THE WISTAR INSTITUTE

focus

spring 2012

Brave Enough to Say "Cure"

Clinical Trial Could Lead to a New Cure Strategy for HIV/AIDS

THE NEED FOR PA CURE FUNDING

THE FINE YOUNG FELLOWS

Only you can make this possible. This is not just about laboratory space and money; this is about building a better future for humanity.

FROM THE PRESIDENT

There are few sights more captivating than construction. As I write this letter to you, workers are using "the cruncher" to tear down our old vivarium, and I admit that I find it hard to tear myself away from the view. As you read in the last issue of *Focus,* we are in expansion mode, undertaking both a transformative building project and a $35 million capital campaign.

Both efforts are well underway. Where the vivarium once stood will be, in less than two years' time, a gleaming seven-story, 89,700-square-foot research tower. Researchers in every laboratory across the Institute will enjoy new or refurbished spaces and exceptional scientific facilities.

The *Building Wistar, Changing the World* campaign is gaining momentum, but we need the help of you and your friends to get us all the way.

Only you can make this possible. This is not just about laboratory space and money; this is about building a better future for humanity. Your investment will enable more "eureka moments" that lead to new treatments, preventions and even cures. We take our motto to heart: Wistar science does indeed save lives.

Already, Wistar has created vaccines that have had a profound, lasting effect on human health. Our Vaccine Center continues this legacy with new vaccines in the pipeline to prevent HIV infection and to treat cancers therapeutically.

Similarly, our new Tumor Microenvironment and Metastasis program within the Cancer Center will provide the insights that will permit us to treat or prevent metastatic cancer. This is a vitally important area of exploration, as most cancer deaths are not caused by primary tumors themselves but, rather, result from the spread of tumors throughout the body.

To support this new program, Wistar's Center for Systems and Computational Biology, which was created largely through the generosity of our donors, will take on an even greater role in collaborating to decipher the complex scientific data our Cancer Center scientists produce. With your help, we are furthering our team science approach to tackle any barriers that might arise between biomedical research and the end of metastatic cancer.

All of these changes, structural and restructuring, alike, will make Wistar a more robust institution, better capable of developing impactful research programs.

So while you might need to "pardon our dust" at the moment, I would like to invite you to join us as Wistar builds for the future.

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

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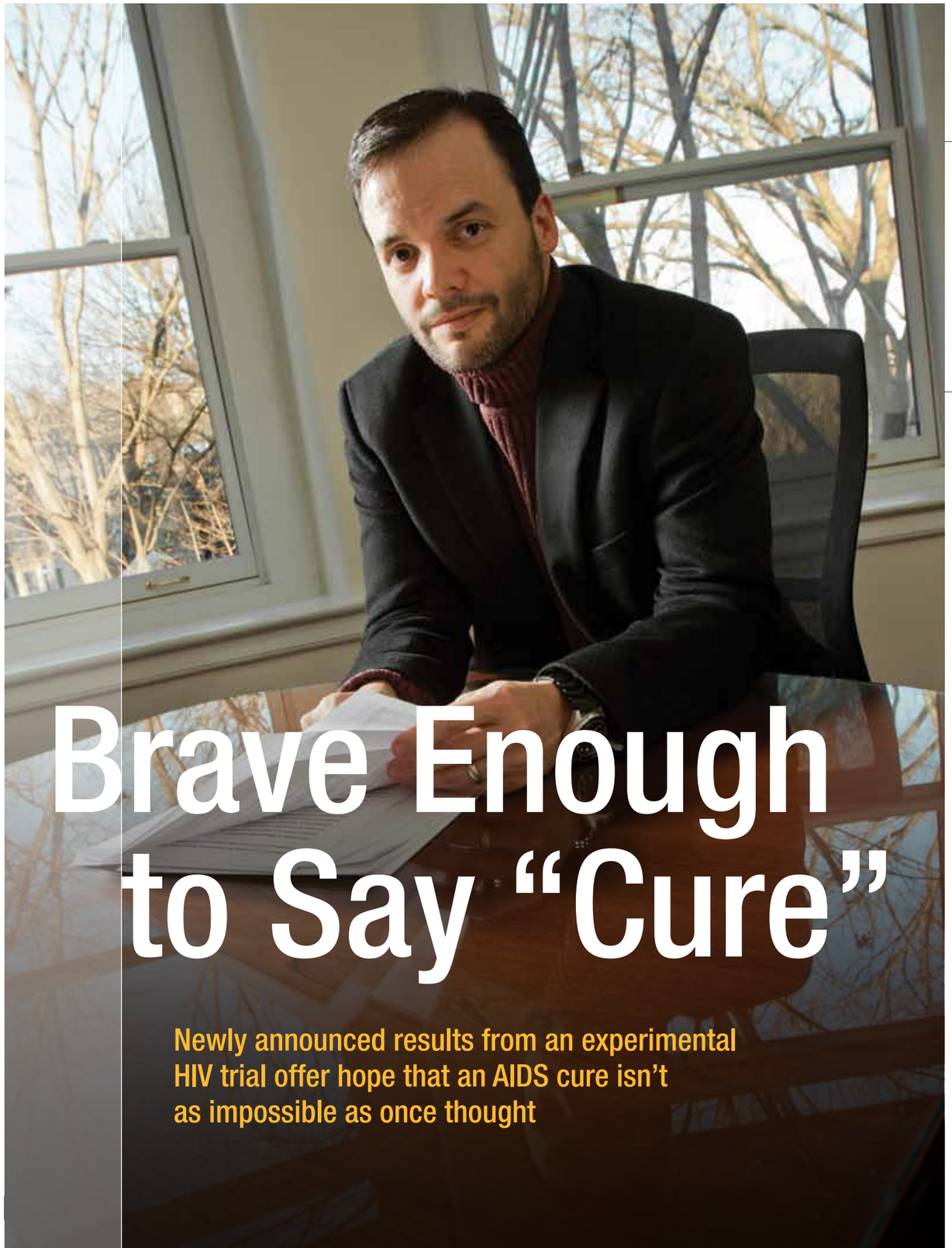

Brave Enough to Say "Cure"

Newly announced results from an experimental HIV trial offer hope that an AIDS cure isn't as impossible as once thought

Wistar's Luis J. Montaner, D.V.M., D.Phil., has announced the results of a clinical trial that shows how the immune system can engage in fighting HIV infection if given the right boost. In his study, HIV-infected volunteers suspended their daily antiretroviral therapy to receive weekly doses of interferon-alpha, an antiviral chemical produced by the human immune system. The study provides the first clinical evidence for a means of reducing the persistent amount of HIV in patients and the ability to control HIV without continued antiretroviral therapy.

Richard Moreau has taken part in many HIV/AIDS-related clinical trials over the years, but this experience was entirely new to him.

"You take part in a trial and that is generally the end of it. There is little, if any, follow-up," he said. "If you happen to remember, and you want to see how it turns out, you try to find what research journal publishes the results. That's about it."

What happened that day at Wistar was different.

On December 12, 2011, some months after taking part in the study, Moreau, along with researchers, physicians, advocates, and fellow participants, gathered to discuss the results of their relatively small clinical trial. It was a collaborative effort, led by Montaner, with contributors at the University of Pennsylvania, Drexel University, and other institutions. In the study, Moreau and other patients who had been on daily regimens of antiretroviral therapy (ART), a mix of three or more HIV-fighting drugs, suspended their treatment in favor of weekly doses of "Pegasys," a form of interferon-alpha. The human immune system manufactures interferon-alpha to "interfere" with the ability of viruses to replicate within cells.

And despite the small size of this particular trial, the news was huge.

"Our data shows that our human immune response can be made to control HIV in people who have otherwise lost that ability and, if sustained by natural interferon production, it establishes proof-of-concept that a functional cure is theoretically possible," said Luis J. Montaner, D.V.M, D. Phil., professor in Wistar's Tumor Microenvironment and Metastasis Program and director of the Institute's HIV-1 Immunopathogenesis Laboratory. "And while we still have much to pursue with this early clinical finding, I firmly believe this gives us hope that one day we can control — and eventually eradicate — HIV in absence of antiretroviral therapy."

According to Montaner, the trial showed that interferon-alpha sustained control of HIV in nine of 20 patients while also decreasing measures of HIV reservoirs — populations of cells that harbor HIV-1 out of reach of the medications available today — in patients otherwise dependent on ART. No other clinical strategy to date has shown an impact on decreasing integrated HIV DNA levels in HIV-infected humans.

Moreau was quick to grasp the consequences of Montaner's words. His doctor had told him that his CD4 (white blood cell) count is as high as it has ever been, and that his viral load — how much HIV-1 RNA is floating in his blood stream, a sign of viral activity — is undetectable. His doctor, however, also noted signs of depression (a common side effect of interferon therapy), which caused Moreau to drop out of the trial despite his clinical gains.

"I consider myself well-informed, but I can't claim to understand all of the things Dr. Montaner said and I certainly appreciate that they all made it a point to talk with us about it," Moreau said. "I did not even finish the trial, and I still feel that I'm a part of this."

"I think it makes a difference in building trust within the community," he added.

That is a sentiment with which the trial's organizers would agree, as institutions have often had difficulty in recruiting patients for HIV research studies locally.

The difference with this trial, according to Montaner, is that they have a lasting partnership with Philadelphia FIGHT, a community HIV/AIDS organization, part primary care facility and part advocacy organization. With FIGHT's involvement, the researchers have been able to conduct a number of small yet powerful HIV-related medical studies.

On March 7, 2012, Montaner's team described their discoveries to colleagues at the Conference on Retroviruses and Opportunistic Infections in Seattle, Washington, and officially announced the trial's results to the world.

continued next page

The Montaner Laboratory knows from experience that it is virtually impossible to begin an HIV/AIDS clinical trial without community support.

PUTTING INTERFERON TO THE TEST

The Pegasys trial is not the first time interferon-alpha was tried in relation to HIV-1. It is just the first time that researchers have been able to find a strategy to sustain HIV-1 suppression using interferon in people on antiretroviral therapy. Interferon can be a very toxic drug, with many side effects when used at doses large enough to achieve clinical effect.

However, Pegasys is a different form of interferon than used in earlier trials. Since human interferon does not persist long enough in the body to serve as a useful antiviral drug, pharmaceutical researchers modified it by adding polyethelyne glycol (PEG) to the interferon molecule, making it last longer in the bloodstream with less toxicity. This “pegylated” form of interferon was approved in 2008 to treat hepatitis B and C infections.

“To be honest, we braced ourselves for the idea that this may not have any effect,” Montaner explained, “but there was enough evidence to believe that this formulation of interferon was worth trying and that a recovered immune system would respond differently if primed with interferon before stopping antiretroviral therapy.”

