The (micro) Environmental Impact of Inflammation

Targeting Cancer’s “Normal” Neighbors to Kill Tumors
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There’s electricity in the air at The Wistar Institute, both literally — not surprising for a biomedical research institute, perhaps — and figuratively. We recently completed a strategic planning cycle that maps a course for advancing our research in novel directions and growing the Institute to new heights of excellence. The excitement is building, as is our sense of accomplishment, as we begin to implement our ideas and bear fruit. In this issue of Focus, you’ll read about the quickening pace of our research progress, and the people and partnerships that make it possible.

People like the Tobin and Kestenbaum families. Motivated by memories of loved ones affected by Alzheimer’s disease and brain tumors, and deeply generous, they recently endowed the Tobin Kestenbaum Family Professorship in Neuroscience. The professorship will enable Wistar to expand our world-class faculty by recruiting a top scientist who studies the brain and its related diseases, such as cancer, Alzheimer’s and Parkinson’s disease.

Regarding partnerships, I’m particularly excited about a collaboration with University of the Sciences in Philadelphia that will help us translate our scientific discoveries into new therapies for cancer and other diseases. Wistar’s experts in chemical and structural biology work to identify small molecules with potential to affect disease processes, for example, by blocking a cellular pathway that leads to cancer. With their expertise in pharmacology, USciences researchers will refine those small molecule candidates into compounds that are ready for early phase clinical testing in humans — the first step in bringing a new drug to patients. What’s remarkable is the depth of our shared commitment to this enterprise. In May, USciences generously assigned its McNeil Professorship to the partnership, formally known as the Center for Chemical Biology and Translational Medicine, and we awarded it to Wistar’s Paul Lieberman, who is the Center director. To my knowledge, this is one of the few, if not the only, inter-institutional professorship of its kind, and I know I speak for the entire faculty in expressing my gratitude and enthusiasm for this partnership.

These two examples confirm a simple truth — research progress, with all the promise it holds for a healthier future for all of us, is made possible by people who share our vision and commitment. I am deeply grateful to you, a friend of The Wistar Institute, for your continued support.

It’s an exciting time at Wistar, as we plan for our future and take giant steps into it. Turn the page, and come along with us.

FROM THE PRESIDENT

Progress and Partnerships
When Puré looks at her garden, she notices more than vibrant color and sweet scents. What surrounds each plant is just as interesting. Soil, insects, sun, rain, wind — all play a vital role in the health of the garden. Attention to this environment is key to treating plant disease, discouraging rabbits from nibbling her hostas, and fending off harmful insects.

Lately, Puré, a professor in the Molecular and Cellular Oncogenesis Program at Wistar, has come to look at cancer cells in much the same way. While most scientists focus on drugs that target the cancer cell itself, Puré is taking aim at the tumor’s microenvironment. By targeting the normal cells that feed the tumor and allow it to grow and spread, Puré believes it’s possible to develop therapies that increase the effectiveness of traditional anti-cancer drugs. Until recently, much of the scientific community viewed this notion with skepticism, a reaction Puré has encountered before. Over the last three decades, her research focus has been the inflammatory system and what role non-immune cells play in inflammation and disease, a connection long dismissed by many scientists. Today, however, it is widely accepted that inflammation is involved in a number of ailments, from heart disease to diabetes, and Puré is now discovering, in cancer.

about the role inflammation played in human disease. The function of inflammation in external injury and infection was well understood and accepted. But the notion that an internal malady such as heart disease or diabetes could trigger an inflammatory response was considered far-fetched, at best. There was a small group of scientists — Puré included — who disagreed.

"Inflammation is much more than swelling," Puré said. Swelling is just the visible side effect of a process that kicked in long before fluid build-up caused tissues to puff up, she adds. Inflammatory cells are part of the body’s natural immune response to anything out of the ordinary— an injury, infection or mutated cells that invade health tissue. "We came to realize that there were too many times we’d observed inflammatory responses that we could not explain or attribute to an infection or external injury," Puré said. The sea change began with the discovery that infectious agents trigger danger signals in the immune system, and that inflammatory mediators are produced by cells in our organs that are not technically components of the immune system.

"We have an innate immunity that allows cells with pattern recognition receptors to recognize the molecules with patterns displayed by pathogens," Puré said. "Then we realized that the system uses the same receptors to see things that have been modified on our own sugars, proteins, molecules, and so on.

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Under the microscope: fluorescence indicates cellular interactions in the tumor microenvironment.

"The inflammation response has evolved to recognize stimulation whether it comes from an infection or external stimuli or if things go wrong in the body without any external injury," she noted. Recently, research began to emerge suggesting that some immune cell receptors are expressed on normal non-immune cells called stromal cells, which include endothelial cells, fibroblasts, pericytes and others found in loose connective tissue. The idea that inflammation played a role in disease processes not associated with infection no longer seemed so outlandish.

"Scientists began to understand how fundamental inflammation is," Puré said, "and it went from speculation to very fundamental inflammation is," Puré said, "and it became a reality. It's no longer a speculation that cancer is a disease of inflammation. We now know that inflammation is, in fact, associated with cancer development and progression."

"And it's not just cancer. Inflammation is associated with a wide range of diseases, including cardiovascular disease, autoimmune diseases, and even depression," she added. "Inflammation is a complex process that involves the interaction of multiple cell types and molecules, and it plays a crucial role in the development and progression of many diseases."
Wistar Garners $14 Million in Economic Stimulus Funding

For most of 2009, one word dominated conversations about economics and politics in the United States: “stimulus.” The American Recovery and Reinvestment Act of 2009 (ARRA), as the stimulus was officially known, was the most visible aspect of the Obama Administration’s economic recovery plan, allotting $787 billion to promote job creation, healthcare modernization, school improvements, infrastructure support, and biomedical research.

