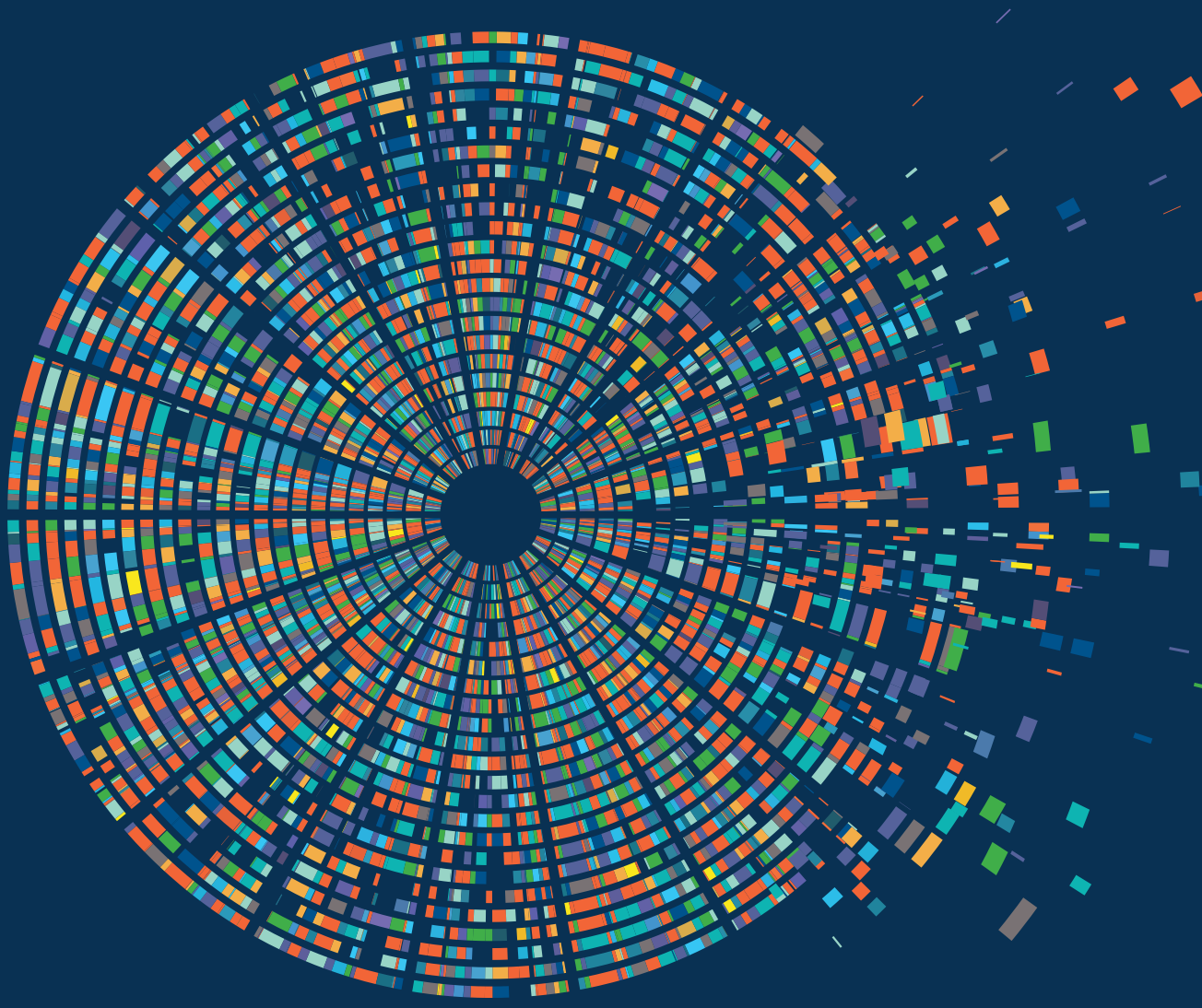
Fall 2020

Focus

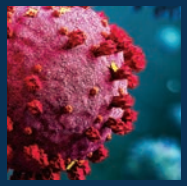
ON THE WISTAR INSTITUTE



Breaking Scientific Barriers

SPECIAL ISSUE:

Updates on COVID-19, Annual Report & More!



Wistar COVID-19 Research Response

Wistar's Impact Through Education

WISTAR SCIENCE: BOLD. IMAGINATIVE. INSPIRED.

CONTENTS

THE WISTAR INSTITUTE

WORKING TO SOLVE THE GLOBAL HEALTH CRISIS THROUGH SCIENCE AND INNOVATION

The first eight months of 2020 have been more different than any other time in our lives. Not only did the COVID-19 pandemic threaten the health and lives of millions of people around the world, it heavily affected our economy and changed the way we live, work, learn and, as social beings, interact with each other and our community.

We were all hit by this storm unexpectedly. Wistar was too. But we quickly reacted to face the impact, ready to continue our scientific mission of improving human health, now more important than ever, while ensuring everyone's safety.

We followed our historic legacy of creating lifesaving vaccines and built on leading-edge expertise in our Vaccine & Immunotherapy Center. The result was the rapid generation and initial clinical testing of an innovative vaccine candidate for COVID-19 in collaboration with a biotech partner. This vaccine uses recombinant DNA technology and an ingenious delivery system and is designed to ensure safety and comprehensive immune response to fight this infectious agent. We do not know if this vaccine candidate, which moved from concept design to clinical trials in 83 days, will ever be approved for clinical use, and we refuse to use the word race when it comes to medicine and biology — we will let the science run its course and speak for itself as to which will be the safest and most effective vaccine platforms to fight COVID-19. But right now, what we do know is that once more, in the midst of one of the most challenging and difficult times worldwide, Wistar heeded the call and was at the forefront of discovery and innovation, upholding its core values of unwavering scientific pursuit, open collaboration and public-private partnership.

Reflecting these unique times, this issue of our *Focus on The Wistar Institute* magazine is indeed special. It summarizes our scientists' research, moving forward quickly and effectively to find solutions for COVID-19, and important initiatives and critical undertakings that took place despite the pandemic.

Our 2019 Annual Report is also included as an abridged version that provides a snapshot of Wistar in 2019. It highlights our scientific and educational accomplishments, our stellar performance attracting federal and private funding, publication of impactful studies, and new promising collaborations. We continue to advance our mission breaking new ground in cancer, immunology and infectious disease research and pandemic preparedness, accelerating scientific advances from the laboratory to patients.

I want to personally thank each one of our supporters for gathering together and propelling our efforts. While we can't all work on the frontline of this emergency, we can all support those in the field including researchers on their quest for life-saving vaccines and therapies for COVID-19.

DR. DARIO ALTIERI
Wistar President and CEO

Wistar Research on the Front Lines of the COVID-19 Pandemic

A HISTORIC LEADER IN INFECTIOUS DISEASE RESEARCH WITH A LEGACY OF CREATING LIFE-SAVING VACCINES, WISTAR WAS WELL-POSITIONED TO JOIN THE RESPONSE SPARKED BY THE COVID-19 PANDEMIC IN THE INTERNATIONAL SCIENTIFIC COMMUNITY.

REWIND BACK TO 2016 when Dr. David B. Weiner, pioneer in DNA-based immunotherapy, arrived at Wistar to establish the Vaccine & Immunotherapy Center (VIC). The intent of the Institute was to create a hub of new technologies and an aggregate of expertise with the capacity to respond to emerging outbreaks and continue Wistar's legacy of advancing scientific discovery for global health. In line with this vision, today the Wistar VIC is at the apex of cancer and infectious disease treatment and prevention, and a force for collaboration, synergy and partnership.