With funding from the National Institutes of Health, the Commonwealth of Pennsylvania’s CURE fund (see The Need for CURE, p. 8), The Philadelphia Foundation Robert I. Jacobs Fund, the Stengel-Miller Family, and a supply of pegylated interferon donated by the drug’s manufacturer, Genentech/Roche, the trial got underway. The clinical team began recruiting patient volunteers from clinics at Penn, Drexel, and Philadelphia FIGHT’s Jonathan Lax Center.

Unlike previous studies, this trial would be conducted after patients had already been on ART. “When someone is first infected with HIV-1, the immune system is overwhelmed, and the natural release of interferon into the blood-stream is ineffective as cells that produce it are quickly impaired,” Montaner said. “But in our study, conducted at a later stage of chronic infection after long-term treatment in an individual, we saw that adding interferon to a recovered immune system can have a dramatic effect in directing responses against HIV-1 to both control and reduce its detection within places we know it can hide.”

The trial followed the progress of 20 men and women of various backgrounds and ethnicities as they started on one of two different doses of interferon while still on ART. The patients then discontinued ART, and maintained interferon treatment for up to 24 weeks. For patients, the trial lasted 24 weeks or until either their HIV-1 levels rose or CD4 T cell counts dropped to a pre-determined level, at which point they would resume ART. Nine patients saw their HIV-1 levels suppressed for three months, while eight patients maintained low HIV-1 levels for the entire 24 weeks.

Remarkably, 45 percent of trial participants were able to sustain viral control under 400 copies of the virus per milliliter by the halfway point of the trial. About as many patients showed more than 50 percent reduction in circulating HIV reservoirs, as measured by the laboratory of Una O’Doherty, M.D., at the University of Pennsylvania.

“In our previous studies, we have seen that when people suspend ART, their viral loads begin to creep upward while their white blood cell count gradually drops,” Montaner said. “We expected to see the same thing during this trial, but we were, frankly, surprised to see patients maintain the gains made through ART using only interferon that modulates our body’s response rather than acting directly against HIV as all current HIV drugs do.”

HOW PEGASYS TOOK FLIGHT

Moreau first found out he was infected with HIV in 1987. Despite almost 25 years as HIV-positive, he still regards himself very fortunate. He responded well to early antiretroviral drugs and is still healthy to this day. He is one of legions of men and women whose HIV status could be considered “chronic.” This status comes with a price: a daily cocktail of drugs for the rest of his life.

In industrialized nations it is a price paid willingly, as seen through declining AIDS-related deaths in the United States despite a steady rate of new cases. In undeveloped nations, especially in Africa, the cost remains far too high for most to reach, and the resulting deaths are far too common.

For years, Moreau has taken part in clinical trials for new HIV/AIDS therapies. When he was younger, he was directly involved with advocacy, which in the late 1980s and early 1990s was militantly focused on getting attention and funding for the AIDS crisis. As the urgency of the crisis abated, however, Moreau continued to look for opportunities to take part in the HIV community. “I’m incredibly fortunate to be as healthy as I am today, and I feel an obligation to take part in trials,” Moreau said.

As the Pegasys trial began recruiting patients, it was Moreau’s physician who recommended he take part. Without patient volunteers medical trials could never happen. And, in turn, useful new therapies would never make it into practice. Many trials never get off the ground due to a lack of willing volunteers.

Without patient volunteers medical trials could never happen. And, in turn, useful new therapies would never make it into practice.

While Montaner and his team have also struggled to accrue patients, he finds it easier than most. Montaner’s relationship with the Philadelphia HIV/AIDS community dates back nearly 17 years, when he first joined Wistar as an assistant professor. It was around the time he first met Jane Shull, executive director of Philadelphia FIGHT, while she was running an informational booth at a college volunteer fair. They discussed his difficulty in getting the data he needed to drive the science of HIV-1 infection forward.

“It became clear to Luis and me that we needed to collaborate, even though we only had a small clinical site in those days,” Shull said. “Luis needed blood samples, which we could provide, and I could see that he was up to do science, which would help everyone.”

Richard Moreau

The association between Montaner and FIGHT (Field Initiating Group for HIV Trials) evolved into a series of small clinical trials testing the assumptions the medical community has made about treating HIV-infected people. One such trial studied ART interruption, temporarily halting a patient’s daily antiretroviral drugs to see if ART has made any lasting changes in how the body responds to HIV. If patients did not require ART daily, it could curb the expense of the drugs and reduce side effects.

“We need to test what we think we know in order to see if it is actually true,” Montaner said. “And, yes, if you halt ART, you begin to see an increase in viral loads within one to two weeks and a decrease in CD4 counts very soon after.”

What the ART interruption trials did, however, was provide a background “control” group for the interferon therapy trial. Data from the ART interruption trials allowed Montaner and his colleagues to compare the effects of interferon in patients to the effects of using of no drugs whatsoever.

According to Shull, FIGHT and Wistar have developed a bond over the years based on mutual respect and a willingness to explore scientific preconceptions about HIV infection.

“If [one of FIGHT’s founders] Jonathan Lax was still alive today, this would be exactly the sort of thing he’d pursue,” Shull said. “He’d be the first in line.”

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Wistar’s Luis Montaner, D.V.M., D.Phil., speaks with Karam Mounzer, M.D., medical director of the Jonathan Lax Center at Philadelphia FIGHT.

The Pegasys Trial participant meeting in December, 2011. Clockwise from top left: Jane Shull, Philadelphia FIGHT; Luis Montaner addresses study participants, colleagues, and supporters; Katie Krauss, AIDS Policy Project.

CHRONIC TO CURED?

For many people, like Richard Moreau, an HIV infection is no longer the death sentence it once was. Instead, it is a chronic infection. In the era of ART, the focus now is on efforts to create improved antiretroviral drugs and prevent infection, including a vaccine.

According to Katie Krauss, a cure for AIDS is not yet on the radar of most HIV/AIDS foundations and politicians. Krauss is executive director and founder of the AIDS Policy Project, a national HIV/AIDS advocacy organization that has, in recent years, turned its attention to the pursuit of a cure for AIDS. Her job, as she describes it, is to try to make things happen: to offer political, organizational — and oftentimes moral — support to those who want to advance progress toward a cure for AIDS. They help untangle red tape at the federal level, find innovative ways of speeding up the research process, and make sure that important cure research is not overlooked.

“I have actually had conversations with researchers where, when they began speaking of their work toward an AIDS cure, they’d start whispering, even with nobody else in the room,” said Krauss. “They would call it the ‘C’ word, or make air-quotes with their fingers; that’s how far out of the mainstream cure research seemed when we began.”

“I have actually had conversations with researchers where, when they began speaking of their work toward an AIDS cure, they’d start whispering, even with nobody else in the room,” said Krauss. “They would call it the “C” word, or make air-quotes with their fingers; that’s how far out of the mainstream cure research seemed when we began.”

“Now, however, there is great momentum toward a cure and very promising research,” Krauss explained. “But there still isn’t enough money, and many private foundations aren’t yet aware that the research is going well or that their help is urgently needed so that we can finish the job and cure this disease for everyone.”

In Krauss’s view, it is up to advocacy organizations to take a stand with researchers who are interested in searching for possible cures. As government research funding is not necessarily focused on a cure, it may be the advocates who can help locate new sources for research grants.

“I think we all worked so hard to get where we are, where there is now hope for a full life despite HIV, that we have downplayed the need for a cure,” Krauss said. “People are still getting AIDS; the disease still kills millions. Only a fraction of people in developing countries can access treatment, and the rest don’t survive. We still need a cure.”

This is where Shull believes that the Pegasys trial might have the biggest impact. “Interferon might not be a cure for AIDS,” Shull said, “but this trial changes the narrative, creates a new storyline where we can show people that it is possible to begin thinking about a cure.”

As Montaner says, this trial was a proof-of-concept. “While our data may not immediately change clinical practice, it identifies the first strategy that shows a clinical response where both viral replication and HIV reservoir indicators are observed to be reduced in absence of current chemotherapy,” Montaner said. “This is the type of response HIV cure research aims to achieve.”

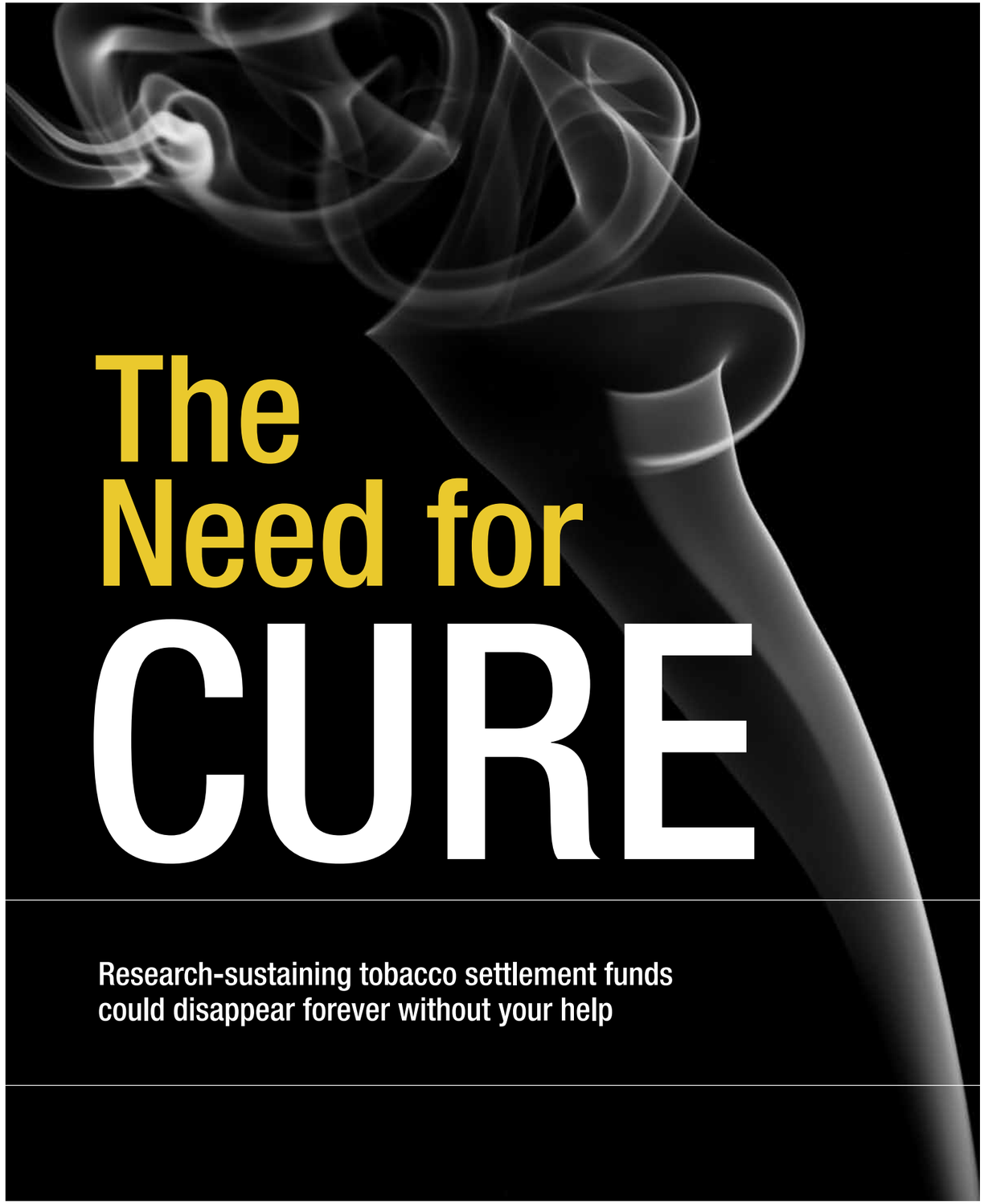
Montaner and his colleagues have submitted their findings to a peer-reviewed journal for publication. Already, the researchers are planning the next trial, and the news of this small trial has gone global as they and others drive their knowledge further in the hope for a cure.

