the presence of mutant NRAS to expression of TERT, a component of the telomerase enzyme that protects the integrity of chromosome ends during replication. Telomerase represents a promising target for cancer therapy because it is absent in most normal adult cells and its reactiva-

tion is required to allow continuous cell divisions in malignant cells. Importantly, mutations in the TERT gene are found in more than 80 percent of melanomas, underscoring its critical role in these tumors.

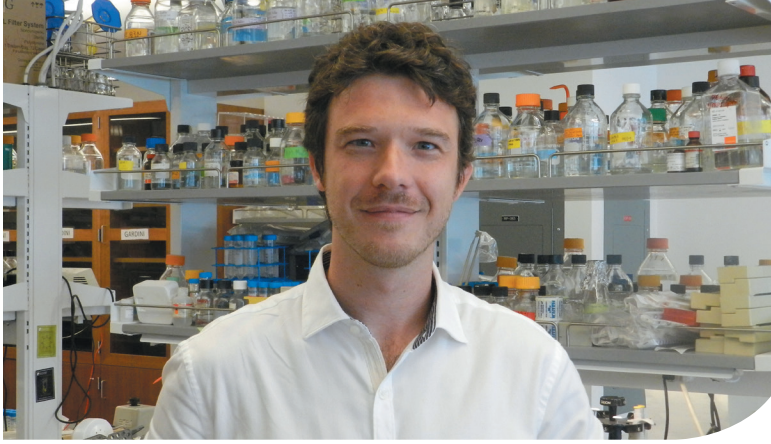
This study showed that NRAS-mutant melanoma cells are highly dependent on telomerase, as inhibition of TERT activity caused extensive DNA damage and cell death in these cells. They also found that targeting mitochondria, the organelles designated to energy production, with the mitochondrial inhibitor gamitrinib (developed at Wistar) enhances the effects of TERT inhibition, providing a proof-of-concept that a combination therapy co-targeting telomerase and the mitochondria may represent a novel strategy for difficult-to-treat melanoma.

The Gardini Lab:
DISCOVERING NEW MECHANISMS OF GENE REGULATION TO UNDERSTAND CANCER

Alessandro Gardini, Ph.D., assistant professor in the Gene Expression & Regulation Program, is interested in epigenetics in healthy conditions and cancer. Epigenetics is the study of the biological mechanisms that cause genes to be switched on and off. Every cell in our body contains the same DNA sequence, yet different cell types have different functions and characteristics. What makes a blood cell and a skin cell mature in different ways and perform their own specialized function is dictated by how and when genes are expressed. Changes in gene expression, which are heritable but do not involve alterations in the underlying DNA sequence, are a normal occurrence that can be influenced by several environmental factors, including age and lifestyle. Research in previous decades has uncovered a prominent role of epigenetics in disease, including cancer.

The Gardini lab studies the role of gene expression regulation in maturation of blood cells in normal and malignant conditions. In particular, they are dissecting the function of certain regulatory DNA elements scattered throughout the genome, called enhancers, and of a large protein complex that binds to them, called Integrator, made up of several protein components.

Gardini and colleagues showed that one of these components, called INTS13, activates enhancers that boost expression of genes associated with immune and blood cell development. Coherently, INTS13 is critical for maturation of monocytes and macrophages — white blood cells that specialize in eliminating foreign substances, cellular debris and cancer cells.



Alessandro Gardini, Ph.D.

Maturation of these cells is disrupted in acute myeloid leukemia and myelodysplastic syndromes. According to Gardini, unveiling the mechanisms that govern this process will provide novel therapeutic targets for these diseases. Study results were published in ***Molecular Cell***.

The lab is also interested in chromatin remodelers, or proteins that modify chromatin structure. Chromatin is a substance within chromosomes, composed of DNA wrapped around proteins to help package the genetic material in a compact form that can fit in the cell nucleus. The structure of chromatin needs to be dynamically modified to allow controlled gene expression in different cellular conditions.