As new outbreaks travel the world spreading much faster than in the past, we need the expertise of talented scientists that understand infectious diseases and new tools that allow for rapid and efficient response. Wistar continues to be an important first responder to infectious disease threats and has built capacity in emerging pandemic preparedness with leading-edge biomedical research.

Lab technician Yaya Dia

In the early days of COVID-19, Wistar scientists quickly implemented a coordinated effort that deployed their expertise and technologies into advancing an array of innovative projects for the discovery of new preventative and therapeutic interventions to tackle the outbreak.

Among their achievements thus far, one of the COVID-19 vaccine candidates is being advanced through clinical trials in collaboration with a publicly traded biotech and other academic institutions.

But scientists do not work and make discoveries in a vacuum. Wistar's research response to COVID-19 was a joint endeavor by everyone at the Institute and our committed community of supporters

DECEMBER 2019

The city of Wuhan, in China, experiences an outbreak of a novel coronavirus that causes pneumonia and rapidly spreads to other countries. Wistar scientists and collaborators start monitoring the outbreak.

JANUARY 11, 2020

SARS-CoV-2 genome sequence becomes available to the scientific community. Design and creation of a synthetic DNA vaccine is initiated by Wistar scientists and collaborators.

JANUARY 23, 2020

The Wistar Institute announces that they are part of a collaboration funded by the Coalition for Epidemic Preparedness Innovations (CEPI) to develop a vaccine.

who came together for the same urgent goal.

The Institute launched the Coronavirus Discovery Fund (CDF) in support of COVID-19 research and, in a matter of weeks, philanthropic support exceeded $1.6 million in new funding from individual donors, foundations and corporate sponsors. This fueled our researchers' efforts and enhanced their ability to quickly advance vaccines and other solutions.

Highlighted below are some of the COVID-19 research projects underway thanks to the generous and pivotal support of CDF donors.

Dr. Weiner, executive vice president, director of the VIC and W.W. Smith Charitable Trust Professor in Cancer Research, and his team with collaborators at INOVIO Pharmaceuticals, Inc. were able to design, develop and begin clinical testing of a synthetic DNA vaccine in just 83 days, thanks to their previous experience responding to recent outbreaks, including Ebola, Zika, and, importantly, MERS, another coronavirus similar to SARS-CoV-2. Their platform allows a plug-and-play approach to stimulate immunity

against virtually any virus for which the genetic information is available. In parallel and in support of clinical studies, advanced testing and modeling is ongoing at Wistar to better characterize immune responses to the vaccine candidate.

Thanks to their expertise in protein modeling and computer simulations, **Dr. Daniel Kulp**, VIC associate professor, and his lab are engineering nanoparticle-based immunotherapies that target SARs-CoV-2. He and his team use synthetic DNA to instruct the body to produce extremely small ('nano') particles displaying multiple copies of critical parts of the virus in order to stimulate immunity. Resembling a tiny ball with viral protein parts sticking out, nanoparticle-based vaccines appear like a virus to the immune system, therefore can elicit extremely strong immune responses. The Kulp lab is also working on other innovative approaches for prevention and therapy and closely monitoring new SARS-CoV-2 mutations that are evolving through viral infection so that the Wistar team can prepare and develop vaccines against future pathogens that have evolved from the current pandemic.

With support from the G. Harold and Leila Y. Mathers Charitable Foundation, the team of **Dr. Hildegund Ertl**, vaccine key opinion leader and professor in the VIC, is developing a SARS-CoV-2 vaccine using genetically modified adenoviruses as vaccine

MARCH 11, 2020

The World Health Organization (WHO) declares the COVID-19 outbreak a global pandemic.

APRIL 2, 2020

The Wistar Institute launces the Coronavirus Discovery Fund to accelerate discoveries and support Wistar scientists in their search for effective solutions to combat the outbreak.

APRIL 6, 2020

The DNA vaccine candidate co-developed by Wistar investigators enters human phase 1 trial with 40 healthy volunteers.

vehicles. Though no adenovirus-based vaccines have hit the market for human use yet, this technology has proven to be safe and effective at inducing neutralizing antibodies and killer T-cell responses. Another COVID-19 vaccine using an adenovirus vector is being advanced by a group of Oxford University scientists in the U.K.

Dr. Luis Montaner, leader of Wistar's HIV Research Program and the Herbert Kean, M.D., Family Endowed Professor, in collaboration with **Dr. Joseph Salvino**, professor in the Cancer Center and a medicinal chemistry expert, are collaborating to find new ways to boost the natural function of the immune system to combat infection by using small molecules that stimulate the interferon response. Montaner and Salvino are repurposing an existing screening project for new HIV drugs, which pointed to molecules that can strengthen the binding of interferon to its receptor.

Dr. Ami Patel, research assistant professor in the VIC.

Dr. Paul Lieberman, leader of the Cancer Center's Gene Expression & Regulation Program and the Hilary Koprowski, M.D., Endowed Professor, and his lab are working to identify FDA-approved small molecules that can directly bind to SARS-CoV-2 RNA and disrupt its function, which is essential for viral infection and disease. Drug repurposing efforts have the potential to identify molecules that are already known to be safe and can be applied for additional uses than the original one in a faster period of time.

Other Wistar researchers actively engaged in Covid-19 research include Drs. Ami Patel, Kar Muthumani, Troy Messick, Ian Tietjen, Yulia Nefedova, Mohamed Abdel-Mohsen, and Bin Tian.

EXPANDING OUR TECHNOLOGY TOOLBOX

Through generous anonymous gifts to the Coronavirus Discovery Fund, the Weiner lab was able to purchase a sophisticated piece of equipment that monitors cells in real time and is instrumental to perform high-throughput assays required to speed up vaccine development. This addition complements the Institute's state-of-the-art technological resources and will hasten our ability to advance critical research in response to future pandemic threats as they arise.

MAY 13, 2020

The Wistar Institute receives $1.6M in philanthropic funding to support research initiatives as part of the Coronavirus Discovery Fund. At the time of publication, support exceeded $1.8M.

MAY 20, 2020

Wistar and collaborators report initial preclinical testing of their DNA vaccine candidate in the journal *Nature Communications*. Immune studies in animals showed induction of robust antibody and T-cell responses following immunization.

JUNE 30, 2020

INOVIO Pharmaceuticals Inc. announces encouraging preliminary results of the DNA vaccine phase 1 clinical trial.

Following Up with DNA Vaccine Creator: DR. DAVID WEINER

THROUGHOUT THIS TIME OF SOCIAL RESTRICTIONS, WITH ANTICIPATION WE LOOK FORWARD, HOPEFUL TO RESUME SOME SEMBLANCE OF NORMALCY TO OUR LIVES. BUT WADING THROUGH A VARIED, STEADY INFO-STREAM OF COVID-19 NEWS BYTES OFTENTIMES BRINGS MORE QUESTIONS THAN ANSWERS.

Drs. David B. Weiner and Ami Patel

RESEARCHERS AND DOCTORS ARE STILL LEARNING how our immune system responds to COVID-19. Some people go through the disease with mild or no symptoms whereas others experience the trauma of a cytokine storm caused by an immune system in overdrive.