While the effects of the recovery plan on the state of the nation continue to be debated, one result is clear — Wistar investigators are busy advancing their research with a $14 million share of ARRA funding.

The stimulus funding could not have come at a better time for the nation’s biomedical research community. After five years without a budget increase, the National Institutes of Health received a $10.4 billion slice of ARRA, and soon took applications for grants and supplements to existing NIH-funded projects.

“As the NIH budget has leveled off in recent years, many — if not most — grant applications do not receive the full amount of money that they requested,” said Marianne O’Neill, Wistar’s director of grants and contracts administration. “As a result, many research projects have to be ‘down-sized’ to stay within budget and progress slows down.” In essence, ARRA is like a booster shot to inject funding and take these projects to the next level.

Historically, Wistar researchers have been competitive in successfully securing NIH funding when compared to their peers at other biomedical research institutions. Here is a glimpse of the ARRA-funded science that will emerge out of Wistar laboratories in the coming months:

**INNATE EFFECTOR FUNCTION AND HIV-1 CONTROL**

Luis Montaner, D.V.M., D.Phil., professor in Wistar’s Immunology Program, received a new grant to investigate why some people infected with HIV-1 exhibit a natural immune response that delays or prevents the virus’s progression to AIDS. In particular, the Montaner lab is examining the innate immunity — the non-specific immune response that serves as the body’s baseline protection against infection — of these people to understand what may protect them from HIV-1.

**CELLULAR INNATE ACTIVATION AS A TACTIC TO PREVENT HIV-1 TRANSMISSION**

The Montaner laboratory also received a new grant to study the factors that appear to protect some women from contracting HIV-1 even after exposure to the virus through high-risk behavior.

**A THERAPEUTIC VACCINE FOR EBV-ASSOCIATED MALIGNANCIES**

Epstein-Barr virus (EBV) infects more than 95 percent of the adult population worldwide and is responsible for the majority of AIDS-associated lymphomas. Unfortunately, EBV is a chronic infection, one that manages to evade the immune system. To create a vaccine against EBV, Paul M. Lieberman, Ph.D., professor in Wistar’s Gene Expression and Regulation Program, proposes a strategy that fuses an EBV protein with a protein from another virus more likely to arouse the immune system; combined, he hopes they will convince the immune system to attack EBV. Lieberman’s funding is through a special ARRA “Grand Opportunity” grant which promotes “high impact” studies that could benefit from short-term support.

**INHIBITORS OF HEDGEHOG SIGNALING FOR BRAIN CANCER CHEMOTHERAPY**

Medulloblastoma, a malignant brain tumor found in children, and glioma, the most malignant and invasive of adult brain tumors, currently have no optimal therapies. Nadia Dahmane, Ph.D., assistant professor in Wistar’s Molecular and Cellular Oncogenesis Program, received a new grant, along with colleagues at the University of Pennsylvania, to investigate new therapeutic targets to help eliminate these brain cancers.

**MicroRNAs AND OTHER NON-CODING RNAs IN COLORECTAL CANCER**

Ramana Davuluri, Ph.D., associate professor in Wistar’s Molecular and Cellular Oncogenesis Program, along with colleagues at M. D. Anderson Cancer Center received a new grant to determine the roles of small segments of RNA, called microRNAs, in regulating the spread of colorectal cancer in order to develop new biomarkers of disease and new targets for drug therapy.
IDENTIFICATION OF OVARIAN CANCER PLASMA BIOMARKERS

Early-stage ovarian tumors usually are asymptomatic, and about 75 percent of cases are diagnosed after the cancer has spread. The laboratory of David Speicher, Ph.D., professor in Wistar’s Molecular and Cellular Oncogenesis Program, earned a new grant to identify proteins in the blood that indicate the presence of ovarian cancer.

CORRELATES OF PROTECTIONS AGAINST SIV/HIV CHALLENGE

Hildegund C. J. Ertl, M.D., professor in Wistar’s Immunology Program and director of The Wistar Institute Vaccine Center, seeks to identify the underlying reasons that Merck’s HIV-1 vaccine reflects a product failure rather than the concept of protection against HIV-1 by triggering T cell responses. (See related story page 12.)

PRE-DOCTORAL TRAINING AT THE CHEMISTRY-BIOLOGY INTERFACE

Ronen Marmorstein, Ph.D., professor in Wistar’s Gene Expression and Regulation Program, received supplemental funding for the continuation of the Chemistry-Biology Interface Training program, run jointly by Wistar and the University of Pennsylvania. The program provides future chemists and biologists with the skills that they will need to work across disciplines in order to solve complex biological problems.

3D HUMAN SKIN MODELS

Meenhard Herlyn, D.V.M., D.Sc., professor in Wistar’s Molecular and Cellular Oncogenesis Program and director of The Wistar Institute Melanoma Research Center, received new ARRA funds to continue studies to establish a three-dimensional model of normal human skin to create experimental conditions for studying cancer that are more “human specific” and predictive. Herlyn’s model has the added benefit of decreasing the number of animals required for preclinical drug toxicology and safety assessment studies.

MAPPING MOUSE REGENERATION GENES

Ellen Heber-Katz, Ph.D., professor in Wistar’s Molecular and Cellular Oncogenesis Program, received a 7 1/2-month supplemental grant to further her studies of the genes that confer regenerative healing capabilities to mice developed in her laboratory. The funds allowed her to bring a visiting scientist into her lab whose contribution to mapping mammalian regeneration genes bore fruit this spring with the publication of a significant paper. (See related story page 15.) The visiting scientist, L. Matthew Arthur, Ph.D., has since applied for — and received — a postdoctoral slot on the Marmorstein training grant, which will allow him to stay on in the Heber-Katz lab.

