On the Cusp: Research Transforming Women’s Healthcare
Dear Friends,

I am delighted to present you with this issue of Lerner Research Institute Magazine. We have had an amazing year in terms of discoveries, innovation, worldwide media attention and philanthropy, and I am excited to share some of these stories with you.

Since breast cancer is a disease that has affected nearly all of us, I am sure you have been closely following the work of Vincent K. Tuohy, PhD, to develop the world’s first preventive breast cancer vaccine. And I hope you all are as thrilled as I am to learn that his vaccine will soon be tested in human trials. The announcement of the creation of the spinoff company Shield Biotech is the culmination of more than 10 years of laboratory work and vigorous, grassroots campaigning to keep the research moving forward.

In light of this exciting development, we have dedicated this issue of the magazine to research related to women’s health. You will read the amazing story of how Qingyu Wu, MD, PhD, discovered a possible cause of preeclampsia, or high blood pressure that develops during pregnancy, and how Margot Damaser, PhD, is investigating the use of stem cells to prevent and treat incontinence in older women. You will learn whether you are a candidate for breast cancer genetic testing from genomics expert Charis Eng, MD, PhD, and read from Giovanni Piedimonte, MD, who leads Cleveland Clinic’s Pediatric Institute, about our efforts to improve the health of pregnant moms and kids.

I am also pleased to introduce you to Shawna Hofstetter, our new Senior Director of Development. Shawna joins us with many years of fundraising experience and new, creative ideas for enhancing our presence and building relationships in the community. She has already revamped our popular Friends of the LRI program, which you can read more about in this issue.

Our research achievements this past year have generated an unprecedented amount of media attention. The world is beginning to recognize the Lerner Research Institute as the hub of innovative, patient-centered research at Cleveland Clinic. Your support has helped us reach these new heights, and I am confident that, together, we will continue to soar.

With warmest regards,

— Paul E. DiCorleto, PhD
It is known that the heart enlarges (hypertrophy) and begins to dysfunction with age, predisposing individuals to a risk of heart failure. Relatively less is known, however, about the biological mechanisms that regulate age-related changes in heart structure and function. The laboratory of S.V. Naga Prasad, PhD, Lerner Research Institute Department of Molecular Cardiology, has identified a protein that may play a critical role in age-related hypertrophy. The image of stained heart tissue demonstrates that, in aged mice, the absence of this protein leads to smaller heart hypertrophy. The image of stained heart tissue demonstrates that, in aged mice, the absence of this protein leads to smaller heart hypertrophy.

On the Cover
Dear Friends,

It is with great respect and enthusiasm that I have joined the philanthropy team of Cleveland Clinic as the Senior Director of Development for the Lerner Research Institute (LRI).

I have enjoyed 25 years working in an exciting career with wonderful institutions, both large and small, in Cleveland. I spent many years with the Juvenile Diabetes Foundation (my first job in development!) and at Case Western Reserve University School of Medicine and many others while I spent four years running my own consulting business.

All of these experiences have now culminated into an opportunity to help advance world-class research that will help improve the quality of life for people all over the world! What an amazing opportunity!

My interest in medicine and research has already become significantly elevated just being in the presence of the impressive scientists housed within the walls of LRI. I am ashamed to admit, but even as a native Clevelander, I never fully understood the depth of the research that goes on in our own community. I am now in awe, every day, of what I am learning!

I am also pleased to introduce you to my colleague John Keller, who just recently joined our team as Director of Development. John comes to us from Oberlin College, where he was Director of Alumni Regional Activities and Education. John, who is a U.S. Navy veteran, worked several years at Case Western Reserve University’s Case School of Engineering. He is also interested in the arts, having worked in fundraising at both the Rock and Roll Hall of Fame and Museum and the Cleveland Institute of Art.

John and I are looking forward to meeting friends and supporters, old and new, and sharing with you all that LRI is offering to our community. One of our major goals is to create an awareness and interest in this research and encourage others to join in supporting life-saving work. I hope you will accept my offer to come for a tour of this marvelous facility and see first-hand the art of discovery!

Please contact me if you wish to make a difference in the lives of patients by supporting research here at LRI. I promise you it will be an investment in the future unlike any other you will make!