For perspective, we reached out to vaccinologist **Dr. David Weiner**, Wistar EVP and director of our Vaccine & Immunotherapy Center, to shed light on the COVID-19 virus that made its entrance on the world's stage a mere nine months ago.

Dr. Weiner's work to develop a DNA vaccine against COVID-19, in collaboration with INOVIO Pharmaceuticals, Inc., and partners, is moving through clinical trials. Daily, he does the heavy lifting to lead a fast-paced research lab: participating in online conferences, publishing articles illuminating the team's latest data, sifting through an onslaught of papers, convening discussions, overseeing experiments, and reviewing data all to move closer to realizing the potential of a novel, effective synthetic DNA vaccine.

Let's start with the basics: how does our immune system recognize and fight an invading virus?

Our immune system has two arms that work cooperatively: the innate and the adaptive immune responses.

The innate immune response is the first line of defense once a pathogen enters our body and starts infecting cells. The adaptive response is specifically engaged to kill that exact virus and destroy infected cells if the innate response isn't effective. It is a more sophisticated response that is built to target each pathogen and "learns" from previous experience to keep memory of infectious attacks and protect us from future encounters. The adaptive response involves T and B cells and other specialized cells of our immune system.

What do we know so far on how the body reacts to SARS-CoV-2 infection?

DAVID WEINER: COVID-19 is complicated. We do not understand innate immunity to COVID-19, but we have a better picture than we did a few months ago. Some people get infected and spread the disease before they develop symptoms, but we isolate them quickly as soon as symptoms appear; and some infectious people are asymptomatic and spread the disease, but of course we don't find them as easily and they are a threat to infect many others. Some people with mild disease recover due to having antibody responses that target SARS-CoV2, and some people can mount T cell responses that are likely able to help clear their infections. However, a significant percentage can progress to more serious disease.

How important are antibodies?

DW: Antibodies are important, but not the whole story. The correlation between antibody levels and duration and severity of disease is not straightforward.

Some research even showed that good neutralizing antibodies correlated with having difficulty fighting infection. Some of the sickest people had the best antibody titers. It doesn't mean antibodies aren't good, it means the picture is more complicated than previously expected.

Researchers are also finding groups where more than 20 percent of infected people have low antibody titers but have memory B cells and have cleared infection rapidly.

We still don't know what an effective antibody response looks like for this virus, and antibodies are just one part of our immune system response.

COVID-19 & Antibodies

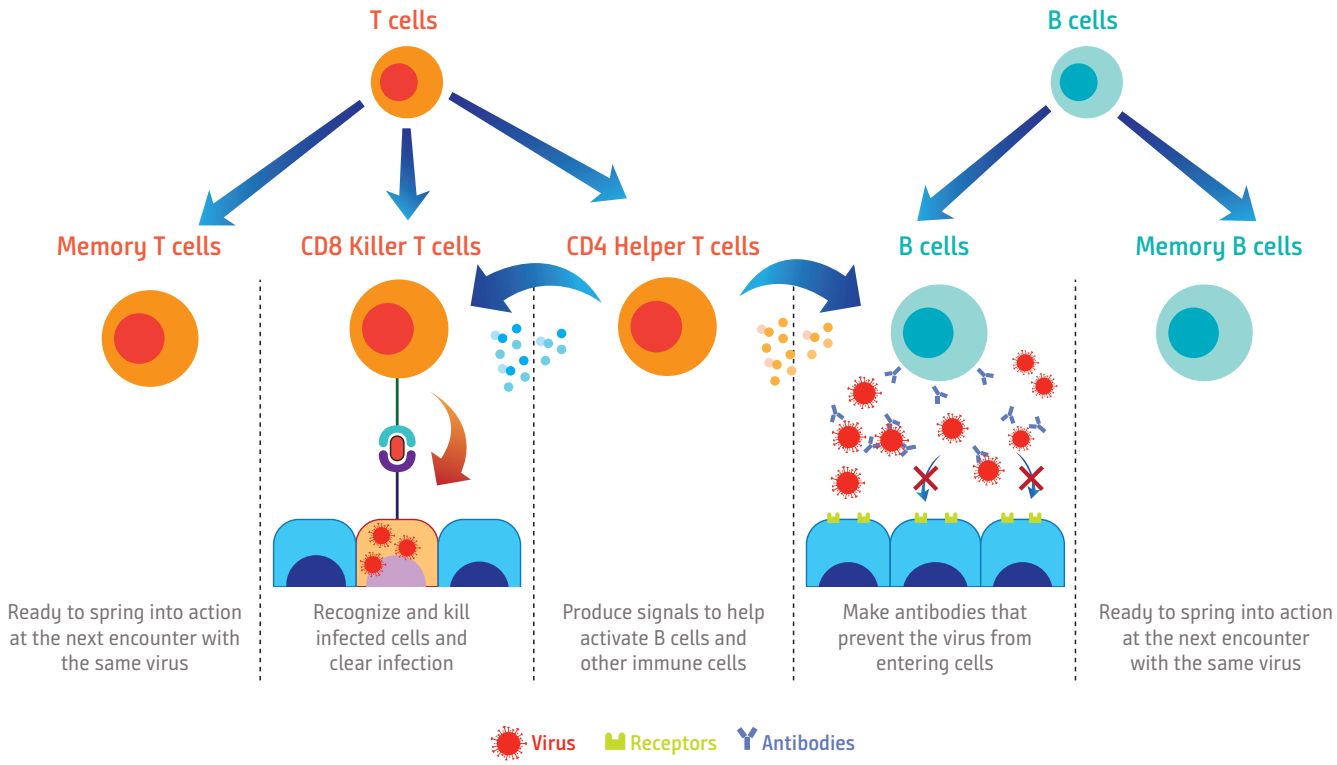
Because this virus is so new, scientists and clinicians are trying to understand the role of antibodies and T cells in the immune system response. B cells produce antibodies against a specific pathogen. They act like a protective barrier coating the pathogen and targeting it for destruction, and limiting its ability to function. There are many types of B cells and some go on to become memory cells — and remember how to fight a pathogen they have already encountered. By better understanding antibodies, we can get closer to creating a vaccine. Yet scientists still don't know what an effective antibody response is, and antibodies are just one part of the story.

What about T cells and who seems to do best against this virus?

DW: T cells are likely very important in our response to COVID-19. A type of T cell, called helper or CD4 T cell, supports B cell responses, but a second type of T cell, called killer or CD8 T cell, functions independently of antibodies to search and destroy viruses hiding within cells, thus helping to clear viral infections.

Some people who have been infected have controlled COVID-19 infection by generating unique T cell responses, likely CD8 T cells, even though they produced weak

T CELLS AND B CELLS IN ADAPTIVE IMMUNITY



antibody responses. Data suggest that T cells might be a key to lasting immunity and that memory T cells remember other coronaviruses we may have come in contact with. Some blood donors who have not had COVID-19 have "cross reactive" T cells because they may have previously encountered coronaviruses that circulate yearly and affect us like the common cold. But we need much more research on this issue.

Tell us about asymptomatic transmission.

DW: Nobody has yet sorted all this out, but we have seen that asymptomatic people either had T cells or low level antibodies to COVID-19, but didn't experience symptoms. Take the aircraft carrier the USS Theodore Roosevelt. Close to one third of the ship became infected, and 30-40% [of that third] had relatively mild cases. They developed T cells but didn't have strong antibody responses. Based on these and other observations on natural infection, having both T cell and B cell responses is likely important for vaccine development.