SPECIFICITY AND FUNCTION OF CD8+ REGULATORY T CELLS

Regulatory T cells play a vital role in preventing the immune system from attacking the body’s own cells and tissues, which can lead to a variety of autoimmune disorders, such as lupus. These cells also have a role in how the immune system works with regard to infection, transplantation, and cancer. Andrew Caton, Ph.D., professor in Wistar’s Immunology Program, received supplemental funding to analyze the processes that govern how regulatory T cells develop and function. In doing so, he seeks to find new ways to utilize T cell biology in the diagnosis and therapy of human diseases.

SHAPING ANTIVIRAL IMMUNITY BY THE INFLAMMATORY, REGULATORY, AND TISSUE ENVIRONMENT

More than two billion people worldwide are infected with HIV, hepatitis B and C, malaria, tuberculosis, and tropical diseases — populations that would benefit the most from improved vaccines. The goal of the laboratory of Assistant Professor E. John Wherry, Ph.D., is to define factors that shape antiviral T and B cell immunity and delineate the mechanisms by which these factors operate. Wherry seeks to understand how unrelated infections impact immunological memory in the hopes of improving vaccines. (Note: As of May, 2010, Wherry has departed The Wistar Institute.)

CONTROL OF CARDIODENESIS BY MICRORNA EDITING

Kazuko Nishikura, Ph.D., professor in Wistar’s Gene Expression and Regulation Program, received new funding for the study of microRNA editing, a process by which a small strand of RNA can influence how cells “read” genes and create proteins. Nishikura hopes the study will reveal critical information about the mechanisms underlying normal and defective heart development and help in formulating new microRNA-based therapies for prevention of congenital heart defects and various cardiovascular diseases.

EARLY INTERACTIONS OF DNA VIRUSES AND HOST

Human cytomegalovirus (CMV) has serious consequences for people with weakened immune systems, such as AIDS and organ-transplant patients and congenitally infected newborns. Gerd Maut, Ph.D., professor in Wistar’s Gene Expression and Regulation Program, received new funding to investigate the immediate-early stage of the CMV infectious cycle to identify new potential targets of therapy.
Fighting Back

Luis Montaner, D.V.M., D.Phil., suggests the body’s best weapon against HIV may be the very system the virus attacks.

In the summer of 1987, while an undergraduate research intern, Luis Montaner peered through a microscope and first laid eyes on the simian immunodeficiency virus. At the time, it was the best model scientists had for studying the human form of the virus that causes AIDS. Scientists had identified HIV years before, but how the virus worked, how it was transmitted, and how to kill it remained a mystery.

By the time Montaner came in contact with that microscope, some 5 to 10 million people worldwide were infected with HIV. According to the World Health Organization, and nearly 100,000 had died from AIDS. Soon after, researchers discovered how the virus crippled the immune system and how it was spread. Stopping HIV, however, was another story, one that Montaner has followed ever since.

Like other scientists studying HIV at the time, Montaner espoused the introduction of antiretroviral drugs in the mid-1990s, which can keep the virus in check. But even then, he knew it wasn’t enough to just restrain HIV. The end goal had to be to rid the body of the virus altogether. And the key to doing that, he thought, would require a different approach to HIV therapies.

Then and now, most research to eliminate the virus centers on how it disables the immune system. However, after more than 20 years of studying HIV, Montaner, a professor in Wistar’s Immunology Program, thinks it’s time to flip that around. Rather than concentrating on what goes wrong, why not look at immune functions that remain despite the viral assault or, better yet, those that seem to activate only after infection?

Called Philadelphia FIGHT, the organization was also a host site for the Community Clinical Trials Research Network, which matched patients with clinical trials. Montaner approached the group with a proposal to do a patient study on the impact of stopping and starting antiretroviral therapy.

HIV drug combinations often have devastating side effects, which led many to study options for stopping their use. Montaner wanted to know how that would affect the immune system and the virus. One possibility in particular intrigued him — that a regimented stop and start drug therapy program would allow the immune system to gradually resist the virus, allowing the body to fight it on its own.

With assistance from Philadelphia FIGHT and philanthropic support, Montaner made plans for a small study of drug interruption in HIV patients. He enrolled about 50 people and divided them into two groups, one received drug therapy throughout the study and the other started and stopped taking the drugs at specific intervals. Their early findings suggested that interrupting therapy had no effect on the level of virus in the patients’ blood. If this held true in a larger study, Montaner thought, it could have a real impact in impoverished areas of the world by, in essence, extending access to drugs to more people: “I’ve always been attracted to the social implications of our research effort,” Montaner said. “Trying to retain some connection to a social agenda has been an important piece to how I decide where I go next.”

In 2003, Montaner met a physician who ran one of the busiest AIDS clinics in Johannesburg, South Africa. The pair devised a study similar to the Philadelphia project which was the first of multiple projects between Wistar and Johannesburg. With help from a National Institutes of Health (NIH) grant and support from Wistar, which covered the cost of antiretroviral drugs, they enrolled 54 participants and launched a project to describe the outcomes of interrupting therapy. Since then, the Montaner lab has initiated additional projects on tuberculosis infection and cervical cancer outcomes following antiviral therapy.

INNATE IMMUNITY

In addition to the effect of antiretrovirals on the adult immune system, Montaner also is interested in the impact HIV drugs have on the innate immune system of infants born with the virus. Unlike the adaptive immune system — which imprints white blood cells with a memory of the invading cell it is sent to fight — the innate immune system reacts quickly to attack a broad spectrum of microbes, but does not store information on the microbes. Some scientists suggest that starting AIDS treatment as soon after birth as possible is the best way to keep the virus in check and allow the immune system to develop. Others have maintained that it’s better to delay treatment until symptoms develop. To figure out which strategy works, Montaner is participating in the Comprehensive International Programme for Research on AIDS in South Africa, the first NIH-sponsored research program to fund foreign institutions directly.