With much gratitude,

Shawna Hofstetter
Senior Director of Development

Pictured: John Keller and Shawna Hofstetter
We just took a big step toward developing a preventive vaccine for the most dangerous type of breast cancer. Cleveland Clinic Innovations has started a new company, Shield Biotech, to develop a vaccine based on our lab research. This research has shown that a vaccine designed for immune prevention of triple-negative breast cancer (TNBC) can work to both prevent and treat the disease.

Now, after a three-year journey, raising money from all kinds of sources who believed in our project, we’ve finally secured the funds to continue development of the vaccine.

A shield against tumors
Our ultimate goal is to give women a defense or shield against developing breast cancer with targeted stimulation of the immune system. The best chance to prevent a tumor is by providing pre-emptive immunity that spots it early and kills it before it can grow.
Our early investigations were very promising. Our data showed that immune protection against breast cancer can be provided by vaccinating against proteins that are no longer expressed in aging breast tissues, but are overexpressed in TNBC.

Vaccination didn’t just inhibit the growth of preexisting tumors — it prevented new ones from forming.

**Targeting a difficult-to-treat disease**

Triple-negative breast cancer is the most aggressive and lethal form of the disease, the predominant form that occurs in women with BRCA1 mutations. As of now, TNBC has a higher recurrence rate than other forms of breast cancer and there’s no targeted therapy for it.

Our aim is to provide protection against recurrence for women diagnosed with the disease. And pre-emptive protection for healthy, cancer-free women against emerging breast tumors, giving them an effective, safe alternative to invasive prophylactic mastectomy.

**How long to develop the vaccine?**

We’re looking at a timeline of around 10 years before the vaccine would be available for women.

- It will take two years to complete preclinical studies and obtain permission from the FDA to test an investigational new drug.
- Shield Biotech will then initiate two Phase I clinical trials, to determine dosage and safety, that will take about three years to complete. We’ll be testing the vaccine in two groups: women with triple-negative breast cancer who have recovered from current standard of care; and healthy cancer-free women at high risk for developing breast cancer who have decided to undergo voluntary bilateral mastectomy to lower their risk.
- If these trials show the vaccine induces immunity and is safe, advanced Phase II and Phase III trials will show us how effective the vaccine is. It should take around five years before these more advanced trials get underway.

Development of a vaccine that will be widely available to prevent this breast cancer will take some time. But we’re well on our way toward discovering whether this vaccine will be effective.
Everyone knows that delivering a baby is a painful experience. But many do not realize that birthing a 7- to 10-pound bundle of joy also can cause lifelong damage to the mother’s pelvic floor — the muscles and connective tissue holding pelvic organs in place. This damage, which is traumatic, can lead to urinary or fecal incontinence or pelvic organ prolapse, in which pelvic organs fall from their normal positions. Collectively termed “female pelvic floor dysfunction” (FPFD), these conditions are common in older women, with up to half of women over age 50 having one or more types.

During the second, “pushing” stage of labor, the baby’s head lies only one millimeter away from the mother’s pelvic bone. When this stage is prolonged, or when the baby is particularly large, the mother is more likely to experience FPFD. Sometimes this damage is not evident until much later in life, or it may occur and resolve immediately after childbirth, only to reappear many years later.

Margot S. Damaser, PhD, of the Department of Biomedical Engineering (BME), studies how childbirth causes FPFD and the post-injury healing process. She is developing a method to treat or even prevent the condition, possibly eliminating the need for surgery. “Surgery does not address the cause,” Dr. Damaser says. “FPFD is a complex disorder, and we are looking at the big picture.”

Dr. Damaser is evaluating the use of stem cell technology to treat FPFD. This technology is being studied extensively in other areas, such as for treatment of blast injuries, like those experienced by soldiers in combat settings. Since Dr. Damaser also is a Research Career Scientist in the Advanced Platform Technology Center of the Louis Stokes Cleveland VA Medical Center, she has a unique perspective on this research.

Stem cells contain “homing factors” that direct them to the site of injury. Depending on the type of injury (brain, pelvis), the cells regenerate to form new, healthy cells and replace the dead or dying tissue. “Stem cells aren’t smart, they’re just responsive,” Dr. Damaser says.

Treatment with stem cells in the year after childbirth may promote pelvic healing and prevent delayed FPFD. Dr. Damaser already has seen promising results in the lab with stem cell transplantation in rodents. She has also found that factors secreted by stem cells may have healing effects. This exciting finding could lead to a fast, inexpensive treatment for FPFD. However, more research is needed before the technology can be tested in humans.