ARID1A is a chromatin remodeler that is found mutated in sporadic ovarian tumors, causing malignant transformation via mechanisms that remained elusive. In a study published in ***Cell Reports***, Gardini and team presented the first systematic, genome-wide analysis of ARID1A activity in ovarian cells, elucidating the oncogenic consequences of its mutation.

Specifically, they found that ARID1A controls a fundamental regulatory step in RNA synthesis from a large fraction of genes in ovarian cells. When this function is compromised, expression of a subset of these genes, involved in DNA repair, cell proliferation and survival, is deregulated, leading to cancer. ■

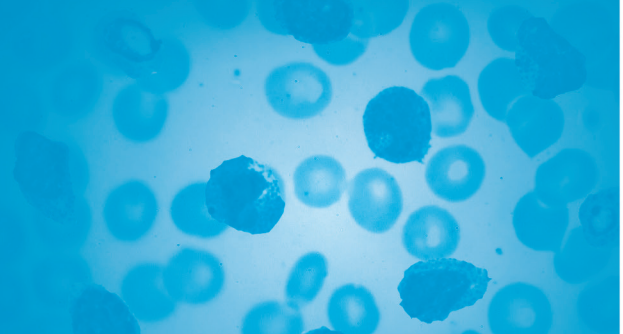
Developing Vaccines

Critical to Global Health

As boundaries disappear due to commercial flights, global trade, urbanization, and population explosions, the spread of emerging diseases rises, causing world health leaders to turn to Wistar for a solution.

2018 WAS A DEFINING YEAR in emerging infectious disease research for the lab of **David B. Weiner, Ph.D.**, executive vice president, director of the Vaccine & Immunotherapy Center and the W.W. Smith Charitable Trust Professor in Cancer Research at The Wistar Institute.

Weiner's groundbreaking synthetic DNA vaccine technology garnered Wistar philanthropic support in the form of a major grant from the **Bill & Melinda Gates Foundation** and global funding from the **CEPI**.



MALARIA VACCINE IN DEVELOPMENT

The **Bill & Melinda Gates Foundation** — the largest private philanthropic foundation in the world — awarded Wistar a $1.49 million grant to create a malaria vaccine through synthetic DNA-based technology.

Malaria is a leading cause of death in infants and children in sub-Saharan Africa and is a complex disease caused by a mosquito bite. The malaria parasite can evade the immune system and enter the bloodstream, eventually migrating to the liver where it establishes infection. There are four common strains of malaria, though Plasmodium (P.) falciparum is the most severe strain prevalent in Africa. A global disease burden, malaria accounted for 219 million cases worldwide and 435,000 deaths in 2017.

Wistar is collaborating with Johns Hopkins Malaria Research Institute at the Johns Hopkins Bloomberg School of Public Health and Inovio Pharmaceuticals, Inc., on this research effort. This funding will enable the team to generate a synthetic DNA vaccine encoding antigens of P. falciparum. This strategy is designed to create the vaccine with the information needed to produce the exact antigen in the recipient's own body, generating a more focused and protective immune response for the development of a next generation malaria vaccine.

People wearing face masks to contain the possible spread of disease during the MERS epidemic in South Korea.

MERS VACCINE MOVES TO PHASE II TRIALS

The **Coalition for Epidemic Preparedness Innovations (CEPI)** is an organization devoted to financing the development of new vaccines as solutions to global epidemics through partnerships between public, private, philanthropic, civil society organizations, and countries. CEPI awarded Wistar a $3.55 million subgrant to advance a Middle East Respiratory Syndrome (MERS) vaccine through phase 2 clinical development. The sub-grant is part of a larger grant awarded to Inovio Pharmaceuticals, Inc., which partners with Wistar in this effort.