“It is exciting to show control against HIV-1 can be regained by way of stimulating natural mechanisms as we had no other example to date to evidence this was possible if you required therapy to begin with,” Montaner said. “Our findings also open the way to determine if we can move this clinical research strategy a step closer towards a cure-based strategy to decrease HIV reservoirs as we have already observed.”

While Moreau recognizes that he might not qualify for a second trial, he certainly wishes that he could continue to take part.

“There are still a lot of people who say HIV is manageable, and leave it at that,” Moreau said. “I don’t think we can stop there. I think we have to keep trying, that a cure is possible.”

With people like Richard Moreau, it just might be. ■



The Need for CURE

Research-sustaining tobacco settlement funds could disappear forever without your help

Just over 10 years ago, in a moment of poetic justice, Pennsylvania passed legislation to establish CURE, the Commonwealth Universal Research Enhancement program, using money from the landmark $200 billion Tobacco Master Settlement Agreement. This innovative program directed tobacco settlement funds to colleges, universities, hospitals, and research institutions across the Commonwealth for research on cancer and many of the other diseases linked to tobacco use.

Thirty percent of CURE funding goes to competitive research grants, submitted by researchers to fund individual projects, while 70 percent goes to so-called formula grants, based on how much an institution receives in research funding from the National Institutes of Health.

Over the last decade, Wistar has been one of 39 formula grant recipients across the Commonwealth, receiving about $1.5 million each year, on average, to support pilot research projects (see sidebar, page 11). It has also been awarded a number of competitive grants, such as the $4.2 million grant to Hildegund C.J. Ertl, M.D., Wistar professor and the director of The Wistar Vaccine Center, to develop a "universal" vaccine to the influenza A virus that will protect against multiple strains of the constantly mutating virus and, thus, would replace the annual influenza vaccine.

Unfortunately, in his budget for fiscal year 2013, Governor Tom Corbett proposes defunding the CURE program, diverting almost $60 million in tobacco settlement funds into the general budget for other purposes.

For Wistar and many other organizations, this decision threatens research jobs and the loss of scientific experiments in which millions of dollars have already been invested. Wistar and its colleagues in the Pennsylvania Cancer Alliance (PCA), an organization that represents the Commonwealth's leading cancer centers, are trying to rally support to see thatthis does not happen.

"Research is a costly endeavor, requiring consistent public support," said Elizabeth O'Brien, Esq., Wistar's Vice President for Legal and External Affairs and the organizer of PCA's campaign to save CURE. "However, our hope is that this public investment in research will lead to new treatments that reduce the immense financial burden of caring for the long-term sick. No matter how well-intended the Governor's budget proposal is, it reneges on a pledge made to the Commonwealth's citizens to invest a portion of the tobacco settlement funds in preventing and curing disease."

According to O'Brien, even if CURE is suspended for just this budget cycle, the effects would be catastrophic for biomedical research across the state. "Imagine setting a book down mid-chapter and picking it up again a year later. Most of us would have to re-read the portions already read," O'Brien said. "If the CURE program is de-funded, we will have to terminate research projects and lay off some staff. And once discontinued, these projects cannot be easily restarted if funding is eventually restored."

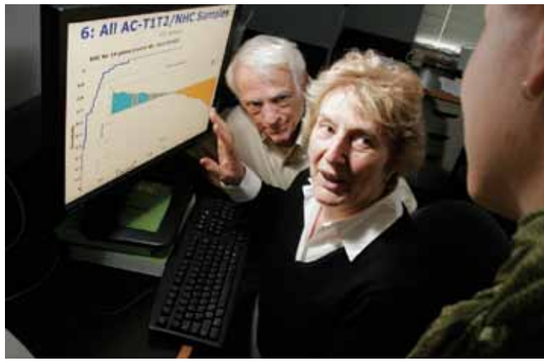
CURE TO EARLY DETECTION OF LUNG CANCER

Wistar scientists know first-hand how CURE funds can make a difference to their research. This March, Wistar's Louise C. Showe, Ph.D., was the lead recipient of a competitive CURE grant designed to change the way we detect and treat lung cancer.

Lung cancer remains the primary cause of cancer-related death, in part, because there is currently no efficient way to screen people for lung cancer at an early stage. In recent studies, Showe demonstrated the possibility of detecting early stage non-small cell lung cancer (NSCLC) by taking a snapshot of gene activity in blood-borne immune cells.

In biomedicine, to take a potentially useful blood test and turn it into a powerful diagnostic tool takes data. To get data, however, you need funding. Now, with a two–year, $1 million CURE grant, Wistar has the support it needs to create the first practical blood test for lung cancer.

With this funding, Wistar researchers will be able to analyze blood samples taken from lung cancer patient volunteers recruited through its partners on the grant at the Helen F. Graham Cancer Center at the Christiana Care Health System and Temple University Health System. The Helen F. Graham Cancer Center, which sees 94 percent of cancer patients in the state of Delaware, has already recruited 400 patients toward this end.



Louise C. Showe, Ph.D.

The aim of their research is to further validate the blood test and create a simplified means of collecting and analyzing blood samples in order to devise a commercially viable test.

"It has become clear to us that we are on the correct path, and we are working to further validate and expand our findings by studying more patient samples so that we have enough evidence to take this concept into clinical trials," said Showe, a professor in Wistar's Molecular and Cellular Oncogenesis Program and director of Wistar's genomics facility. "With a simple blood draw, we can detect lung cancer, show the effectiveness of

continued on next page

cancer surgery, by sampling the same patient's blood for analysis after surgery and hopefully even determine if the cancer may return."

"This funding will enable us to take that next step and turn biomedical discovery into medical reality," Showe said.

In a 2009 study, Showe and her colleagues first demonstrated the correlation between the presence of NSCLC and gene expression patterns — changes in gene activity — within peripheral mononuclear blood cells (PBCs), white blood cells like leukocytes and lymphocytes important for an immune response.

In 2011, the researchers further showed that such gene expression patterns change after a tumor is successfully removed by surgery and in many cases could return to normal. They also found a panel of genes that could distinguish between malignant tumors and non-cancerous lung nodules, suggesting that such a blood test could also guide treatment decisions and help prevent unnecessary surgeries.

This project began with a $3.4 million competitive CURE grant in 2003 to Wistar Professor David Speicher, Ph.D., who received funds to, in collaboration with Showe, begin screening blood for proteins and genes that might indicate lung cancer.

"Genomics technology, the ability to detect and determine gene activity, has dramatically improved in just the last decade, and so have the costs associated with scanning for gene activity," Showe said. "However, there is little doubt that we could not go on without this CURE grant."

RESEARCH TODAY FOR A HEALTHIER TOMORROW

The efforts of the Showe laboratory and their colleagues highlight yet another way CURE benefits Pennsylvanians. Biomedical research is an inherently hopeful process, one that makes the wise assumption that hard work now will yield benefits in the future. Showe's work may likely lead to a commercially-viable blood test for lung cancer. And indeed, this groundbreaking genomics-based technology may lead to blood tests for a host of other diseases.

"Pennsylvania's investment in Dr. Showe's work could save tens of thousands of lives otherwise lost to lung cancer and millions of dollars in medical expenses," O'Brien said. "It seems shortsighted to end a program that can generate such useful healthcare solutions."

Indeed, in the proposal to defund the CURE program, the Governor suggests applying the funds to long-term care. However, a brief look at health statistics in the Commonwealth provides compelling reasons to leave the program as is. One in three Pennsylvanians will be stricken with cancer in his or her lifetime; and, the Commonwealth's proportional share of elderly and obese residents is among the highest in the nation. Age and obesity are both risk factors for cancer and a host of other diseases.

Currently, through the CURE program, the Commonwealth is taking appropriate steps to address the growing disease-related needs of the state's population for the foreseeable future. Research efforts across the state have already furthered our ability to prevent and control disease (see sidebar), which will lead to significant healthcare savings in the long term.

An ounce of CURE, it would seem, could lead to pounds of disease prevention.

A SOUND RETURN ON INVESTMENT

Pennsylvania is, by any measure, a national leader in biomedical research. Few states can boast such a thriving, collaborative set of academic and commercial biomedical institutions. In a competitive national landscape, however, one of the most worrisome aspects of the Governor's proposal to defund CURE is the potential loss of leadership for the Commonwealth in this all-important economic sector.

CURE funding is critical to our ability to compete with other states for federal research dollars. Eliminating CURE support will cripple our competitiveness with research institutions in other states and countries, resulting in a long-term structural drag on the Commonwealth's economy and its ability to create jobs. ■

A Call to Action

TIME IS RUNNING OUT FOR CURE.

As this issue of *Focus* goes to print, the budget is still up for debate in Harrisburg with the deadline for a final budget in June. As you are reading this, you still have time to contact your state representatives to ask them to keep CURE funded.