So how does a PhD engineer become involved with patient-related research? Interest and collaboration. “Here at the Lerner Research Institute, we are in such proximity to physicians that they can literally stop by the lab on their way to lunch to share their ideas with me, and vice versa,” she says. “This kind of interaction happens in very few places.” In addition to her VA Medical Center and Biomedical Engineering appointments, Dr. Damaser holds a joint appointment in Cleveland Clinic’s Glickman Urological & Kidney Institute. Reflecting on the many roles she plays as a translational investigator, she adds, “It was never my intention to do research in an ivory tower.”

Stem Cell Technology May Alleviate Incontinence in Older Women

Pictured: Margot S. Damaser, PhD, and student, Brittaney Wilson-Harris
Making Ends Meet

While working as a basic science researcher at the National Institutes of Health, Brittaney Wilson-Harris couldn’t shake a nagging desire to work with patients. It was when a colleague suggested she go to medical school that she realized she could do both.

Because she wanted to help patients in the lab and at the bedside, Ms. Wilson-Harris was attracted to the Cleveland Clinic Lerner College of Medicine. This unique medical school’s mission is to train physician-investigators by integrating basic science, research, and clinical medicine into every facet of its curriculum. Students complete a one-year, master’s level research thesis to gain hands-on laboratory experience and graduate with a medical degree with special qualifications in biomedical research.

After three-and-a-half years in the program, and prior to beginning her research year, Ms. Wilson-Harris learned that she was pregnant. At six months into her pregnancy, she joined Dr. Margot Damaser’s Urological Biomechanics in the Department of Biomedical Engineering, where she studied a potential stem cell treatment for pelvic organ prolapse, the leading cause of hysterectomy in the United States. To support her project, she applied for and was awarded the Urology Care Foundation’s Herbert Brendler, MD, Summer Medical Student Fellowship, which provides a stipend for outstanding students interested in urological research.

Ms. Wilson-Harris delivered a healthy baby girl in October 2012, but complications led to emergency surgery for mom and time in the intensive care unit. Several weeks later, when she was ready to return to work from a brief maternity leave, Hurricane Sandy destroyed her family’s home and belongings. After several weeks of living in hotels and then finding a new home, she finally was able to return to the lab and continue her research.

Throughout all of these events, she did not miss a beat. She completed her research in Dr. Damaser’s lab and began clinical rotations in her final year of medical school. She now is applying for residencies in obstetrics and gynecology.

Ms. Wilson-Harris says she is grateful for the opportunity to gain research experience and contribute to a project that may directly affect patient care. “The Brendler fellowship came at the perfect time in my life because with all the chaos, I was able to concentrate on my research and not have to worry about how to make ends meet.”
Preeclampsia, or high blood pressure that develops during pregnancy, can cause dangerous complications in the mother and fetus. It occurs in six to eight percent of all pregnancies in the U.S., yet the cause of the disease eluded researchers for more than a century. However, in 2012, a researcher in Lerner Research Institute’s Department of Molecular Cardiology uncovered a possible cause. How he found it reads like a detective story.

It begins in the 1990s, when a young physician-scientist, Qingyu Wu, MD, PhD, went to California during the “gene rush.” He was particularly interested in finding genes that encode a specific type of protein called a serine protease. Serine proteases are known for their ability to cut sequences of amino acids. An expert in cardiovascular biology, Dr. Wu was the first to discover a serine protease in the heart. He called it corin (cor is Latin for “heart”). He went on to determine that corin cleaves a protein that regulates blood pressure.

Dr. Wu searched for corin in other organs, too, but came up empty-handed. Then, one day, a researcher on his team was looking through a batch of heart tissue slides purchased from an outside company. Somehow, a slide with uterine tissue inadvertently was mixed in with the heart slides. The uterine cells lit up with corin.

“How could this be?” he wondered. Dr. Wu’s team already had searched for corin in the uterus. How could they have missed it? On further investigation, they discovered that the tissue they were looking at was not from a typical uterus — it was from a pregnant uterus. The plot thickened.

Knowing that blood volume is greatly increased during pregnancy, Dr. Wu began to suspect that corin, which regulates blood pressure, was involved in preeclampsia. For a long time, researchers had known that preeclampsia was related to the placenta, but this area of research was considered a “black box.” Dr. Wu was entering dangerous territory for a scientist.