Should we take an antibody test and if antibody levels drop what does that mean for immunity?

DW: Antibody tests provide a good measure for what percentage of the total population has had COVID-19. But antibody tests are not perfect. If taken too soon they might give an incorrect assessment of the future. Antibody levels have shown they can fade a few months post-infection and have been reported to become undetectable. However, these data are early, and more studies may clarify this emerging picture.

What does this all mean for vaccine development?

DW: Lots has been written about neutralizing antibodies and how long antibodies remain in our body after COVID-19 infection. We look to past outbreaks to infer and better understand outcomes based on past diseases stopped by effective vaccines.

At the far ends of the spectrum we have the live measles vaccine, which confers lifetime immunity with just one shot, and the influenza vaccine, which we need every year.

Year to year, many different flu strains circulate throughout the world and scientists try to track strains in other parts of the world to best gauge what seasonal influenza strains will be circulating in the U.S. Unlike measles but similar to what scientists are noticing with flu, antibodies created to COVID-19 appear to wane over six months.

As we analyze outcomes in patients naturally recovering from COVID-19, we are seeing antibody levels wane, but more data are needed.

Does SARS-CoV-2 mutate?

DW: The SARS-CoV-2 genome is three times as large as HIV, but has a very low level of mutation due to its built-in proofreading activity. We know it's mutating at a low level, partly because we have so much infection and, moving through so many people, the virus has a lot of opportunity to change. All in all, those changes are currently limited. We have studied this and the vaccine we are working on is protective against the major mutation change so far observed.

Can we be re-infected?

DW: Right now, it's not clear. With more than 28 million cases, there have only been a few confirmed cases of reinfection so far. Animal studies, particularly in non-human primates, have pointed to no reinfection after a month, but it's a very short time frame for immune memory and still a guessing game. We will need longer-term follow up. An effective vaccine could be used to boost immunity for previously infected persons to help ensure they remain protected.

What will make a good vaccine?

DW: We can't be sure but it is likely a vaccine that is safe for diverse populations and one that will induce antibodies and T cells. Antibodies provide the first level of protection against viral infection, while T cells are important to expand B cell responses and to clear infection and contribute to immunological memory.

Tell us about your vaccine

DW: We tailor our DNA platform to the desired virus, in this case SARS-CoV-2. The DNA vaccine technology does not make use of proteins or virus at all. We develop our vaccine synthetically: it is non-live and non-spreading, has been well tolerated in the clinic, and can generate both T and B cell responses. Our collaborators at INOVIO have done a lot of tests to monitor the DNA platform stability over time and demonstrated that it's stable at room temperature for more than a year and for more than three years in refrigerated conditions, which is important in resource-limited settings. You can transport the vaccine, and it's simple to distribute.

For the SARS-CoV-2 synthetic DNA vaccine, as has been reported, we have obtained promising data. It generated both antibodies and T cells in small and large animal models including non-human primates. It induced protection in the non-human primate challenge model. INOVIO has announced safety and top-line immunology data regarding the human clinical trial, reporting that the vaccine induced antibody and T cell responses in most vaccinated subjects, with a very strong safety profile. The team is continuing studies in animal models even as we study the vaccine in humans to generate as much data as possible on safety and immunogenicity through the most rigorous assays and tests. First and foremost, we are focused on generating a safe and effective vaccine.

New Faculty Join Wistar

THE WISTAR INSTITUTE RECENTLY WELCOMED THREE NEW SCIENTISTS WHO WILL LEAD THEIR LABORATORIES IN THE GENE EXPRESSION & REGULATION (GER) AND MOLECULAR & CELLULAR ONCOGENESIS (MCO) PROGRAMS. THESE ARE TWO OF THE THREE CANCER CENTER RESEARCH PROGRAMS CENTERED AROUND UNDERSTANDING TUMOR INITIATION, THE TUMOR MICROENVIRONMENT AND CANCER METASTASIS.

"I am thrilled to have these remarkable scientists on board," said Dr. Dario Altieri, Wistar president and CEO. "In this time of uncertainty, it is exciting to bring new perspectives to our Institute. It reinvigorates our scientific commitment to finding new ways to understand, diagnose and cure cancer, a different but equally important pandemic."

Dr. Italo Tempera joined Wistar as an associate professor in the GER Program on April 30. He is a molecular virologist with special expertise in the study of the Epstein Barr virus (EBV) and underlying mechanisms that contribute to the virus' ability to infect people and cause diseases such as mononucleosis and cancer.

EBV is a common infection that has been linked to the development of some cancer types including Burkitt's lymphoma, nasopharyngeal carcinoma and lymphomas. These malignancies are challenging to target, partly because EBV establishes a long-term, latent infection through complex and dynamic gene expression patterns. "Research in my laboratory is aimed at understanding and interfering with these gene expression patterns as a new approach for targeting and treating EBV-associated cancers," said Dr. Tempera.

He comes to Wistar from the Fels Institute for Cancer Research and Molecular Biology at the Lewis Katz School of Medicine of Temple University, where he established his lab in 2012 and was promoted to associate professor in 2017.

Fun fact, he received his postdoctoral training at Wistar in the laboratory of Dr. Paul Lieberman. Returning to Wistar as an independent established investigator, he brings expertise that is a perfect complement to our ongoing research on the viral causes of cancer.

When not in the lab, Dr. Tempera 'experiments' in the kitchen making dishes inspired by the Italian culinary tradition. He also likes photography and figurative arts. In his office, you can admire some paintings by his mother-in-law. "My favorite is the one she painted in Italy with a view of my grandparents' country home," he said. "I like to look at it while I work, it makes me feel at peace and closer to my birthplace."

Dr. Bin Tian, a molecular systems biologist, joined the GER Program as professor on June 1. Dr. Tian is an RNA biology expert whose research focuses on the mechanisms through which genetic information is decoded. Messenger RNA (mRNA) is an intermediate molecule that carries the genetic blueprint from

our genes to proteins that build cellular machineries in our cells. The Tian laboratory studies how mRNA molecules are modified to control and regulate how genetic instruction is executed.

Utilizing interdisciplinary approaches that span genomics and molecular and computational biology, the Tian lab studies RNA biogenesis and metabolism in normal conditions as well as in cancer and neurological diseases. Dr. Tian's investigations will expand Wistar's RNA biology research capabilities and brings critical expertise that will synergize with the work of our scientists across our research programs.

His lab is also focused on developing novel therapeutics for COVID-19 by controlling production and metabolism of a wide variety of genes that encode inflammatory molecules, to mitigate the uncontrolled immune response that causes respiratory failure and organ damage.

Dr. Tian joins Wistar from Rutgers New Jersey Medical School where he was a tenured professor.

An avid traveler, Dr. Tian loves to explore different cultures and cuisines from around the world. In his down time, he is a regular swimmer and enjoys playing tennis.

"When I started my lab in 2003, I planned to study one aspect of RNA biology that was hot at the time, but our discoveries took us in an alternate direction and, along the way, we ended up with many unexpected findings that opened into new interesting paths," said Dr. Tian. "Science really is like a box of chocolates. You never know what you're gonna get."

Dr. Chengyu Liang, who joined Wistar as a professor in the MCO Program on July 6, also landed in her field of research through an unexpected discovery that opened a new and interesting avenue for her laboratory. "Science is full of surprises," she said. "That's also what I love about it."