For his part of the study, Montaner and his colleagues examined data from 377 infants who were HIV positive at birth. At about 7 weeks of age, the children were randomly assigned to one of two groups. Antiretroviral therapy was delayed in the first group until the infants were 40 weeks old. The second group received the drugs immediately. The results clearly point to an advantage of early treatment, which reduced infant mortality by 76 percent and slowed the progression of the virus by 75 percent.

When the scientists examined the level of various immune factors in the blood of infants who were treated early and compared it to blood samples from adults in the treatment interruption
Lessons from a Failed Vaccine Trial

Scientists may not know what caused the widely publicized failure of one of the most promising HIV vaccines in history, but a new study by Wistar researchers shows what didn’t.

Merck launched its study — called STEP — of the experimental vaccine in 2004, using a common cold virus, Ad5, to transport HIV genes through the body. The idea was to introduce the immune system to a weakened form of HIV so that it would recognize the virus if or when the person became infected. Three years later, Merck announced that preliminary findings suggested the vaccine didn’t prevent HIV, and ended the trial. Scientists were eager to discover why the vaccine failed so that future vaccine development efforts could avoid those problems.

A preliminary analysis suggested that participants who had high levels of antibodies to this strain of cold virus before receiving the first vaccine actually showed an increased risk of HIV infection. Researchers theorized that when the immune system was exposed to Ad5 in the vaccine, it created large numbers of disease-fighting CD8 T cells — the very cells that HIV attacks. The increase in these T cells gives the virus more targets to latch onto and the HIV infection spread.

But last fall, a study published in the journal Nature Medicine disproved that theory. Hildegund C. J. Ertl, M.D., director of the Wistar Institute Vaccine Center, was part of a team that examined blood samples with varying amounts of Ad5 antibodies taken from 43 healthy participants prior to vaccination. When they compared the pre-vaccine samples to those taken afterward, they found no correlation between the level of Ad5 antibodies before vaccination and an increased HIV risk after vaccination. Researchers examined 10 subsets of T cells designed to fight Ad5 to see if the vaccine caused any changes in the cells’ behavior. Again, they found no differences in the before and after.

Since the vaccine used a common cold strain, Ertl and her colleagues believe that most people would already possess Ad-speciﬁc T cells. “It doesn’t appear that vaccination increases the pool of potentially infectable CD8+ T cells in people with pre-existing immunity to Ad5,” Ertl said. “When you look at the data together, they suggest we must look elsewhere to explain the link between previous Ad5 immunity and increased acquisition of HIV infection.”

Rule Nothing Out

Joe Kissil’s early memories of playing outside with his father were actually recollections of his first science experiments. His father, a marine biologist, moved his family to southern Israel near the Red Sea when Kissil was young. “We were doing science while snorkeling and sailing,” Kissil recalled. “It wasn’t that bad.”

Kissil’s love of science stayed with him over the years. After leaving the Israeli Army in 1990, he enrolled at Ben-Gurion University in 1990, majoring in life sciences, before heading to graduate school at the Weisman Institute. His doctoral studies dealt with cell death in mammalian systems, a pursuit he continued as a postdoc at the Massachusetts Institute of Technology. It was there that Kissil began to research a disorder called neuroblastoma 2 (NF2), a hereditary disease that can cause benign brain tumors and spinal and eye lesions. Research by Kissil and others found that a mutation in a tumor-suppressor gene called Merlin leads to NF2. Merlin regulates a family of small binding proteins called Rac, which were originally thought to have a role in cancer. When early studies found no link, however, many scientists turned their attention elsewhere.

Kissil stuck with it. What if, he wondered, Rac’s involvement in cancer had nothing to do with its relationship to the Merlin gene, but rather with something else? Rac was linked to a number of other genes, including a gene called Ras, which is mutated in a variety of cancers. After joining The Wistar Institute in 2004 as an assistant professor, Kissil developed animal models to explore this possibility. In 2007, Kissil’s lab published a paper in the journal Cancer Research that for the first time showed a definitive link between Ras and Rac.

One of his newest studies stems from his postdoc work on Merlin. Kissil’s team has shown how the gene inhibits cell signaling through Rac by upregulating a family of proteins called Pak, which causes cells to grow. In the case of NF2, this allows cancer cells to flourish and spread. By blocking the Pak proteins, Kissil was able to stop tumor development in mice. This work is supported in part through a grant from the American Cancer Society.

Kissil’s group also is looking at Ras function with Notch, a family of proteins crucial to embryonic growth that can either help cancer grow or prevent it from spreading. Specifically, he wants to know how Notch proteins are involved with pancreatic cancer. “A lot of these molecules that are involved in development also have roles in cancer,” Kissil said. “In the end, almost everything plays a role in everything.”

That is an underlying theme in Kissil’s lab. Rule nothing out.

“There may be preconceived ideas of what we want a project to look like but in many cases we just don’t know the answer,” said Kissil. “If the idea is based on sound literature and good precedent, it’s worth looking at.”
One Gene May Hold the Secret to Human Regeneration

Humans should rightfully feel that we have done fairly well in the evolutionary lottery: We cannot fly like birds, of course, but intelligence, social skills, and opposable thumbs have gotten us far. Our entire mammalian lineage, however, has missed out on something common to the lowliest flatworms and sponges: regeneration, the ability to heal without scarring or even to replace limbs and organs. But just as humanity has learned to fly higher than any bird dares dream, could we also one day replicate regeneration?

This spring, one Wistar researcher’s quest to tap the potential of regeneration has reached a milestone: the identification of a gene that may hold the secret to regeneration in mammals. The laboratory of Ellen Heber-Katz, Ph.D., a professor in Wistar’s Molecular and Cellular Oncogenesis Program demonstrated the loss of a single gene, called p21, confers a healing ability to mice that scientists thought had been lost to mammals through evolution. Their findings were reported in the Proceedings of the National Academy of Sciences.