Please visit PCA online today to see how you can help save CURE for tomorrow: www.pennsylvaniacanceralliance.org

How Wistar Puts CURE Formula Grants to Use

Since 2001, Wistar has received over $17 million in CURE grants, which it has then distributed to its scientists as starter funding for nearly 50 research projects. These funds help researchers tackle projects with great potential, for example:

GENE PROMOTER DATABASE:

An endless bounty of information hides within our genomes. Wistar Associate Professor Ramana Davuluri, Ph.D., used CURE funds to help build the Mammalian Promoter Database (MPromDb), which helps researchers mine the extensive genetic data available to help find gene promoters—regions along a DNA strand that tell a cell's transcription machinery where to start reading in order to create a particular protein. With this information, researchers can design personalized diagnostics and therapeutics, or delve deeper into the study of gene regulation than previously thought possible.

THE CARE AND MAINTENANCE OF TELOMERES:

Our chromosomes are protected by stretches of DNA called telomeres, the gradual erosion of which is partly responsible for both aging and cancer cell evolution. When Wistar Associate Professor Emmanuel Skordalakes, Ph.D., joined the Institute in 2006, he received CURE funds to learn more about how telomeres work. In 2008, he published structure of the active region of telomerase, the enzyme that helps rebuild telomeres. It is an important step if researchers are to make cancer drugs that work by blocking the enzyme.

PREDICTING WEAKNESS IN INFLUENZA:

Influenza is constantly evolving, which means we need a new vaccine each year for protection. It was once thought that influenza viruses easily accepted the mutations that allow them to evade vaccines, but the lab of Wistar Assistant Professor Scott Hensley, Ph.D., has data that suggest that influenza viruses are actually crippled by these mutations and must acquire even more mutations to be able to survive. Predicting how flu evolves will allow scientists to create more effective and longer-lasting vaccines.

An ounce of CURE, it would seem, could lead to pounds of disease prevention.

The Fine Young Fellows

Postdoctoral fellows trade long hours and hard work for mentoring and career momentum

If The Wistar Institute was an independent company, it would dwarf many of the biotech start-ups in the area, with one notable difference: junior researchers like Wistar's postdoctoral fellows — or postdocs, as they're more commonly called — don't bring home stock options or high salaries. Instead, they get paid in a different coin of the realm — the chance to build their own research programs while working alongside world-renowned senior scientists.

On a day-to-day basis, a given laboratory does run a bit like a company, with a principal investigator (PI) acting as president and the postdocs as research directors who oversee other members of the lab. "The specific projects and the day-to-day bench work are the province of postdocs," said Harold Riethman, Ph.D., associate professor in Wistar's Gene Expression and Regulation Program and associate director of training.

Postdocs, Riethman says, are a crucial part of Wistar's success. "Besides bench work, postdocs train and supervise junior lab members, help write grants and papers, and give talks."

"Accepting a postdoc into the laboratory today involves more than bringing on a highly skilled technician," said Riethman. "Taking on a postdoc involves a significant mentoring investment. Mentoring does not just involve overseeing the individual, but committing to the promotion and success of the protégé's career."

Currently, more than 100 Ph.D.-level scientists are engaged in biomedical research at the Institute. So what is it that draws freshly minted Ph.D.s to Wistar for their postdocs?

"The breadth and quality of research going on at Wistar was one of the things that attracted me to the Institute," said Lisa Chang, Ph.D., postdoctoral fellow in the lab of Ellen Puré, Ph.D.

"My background is in developmental biology, studying the regulatory pathways involved in early development, how fetal cells of the mesoderm transform into muscle, skeleton, organs, and the like," Chang said. "But I knew that in continuing my research I wanted to become more involved in cancer biology."

Chang, now in her second year of postdoctoral work, expanded upon her Ph.D. research after joining the Puré lab, and is now investigating the way in which fibroblast activation protein expressed on the surface of certain "normal" cells within the tumor microenvironment contributes to the metastasis of breast and lung cancer.

ONE PART RESEARCHER, ONE PART ENTREPRENEUR

Increasingly, as federal funding for biomedical research becomes more competitive, postdocs have had to work harder to obtain the funding necessary to get their own research projects off the ground. Obtaining support from the National Institutes of Health (NIH), for example is a long-term process, with researchers often spending months or years doing experiments and gathering preliminary research data to put together research-program proposals.

Chang was fortunate to have earned an NIH F32 postdoctoral fellowship grant this year, an award which provides up to three years of support for promising postdocs who have the potential to become productive, independent investigators within the broad scope of biomedical, behavioral, or clinical research — great news in this often bleak funding climate.

After a dramatic expansion between 1998 and 2003, the budget for the entire NIH has been essentially flat for nearly a decade. Grant proposals from young researchers, often inexperienced at grant writing, are ranked against seasoned and successful senior researchers. In this competitive environment, many well-trained, talented young researchers fail to secure grants. This lack of grant funding keeps many postdocs from making the jump to running their own labs.

LIFE IN AND OUT OF THE LAB

Biomedical research today, compared with a decade ago, requires more work-hours, giving postdoctoral work a reputation for being difficult and time-consuming, as each fellow tries to distinguish him – or herself among their peers.

"Postdocs set their own hours," Chang said, "but it isn't unusual to work 12-hour days and four or five hours over a weekend, if that's what's called for by a particular project."

Most postdoctoral fellows are in their 30s by the time they begin working toward obtaining a tenure-track faculty appointment. Not coincidentally this is also when the greatest number of female postdocs tend to drop out of science or move into either the private sector or a government agency.

"I've heard this a lot, people wondering how postdocs can reconcile family life with a scientific career, but a lot depends on your relationship with your PI," explained Chang. "The hours may be long, but for the most part they're flexible, which can make starting a family as a postdoc easier."

They may not have their own laboratories and they may not be faculty, but Wistar's postdoctoral fellows are the foundation of the Institute's research might.

Finding the right balance of career and family can be a challenge in a culture where scientists face a limited amount of time to prove themselves worthy of tenure.

There is also the pressure of the job market to contend with. In recent years tenure-track jobs have been harder to come by, noted David Friedmann, Ph.D., a third-year postdoc in the lab of Ronen Marmorstein, Ph.D.

As part of Marmorstein's crystallography laboratory, Friedmann's work focuses on the molecular structure of acetyltransferase, an enzyme capable of transferring acetyl groups from one compound to another, adding a chemical modification to other proteins. This alteration helps to regulate the transformation of countless biological molecules.

continued on next page

Opposite: David Friedman, Ph.D. and Lisa Chang, Ph.D.

Biomedical research today, compared with a decade ago, requires more work-hours, giving postdoctoral work a reputation for being difficult and time-consuming, as each fellow tries to distinguish him- or herself among their peers.

"It used to be, if you went through these formulaic steps of getting your Ph.D. and completing postdoctoral training with a well-known PI, then your ticket was written. But these days you can work at a world-renowned lab and still not get the job of your choice," Friedmann said.

MENTORING IN A NEW ERA

Recognizing the need for expanded postdoctoral training outside of the lab, Wistar President and CEO Russel Kaufman, M.D., and Wistar's training committee took action. Wistar postdocs are now able to take part in the University of Pennsylvania's Biomedical Postdoctoral Programs (BPP). Through the BPP program, postdocs participate in workshops on career and personal development.

"Mentorship can take any number of forms, and postdocs need to take responsibility for their non-bench education," Friedmann said. "I've learned to keep a conversation going with my peers and other PIs. It's a great way to get some insight on your research, and Wistar's size and location help make these collaborative relationships easier to facilitate."

Friedmann also serves as the postdoc representative on Wistar's training committee and was instrumental in forming the partnership between the BPP and Wistar. Wistar hopes to further expand upon its postdoctoral training program.

"It is my goal to enhance what is already an extremely strong postdoctoral program here at The Wistar Institute," said Maureen Murphy, Ph.D., professor and program leader of Wistar's Molecular and Cellular Oncogenesis Program and associate director of faculty development and education.

Before coming to Wistar in December of 2011, Murphy helped build a postdoctoral training program at the Fox Chase Cancer Center in Philadelphia. "We already have world-class postdocs here at Wistar, now we just have to design a world-class program around them. In the near future, we foresee offering things like in-house grant writing courses, workshops on mastering imaging techniques and seminars designed to expose postdocs to alternative career paths," Murphy said.

"A lot goes into training a postdoc, and a good training program should give postdocs 'lines,' on their résumé," Murphy said. By "lines," Murphy means fellowship awards, prizes for recognition of research, and opportunities to attend workshops and other training venues. "Ideally we will be able to maximize productivity and equip postdocs to make informed career choices upon completing their training at Wistar."

The postdoctoral experience varies from person to person, and pushing the frontiers of science can be a rather nebulous job description, but these postdocs know that there are no worthwhile rewards without hard work. ■

Ronen Marmorstein, Ph.D.

Ronen Marmorstein, Ph.D.

Ronen Marmorstein, Ph.D. worked his way up from the very bottom rung. Literally.

As a graduate student at the University of Chicago, he was part of one of the first research labs using X-ray crystallography, a process that reveals the three-dimensional structure of molecules, to study how proteins interact with DNA.

"I was the low man on the totem pole. I did all the biochemical work that led to the X-ray crystal structure but never actually got to do the structure myself," Marmorstein said.

That didn't come until a postdoctoral fellowship at Harvard University where he learned how to produce the structures – and the technology has improved much more since.

"The methodology and computation has improved," he said. "So now one person completes the project from soup to nuts," which is how members of the Marmorstein laboratory work today.

Marmorstein is the Hilary Koprowski, M.D. Professor and Program Leader of the Gene Expression and Regulation Program at The Wistar Institute.

His research exploits the use of X-ray crystallography and other complementary biochemical techniques to study proteins involved in epigenetics, and how signaling molecules, like protein kinases, direct epigenetic programs.

"Epigenetic differences are what causes cells that have identical genetic information to do different things," Marmorstein said. It's what makes one cell a skin cell and another a stomach cell, for example.

"The molecular basis for how this occurs is poorly understood," Marmorstein said, and diseases like cancer, metabolic disorders or neuropathies are often mediated by epigenetic factors gone awry.

If researchers can understand the molecular basis for such misregulation, they can create drugs for epigenetic targets that could hopefully fix the disease.

Marmorstein, who was born in Israel and raised in New York, came to Wistar to start his own laboratory in 1994. "The science at Wistar was exciting, the Philadelphia research community was vibrant and interactive and the graduate students were talented," he said, thus drawing him to relocate here. "This all turned out to be true."

Marmorstein lives in Swarthmore with his wife, Shoshanna Gottleib, who he met while in graduate school and who is now a middle school biology teacher, and their three children. His oldest daughter Anna is studying advertising at Penn State while his 17-year-old son Andrew, who worked in the lab with Marmorstein last summer, will be headed to Case-Western University in the fall to study engineering.