The Liang lab studies the mechanisms that regulate fundamental cellular processes such as cell death, DNA damage repair and membrane trafficking in cancer and infectious disease, in a continuum of basic and translational science. They focus on autophagy, the natural ability of cells to "self-eat" to digest, remove and recycle damaged or unwanted components. In addition to its quality control function, autophagy also constitutes a barrier against malignant transformation and the Liang lab studies its role in leukemia, colorectal cancer, melanoma, and viral infections.

During her postdoctoral training, Dr. Liang was studying a virus which led her to discover a novel autophagy pathway that is involved in DNA repair and chromosomal stability in mammalian cells. "Viruses are bad for us, but they are also valuable tools to understand the cause of human disease," she said.

This pathway preserves genome stability in response to UV radiation exposure and is impaired in skin cancer. Therefore, Dr. Liang's work has a strong focus on melanoma and ideally complements the Institute's melanoma research program.

In her private life, Dr. Liang cultivates her spirituality through meditation and reading books by philosophers and spiritual leaders such as Jiddu Krishnamurti. "Meditation helps me clear my mind, relax and be more focused on my work," she said. "When I observe my mind and my heart from a different perspective, I feel myself closer to the true merit of science."

As a little girl, Dr. Liang wanted to become a doctor because she wanted to save lives. Many years later at medical school, during her clinical rotation, she realized that clinical practice without a deep understanding of disease was rootless. This new awareness gradually led her to the path of scientific investigation, though she values her medical training that allows her to bridge basic findings with clinical significance.

All three new faculty are excited to be at Wistar, a premier research institution with a long and distinguished history of discoveries. They value its high-caliber scientific environment, its collaborative culture, and the wide spectrum of technology support, and look forward to forging new collaborations and advancing their research at the Institute. ●

The Wistar Institute gratefully acknowledges support from The Pew Charitable Trusts to aid in our recruitment efforts and expand the breadth of research in Wistar's Cancer Center and Vaccine & Immunotherapy Center. Pew's award of $1M in 2019 partially supports the labs of Drs. Tempera, Tian and Liang.

A Life at the Intersection of Music, Biotechnology and Business

A CONVERSATION WITH ANNE SCHOEMAKER ABOUT HER VISION TO SPONSOR THE WISTAR-SCHOEMAKER INTERNATIONAL POSTDOCTORAL FELLOWSHIP, A PARTNERSHIP LAUNCHED IN 2019 BY WISTAR AND LEIDEN UNIVERSITY MEDICAL CENTER (LUMC) IN THE NETHERLANDS TO BRING LUMC GRADUATES TO WISTAR FOR POSTDOCTORAL TRAINING.

As a trained pianist, can you explain why you feel so passionately about biomedical research training and education?

I am a Juilliard-trained pianist, and music remains an integral part of my life, but I never made a living performing. I pivoted away from that life through a graduate degree in business which is what led me, serendipitously, I might add, into the world of biotechnology. As fate would have it, it also led me to my late husband, Hubert J.P. Schoemaker, whom I met during a meeting.

My career in biomedical technology management and licensing explains part of my interest in biomedical research and education. I joined the University of Pennsylvania's technology transfer group at its inception. I had always enjoyed studying science, had business credentials, and wanted to work in a nonprofit environment, so I found the opportunity to join this nascent effort interesting. But I would not have predicted how much I would enjoy my interactions with scientists and the diversity of the work. That environment also provided something else: a window into the world of research, discovery and innovation and, importantly, an understanding of what is required to fuel the scientific endeavor. I remember thinking that I wished I had paid more attention in high school chemistry class (I was too busy practicing), and I learned that, not unlike mastering a musical instrument, cultivating a research scientist necessitates a program of intellectual discipline and training that begins early and continues over many years.

The other part of my interest derives from my husband's background as a person who also fell, somewhat serendipitously, into the world of science. As a young student in the Netherlands, academics in general were not of particular interest to him, and only because his father sent him to the U.S. to "improve his English" did he somewhat accidentally find his way to the University of Notre Dame and the study of chemistry. Two years later, he was hooked – on the subject matter and what the scientific tools and repertoire enabled. He later completed a Ph.D. at Massachusetts Institute of Technology in record time, and he often reflected on the value of his education and training at both institutions as fundamental to enabling his seminal contributions to the field of biotechnology.

Why, as a philanthropist, did you choose Wistar to establish a postdoctoral fellowship collaboration with the Leiden University Medical Center?

First of all, I'm a Wistar alumna. Former director Hilary Koprowski hired me in the early 90s to establish the Business Development Department at Wistar, and I was fortunate to work with wonderful colleagues for several

Anne Schoemaker with her late husband Dr. Hubert J.P. Schoemaker

years during a very exciting time when the rabies and rotavirus vaccine technologies were commercialized. Importantly, fundamental research on the monoclonal antibody technology that formed the basis of Centocor, the company my husband co-founded, came out of Wistar. If all of these connections weren't enough, several researchers at LUMC, our inaugural Postdoctoral Fellowship partner, were Centocor collaborators. There are many important and deeply meaningful connections among Wistar, Centocor, my husband, and myself. The choice was, therefore, pretty obvious to me.

What does an international collaboration like this bring to the trainees from Leiden and the Wistar community?

Hubert fiercely believed that collaboration was the surest path to success. In the early days of Centocor, he elevated collaboration very nearly to an art form, replacing a corporate research and development department with many highly cultivated relationships with academic institutions and scientists whose discoveries ultimately became Centocor's products. These relationships were international: from LUMC to the Max Planck Institute in Germany, the Pasteur Institute in France, and the Imperial College London in the U.K., among others. He celebrated diversity of thinking and culture and believed the energy created by these contrasts provided creative fuel for his

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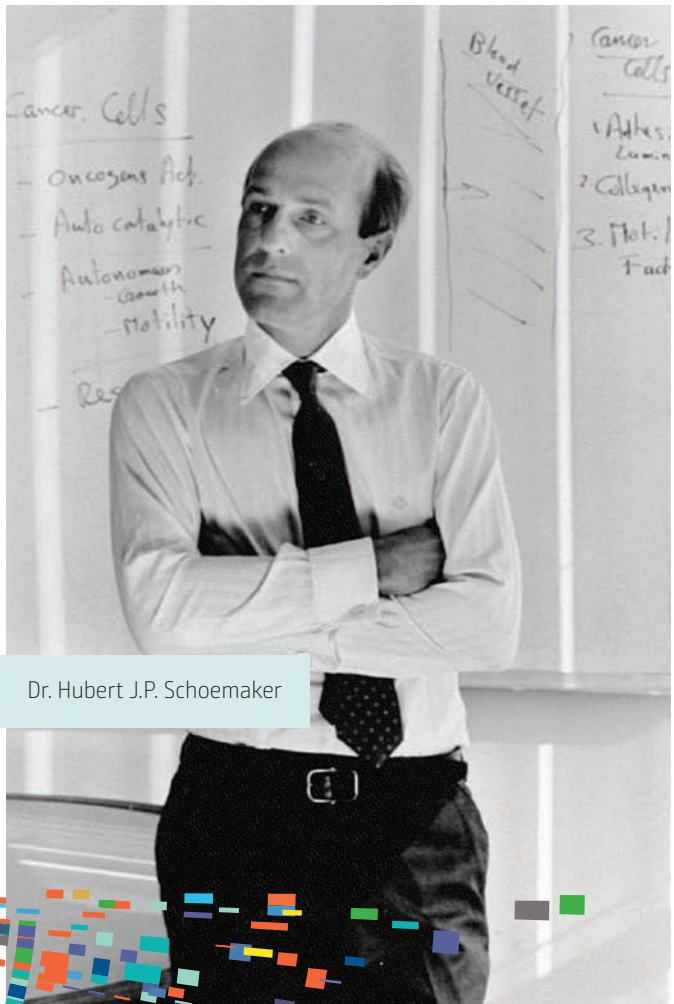
"We are grateful to Anne for serving as a valuable connection, having the foresight to lay the foundations for the Wistar-Schoemaker International Postdoctoral Fellowship with the Netherlands and introducing us to former Centocor colleagues and friends who helped cultivate the relationship between Cheyney and Wistar."