Unlike mammals, which heal wounds by forming a scar, these mice begin by forming a blastema, a cell structure associated with regeneration as seen in amphibians. “Much like a newt that has lost a limb, these mice will replace missing or damaged tissue with healthy tissue that lacks any sign of scarring,” said Heber-Katz.

According to Heber-Katz, the journey toward this discovery began with a moment of serendipity. In 1996, her laboratory acquired a strain of mice, known as MRL mice, for use in a study related to lupus. The mice get a comparable autoimmune disease. Heber-Katz asked a postdoctoral student to pierce small holes into the ears of the experimental mice, a common practice in order to distinguish them from the untreated control group of mice.

A few weeks later, however, the investigators discovered that these holes had closed without a trace. While the experiment was ruined, it left the researchers pondering if this MRL mouse was a window into the potential for human regeneration.

In their recent study, they found that p21, a gene that helps control the ability of cells to divide, was consistently inactive in cells from the MRL mouse ear. So Heber-Katz procured p21 knockout mice, which were readily available, and widely used in many studies. What had not been noted was that these mice could also heal their ears.

“In normal cells, p21 acts like a brake to block cell cycle progression in the event of DNA damage, preventing the cells from dividing and potentially becoming cancerous,” Heber-Katz said. “In these mice without p21, we do see the expected increase in DNA damage, but surprisingly no increase in cancer has been reported.”

In fact, the researchers saw an increase in apoptosis — also known as programmed cell death — the cell’s self-destruct mechanism that is often switched on when DNA has been damaged. This is exactly the sort of behavior seen in naturally regenerative creatures, says Heber-Katz.

While the researchers caution that the clinical use of their findings remains years away, they are hopeful that their findings will form the basis for useful therapies. “While we are just beginning to understand the repercussions of these findings, perhaps, one day we’ll be able to accelerate healing in humans by temporarily inactivating the p21 gene,” Heber-Katz said.

Discovery Suggests a Rethinking of Melanoma Therapy

One of the reasons that melanoma is the deadliest form of skin cancer is its persistence. The survival rate of late-stage melanoma is less than 15 percent, and the disease often comes back even after seemingly effective treatment, a trait that many researchers attribute to cancer stem cells that continually renew melanoma tumors with fresh cancer cells.

Scientists at Wistar have a new theory that turns the cancer stem cell model on its head: individual melanoma cells are neither stem cells nor conventional cancer cells — they’re both. They call it “dynamic stemness” and it means that all melanoma cells equally harbor cancer stem cell potential that enables them to induce new tumors.

Their findings, published in the journal Cell, reveal the unique biology of melanoma, and suggest that the disease requires an entirely new therapeutic approach.

“Targeting only the bulk tumor population, as most conventional anticancer therapies do, is pointless in melanoma, in that each cell can act as a seed for the tumors to rebound,” said Memhard Herlyn, D.V.M., D.Sc., professor and leader of Wistar’s Molecular and Cellular Oncogenesis Program. “The other implication is that we should stop hunting for a cancer stem cell, because it won’t be there.”

The traditional view of cancer holds that cancers arise following a random accumulation of malignant events, e.g., mutations, gradually imparting enough unchecked. In the classic model, a single malignant stem cell produces both copies of itself and “normal” cancer cells that make up the bulk of the tumor. Over the last decade, scientists have developed a cancer stem cell concept that explains how the slow growth and persistence of these stem cells allow tumors to persist following treatment. Melanoma, for one, seems to follow a third path, dynamic stemness, where every melanoma cell can serve as a stem cell, continually replenishing the tumor, Herlyn says.

In the study, Herlyn and his colleagues describe a slow-growing subpopulation of melanoma tumor cells, defined by the protein JARID1B, which is required for tumor maintenance. Genetically blocking the ability of cells to produce this protein “exhausts” the tumor, preventing its proliferation. Yet unlike classic cancer stem cells, this subpopulation is highly plastic: JARID1B-expressing cells can turn off the gene, and JARID1B-non-expressing cells can turn it on.

Their findings suggest that melanoma requires a two-pronged therapeutic approach, says Herlyn. One is needed to target the bulk of the tumor, while another one should specifically target the JARID1B-positive subpopulation.

“It’s a dual therapy that we are proposing,” said Herlyn.

Herlyn and his colleagues are now exploring ways to create new drugs that specifically target JARID1B cells.
A Pattern For Early Lung Cancer Detection

In 2009, more than 219,000 people in the U.S. found out they had lung cancer. The cancer had already spread in about half those patients, according to the American Cancer Society, cutting their five-year life expectancy in half.

Symptoms of lung cancer are hard to spot when the disease first strikes, making early diagnosis difficult. Physicians long for an easy-to-administer screening test that could be given regularly to smokers, those with a family history of lung cancer, and others at high-risk of the disease. At the moment, diagnosis is made most often through X-rays or invasive biopsies. But new research by scientists at Wistar could lead to a simple blood test to find cancer early before it has a chance to spread. Led by Wistar investigators Louise C. Showe, Ph.D., and Michael K. Showe, Ph.D., the study, published in the journal of Cancer Research, identified a 29-gene signature found in the immune systems of lung cancer patients. The project included analyses of peripheral blood — in particular the white blood cells that circulate through the body and are important immune cells.

When the Showes first began the study in 2004, the idea of looking for a sign of cancer anywhere other than a suspected tumor was shunned by most scientists and physicians — even the doctors who collected the initial blood samples for the study. “This was not a popular idea when we first started because people thought you had to look at the tumor itself to learn something about cancer,” said Louise Showe, professor in Wistar’s Molecular and Cellular Oncogenesis and Immunology programs. “As the study went on, the doctors became some of our biggest supporters.”