Word is still out on what their 12-year old son Jason will do, but he wants to be a baseball player. "He's really into baseball right now," said Marmorstein, who admits that his alternate dream job would be as a baseball player – even if he is outnumbered in his house and his adopted city as a Yankees fan.

"Jason is a Yankees fan," he said. "But I was not able to convert the rest of the family."

"That will never happen – they're Phillies fans." ■

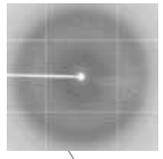


image 1

The Marmorstein lab uses X-ray crystallography to "see" the shape of the molecules they study. As X-rays bounce off of a crystallized form of the molecule(s) they study, they create a pattern (image 1) that can then be analyzed to create a computer model. The model (image 2) shows how a molecular inhibitor (yellow) binds to the active site of an enzyme (blue). The model helps the lab better understand how such small molecule inhibitors can be developed into useful drugs.

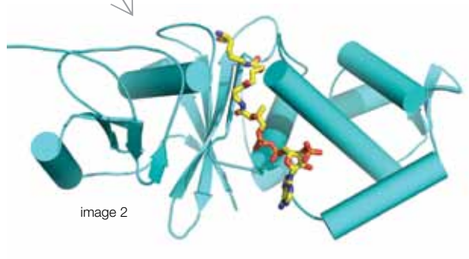


image 2

$4.7 Million to Develop Drug Against Epstein-Barr Virus-related Cancers

The laboratory of Wistar Professor Paul M. Lieberman, Ph.D., has undertaken a historic, groundbreaking project that may change the way doctors treat a variety of human cancers. Historic, because his is the first laboratory in the United States to receive a Seeding Drug Discovery Award from Wellcome Trust, a United Kingdom-based charity. Groundbreaking, because the award will support the development of what may be the first drug to treat Epstein-Barr virus (EBV)-related cancers by attacking the virus as it remains dormant within a patient's cells.

The project is a three-year, multi-stage effort where funding is based on the achievement of defined research milestones, outlined by Lieberman and Troy Messick, Ph.D., a staff scientist in the Lieberman laboratory and co-leader on the project. If successful at each milestone, the laboratory will receive up to $4.7 million in support of their efforts.

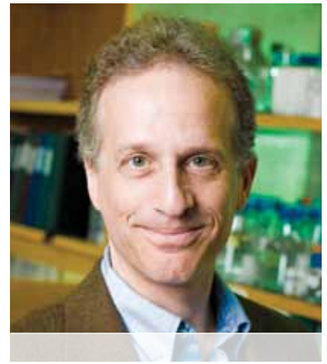
The World Health Organization defines EBV as a Class I carcinogen, and it is estimated to cause a small but significant portion of all human cancers. The virus may persist in the human body for decades and cause infected cells to become cancerous. It is estimated that EBV causes nearly 400,000 cases of cancer each year, including Burkitt's lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, gastric carcinoma and certain oral and throat cancers.

According to Lieberman, EBNA1, a protein produced by EBV, is a prime target for therapeutic intervention. The protein acts as the master switch that regulates viral gene activity and guides the ability of EBV to remain dormant in the body.

"Knocking out EBNA1, therefore, could likely eliminate latent Epstein-Barr virus and control the growth of EBV-associated cancer."

"EBNA1 is expressed consistently in all EBV-related cancer and is essential for the virus to reproduce," said Lieberman. "Knocking out EBNA1, therefore, could likely eliminate latent Epstein-Barr virus and control the growth of EBV-associated cancer."

To develop an anti-EBV drug, the researchers began a complex screening process to find a small molecule that could chemically bind to EBNA1 and inhibit its ability to function. They began with a library of 600,000 molecular compounds, eventually narrowing the pool down through a series of tests to a handful of leading candidate molecules that have the most potential to serve as the basis of a new anti-EBV drug.



Paul M. Lieberman, Ph.D.

With funds from the Wellcome Trust, the Wistar researchers will further optimize their candidate small molecule inhibitors, with the aim of developing at least one chemical compound into a viable drug candidate. This drug candidate could then be used in clinical trials designed to determine its safety and effectiveness for humans.

"This is an investment in drug discovery, enabling a small team of experts to do the type of translational research typically seen in large drug companies," said Messick. ■

Wistar Recruits Noted Cancer Biologist, Gains New Face for Mentoring

Maureen Murphy, Ph.D., already had a lot on her plate when she joined The Wistar Institute in December of 2011. Murphy, a noted expert on the role of the p53 gene in cancer, brought with her a full research agenda (and all of her research staff) from her laboratory at Fox Chase Cancer Center in Philadelphia.

Shortly after becoming a professor at Wistar, it was announced that Murphy would be taking a much larger role in administration. First, she was named leader of the Molecular and Cellular Oncogenesis Program along with co-leader David Speicher, Ph.D. But she will also have a strategic and guiding role for both junior faculty and young researchers.

As associate director of faculty development, she will be responsible for developing programs intended to train and mentor the careers of Wistar's junior faculty members. And, as associate director of education, she will develop programs designed to engage and better train students and postdoctoral fellows. [See The Fine Young Fellows on page 12]

"I intend to create a face for Wistar's internal mentoring and education efforts," Murphy said. "We want to ensure that, in addition to remaining at the forefront of breakthrough medical research, Wistar also continues to excel as a place of education, preparing the next generation of scientists for the discoveries that lie ahead."

Murphy began her career locally with an undergraduate degree in biochemistry from Rutgers University, followed by a doctorate in molecular biology from the University of Pennsylvania School of Medicine.

In 1994, she began postdoctoral research at Princeton University in the laboratory of Arnold J. Levine, Ph.D., co-discoverer of the p53 tumor suppressor gene, which is the most frequently mutated gene in human cancer. She began her independent career studying p53 at Fox Chase in 1998, where she was promoted to full professor in 2011, and where she ran the Postdoctoral Training Program for seven years.

The Murphy laboratory focuses on how tumor suppressor genes, such as p53, regulate two cell death pathways, apoptosis and autophagy. Apoptosis (programmed cell death) and autophagy (literally, the cell eating itself) are what Murphy describes as the cell's most important defense mechanisms against cancer. Murphy's interest centers on the discovery of how tumor suppressor genes normally defend against cancer. Her research uses small molecule therapeutics designed to target the pathways of apoptosis and autophagy, in efforts to improve the treatment of cancer. Murphy has also developed an interest in how genetic variants in p53 that naturally exist in human populations affect how we combat tumor development. Her studies have relevance for understanding racial differences in cancer risk and progression, particularly in ethnic populations where these variants occur with high frequency.

> "I have great ideas for expanding an already strong program that will enhance the scientific repertoire and skill sets of our outstanding trainees."

Murphy's plans for the training program are admittedly ambitious. "I have great ideas for expanding an already strong program that will enhance the scientific repertoire and skill sets of our outstanding trainees." In particular, Murphy envisions "…giving the trainees more control of their education, by awarding them slots for Distinguished Lectures, more internal fellowship opportunities, and more opportunities to present their research to the Wistar community. "On top of this, I am designing grant writing and image preparation workshops that will enable our trainees to leave here with a unique and impressive skill set," she said.

Maureen Murphy, Ph.D.

"Maureen brings with her a vibrant and productive laboratory program focused on mechanisms of p53-dependent cell death and the cellular stress response in cancer," said Dario Altieri, M.D., executive vice president, chief scientific officer, and director of the Institute's Cancer Center. "Maureen will also play a pivotal role in strengthening our mentoring and career development initiatives for junior faculty and trainees, thereby positioning The Wistar Institute for even greater success during the current institutional expansion." ■

Boosting Immunity for the Long Term

Vaccines take advantage of a remarkable ability of our immune system: it can remember viral infections for years, even decades, after they have first been encountered and defeated. While each individual antibody we make lasts only about a month, we retain the means of making that individual antibody for a lifetime, with rare exceptions.

Until now, the exact mechanism behind this was poorly understood, but researchers at The Wistar Institute have discovered some of the protein signals responsible for keeping the memory of distant viral infections alive within our bodies. Their research may aid scientists in creating better, more effective vaccines for diseases like influenza.

"We are particularly interested in how our bodies generate antibodies against viruses and how we maintain anti-viral antibody secreting cells as a hedge against future infection from the same virus," said Jan Erikson, Ph.D., senior author of the study, professor in the Tumor Microenvironment and Metastasis Program and a member of The Wistar Vaccine Center. "We know protein signals sustain the cells that make antibodies against viruses in perpetuity, which we believe is crucial knowledge for the development of vaccines for lasting protection."

The main role of vaccines is to stimulate the production of antibodies that bind to portions of the infectious agent. Once bound, the antibodies provide a target for the immune system, allowing immune cells to attack it or any infected cells in order to clear away disease.

Antibodies are highly variable proteins that are produced in huge quantities by a subset of white blood cells, called B cells, that have transformed into antibody factories, termed antibody secreting cells (ASCs). Our immune system produces a broad array of antibodies, but during an infection with a virus, for example, the immune system allows the predominant production of antibodies that are directed against the virus. The cells making these particular antibodies are then selected for preservation.

According to Erikson and her colleagues, this act of preservation — essentially immune memory — requires signals, provided by proteins called BLyS and APRIL. Mice that have been exposed to influenza require these proteins in order to sustain anti-influenza ASCs in their lungs. The researchers found that neutralizing BLyS and APRIL reduced the numbers of anti-viral ASCs found in the lungs and bone marrow, yet interestingly, did not affect the ASCs found in the spleen or in lymph nodes near the lungs.

> It might be possible to manipulate ASC behavior to prolong or strengthen the effectiveness of vaccines to viral diseases, such as influenza.

BLyS and APRIL bind to another protein called TACI, a receptor found on the surface of ASCs, which the researchers see as an important translator for marking the ASCs that will become long-lived.

"Our studies show that mice that lack TACI can mount an initial B cell response to viral infection — and are able to produce antibodies to influenza — but these mice fail to maintain anti-viral ASCs over a long period of time," said Amaya I. Wolf, Ph.D., the study's lead author and a postdoctoral fellow in the Erikson laboratory. "Importantly, we show that this results in lower anti-viral antibody levels, and mice are less protected against a secondary viral attack at a later time."

Jan Erikson, Ph.D.

According to Wolf, it might be possible to manipulate ASC behavior to prolong or strengthen the effectiveness of vaccines to viral diseases, such as influenza. Drugs that induce targeted release of ASC survival factors, such as BLyS and APRIL, could theoretically help to maintain the production of specific antibodies, making for a more effective flu vaccine. While the seasonal flu is constantly mutating — necessitating an annual vaccine — even weakly reactive antibodies could be protective if there are enough of them and if the immune system can retain the memory to produce them over the long-term. ■

José Conejo-Garcia, M.D., Ph.D.