MERS is a highly infectious respiratory disease spread from camels to humans and is prevalent to the Middle East. In 2015, an outbreak occurred in Seoul, Korea, that dramatically impacted the country. The World Health Organization listed MERS as a potential public health emergency in the 2018

The Weiner Laboratory

at Wistar is dedicated to accelerating DNA-based vaccine technology. Weiner is igniting collaborations to advance new vaccines for Zika, Influenza, HIV, Ebola, CHIKV, and immunotherapies for ovarian, prostate, and other cancers. Having fostered national and global relationships between academia, industry, and government, Weiner's research expands upon Wistar's mission to create new treatments for the most uncompromising diseases and make lifesaving contributions to human health.

David B. Weiner, Ph.D.

annual review of the Blueprint list of priority diseases. CEPI picked MERS from among the top three infectious diseases for which vaccine development and rapid deployment is critical.

The synthetic DNA vaccine against MERS is based on key technology generated in the Weiner lab. This technology shows a significant public health advantage against rapidly emerging pathogens due to its temperature stability, optimized design and rapid strategy for development. These types of new synthetic DNA vaccines are conceptually safe and potent, can be manufactured quickly, and are more stable than traditional vaccines, making them ideal to distribute during outbreaks. ■

The **G. Harold and Leila Y. Mathers Charitable Foundation** awarded two grants totaling $1.65 million to Wistar scientists **Farokh Dotiwala, M.B.B.S., Ph.D.**, assistant professor in the Vaccine & Immunotherapy Center, and **Alessandro Gardini, Ph.D.**, assistant professor in the Gene Expression and Regulation Program of Wistar's Cancer Center. Each three-year grant will provide $825,000 in funding to advance important projects in their labs.

Dotiwala's project centers on a process called microptosis to combat anti-microbial resistance in bacteria, which is causing diseases like pneumonia, tuberculosis and malaria to return as the mass-killers they were in the pre-antibiotic era. Dotiwala was one of the discoverers of microptosis, a very ancient mechanism through which our immune system kills cells infected with intracellular parasites to protects us from disease. Dotiwala plans to further explore this mechanism to expose potential bacterial vulnerabilities that could be used as a novel target for future antimicrobial therapies.

Gardini's project aims at discovering new molecular players in a process called cell fate determination. Thanks to this process, genetically identical stem cells present in the bone marrow mature into different blood and immune cells that are morphologically and functionally distinct. At the molecular level, these cells carry out different gene expression programs that allow different sets of genes to be turned on and off. Gardini's research delves into these mechanisms to uncover novel regulators and reveal druggable targets for certain types of leukemia.

Gardini also received a three-year Research Scholar Grant from the **American Cancer Society** for $792,000 to further his investigations into the role of the ARID1A protein in ovarian cancer. ARID1A is mutated in a large proportion of ovarian cancers and mutations alter its function as a regulator of gene expression. ■

Thinking Locally & Globally

When it Comes to Wistar Partnerships

The Business Development Team opens doors to life science-focused business opportunities that may benefit Wistar and the region.

The mission of Wistar's Business Development team led by **Heather A. Steinman, Ph.D., MBA**, is to create meaningful biomedical research collaborations and opportunities with potential partners from the life sciences industry, including biotech, biomedical and life sciences companies and venture capital firms, and other academic institutions. The team is focused on accelerating the pace of early stage Wistar discoveries toward commercial applications with an approach that is nimble, flexible and accessible. Through collaboration, Wistar scientists together with Wistar's business development team take a proactive approach to translational science to drive meaningful collaborations that may become future life changing therapeutics and diagnostics.

Neetu Singh, Ph.D., Heather A. Steinman, Ph.D., MBA, and Kathy Day

WISTAR OPPORTUNITIES FLOURISHED IN 2018:

1) Virion Therapeutics, LLC was spun out of Wistar and is advancing innovative, immune-based therapies for the treatment of chronic, viral-associated cancers and viral infections. Co-founded by **Hildegund C.J. Ertl, M.D.**, professor in the Vaccine & Immunotherapy Center at Wistar, and life science entrepreneurs Andrew D. Luber, Pharm.D., and Bernard Rudnick, MBA, Virion utilizes a novel genetically encoded checkpoint inhibitor in combination with chimpanzee adenoviral vectors to deliver potent antitumor and antiviral responses.