Showe got the idea to examine peripheral blood for cancer markers while working on a skin cancer study in 2003. Cancer cells survive by drawing nutrients from the blood. Some cancer cells can travel to other parts of the body via the bloodstream. The question the Showes’s tried to answer was whether, as the disease interacts with the blood and spreads, was it possible that it left a trail behind in the bloodstream? To answer this question, they collected blood samples from more than 200 patients with lung cancer or other, nonmalignant lung diseases. They wanted to find out if lung tumors — even at their earliest stage — left their mark on circulating blood cells. They extracted RNA from the blood and used microarrays to search for a gene signature that indicated the presence of a cancer.

They identified a 29-gene pattern that allowed them to separate 137 people with lung cancer from 91 patients with benign lung tumors with 86 percent accuracy. “Most tumors are found late — primarily by accident — and treatment options at that point are limited,” Showe said. For early detection to be successful, the process must be easy, safe, and inexpensive. X-rays and biopsies are neither. Drawing blood, on the other hand, is routine at physician check-ups. “Of course,” she added, “if we’re ever going to make this test clinically useful, it has to be something that is accurate and easy to apply.”

Showe and her colleagues are now working on a way to streamline the process necessary to draw, store and ship blood samples in a way that protects the RNA. The institute also has filed for a patent on the 29-gene signature and method the researchers used to analyze the data — the first step toward partnering with a company to develop the test for widespread use.

Co-authors of the study include lead author Michael K. Showe, Andrew V. Kossenkov, Ph.D., Elena V. Nikonova, M.D., Celia Chang, Ph.D., Calen Nichols and David A. Sprich, Ph.D., all of The Wistar Institute; Steven M. Albroda, M.D., Anil Vachani, M.D., John Kucharzuk, M.D., Bao Tran and Elliot Wakeam, all of the University of Pennsylvania School of Medicine; and William N. Rom, M.D., M.P.H., and Ting an Yie, M.S., both of the New York University School of Medicine.

This study was supported by the Pennsylvania Department of Health (PA DOH) Tobacco Settlement Grants, the PA DOH Commonwealth Universal Research Enhancement Program, the National Cancer Institute and a Wistar Cancer Center Support Grant.
In most of the more than 40,000 women in the U.S. who died from breast cancer last year, the disease had infiltrated the bloodstream and scattered throughout the body. From the moment the cancer escaped the breast tissue, those patients’ prognoses grew grim. This process — called metastasis — remains a puzzle for scientists. And though many of the individual pieces involved in metastasis have been identified over the last 10 to 15 years, just how they fit together is not fully understood.

A new study by scientists at The Wistar Institute has identified two important pieces of this puzzle and how they interlock, work that could not only help scientists better understand metastasis, but may one day be used to help physicians predict metastasis risk in patients.

In studies of two genes thought to be involved in cancer, research led by Qihong Huang, M.D., Ph.D., assistant professor in Wistar’s Gene Expression and Regulation Program, suggests that one of those genes — KLF17 — plays a crucial role in preventing metastasis. The team studied two groups of mice with a type of breast cancer that usually doesn’t spread, and in one of those groups, blocked the expression of KLF17. After only a few days, the cancer in those mice had traveled to the lungs. To see if KLF17 was also involved in preventing cancer metastasis in humans, Huang and his colleagues then injected human breast cancer cells into mice, some of which had a faulty KLF17 gene. Within eight to 10 weeks, the cancer in the latter group had spread to the lungs. “The lower the expression of KLF17, the more invasive the cancer,” Huang said.

To better understand what happens when KLF17 is suppressed, the scientists looked for genes whose expression was either increased or decreased when KLF17 expression was hampered. They identified several, including Id1, a gene known to be involved in tumor metastasis. They found that too little KLF17 caused an overproduction of Id1, which in turn allowed tumor cells to invade neighboring tissue. Now Huang wants to find out what happens if they stimulate expression of KLF17. If doing so slows the function of Id1 — and stymies spread of the disease — scientists could use the gene interaction as a marker to identify patients whose breast cancer is more likely to spread. He also plans to search for other genes that are affected by KLF17, as well as genes that control KLF17 itself.

Study co-authors included Krunmar Gummireddi, Ph.D., lead author of the study; Louise C. Showe, Ph.D., and Anping Li, all of The Wistar Institute; Andres J. Klein-Stant, M.D., of the Fox Chase Cancer Center; and Phyllis A. Gimotty, Ph.D., Distinguished Katsanos, M.D., Ph.D., and Lin Zhang, M.D., all of the University of Pennsylvania.

The project was supported by the Breast Cancer Alliance, Fannie Foundation, V Foundation, Commonwealth Universal Research Enhancement Program of the Pennsylvania Department of Health, the National Cancer Institute and the Mary Kay Ash Charitable Foundation.

Grant Highlights

**KAZUKO NISHIKURA, Ph.D.**

Kazuko Nishikura, Ph.D., a professor in Wistar’s Gene Expression and Regulation Program, received a Senior Scholar in Aging Award from The Ellison Medical Foundation. The four-year grant totaling more than $1 million, will support Nishikura’s research focused on telomerase-repeat-encoding RNA (TERRA) and the significance of TERRA editing in controlling the length and preserving the integrity of telomeres. Telomeres function has been shown to play a role in aging, cancer, and certain inherited diseases. The Ellison Medical Foundation supports basic biomedical research on aging relevant to understanding lifespan development processes and age-related diseases and disabilities.