Reprogramming Traitors with Nanotechnology

NEW FINDINGS MAY LEAD TO A NEW THERAPY FOR AGGRESSIVE OVARIAN CANCER

Admittedly, it sounds like a dark sci-fi plot, possibly starring Keanu Reeves: "reprogram" treacherous double agents using nanotechnology — synthetic, engineered molecules — designed to silence a specific gene.

According to Wistar's José R. Conejo-Garcia, M.D., Ph.D., the scenario is not only real, it's happening. Recently, his laboratory identified the traitorous cells of our own immune system that help ovarian cancers become so aggressively metastatic. Fortunately, his laboratory has also developed a tool to win back the allegiance of these cells and restore their ability to suppress tumors.

"Ovarian tumors don't necessarily break 'free' of the immune system, rather dendritic cells of the immune system seem to actively support the tumor's escape," said Conejo-Garcia, a Wistar associate professor and leader of the newly-formed Tumor Microenvironment and Metastasis Program in Wistar's Cancer Center. "More importantly, we show that by depleting these dendritic cells of the immune system, we can reverse the effect."

This winter, in the *Journal of Experimental Medicine*, Conejo-Garcia presented the first successful attempt to reproduce the tumor microenvironment of human ovarian cancer in a mouse model of the disease. In essence, the model replicates the inflammatory surroundings that ovarian tumors experience in humans, providing a better tool for researchers to understand, prevent, and treat tumors.

With support from National Cancer Institute and the U.S. Department of Defense, the Conejo-Garcia laboratory combines emerging tumor microenvironment science and the latest molecular tools to combat ovarian cancer, one of the most deadly forms of cancer in women.

What they found confirmed their suspicions that, within the ovarian tumor microenvironment, a traitor lurked. In healthy tissue, dendritic cells function as sort of alarm system to alert the immune system to potential threats. They work as antigen-presenting cells, offering foreign or disease-causing molecules (called antigen) to the white blood cells that can then respond to an infection or, in this case, tumorous growths. Amid the ovarian cancer microenvironment, dendritic cells induce the immune system to attack tumor cells and inhibit their growth.

Except, Conejo-Garcia found, there comes a point where dendritic cells may switch sides and actively encourage tumors to spread.

"We see a change in the dendritic cells themselves, which allows tumors to progress to terminal disease in a very short time," Conejo-Garcia said. "Interestingly, the tumors are still immunogenic — they could still otherwise elicit an immune response — it is just that the dendritic cells are actively suppressing the involvement of other anti-tumor immune cells, primarily T cells."

Conejo-Garcia and his colleagues believe that their findings offer a twist on the emerging theory of "cancer immunoediting." In immunoediting, the immune system actively "edits" tumors to eliminate the individual cancer cells that express recognized antigen, thereby preventing small tumors from becoming symptomatic. All symptomatic tumors, therefore, represent a failure of the immune system, where tumors lose their immunogenicity — their ability to trigger and be recognized by our immune system.

According to Conejo-Garcia, these findings presented a new strategy to treat metastatic ovarian cancer. If they could somehow target these traitorous dendritic cells, it may effectively "reactivate" anti-tumor T cells.

PUTTING THEORY TO THE TEST

Indeed, this winter, in the journal *Cancer Research*, the researchers demonstrated how artificial RNA molecules could win back the allegiance of dendritic cells and restore immunoediting.

For years, the Conejo-Garcia laboratory has explored methods of using nanoparticles — synthetic molecules built at the same billionth-of-a-meter scale on which proteins and genes operate — for therapeutic effect. In this instance, they built a nanoparticle that carries a replication, somewhat, of a form of "micro-RNA" called miR-155.

As the name implies, micro-RNA are small snippets of RNA molecules. One of the central tenets of biology is that RNA carries the instructions encoded as genes within segments of DNA to the cell's protein-making machinery. As scientists have found out over the last decade, not all RNA molecules are fated to serve as operating instructions for protein factories. So-called silencing RNA, like miR-155, can serve to turn off genes by binding to DNA and, in effect, smothering individual genes to prevent them from being read or expressed into protein.

Previous research has shown that miR-155 has a distinct role in maintaining the immunoediting of ovarian cancer, so the Conejo-Garcia laboratory went about developing nanoparticles that carried segments of RNA-mimicking miR-155 to test their effect. According to Conejo-Garcia, their nano-RNA molecules restored dendritic cell function in their ovarian cancer mouse model.

"For us, this is a one-two proof of concept in that we can see further evidence that our model works and we have a path for developing a potential new drug for aggressive ovarian cancer," Conejo-Garcia said. "We are beginning to see this remarkable world where we can silence individual genes for therapeutic effect."

In essence, turning science fiction into medical reality. Or, to quote Keanu Reeves: "Whoa." ■

Grant Highlights

THE WISTAR INSTITUTE

The Wistar Institute Cancer Center is the recipient of a $100,000 Institutional Research Grant from the American Cancer Society. With these funds, Wistar can offer staff and junior faculty who currently have no national peer-reviewed research grants support in the form of $20,000 over a three-year period as seed funding for pilot projects. The intent is to help those in the early stages of their careers initiate cancer research projects so they can obtain preliminary results that will enable them to compete successfully for national research grants.

MAUREEN MURPHY, PH.D.

Murphy, a professor and leader of Wistar's Molecular and Cellular Oncogenesis Program, received a three-year $584,000 grant from the National Cancer Institute to study the biology of the ARF tumor suppressor. While many researchers work on the pathway whereby ARF activates p53, a well-known gene that is often mutated in cancer, the Murphy lab works on the pathway whereby ARF induces autophagy (literally, "self-eating"), a key cell survival pathway that is often commandeered by tumor cells. Murphy's lab will try to better understand how ARF induces autophagy, and whether mutations of ARF in cancer affect this process.

GRANT AWARDS

The Wistar Institute and its scientists continue to compete successfully for grants to support research and programs. Here is a sampling of recent awards.

PRIVATE GRANTS

AMERICAN CANCER SOCIETY
Dario Altieri, M.D.
Institutional Research Grant
Three years, $120,000

UNIVERSITY OF PENNSYLVANIA TAPITMAT
Scott Hensley, Ph.D.
Human influenza vaccine
One year, $89,965

BOEHRINGER INGELHEIM
Meenhard Herlyn, D.V.M., D.Sc.
Melanoma research
One year, $93,000

MELANOMA RESEARCH FUND
Meenhard Herlyn, D.V.M., D.Sc.
Melanoma research
One year, $125,000

ROGERS CHARITABLE TRUST
Hui Hu, Ph.D.
Ovarian cancer
One year, $24,500

W.W. SMITH CHARITABLE TRUST
Qihong Huang, M.D., Ph.D.
Cancer molecular biology
One year, $98,000

SEAMON CORPORATION
Luis Montaner, D.V.M., D.Phil
Scholarships for 8th International Macrophage Conference
One year, $20,000

FERRIS CHARITABLE FOUNDATION
Ramin Sheikhattar, Ph.D.
Breast cancer
One year, $25,000

BIOTIME, INC.
Louise Showe, Ph.D
Sponsored research agreement
Two years, $200,000

FEDERAL GRANTS

NATIONAL CANCER INSTITUTE
Lisa Chang, Ph.D., Puré lab
Breast cancer
One year, $48,000

NATIONAL CANCER INSTITUTE
Maureen Murphy, Ph.D.
Analysis of p53 variants
Three years, $584,000

NATIONAL CANCER INSTITUTE
Frank Rauscher, Ph.D.
Melanoma
Five years, $1,000,000

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE
Italo Tempera, Ph.D., Lieberman Lab
Epstein Barr virus
One year, $100,000

(l to r) James Manser, Staci Vernick Goldberg, and Leadership Council member Erin Murphy Boyle discuss the art of photomicrography at the opening reception for the 2012 Nikon Small World Exhibition.

Leadership Council chair Dan Wheeler, Amy Fox, Board Secretary Maida Milone, and Jo-Ann Zoll pose at the Small World opening.

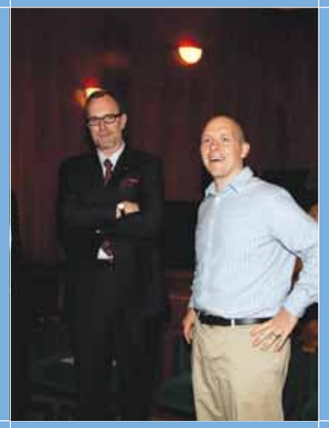
Elyse and Max Berger chat with a fellow guest at the Small World opening.

Guests enjoy the artful imaging of a marine crustacean at the Nikon Small World Exhibition opening.

Leadership Council member Anne Ravert, J.D., at the Small World exhibit.

Guests take a hands-on look at the microscopic world at the opening reception for the 2012 Nikon Small World Exhibition.

Rob Dunn, Ph.D., author of *The Wild Life of Our Bodies: Predators, Parasites, and Partners That Shape Who We Are Today*, signs copies of his book for guests at the November 2011 Authors Series event.



Dan Wheeler and Rob Dunn

Guests discover the beauty and complexity of life as seen through today's advanced microscopes at the opening of the Nikon Small World Exhibition.

Winner of the 2011 Dr. Monica H.M. Shander Memorial Fellowship, Glen Liszczak a graduate student in the Marmorstein Lab, is flanked by Harold C. Riethman, Ph.D., (l) and Ronen Marmorstein, Ph.D.

Paula Dvorak (l) and Leadership Council member Donna Weinraub at the Dunn Authors Series event.

Wistar Supporters Look to the Future with Gifts of Life Insurance

Bruce and Judi Goodman are not only generous contributors to The Wistar Institute; they also put a great deal of thought into their gifts, both present and future. The Goodmans, owners of Jenkintown-based Goodman Properties, came to Wistar offering to make the Institute the beneficiary of a significant life insurance policy. Since then, they have become advocates for using life insurance policies as a means of planned giving.

"Life insurance policies are a great way to demonstrate a commitment to an institution over a longer period to time," said Bruce Goodman. "I think most people are unaware of this type of donation and would be surprised to realize how many benefits it has for both the donor and the charity."

Bruce first became involved with Wistar through two good friends, Robert Fox and the late Ed Sickles.

"These are very dear friends of mine and they told me about Wistar, and I soon realized that it was a great facility engaged in outstanding research," said Goodman. "Judi and I wanted to do something that would provide substantial benefits to Wistar. Life insurance is an approach that leverages the gift over time."

Robert Fox is also the person responsible for linking another donor, Robert Miller, CLU, ChFC, president of Charlap & Miller, Inc., to Wistar. A life insurance broker, Miller shares Goodman's enthusiasm for turning policies into donations.