DARIO C. ALTIERI

company. International collaboration creates a unique form of experiential learning, and this is what trainees can expect from joining us at Wistar as Fellows.

How does the program change due to the global experience of COVID-19?

Sadly for all of us, we have hit a physical pause. The health and safety of the Wistar community and future researchers and staff is paramount, so international travel and relocation is not possible at this time. The program is fully established and ready to be implemented as soon as it is safe to do so, and there is much excitement and anticipation on the part of our Dutch colleagues to operationalize the Fellowship. In the meantime, we continue to engage with our colleagues at LUMC and cultivate additional relationships with interested parties, albeit through digital platforms, as we believe this Fellowship program could be replicable worldwide.



Dr. Hubert J.P. Schoemaker

WISTAR AND CHEYNEY UNIVERSITY FORGED STRATEGIC COLLABORATION FOR LIFE SCIENCE RESEARCH TRAINING AND BUSINESS DEVELOPMENT

Wistar believes access, inclusion, equity, and equal opportunity are essential and at the intersection of the sciences.

The Wistar Institute and **Cheyney University of Pennsylvania** recently forged a special collaboration to expand life science research training opportunities to Cheyney students. It unites the nation's first independent biomedical research institute and the nation's first historically Black college and university (HBCU) to make Cheyney a hub for life science research education and training.

Through this union, Cheyney students will participate in Wistar's biomedical research and training curriculum and gain hands-on laboratory experience through laboratory courses and internships that can progress into Wistar's credentialed apprenticeship program. In addition, Cheyney University becomes a new member of the Philadelphia Research Consortium (PRC), through which Cheyney University and its on-campus life-science companies will be able to leverage the research and business communities coalesced around the PRC.

"Tapping into our strong network of partners and continuing scientific exchange with our community and beyond are key elements to ensure inclusive and essential training of the next generation of scientists at Wistar," said Dario C. Altieri, president and CEO.

HIGHLIGHTS FROM 2019 AT WISTAR

2019 Science Highlights

In 2019, Wistar laboratories made important advancements in cancer, infectious disease and vaccine research, reflecting the Institute's scientific commitment to these fields. These efforts were published in high impact research journals. The following is a selection of studies that represent the spectrum of Wistar discoveries during this year.

Dario Altieri

LABORATORY

The laboratory of Dr. Dario Altieri discovered a new mechanism that controls **cancer cells' ability to adapt to their surroundings and grow, a process called plasticity**. This finding may potentially open a new therapeutic avenue.

- New mitochondrial pathway controlling survival of cancer cells: Mitochondria, the cell's powerhouse, adjust their metabolism and morphology during cancer development and metastasis. The discoveries uncovered new players and pathways in this process, opening therapeutic opportunities to selectively target cancer cells in patients.
- New molecule targeting cancer cell mitochondria delivered anticancer activity in preclinical studies: Targeting the newly discovered pathway, this molecule may translate into a novel therapy with potential to be effective in multiple cancer types and less prone to drug resistance.

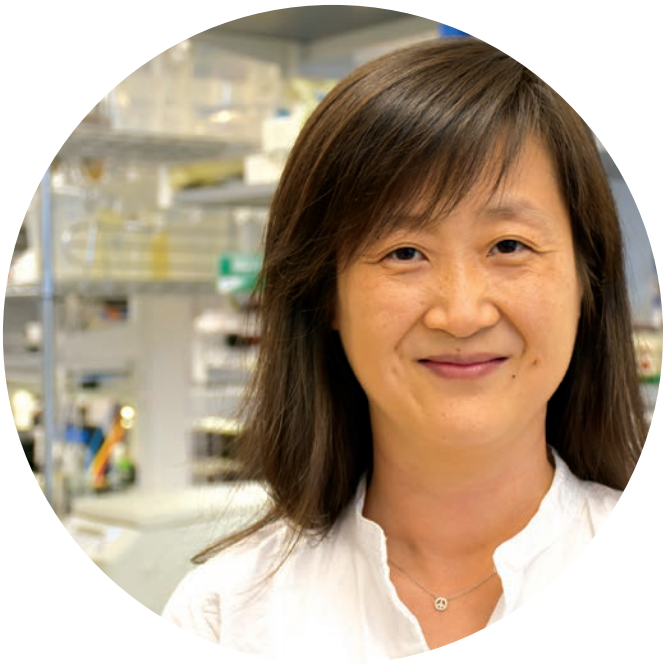
Qing Chen

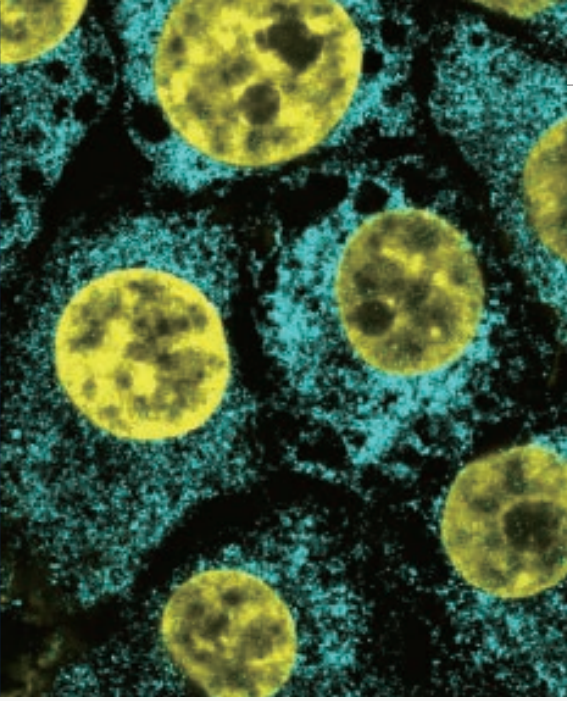
LABORATORY

New Mechanism Fueling Brain Metastasis

Brain cells called astrocytes enhance metastatic growth by providing fatty acids as a nutrient source for cancer cell metabolism and proliferation.

Fatty acids activate a pathway called PPAR-gamma in cancer cells. Genetic and pharmacologic blockade of this pathway decreased the brain metastatic burden in mouse models, suggesting this could be a viable therapeutic strategy to control brain metastasis. In support of this research, Chen received the 2019 Legacy of Hope Merit Award.





Rugang Zhang LABORATORY

The laboratory of Dr. Rugang Zhang explored new mechanisms of cancer development and identified **novel strategies for therapy resistance**.

- The dynamic role of cellular senescence in cancer: New mechanism that controls ability of senescent cells to release molecules that stimulate cancer growth may be modulated during chemotherapy to sensitize cancer cells to immunotherapy.
- New therapeutic strategy for chemotherapy resistance in ovarian cancer: In combination with standard chemotherapy, this class of inhibitors suppress the outgrowth of resistant cancer cells and prolong survival in a preclinical model.