**JOSEPH KISSIL, Ph.D.**

Joseph Kissil, Ph.D., an assistant professor in Wistar’s Molecular and Cellular Oncogenesis Program, received a Research Scholar Grant from the American Cancer Society. The three-year grant totaling $582,000 will support Kissil’s research aimed at developing a new treatment approach for neurofibromatosis type 2, an inherited disorder that causes brain tumors leading to hearing loss, balance problems, and compression of the brainstem.
Immunologist Scott Hensley Joins Wistar’s Anti-Flu Crew

Each winter, just as the flu infection rate hits its peak in the United States, scientists at the Centers for Disease Control and their counterparts at the World Health Organization make an educated guess about the seasonal influenza vaccine for next year. The seasonal influenza virus is constantly changing — altering its outer coat — as it moves around the globe, and the scientists must decide which strains of the virus ought to become targets for the next vaccine. The consequences for their decision are enormous, and even with a robust vaccination program in place, 16,000 people in the United States, alone, are expected to die from the flu each year.

Scientists at The Wistar Institute Vaccine Center are hoping to make that annual flu shot a thing of the past with a “universal” vaccine, which would grant broad immunity to the flu, no matter how it changes.

In June, Scott Hensley, Ph.D., an expert on the seasonal variability of the flu, joined The Wistar Institute as an assistant professor in the Immunology Program. Hensley comes to Wistar from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.

Hensley has distinguished himself in immunology circles for his work on antigenic drift, the technical term for the evolutionary changes that make the outer coating of the influenza virus such a moving target for public health researchers.

“Each influenza vaccine could potentially save countless lives, and I believe that the team we have assembled, with its distinct yet complementary approaches, has a great chance of making such a vaccine a reality.”

The Hensley laboratory will continue this work by studying the molecular mechanisms that allow antigenic drift to occur, as well as describing how the human immune system generates antibodies to influenza. Hensley hopes to combine these two paths in order to create a vaccine that will generate antibodies against targets that are less likely to mutate from season to season.

“Scott is an excellent addition to our program, as his expertise and research goals are so well aligned with ours,” said Professor Hildegund C. J. Ertl, M.D., leader of Wistar’s Immunology Program, and director of the Vaccine Center. “A universal influenza vaccine could potentially save countless lives, and I believe that the team we have assembled, with its distinct yet complementary approaches, has a great chance of making such a vaccine a reality.”

In addition, his research will also include an analysis of the 2009 pandemic H1N1 influenza strain and its descendents. The goal of these studies is to identify antigenically distinct variants before they spread globally among the human population. This line of research will also answer lingering questions about how past exposures to strains of H1N1 may have protected some older Americans from the disease.

Keinath Tapped to Head AIRI

Larry Keinath, vice president for finance and administration at The Wistar Institute, has been named president-elect of the Association of Independent Research Institutes (AIRI), a group representing close to 100 independent, nonprofit research institutes in the United States, including Wistar. An AIRI member since the late 1980s, Keinath has served in a number of leadership roles for the organization, including treasurer and program chair of the group’s 2006 annual meeting. As president-elect, Keinath will work on legislative issues of interest to member institutes, as well as planning the 2010 annual meeting and help select new officers and board members. Keinath, who has been with Wistar for more than 25 years, took over his new AIRI post in October 2009. When his term ends in 2011, he will begin a two-year term as AIRI president, followed by a final two-year term as AIRI past-president. For more information on AIRI, visit www.airi.org.
The Wistar Institute and University of the Sciences in Philadelphia (USciences) recently named Wistar Institute researcher Paul M. Lieberman, Ph.D., the McNeil Professor of Molecular Medicine and Translational Research. Lieberman, an expert in gene expression and regulation, will provide leadership of the Center for Chemical Biology and Translational Medicine (CCBTM) at Wistar and USciences.

The CCBTM combines Wistar’s strengths in basic biomedical research with USciences’ expertise in medicinal chemistry and pharmacology. The partnership will enable more rapid translation of basic science discoveries into compounds with potential for refinement into new medicines and therapies for patients.

The Center’s researchers develop and use small molecules to study the biology of living systems. Their goal is to find new chemical agents that can be developed to work against targets — such as genes and proteins — that are involved in human disease. They identify these “hits” using robotic equipment at Wistar’s Molecular Screening Facility. These compounds are then handed off to computational and medicinal chemists at USciences for further refinement into potential new drugs.

Lieberman is a professor in the Gene Expression and Regulation Program at Wistar. His research focuses on understanding how cancer-associated viruses such as Epstein-Barr virus and Kaposi’s sarcoma-associated herpes virus persist in the body in a latent state, and the biochemical pathways that spark the viruses to awaken, leading to cancer. The Lieberman team has defined several of the pathways that control the stability, replication and gene expression patterns of the latent viruses. He also has identified small molecule “hits” that inhibit Epstein-Barr virus pathways, and is currently characterizing them through chemical biology.

Douglas Briggs served as president and CEO of the cable television home-shopping network QVC, Inc., from 1995 until his retirement in 2006. Prior to joining QVC, Briggs was vice president for marketing at The Franklin Mint. Briggs has received numerous awards for his philanthropic work, including the humanitarian award from the Shangri-Cornell Breast Center and the Fashion Footwear Association of New York Humanitarian Award for his advocacy and fundraising for breast cancer research.

Ronald L. Caplan founded Philadelphia Management Corporation, which specializes in the re-development of older properties, many of which are listed on the National Register of Historic Places. Caplan — who currently serves as the business’s president and CEO — works with a number of nonprofit organizations, including the Abington Cancer Center of the University of Pennsylvania, where he founded the Ronald and Ellen Caplan Patient Education Center.

Maida Milone has practiced law and managed nonprofit organizations for 20 years, specializing in the pharmaceutical industry. She participates as a board member for a number of organizations, including the Field Center for Children’s Policy, Practice and Research at the University of Pennsylvania and St. Christopher’s Foundation for Children, and is a member of the Women’s Health Leadership Council of the University of Pennsylvania Health System.