"Life insurance is cost effective and mutually beneficial to the donor and the institution," Miller said. "This is a way of doing something meaningful that allows the donor to make a substantial gift while still retaining the assets for family members."

The Goodmans' gift involved purchasing the policy and naming

Robert Miller, CLU, ChFC

Wistar as the beneficiary. The annual premiums are paid in the form of a charitable donation to the Institute. Wistar will receive the full payment after the deaths of both Bruce and Judi, or Wistar can opt for the cash value of the policy at any time.

"My wife and I are comparatively young, and we hope to live for a long time," he said, "but this is a way of thinking of gifts today that make a difference for tomorrow."

Miller has put his professional advice into practice buying life insurance policies for several beneficiaries, including Wistar. "This is really a good way to meet your charitable goals at different stages of your life," Miller explained.

Both Miller and Goodman stress that giving life insurance is not a substitute for other forms of giving. The Goodmans have backed up that statement with a very generous gift to Wistar's capital campaign *Building Wistar, Changing the World.* Judi Goodman is also very active with the IMAJNZ Foundation, whose "A Date with a Plate" event raised over $500,000 for the Noreen O'Neill Foundation for Melanoma Research to benefit the research of young scientists at Wistar.

"When you support the work being done at Wistar, you are really seeing the big picture for research, the work that is going to make a difference for people who are suffering with melanoma and other diseases in the future," Goodman said. "I want to be thinking of that future in a strategic way, and I think that life insurance is an excellent way to do that." ■

GIFTS OF LIFE INSURANCE POLICY

Advice from an Expert

Albert E. Gibbons, CLU, ChFC, AEP, president of AEG Financial Services works with clients to address their full range of life insurance needs. He views gifts of life insurance policies to charitable institutions as an excellent option for many individuals interested in making planned gifts.

"There are so many positive aspects to this kind of gift," said Gibbons. "It's simple. It's guaranteed, and it has a predictable value — unlike stock for instance."

As Gibbons explains, the charity is the owner and beneficiary of the life insurance policy from the beginning. The donor then pledges to forward a gift every year to the charity that the charity can use to pay the premium.

"If you do it this way, there are no real tax issues," Gibbons said. "The premiums are deductible to the extent that deductions are allowable under the law."

Life insurance is what is termed a "self-completing" gift, meaning that once the donor dies, the money passes directly and almost immediately to the beneficiary without going through probate. The gift cannot be successfully contested and does not generate any legal fees.

Gibbons advises working through an established, knowledgeable life insurance professional who can help choose the type and amount of the policy, and emphasizes the importance of having a relationship with the beneficiary institution.

"The one thing that donors need to be aware of is that they are making a pledge to pay the required annual premium payments per their agreement with the charity," he said.

"It also means that it is critical to assure that the product they purchase fits their needs and financial abilities, Gibbons said. "If those issues are addressed, then this is a very clean, straightforward way to make a significant contribution. There's no way I can think of to improve it, and no downsides."

To learn more visit **www.algibbons.com**

A Celebration of Science

PHILADELPHIA SCIENCE FESTIVAL

The second annual Philadelphia Science Festival takes Philadelphia by storm in April of 2012. Join Wistar once again at our booth on the Ben Franklin Parkway for the Science Carnival April 21, 2012 from 11:00 am to 4:00 pm

The Wistar Institute Leadership Council hosts what is bound to be this year's most talked-about event. On Tuesday, April 24, at the Academy of Natural Sciences (19th Street and the Parkway), Wistar Professor Hildegund C.J. Ertl, M.D. will host a panel discussion of the new book *Vaccine: The Debate in Modern America*.

Ertl's panelists include the book's author, Mark Largent, Ph.D. (professor at Michigan State University), Paul Offit, M.D. (chief of the Division of Infectious Diseases at the Children's Hospital of Philadelphia and author of the *Deadly Choices: How the Anti-Vaccine Movement Threatens Us All*), and Jason Schwartz (associate fellow at the University of Pennsylvania Center for Bioethics).

The event begins at 6:30 pm. This event is free, but registration is required. Go to wistar.org/events for more information.

Also, on April 27, 6:00 p.m., Wistar Archivist Nina Long will lead "Visualizing the Body Beautiful," a discussion on the art of medical illustration, at the Pennsylvania Academy of Fine Arts. Visit philasciencefestival.org for details.

Ronen Marmorstein, Ph.D. and guest at last year's Science Carnival.

Designs on a Cure

The Wistar Institute honors designer and cancer survivor Carmen Marc Valvo with the 2012 President's Award.

From Princess Madeline of Sweden to Queen Latifah, he designs for both royalty and those who just want to feel like royalty. Carmen Marc Valvo, whose couture creations are synonymous with glamour and celebrity, is one of the most sought-after fashion designers in the world.

He is also a survivor. Diagnosed in 2003, Valvo has become an outspoken colon cancer survivor who uses the fashion runway as his platform from which to advocate for early screening for colon cancer. For this reason, he was honored with The Wistar Institute's 2012 President's Award.

The President's Award recognizes a public figure who has been personally touched by cancer, and who advocates for improvements in cancer education and research. Previous honorees of The Wistar Institute's President's Award include U.S. Sen. Arlen Specter, General H. Norman Schwarzkopf, ABC News correspondent Sam Donaldson and "Good Morning America" co-anchor Robin Roberts.

"Carmen Marc Valvo embodies the spirit of The Wistar Institute President's Award," said Wistar President and CEO Russel E. Kaufman, M.D. "From his very public platform — the fashion runway — he advocates for cancer research and delivers a simple yet profound message: no one needs to die from colorectal cancer. Get screened."

Valvo was diagnosed just shy of his 50th birthday, the recommended age to begin colon cancer screening. Sensing that something "was off" regarding his health, Valvo insisted on a colonoscopy, allowing doctors to find and successfully treat his cancer.

Valvo began his professional career as a designer for Nina Ricci in Paris, then Christian Dior. He launched his own label in 1989 and quickly established a solid reputation with his Carmen Marc Valvo Collection. With a true passion for designing eveningwear, Valvo launched Carmen Marc Valvo Couture in 1998, earning the favor of socialites and celebrities including Beyoncé, Queen Latifah, Catherine Zeta-Jones and Eva Longoria.

Valvo spoke publicly about his colon cancer for the first time in 2005, when fashion serendipity brought him together with the National Colorectal Cancer Research Alliance, which was launching a colorectal cancer awareness initiative during the 2005 Spring/Summer Fashion Week in New York City. The experience helped launch Valvo into his second "career" in cancer advocacy. Today, serving as an ambassador of the Entertainment Industry Foundation, Valvo has helped raise millions of dollars for colon cancer research, and has appeared in national broadcast and print public service campaigns to encourage early screening for colon cancer. ■

Diagnosed in 2003, Valvo has become an outspoken colon cancer survivor who uses the fashion runway as his platform from which to advocate for early screening for colon cancer.

(l to r) Carolyn Curci, Joan Farkas, Phyllis Liebert, and Caryl Levinson.

Models show off the latest Valvo designs.

(l to r) Debbie McKenna, Mary Smith, and Louise Havens.

Russel E. Kaufman, M.D., (l) and Carmen Marc Valvo.

Valvo receives his white lab coat, a President's Award tradition.

Lanny Newman (l) and Wistar board secretary Maida Milone.

Sue Golden (l) and Beth Paterno.

Guests enjoy the President's Award luncheon.

Sam Donaldson

MELANOMA RESEARCH ADVISORY BOARD MEMBERS

MAURY ALSHER
Sr. Vice President,
Hub International PA, LLC

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Sam Donaldson Becomes Honorary Member of Melanoma Advisory Board

Legendary ABC News correspondent and cancer research advocate Sam Donaldson has been named to an honorary position on Wistar's Melanoma Research Center Advisory Board.

Donaldson joins a team of melanoma research advocates in furthering the mission of The Wistar Institute Melanoma Research Center (MRC) to create new and more effective treatments against the disease. The advisory board performs a crucial role in expanding the influence of the center so that it may meet its goals of advancing the science of melanoma and driving new treatments into the hands of oncologists.

"I'm glad to enter into this partnership with Wistar," said Donaldson, who is also a survivor of the disease. "No one person can fight melanoma alone, and it's vital that we continue to invest in melanoma research to unlock better therapies and ultimately find a cure."

Launched in May 2010, the MRC was designed to expand upon Wistar's prominence in the study of melanoma, an often deadly form of skin cancer diagnosed in over 68,000 Americans every year. While the incidence of many cancers has begun to decrease in the U.S., the opposite is true for melanoma. The numbers of new cases and deaths have been rising sharply, doubling over the last 30 years, and are expected to continue to do so for years to come. Melanoma currently kills 8,600 people in this country every year with 85 percent of patients dying within five years of diagnosis.

The Melanoma Research Center (MRC) brings together a critical mass of scientists and clinicians to share tools, ideas and expertise with the goal of developing effective new therapies to lessen the enormous burden of suffering and death caused by this disease.

"We are extremely pleased to have Donaldson on board in an advisory role," said Meenhard Herlyn, D.V.M., D.Sc., Wistar professor and director of the MRC. "He has always been a great advocate for improvements in cancer education and greater increases in melanoma research funding."

Donaldson, a 45-year veteran of the ABC News Network, has also served two appointments as ABC's chief White House correspondent, covering the Carter, Reagan and Clinton administrations. Today, Donaldson occasionally appears as a panelist on ABC's "This Week" and participates in a weekly roundup of ABC News Radio affiliate shows. He also sits on the board of the advocacy group Research!America, an organization promoting research into cancer treatment and prevention.

In 2004, Donaldson received The Wistar Institute's first President's Award in recognition of his work championing the advancement of cancer research and treatments. ■

Meet Our New Chair: Helen Pudlin Takes on the Role of Board Leader

During this spring's quarterly board meeting, The Wistar Institute proudly announced the election of Helen P. Pudlin, Esq. as chair of the Institute's board of trustees.

Pudlin, executive vice president and general counsel of The PNC Financial Services Group, is the 18th chair of the board and the first woman to hold the position since the independent biomedical research institute was founded in 1892.

Pudlin has been a member of Wistar's board since 2001, serving as co-vice chair since 2007, and as chair of the board's nominating and governance committee.

"It has been a pleasure to work with Ms. Pudlin over the last decade, and her guidance has directly contributed to the Institute's success," said Wistar President and CEO Russel E. Kaufman, M.D. "Wistar is expanding, growing its faculty, its programs, and building a new research facility for its scientists. I can think of no one better suited than Helen to help lead us into our very bright future."