2) Wistar and **Harbour BioMed** joined forces to advance an academia-industry collaboration to identify commercially viable novel antibody therapies for cancer and infectious diseases. The partnership combines Wistar's cancer biology and immunology expertise with Harbour's proprietary transgenic mouse platform for generating and validating novel monoclonal antibodies against tumor and infectious antigens.

3) Wistar and **Ben Franklin Technology Partners of Southeastern Pennsylvania** (Ben Franklin), a nonprofit conglomerate of partners providing direct/seed funding, mentorship and networks to strengthen enterprise development, have signed a memorandum of understanding (MoU) to advance early stage life sciences startups coming out of Wistar. Under the MoU, Ben Franklin and Wistar cultivate a mentoring program called "Ben-In-Residence" around technology development for translational scientists and entrepreneurs at Wistar. Ben Franklin experts will contribute support and guide scientists on technology commercialization, with the potential to fund Wistar startups.

4) Ben Franklin granted seed funding to **ISOMA Diagnostics**, a Wistar spin-out dedicated to identifying targeted therapies for glioblastoma patients. Based on intellectual property licensed from Wistar and the University of Pennsylvania, funds are used for assay development and clinical validation of a novel molecular test useful for stratifying patients with glioblastoma, the most common and deadly type of primary malignant brain cancer in adults. ■

Shared Resources

The Wistar Institute Shared Resources, or core facilities, provide state-of-the-art technological support and professional expertise to assist investigators at Wistar and other institutions with their research needs, representing a strong asset of the Institute's scientific enterprise.

The new BSL-3 facility at Wistar.

A Closer Look at a Few Cores

Bioinformatics is an interdisciplinary field of science that combines expertise in biology, computer science, information engineering, mathematics, and statistics to help researchers analyze and interpret biological data. The **Bioinformatics** facility continuously develops new and efficient approaches to data analysis as a response to emerging research needs.

The **Biosafety Level-3** or BSL-3 facility provides a safe environment for handling airborne infectious agents that may cause serious or potentially lethal disease. BSL-3 facilities are specially equipped with a directional airflow system that draws air from clean areas towards potentially contaminated areas and does not re-circulate exhaust air, and a self-closing set of locking doors with access away from common use areas.

BSL-3 work follows strict federal regulations with oversight from the institutional biosafety departments. Access to the BSL-3 lab is restricted to trained personnel and controlled at all times. Besides following the standard practice for biomedical research, researchers that work in a BSL-3 facility are required to wear additional protective equipment. The Wistar BSL-3 facility opened in 2018 and expanded the range of infectious agents being studied at the Institute.

The **Molecular Screening & Protein Expression** facility enables researchers to discover small molecule compounds and study novel molecular targets. The facility provides expertise in biochemical and cell-based assay development, which enables researchers to discover small molecule compounds that interact with a protein of interest. These novel compounds can then be used as tools to study the target protein's function and can be further developed as therapeutics. ■

Many of Wistar's Shared Resources are approved by the National Cancer Institute (NCI) and supported by the Cancer Center Support Grant (CCSG). The high-caliber technologies and services provided by the Institute's Shared Resources were considered critical components that were evaluated in the CCSG grant renewal process in 2018.