Chih-Chi Andrew Hu LABORATORY

Enhanced Anticancer Compound May Allow for Precise Activation and Tracking of Treatment

Interfering with the ability of cancer cells to deal with a stressful environment has shown therapeutic promise; through smart chemical modifications, the new compound can be activated where needed and emits fluorescence that could potentially be tracked in the body, providing a real-time therapy readout.

Paul Lieberman LABORATORY

First-in-class Drug for Epstein-Barr Virus-associated Cancers

New small molecule inhibitors reduced tumor growth in preclinical models, opening the way for clinical trials.

Luis Montaner LABORATORY

Repeated Semen Exposure Promotes Resistance to Infection in Preclinical Model of HIV

This study found that semen exposure can change the characteristics of the circulating and local immune cells that are targets for HIV infection, reducing the susceptibility to a future infection.

Kar Muthumani LABORATORY

DNA Vaccine Against Mayaro Virus

A synthetic DNA vaccine shows promise in preclinical models against the mosquito-borne infection endemic to South America that has the potential to become a global emerging viral threat.

2019 Grant High Points

As part of federal funding that fueled Wistar research in 2019, researchers at the Institute received major grants supporting new, innovative and out-of-the-box research expected to significantly impact the fields of cancer and infectious disease.

Dr. Emma Reuschel, postdoctoral fellow.

1

The National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, awarded two major grants totaling more than $12 million to **Dr. Luis J. Montaner**, director of the HIV-1 Immunopathogenesis Laboratory and the Herbert Kean, M.D., Family Professor. He spearheads an international multidisciplinary clinical research consortium that will investigate the impact of opioid use disorder (OUD) and medications for opioid use disorder (MOUDs) on immune recovery in response to antiretroviral therapy (ART) in HIV-infected people.

NIDA provided funding for two clinical studies: an international trial to evaluate the impact of different MOUDs (methadone, extended-release naltrexone or buprenorphine) on immune restoration in HIV-infected people who inject drugs and are initiating ART; and a mechanistic study conducted on Philadelphians living with HIV on ART and taking MOUDs, aimed at dissecting the mechanisms that regulate persistent immune activation and residual HIV expression.

"We expect the results of this major collaborative effort, which has its hub in Philadelphia, to have broad clinical implications to inform the best pharmacologic strategy for the management of opioid-use disease in HIV-infected people starting ART," said Montaner.

Collaborators in these efforts include the Vietnam Ministry of Health, the Perelman School of Medicine at the University of Pennsylvania, the Pasteur Institute and the Institute of Applied Medicine and Epidemiology in France, Jonathan Lax Treatment Center, and the Icahn School of Medicine at Mount Sinai.

2

A grant totaling $12.5 million over five years was bestowed by the National Institutes of Health (NIH) upon a collaborative team led by **Dr. Meenhard Herlyn, D.V.M., D.Sc.**, director of Wistar's Melanoma Research Center and professor in the Molecular & Cellular Oncogenesis Program, and Dr. Ashani T. Weeraratna, former Wistar faculty now at Johns Hopkins University.

This funding extends a preexisting grant that was continuously renewed for 10 years and produced numerous advancements in the field of new melanoma targeted therapies. Through different multidisciplinary research projects, this new grant cycle will further this research integrating the role of the tumor microenvironment in influencing therapy response and development of resistance.

"It is not effective to just target specific genetic drivers in the tumor cells or specific immune response mechanisms because the tumor eventually finds ways to bypass that initial roadblock," said Herlyn. "Our team brings together diverse expertise so that we can tackle the whole picture of tumor resistance from different angles."

3

Dr. Zachary T. Schug, assistant professor in the Molecular & Cellular Oncogenesis Program, received the prestigious NIH Director's New Innovator Award in support of his research on the link between a high sugar/fat diet and alcohol use with cancer.

NIH Director's Awards for High-Risk, High-Reward Research are given to exceptionally creative scientists and were launched to support innovative approaches to major challenges in biomedical and behavioral research that call for high-risk, high-impact proposals.

This grant, totaling $2,679,000 given over five years, will advance Schug's research on the molecular mechanisms through which obesity and heavy drinking increase cancer risk.

"Zachary's research may have important clinical implications," said Dr. Dario C. Altieri, Wistar president and CEO, director of the Wistar Cancer Center and the Robert and Penny Fox Distinguished Professor. "Because of its relevance and innovation, this work embodies the type of research the NIH plans to support with this award."

4

An NIH grant of approximately $4.6 million was awarded to **Dr. David B. Weiner**, executive vice president, director of the Vaccine & Immunotherapy Center, and the W.W. Smith Charitable Trust Professor in Cancer Research, in support of innovative research to tackle antibiotic resistance, an expanding global public health concern.

Dr. Weiner's team is advancing a nontraditional approach based on a synthetic DNA technology to combat multidrug-resistant P. aeruginosa. They developed DNA-encoded monoclonal antibodies (DMAbs) that can effectively control this multidrug-resistant infection in mice.

This grant allows for extension of these studies by providing $4,624,553 over four years to further implement the DMAb strategy and move it forward toward clinical development.

"This support will move us closer to creating an out-of-the-box tool to fight antibiotic-resistant infections that threaten the lives of thousands every year just in the U.S.," said Dr. Weiner.

Wistar's Impact Through Education

The Institute continues to build educational programs, curricula, teaching and laboratory space through tapping into its strong network of partners and through scientific exchange with the community, to ensure inclusive and essential training of the next generation of scientists.

Inaugural Caspar Wistar Fellow Joined Wistar

In 2019, the Caspar Wistar Fellows Program launched to fast-track the most promising, early career scientists to pursue creative, out-of-the box biomedical research for the benefit of humanity. Dr. Rahul Shinde was the inaugural Fellow selected into the Program, which invites accomplished, intellectually driven postdoctoral scientists from across the U.S. and beyond to Wistar to receive both mentorship and freedom to pursue a strong, independent research program in their chosen field.

Dr. Shinde's research is in cancer immunology, focusing on the role of specialized cells that act as a front-line defense system for our immune systems, called macrophages. His lab investigates how these cells alter the microenvironment surrounding the tumor, which is a key determinant of cancer development and therapy resistance. Dr. Shinde is also interested in the gut microbiome and its connection with tumor progression.

Through generous support of Doug and Peggy Briggs, Wistar will continue to attract the best and brightest in the field of cancer and infectious disease research.

Dr. Rahul Shinde and lab technician Akwasi Gyampoh

Dr. Shinde's research is in cancer immunology, focusing on the role of specialized cells that act as a front-line defense system for our immune systems, called macrophages.

Launch of the Wistar-Schoemaker International Postdoctoral Fellowship

This program is a partnership with Leiden University Medical Center (LUMC) in the Netherlands to bring to Wistar recent LUMC graduates, supported by a three-year fellowship, for postdoctoral training under the mentorship of a Wistar faculty member.

The program promotes scientific and intellectual exchange and collaboration between investigators in the Netherlands and the United States.