As chair, Pudlin replaces Brian H. Dovey, who has served in the role since 2005. During his time as chair, Dovey, a partner in the venture capital firm Domain Associates, oversaw changes in Wistar's executive and scientific leadership and the development of the Institute's current research agenda, culminating this past September with the groundbreaking of a seven-story advanced research tower on Wistar's campus. Dovey will remain an active member of the Wistar board, which he joined in 1998.

"We are grateful to Mr. Dovey for his leadership and strategic vision, which set Wistar on the path toward our new building, and established partnerships within the life sciences industry to help move our scientific discoveries out of the laboratory and into the marketplace where they can improve public health," Kaufman said. "For more than a century, each chair of Wistar's board of trustees has left his own legacy at the Institute. Brian's legacy of excellence will be long-remembered."

"I greatly appreciate the support and kindness from, not only my colleagues on the board, but the leadership, faculty, and staff of the entire institute. We are all stakeholders in Wistar's continued success," said Pudlin. "Wistar is a remarkable place with a fascinating history and a promising future in scientific discovery, and I am privileged to be a part of it."

Pudlin joined PNC, Philadelphia, as general counsel in 1989 from the law firm of Ballard, Spahr, Andrews & Ingersoll in Philadelphia, where she was a partner. She was elected senior vice president and deputy general counsel for PNC in 1992 and became a managing general counsel and subsequently general counsel in 1994. She was named executive vice president in February 2009.

In addition to her service on Wistar's board, Pudlin is on the board of overseers of the University of Pennsylvania Law School, the board of managing directors of The Clearing House Association L.L.C., the Lawyers Council of the Financial Services Roundtable and the board of directors of the Pig Iron Theater Company. She also is a member of the International Women's Forum of Western Pennsylvania.

Helen P. Pudlin, Esq.

Pudlin also has served as a lecturer at the University of Pennsylvania Law School, served on the Board of Governors of the Philadelphia Bar Association, the House of Delegates and Judiciary Committee of the Pennsylvania Bar Association. In 1997, she was honored as one of Pennsylvania's Best 50 Women in Business. In 2005, she received the Alumni Award of Merit from the University of Pennsylvania Law School. In 2007, she was named to *Diversity Journal*'s list of "Women Worth Watching" in 2008. In 2010, she was honored as a Woman of Distinction by *The Legal Intelligencer*. In 2011, she was honored at the Girls Inc. New York Luncheon Celebrating Women of Achievement and received the Pennsylvania Most Powerful and Influential Women Award by the National Diversity Council.

Pudlin graduated from the University of Pennsylvania, where she received a bachelor of arts degree and was elected to Phi Beta Kappa. She earned a master's degree from the University of Pennsylvania and her juris doctorate degree from that University's School of Law. ■

Adele Schaeffer Honored at 2011 Wistar Gala

Presented at the Wistar Gala, the Wistar Award is a biennial award given to an individual who reflects the qualities of compassion, integrity, generosity, commitment, and vision that the Institute's founding members demonstrated. In October, 2011, Wistar honored Adele K. Schaeffer, a lifelong champion and advocate for biomedical research.

Schaeffer has been an active trustee of The Wistar Institute board for more than 20 years and has helped raise over $1 million for Wistar research.

This year's Wistar Gala raised $153,000 and will benefit the *Building Wistar, Changing the World* campaign, the five-year, $35 million initiative that will support the construction of a seven-story research tower and the recruitment of new faculty members.

Adele Schaeffer and U.S. Senator Arlen Specter.

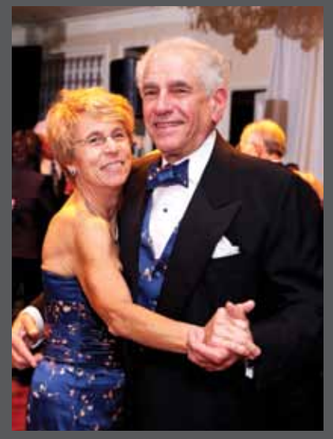
(l to r) Dario Altieri, M.D., Jane Kaufman, Russel E. Kaufman, M.D., Richard G. Pestell, M.D., Ph.D., and Nataliia Pestell.

David and Judy Wachs.

Wistar Assistant Professor Scott Hensley, Ph.D. and Kristin Hensley, Ph.D.

Graham and board member Susan McDonald.

Guests groove at the Gala.



Frances Batzer and Michael Baylson.

(l to r) Wistar board member and capital campaign chair Robert Fox, David Wachs, Richard Rothman, and Dick Fox.

Issac J. Wistar at age 55, painted in 1882 by Bernard Uhle.

The sisters of Issac J. Wistar in November 1861. Top row, L to R: Lydia Kendall, Kate Wistar, Hannah Hacker, Sarah Rhoads. Bottom row, L to R: Margaret Haines, Mary Brown.

When Service is Tradition

This winter, when I. Wistar Morris III joined the Institute's board of trustees, he became the latest part of a proud tradition that began with the birth of The Wistar Institute in 1892.

When the Institute's founder, General Issac J. Wistar, drew up the Deeds of Trust that dictated the Institute's terms of management, he required that a male heir directly descended from his grand-uncle, Caspar Wistar, M.D., must always be a member of Wistar's board of trustees. Since that time, the Wistar family has done more than just lend its name to the Institute: they have given service.

In florid Victorian style, the Deeds of Trust state: "Such descendant of Caspar Wistar, M.D., the father of this Donor, who was born A.D. 1801 and died A.D. 1867, as would at this time be the oldest of his nearest lineal heirs in the same degree, provided such descendant shall be a male of not less than twenty-one years of age, and if not, then the next oldest of his nearest lineal heirs in the same degree possessing these qualifications, or such other person in his stead as such heir shall from time to time indicate…"

And so, The Wistar Institute has been favored with the leadership of many generations of Wistars, some acting in the role of the official family representative, and others, simply serving to further the Institute's mission.

In fact, I. Wistar Morris III is not the family representative. Samuel Rhoads currently holds that distinction; more on him later. Instead, Morris serves as a representative of the Academy of Natural Sciences of Drexel University, which was also a relationship established in the Deeds of Trust.

Although the terms of the Deeds of Trust specifically state that the family representative on the board must be a male descended from the male line, these terms became challenging to fulfill. Sometimes, direct descendants didn't have sons, or they chose not to serve. In such circumstances, the language in the Deeds of Trust that state "such other person in his stead as such heir shall from time to time indicate" opened the doors to allow the male heirs descended from the female line to fill the family representative role. Issac J. Wistar's sister Margaret had married Robert Haines, who lived in Germantown. Their son, Caspar Wistar Haines, in 1915 became the first family representative on the board who was descended from the female line, and was then followed as family representative by his son, Caspar Wistar Haines, Jr.

In this same period, Effingham B. Morris, who was descended directly from the first Caspar Wistar (founder of the first glassworks in the American colonies, Wistarburgh Glass), was president of the board from 1915 to 1937.

Samuel Rhoads, the current family representative, took over from his father Donald Vail Rhoads, M.D., in 2004, and is descended from Issac J. Wistar's sister Sarah. Rhoads has played an active role on the board, including providing testimony to the Pennsylvania Orphans' Court in a proceeding to gain approval for the Institute's new research tower, currently under construction.

In over a century since The Wistar Institute has begun its evolution from anatomical museum to a world-renowned destination for cancer and vaccine research, it is nice to consider that, in many ways, Wistar remains a family organization. ■

WISTAR FAMILY MEMBERS WHO HAVE SERVED ON THE BOARD OF MANAGERS WITH DATES OF SERVICE

1 ***GEN. ISAAC JONES WISTAR**
1892–1905; Secretary 1892-1905

EDWARD D. TOLAND
(related to Sarah Toland Wistar, Isaac Wistar's wife)
1893–1903; Treasurer 1898-1903;
Co-Trustee 1893–1913.

WILLIAM WYNNE WISTER, JR.
1893–1900

DR. ARTHUR E. BROWN
1901–1910

2 ***DR. THOMAS WISTAR**
(brother of Isaac J. Wistar)
1905 –1913

***CASPAR WISTAR HAINES**
1913–1935

GEORGE VAUX, JR.
(Isaac Wistar's aunt, Margaret, married Roberts Vaux, 1814.)
1910 –1928

3 **EFFINGHAM B. MORRIS**
(President of the Board of Managers)
1915 –1937

EFFINGHAM B. MORRIS, JR.
1937 –1952

***DIEDERICK JANSEN HAINES**
1937 –1943; Secretary 1937

***WILLIAM GIBBONS RHOADS**
1943–1958

***CASPAR WISTAR HAINES, JR.**
1958–1973

OWEN JONES TOLAND, JR.
(related to Sarah Toland Wistar, Isaac Wistar's wife)
1964–1999; Treasurer 1968–1987

MARGARET LEONARD BROWN
(Mrs. T. Wistar Brown)
1968–1998

4 ***DR. DONALD VAIL RHOADS**
1974-2003; Secretary 1983-1991

***SAMUEL RHOADS**
2004–present

ISRAEL WISTAR MORRIS III
2012–present

* Denotes served as designated Wistar family representative

Our information is drawn from our historical archives, and may be incomplete. We welcome any additions or information you may have to share!

Tintype photo taken in late 1856 or early 1857. Top row, L to R: Issac J. Wistar, age 29; Sarah Wistar, age 17; Thomas or William Wilberforce Wistar (twin), age 19; Hannah Wistar, age 21; Katherine Wistar, age 13. Bottom row, L to R: Elizabeth Waln Wistar ("Aunt Betsy"), age 68; Thomas or William Wilberforce Wistar (twin), age 19; Robert Haines, age 29; Margaret Wistar Haines, age 25.

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Join us at the 17th Annual Albert R. Taxin Golf & Bridge Classic

MAY 21, 2012 AT GREEN VALLEY COUNTRY CLUB

This event was established to honor the memory and legacy of Albert R. Taxin, a beloved Philadelphian who died in 1993 of a brain tumor. All proceeds from the Classic support the work in the Albert R. Taxin Brain Tumor Research Center at The Wistar Institute.

Learn more at Wistar.org/events

ON TWITTER?
Join us as we live-tweet Wistar's Author Series event April 24th, beginning at 6:30 pm. Follow us at @TheWistar

ON FACEBOOK?
Keep track of Wistar news and events while sharing with your friends at: Facebook.com/thewistarinstitute

Wistar.org

REFUNDS FOR BREAST CANCER RESEARCH
Look for the PA Breast Cancer Coalition's Refunds for Research line (line 35) on your state income tax form and donate your refund to breast cancer research.