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Bioinformatics

Biomedical Research Support Core

Biosafety Level-3

Cell Culture
(at Fox Chase Cancer Center)

Flow Cytometry

Gene Editing Institute
(at Helen F. Graham Cancer Center & Research Institute)

Genomics

Histotechnology

Imaging

Molecular Screening & Protein Expression

Proteomics & Metabolomics

Research Supply Center

Transgenic Mouse Facility
(at Fox Chase Cancer Center)

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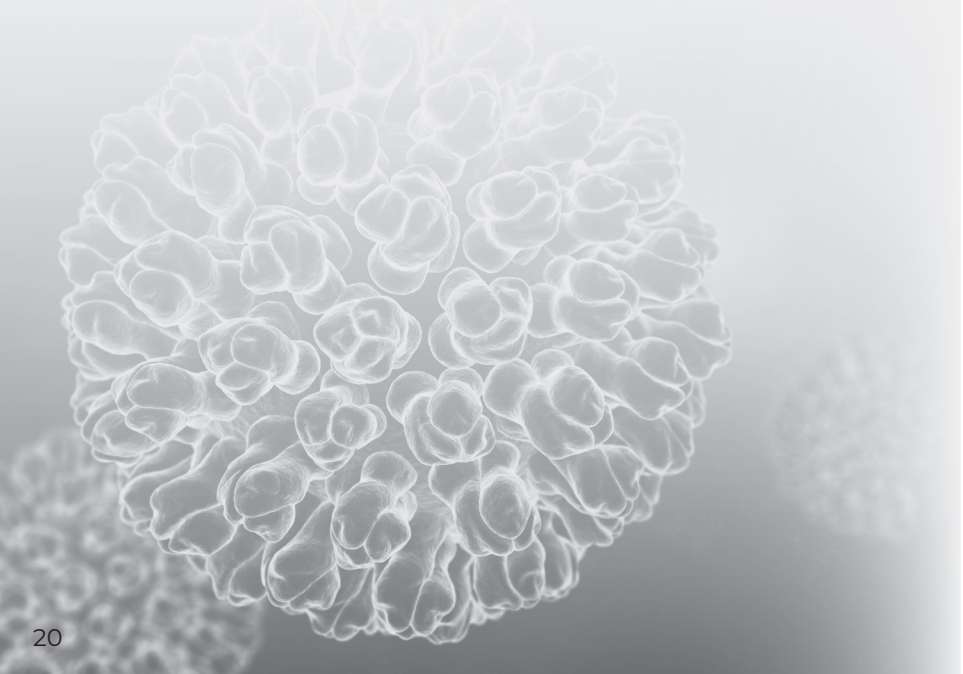

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The Wistar Institute's 1892 Legacy Society is a special group of supporters who have named Wistar in their estate plans or established deferred gifts in support of lifesaving biomedical research.

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Wistar family celebrating the 300th anniversary of the family's arrival in the United States.

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The Wistar Institute was founded in 1892 through a generous gift 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 respected Philadelphian physician and anatomy professor, and the author of the first American textbook on anatomy. Wistar descendants continue to support the Institute to this day.

Wistar gratefully acknowledges the following family members who made contributions in 2018:

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Philadelphia Science Festival

During the 2018 Science Festival, Wistar scientists and staff made science fun and accessible at two community events using microscopes, vaccine and cancer cell games and biology concepts to educate families about Wistar science.

Science in the National Park

APRIL 26

INDEPENDENCE NATIONAL HISTORICAL PARK

1.


2.

1. Jessica Palmer explains the different phases involved in the development of a vaccine.

2. Aubrey Leso helping a Philadelphia Public School student understand what she is seeing though the microscope.


3.

Science Carnival

APRIL 28

BENJAMIN FRANKLIN PARKWAY

4.


5.

3. Scientists Gloria Marino and Kevin Alicea-Torres talking cancer research through playful interactives representative of the tumor microenvironment.

4. Scientist Michael Young explains how vaccines are created and Wistar's rich history developing rabies, rubella and rotavirus vaccines.

5. Scientists Patricia Reyes-Uribes (L) and Cindy Lin, Ph.D. (center) interacted with hundreds of people who descended on the Carnival, the grand finale event of the weeklong Science Festival celebration.