> "We strive to make our science education positively impact our community, in microcosm, and the rest of the world."
>
> DR. DARIO ALTIERI
> *Wistar president and CEO*

Important Recognition for the BRT Apprenticeship

Wistar's Biomedical Research Technician (BRT) Apprenticeship was named the 2019 Outstanding Nontraditional Apprenticeship Program by the Pennsylvania Department of Labor & Industry. Established in 2017, the BRT Apprenticeship is the first registered, nontraditional apprenticeship program for biomedical research ratified by the Pennsylvania Department of Labor & Industry. It is a flagship model of how unconventional workforce development opportunities can be created to bring competitive job opportunities to a flourishing life sciences sector.

The Apprenticeship offers a career pathway to becoming biomedical research technicians in a research laboratory environment. This apprenticeship model successfully creates cross-boundary collaborations between industry, academia and research institutes, offers in-depth training and education while providing students a wage, and gives trainees the competence sought after by the life sciences industry.

Wistar by the Numbers

128
PAPERS PUBLISHED

15 New National Institutes of Health (NIH) Grants

9 of which from the National Cancer Institute (NCI)

30 New Grants Awarded by Philanthropic Foundations

RANKING IN THE TOP 1% OF INSTITUTIONS FOR INNOVATION GLOBALLY

(TOP 4% IN THE U.S.)

Source: SCImago Institutions Rankings

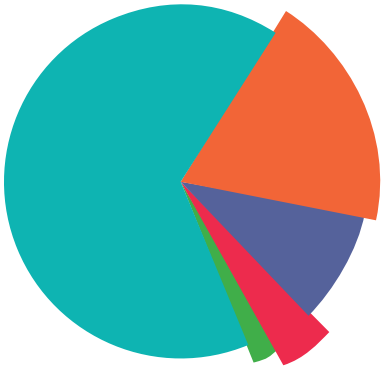
To learn more about Wistar's discoveries and technology commercialization, please contact the Business Development department at busdev@wistar.org or Dr. Heather Steinman, VP for Business Development & Executive Director of Technology Transfer, at hsteinman@wistar.org

Financials

As of December 31, 2019

OPERATING SOURCES

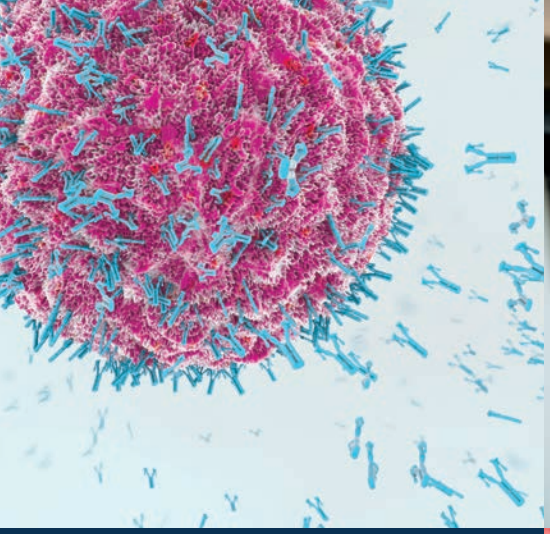
Federal grants	$37,241,000	56%
Non-federal gifts, grants and contracts	$15,546,000	23%
Investment draw and other income	$6,499,000	10%
Licensing	$5,383,000	8%
Unrestricted annual giving	$1,830,000	3%
Total Sources	**$66,499,000**	**100%**

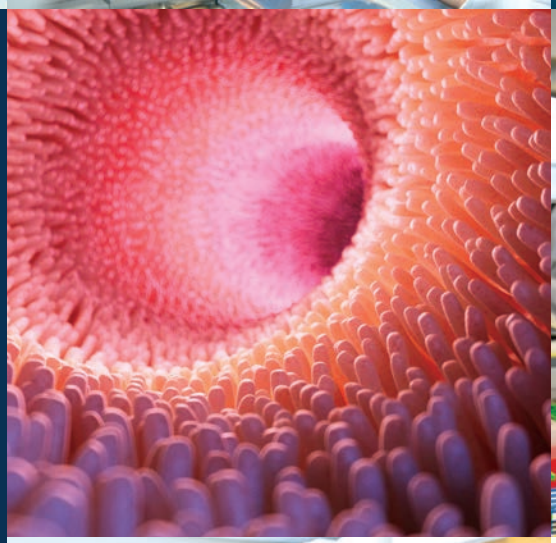


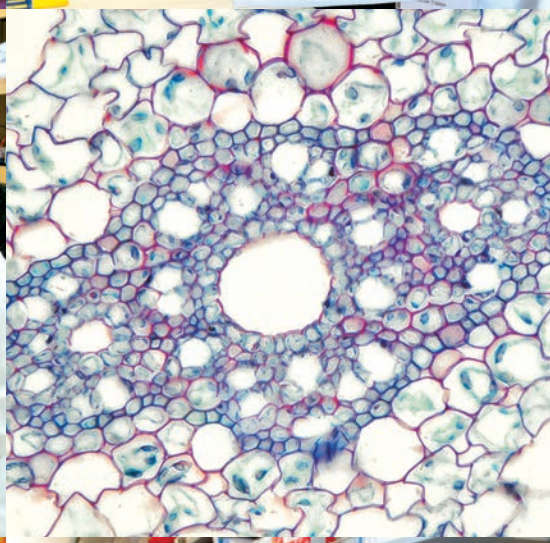
OPERATING USES

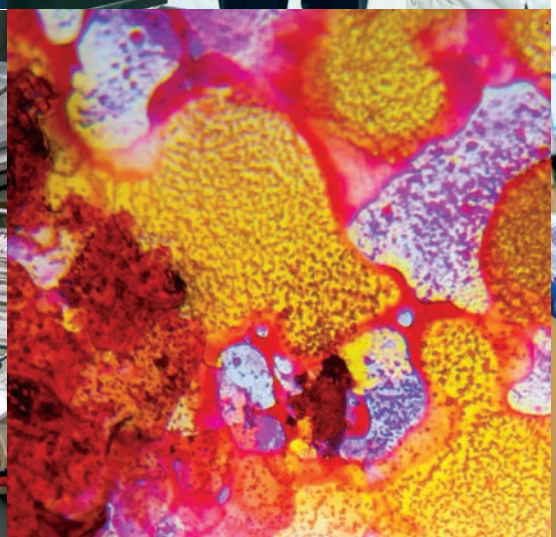
Research	$41,877,000	66%
Administration	$12,146,000	19%
Plant operations	$5,926,000	9%
Capital outlays	$2,722,000	4%
Interest expense	$1,326,000	2%
Total Uses	**$63,997,000**	**100%**

Operations Cash Flow	**$2,502,000**









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"Stronger than ever in this challenging time are the scientific quest for knowledge and the drive to make a difference in human health that inspire our scientists every day."

DR. DARIO ALTIERI
Wistar president and CEO

THE WISTAR INSTITUTE is an international leader in biomedical research with special expertise in cancer, immunology, infectious disease research and vaccine development. Founded in 1892 as the first independent nonprofit biomedical research institute in the country, Wistar has held the prestigious Cancer Center designation from the National Cancer Institute since 1972. The Institute works actively to ensure that research advances move from the laboratory to the clinic as quickly as possible.

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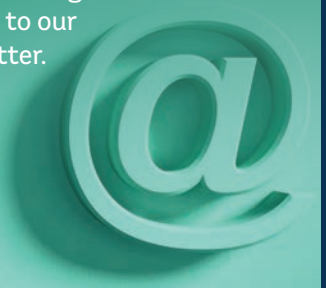
Please send an email to development@wistar.org so we can add you to our monthly e-newsletter.



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NCI Cancer Center

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