Richard E. Fitzpatrick, a dermatologist noted for improving medical procedures and advancing dermatologic laser technology, is the director of cosmetic dermatology at La Jolla Cosmetic Surgery Centre in California. He is also an associate clinical professor in medicine and dermatology at the University of California, San Diego and serves on the medical staff at Scripps Memorial Hospital La Jolla.

Susan Schwartz McDonald is president and CEO of the Philadelphia-based Philadelphia-based National Analysts Worldwide, where she specializes in healthcare markets. She is on the board of directors for the Council of American Survey Organizations, and chairs the group’s pharmaceutical marketing research task force. Prior to joining Wistar’s board of trustees, McDonald also served on Wistar’s leadership council, an external advisory group that supports Wistar’s mission through community engagement and resource development.

Gail Walker Heam is a biology professor at Drew University in Philadelphia and founder of the Bokko Biodiversity Protection Program, a wildlife conservation program for rare species of primates, sea turtles, and large vertebrates on Boko Island in Equatorial Guinea, Africa. Heam serves on boards of the Academy of Natural Sciences, First Hospital Foundation, Penn Medicine, and Pennsylvania Hospital.

Douglas S. Briggs, Ronald L. Caplan, Gail Walker Heam, Ph.D., Maida R. Milone, Richard E. Fitzpatrick, M.D., Milton S. Schneider, and Susan Schwartz McDonald.

New Members Join Board of Trustees

The Wistar Institute’s board of trustees recently gained seven new members:

1. Douglas Briggs served as president and CEO of the cable television home-shopping network QVC, Inc., from 1995 until his retirement in 2006. Prior to joining QVC, Briggs was vice president for marketing at The Franklin Mint. Briggs has received numerous awards for his philanthropic work, including the humanitarian award from the Shangri-Cornell Breast Center and the Fashion Footwear Association of New York Humanitarian Award for his advocacy and fundraising for breast cancer research.

2. Ronald L. Caplan founded Philadelphia Management Corporation, which specializes in the re-development of older properties, many of which are listed on the National Register of Historic Places. Caplan — who currently serves as the business’s president and CEO — works with a number of nonprofit organizations, including the Abington Cancer Center of the University of Pennsylvania, where he founded the Ronald and Ellen Caplan Patient Education Center.

3. Maida Milone has practiced law and managed nonprofit organizations for 20 years, specializing in the pharmaceutical industry. She participates as a board member for a number of organizations, including the Field Center for Children’s Policy, Practice and Research at the University of Pennsylvania and St. Christopher’s Foundation for Children, and is a member of the Women’s Health Leadership Council of the University of Pennsylvania Health System.

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6. Gail Walker Heam is a biology professor at Drew University in Philadelphia and founder of the Bokko Biodiversity Protection Program, a wildlife conservation program for rare species of primates, sea turtles, and large vertebrates on Boko Island in Equatorial Guinea, Africa. Heam serves on boards of the Academy of Natural Sciences, First Hospital Foundation, Penn Medicine, and Pennsylvania Hospital.

7. Milton “Tony” S. Schneider is the founder and principal of The Glenville Group, a real estate development and investment firm in Plymouth Meeting, Pa. Schneider is a member of the National Advisory Board of the Barbara and Edward Netter Center for Community Partnerships at the University of Pennsylvania. Schneider is president of the Anti-Defamation League Foundation and serves as a member of the League’s National Executive Committee. He also serves on the board of directors of the Jewish Federation of Greater Philadelphia.
It’s not uncommon to find hidden treasure at The Wistar Institute. Usually, however, those treasures are discovered in a lab and come in the form of a newly identified gene, a technology to improve drug delivery, or the isolation of a protein that plays a key role in fighting disease.

Last summer, Wistar archivist Nina Long came across a treasure of a more traditional nature. While going through the Wistar vault, the Wistar Museum Collections curator spotted a dusty black box with a handwritten label. Much to her surprise, the box contained a collection that had not been seen since it was inventoried in 1958 — colonial currency dating from before the American Revolution.

Long, also the director of Library Services for Wistar, counted 74 notes, printed between 1758 and 1777 from the Pennsylvania, New Jersey and Delaware colonies. Even though money had expiration dates during that time, many people chose to keep the bills, believing them to be valuable even after the notes were expired. The label on the box and a note that lay atop the bills were written by the Institute’s founder, Isaac Wistar, who indicated that the money had been passed down from his maternal grandfather, former Philadelphia mayor Isaac Cooper Jones, upon his death in 1885.

Some of the bills in the box were printed by Benjamin Franklin and his business partner David Hall in Philadelphia. Others bore signatures of Charles Thomson, John Morton, and Francis Hopkinson — all signers of the Declaration of Independence. The collection is valued at $18,000, according to John Kraljevich, a renowned numismatist in New York City. The bills, which were placed in protective coverings, are part of the Wistar Archives Collections.
Melanoma Research Center Opens

A Wistar supporter takes an extremely close look at some of the work in the Melanoma Research Center while touring the facility during the Center's opening day celebration.

Learn more about melanoma and Wistar’s pioneering efforts to fight the disease in our next issue, Winter 2011.

This May, The Wistar Institute announced the creation of The Wistar Institute Melanoma Research Center. The Center brings together scientists, physicians, the life sciences industry, and melanoma advocates in saving lives by advancing new and better therapies for this deadly disease.

Unlike most cancers, the incidence of melanoma is increasing, doubling in the past 30 years, despite better detection and a greater awareness of the dangers of sun and ultraviolet ray exposure. There are currently no effective treatments for advanced melanoma, a fact the Center hopes to soon change.

The director of Wistar’s Melanoma Research Center, Meenhard Herlyn addresses attendees of the Center’s opening on May 27.