WOMEN & SCIENCE
PROGRAM

Helen Dean King Award Ceremony

APRIL 12

THE WISTAR INSTITUTE

Wistar's Helen Dean King Award honored Shirley Tilghman, Ph.D., a pioneer in the field of molecular biology and Princeton's first woman president. Tilghman discussed her scientific career, tenure as president, and leadership on behalf of advancing the early careers of young scientists.

1. Shirley Tilghman, Ph.D.
2. Cackie Rogers, Liz Anderson, Helen Pudlin, and Ellen Harvey
3. Women & Science guests mingle before the program presentation.

Fireside Chat: Women's Health

FEBRUARY 1

THE WISTAR INSTITUTE

WHYY's Naomi Starobin led a discussion with Phillippa Marrack, Ph.D., distinguished immunologist from National Jewish Health, on Marrack's work to elucidate the immune system and how it protects us.

1. Susan Schurr, Naomi Starobin and Phillippa Marrack, Ph.D.
2. Amy Fox and Adele Schaeffer
3. Ilona Vovk, Alixandra Papaharis and Samantha Audia

Fireside Chat: Breast Cancer Metastasis

JUNE 20

THE WISTAR INSTITUTE

WHYY's behavioral health reporter Maiken Scott spoke with Qing Chen, M.D., Ph.D., Wistar assistant professor in the Immunology, Microenvironment & Metastasis Program, about research on breast cancer metastasis.

1. Maiken Scott with Qing Chen, M.D., Ph.D.

2. Carrie Boxer, Ken Davis, John Boxer, and Leslye Silver

3. Stacey Spector and Dario Altieri, M.D., Wistar president & CEO

Innovating, Funding & Delivering Vaccines for a Changing World

NOVEMBER 1

THE WISTAR INSTITUTE

Merck VP of Public Health and Scientific Affairs Ruxandra Draghia, M.D., Ph.D., discussed her work to improve human health by harnessing innovative research to develop vaccines capable of combating the next global epidemics.

1. Elizabeth Dougherty and Sophie Mohin

2. Ruxandra Draghia, M.D., Ph.D.

3. Jane and Joe Goldblum with Serge Pepper

Discovery Gala

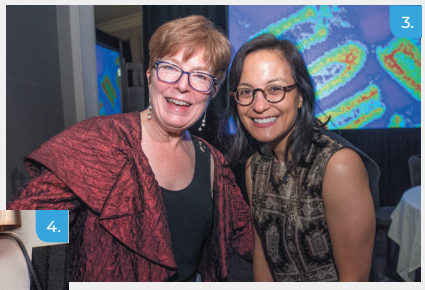
SEPTEMBER 21

THE LOGAN PHILADELPHIA

Nearly 300 friends of the Institute came together for the Discovery Gala, hosted by Wistar's Leadership Council & Ambassadors. Attendees celebrated the Wistar research that will one day lead to therapies and vaccines for some of the most devastating cancers and infectious diseases.


1.

2.


3.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6.

1. Luis Montaner, D.V.M., D.Phil.

2. Dario Altieri, M.D., Wistar president & CEO

3. Mary Bak, Esq. and Josie Burri

4. Charlie and Lisa Martin, Elizabeth McKee Anderson, and David Anderson

5. Brotherly Love, Select Ensemble of the Philadelphia Gay Men's Chorus, performing at the Gala

6. Greg and Alex Stanbach

Group photo of the speakers: (L–R back row) Thomas Tuting, M.D., Meenhard Herlyn, D.V.M., D.Sc., Patrick Hwu, M.D., Richard Marais, Ph.D., Sergio Quezada, Ph.D., Ashani Weeraratna, Ph.D. (L–R front row) Jessie Villanueva, Ph.D., Donita Brady, Ph.D., Carmit Levy, Ph.D., Suzanne Topalian, M.D., and Timothy Chan, M.D., Ph.D.

2nd Annual Noreen O'Neill **Melanoma Research Symposium** Host Response in Melanoma

1. Amanpreet Kaur and Lea Schuh

2. Symposium co-chair Ashani Weeraratna, Ph.D. discussed her seminal work on aging and how it influences melanoma progression

3. Wistar melanoma scientists Filipe Almeida, Ph.D., Gretchen Alicea, Vito Rebecca, Ph.D., Meaghan Kiernan, and Mitchell Fane, Ph.D.

JUNE 26
THE WISTAR INSTITUTE

Wistar assembled top melanoma experts from across the nation and globe to discuss latest developments in melanoma research.

More than 200 basic and clinical melanoma research experts convened at Wistar to assess progress and challenges in the treatment of melanoma. Targeted therapies and immunotherapies have revolutionized treatment options for melanoma patients, yet a substantial proportion of them do not benefit from these new approaches. Researchers continue to look for factors that affect the patient response and how to modulate these responses to improve survival.

Panelists discussed hot topics in melanoma research, including progress in treating advanced melanoma patients with immune checkpoint blockade therapy; the impact of aging on melanoma progression and metastasis; the role played by the microbiome in the patient response to immunotherapy; and the molecular factors that predict patient response to targeted therapies, immunotherapies and combination therapies.

The annual event is made possible through the generous support of **The Noreen O'Neill Foundation for Melanoma Research** (NOFMR) founded in 1998 by Noreen O'Neill, a melanoma patient and fierce research advocate. Noreen passed away in 2000 after a courageous fight against malignant melanoma, but her legacy lives on through the Symposium and the work of her Foundation, which continues at Wistar as the Noreen O'Neill Melanoma Research Fund to advance transformative melanoma research. ■

Cores Day 2018

SEPTEMBER 13

CHILDREN'S HOSPITAL OF PHILADELPHIA CAMPUS

Wistar, Penn and CHOP researchers and staff joined forces to talk about the scientific services and state-of-the-art technologies that the West Philadelphia community of core facilities offer to support research efforts and continue the tradition of scientific excellence in the research community.

2.

1.

1. Researchers interested in Wistar's core facilities spoke with many of the directors on hand throughout the day.

2. (L–R) Livio Azzoni, M.D., Ph.D., Carlos Carmona, Denise DiFrancesco, Sonali Majumdar, M.S., Silvia Licciulli, Ph.D., and Tara Yates ready to engage researchers about Wistar's Shared Resources.

Nikon Small World

JANUARY 19

THE WISTAR INSTITUTE

Wistar hosted top winners of the 2017 Nikon Small World Photomicrography Competition with an Opening Reception.

1.

3.

2.

1. Guests saw winning images on display.

2. James Hayden, Wistar Imaging Facility managing director, discussed how scientists use microscopy to improve their understanding of biological processes.

3. (L–R) Clive Baron, Robin Cohen, Susan Charleston, Ken Davis, and Merle Gilmore

Innovate, Collaborate, Ignite 2018!

OCTOBER 2

UNIVERSITY OF THE SCIENCES

The Philadelphia Research Consortium celebrated its first gathering and welcomed more than 150 attendees from throughout the life sciences community to network and connect over the possibility of forming new preclinical research collaborations.

Team Elbo & Team Patio Melanoma Walk

OCTOBER 28

SOUTH PHILADELPHIA

The 3rd Annual Team Elbo/Team Patio Melanoma Awareness Walk drew more than 150 friends and family members of organizers Eleanor Armstrong and Patrick Dean for a special walk day to raise much-needed awareness and integral funds for Wistar's melanoma research.

1

2

1. Patrick Dean and Eleanor Armstrong

2. (Standing L – R) Ava Heinly, Lauren Heinly, George Heinly, Sue Gallagher and (in the stroller) Mick and Alli Heinly


1.

Champion Run for Research

NOVEMBER 26

WISTAR TO THE PHILADELPHIA MUSEUM OF ART

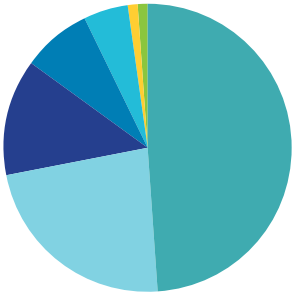
The commitment and advocacy of Wistar scientists and staffers raised key funds and awareness in support of Wistar trainees.


2.

1. Some of the participants at the end of the 2018 Champion Run for Research

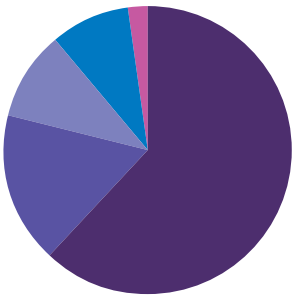
2. Taekyoung Kwak, Livio Azzoni, M.D., Ph.D., and Krzysztof Wojtak

2018 Financials



REVENUES

Federal Grant Funding	$39,871,000	49%
Technology Transfer	$18,886,000	23%
Foundation & Other Private Funding	$10,327,000	13%
Investment & Other	$6,122,000	8%
Corporate-sponsored Research	$3,948,000	5%
Unrestricted Contributions	$1,035,000	1%
State Funding	$865,000	1%
Total	**$81,054,000**	**100%**



EXPENSES

Direct Research	$43,248,000	62%
General & Administrative	$11,658,000	17%
Depreciation	$7,054,000	10%
Operation & Maintenance of Plant	$6,070,000	9%
Interest Expense	$1,332,000	2%
Totals	**$69,362,000**	**100%**

Other Changes in Net Assets

Investment Return and Other	**$16,438,000**
Change in net assets	**$4,746,000**

WISTAR BY THE NUMBERS

60 Postdoctoral Fellows

19 Predoctoral Trainees

298 Total Paid Employees

6 Visiting Scientists

31 Labs

22 Countries Represented

PATENTS ISSUED

U.S. PATENT NO. 10,113,201
Methods and Compositions for Diagnosis of Glioblastoma or a Subtype Thereof
ISSUE DATE: October 30, 2018
INVENTORS: Louise C. Showe, Donald O'Rourke, Ramana Davuluri, et al.

U.S. PATENT NO. 10,010,560
Small Molecule HSP70 Inhibitors
ISSUE DATE: July 3, 2018
INVENTORS: Maureen E. Murphy, Donna George and Julia I-Ju Leu

U.S. PATENT NO. 9,983,215
Methods and Compositions for Diagnosis of Ectopic Pregnancy
ISSUE DATE: May 29, 2018
INVENTOR: David W. Speicher, Kurt T. Barnhart and Lynn A. Beer

U.S. PATENT NO. 9,920,375
Biomarkers in Peripheral Blood Mononuclear Cells for Diagnosing or Detecting Lung Cancers
ISSUE DATE: March 20, 2018
INVENTORS: Louise C. Showe, Michael Showe, Andrew V. Kossenkov and Elena Nikonova

U.S. PATENT NO. 9,903,870
Methods and Compositions for the Diagnosis of Ovarian Cancer
ISSUE DATE: February 27, 2018
INVENTORS: David W. Speicher, Hsin Yao Tang and Lynn A. Beer

U.S. PATENT NO. 9,868,951
Methods and Compositions for Enhancing the Therapeutic Effect of Anti-Tumor T Cells
ISSUE DATE: January 16, 2018
INVENTORS: Jose R. Conejo-Garcia, Hui Hu and Tom-Li Stephen

U.S. PATENT NO. 9,856,214
EBNA1 Inhibitors and their Method of Use
ISSUE DATE: January 2, 2018
INVENTORS: Paul M. Lieberman, Troy E. Messick, et al.

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