Dr. Wu, however, shattered expectations when he discovered that corin levels not only were present in pregnant women, but they also were dramatically reduced in women with preeclampsia. Furthermore, some women with preeclampsia had genetic mutations that interfered with corin’s function. Dr. Wu’s team demonstrated that corin is involved in expansion of the spiral artery—the thin, curly artery that expands to accommodate an increase in blood volume during pregnancy. If that artery does not enlarge (because of low levels of corin), the body is forced to pump a lot of blood through a very small opening. The mother’s blood pressure then rises to ensure that the fetus receives enough blood.

Dr. Wu’s results were published in the journal Nature, and the National Heart, Lung, and Blood Institute named his discovery one of the top research findings of 2012. The discovery opened the door for researchers to study preeclampsia in more detail. Identifying additional mutations could lead to a genetic test for identifying women who are at high risk, indicating to their doctors that the pregnancies should be monitored closely from an early stage. The research also could lead to potential new drugs to increase corin levels in women at risk for preeclampsia.

Despite his significant findings, Dr. Wu does not consider himself a great mystery solver. “I was really just pursuing my curiosity,” he explains. “I went to California looking for that golden nugget. All these years later, I found it in Cleveland.”

Pictured: Qingyu Wu, MD, PhD
The more education you have, the lower your risk of heart disease.

A normal heart valve is about the size of a half dollar.

The first heart pacemakers plugged into a wall socket.

Happiness and a strong sense of emotional vitality helps lower your risk of heart disease.

The number of heart attacks peaks on Christmas Day, followed by December 26th and New Year’s.

The first heart cell starts to beat as early as 4 weeks.

The first “study” showing benefits of a vegetarian diet appears in the Bible’s Book of Daniel (600 BCE).

In men, baldness has been associated with a higher risk for heart disease (although baldness does not cause heart problems).

Modesty prompted the invention of the stethoscope. Before it existed, doctors had to press their ears directly to each patient’s chest.

Heart disease has been found in 3,000-year-old mummies.

Your heart is about the size of your two hands clasped together.

It beats 100,000 times a day.

Regular exercise is the single most important key to heart health. And it is free.

Heart disease is your greatest health threat (and is a greater danger than breast cancer in women and prostate cancer in men).

The beating sound is the clap of valve leaflets opening and closing.

Each minute your heart pumps 1.5 gallons of blood.

Your heart is a coordinated machine. The right side pumps blood into your lungs, while the left side pumps it back into your body.

Celebrities who’ve had open heart surgery in recent years include David Letterman, Bill Clinton, Robin Williams, Barbara Walters, Arnold Schwarzenegger and Regis Philbin.

You control your heart health through diet, exercise and managing stress.

clevelandclinic.org/healthhub

*U.S. News & World Report
Actress Angelina Jolie made headlines this year when she announced that she had undergone a preventive double mastectomy. With a genetic mutation in the \textit{BRCA1} gene, Ms. Jolie made her decision based on a likelihood — about 80 percent — that she could develop a deadly form of breast cancer. After her announcement, print and online media, television and radio and news stations erupted with information about the \textit{BRCA1} mutation, and women around the world wondered: “Do I have this, too?”

One expert widely featured in these news stories was \textbf{Charis Eng, MD, PhD}, who chairs the Genomic Medicine Institute and directs the Center for Personalized Genetic Healthcare at Cleveland Clinic. Her advice to women concerned about \textit{BRCA} mutations was simple: Talk to your doctor and seek genetic counseling if advised. Dr. Eng emphasized that certain characteristics, such as being of Ashkenazic Jewish descent and having a family history of breast cancer, are warning signs, and that women with one or both of these risk factors should speak with a genetics expert to determine whether testing is necessary. Ultimately, Dr. Eng stressed, there is no one correct course of action and each woman’s case needs to be considered individually.

The concept of individualized medicine, or tailoring treatments based on a person’s genetic makeup, is the cornerstone of Dr. Eng’s work. While factors such as environment and lifestyle choices affect a person’s overall health, genes are a strong, predetermining factor for disease development, especially for cancer. “Ten to 15 percent of all breast cancers, which is a lot, are due to strong genetic causes that can be inherited and passed on,” says Dr. Eng.

Dr. Eng, who holds the Sondra J. and Stephen R. Hardis Endowed Chair in Cancer Genomic Medicine, has spent most of her career searching for genes related to cancer. Sometimes called a “gene hunter,” she discovered two — called \textit{PTEN} and \textit{KILLIN} — that, when mutated, cause a disease called Cowden syndrome. With this disease, patients are at increased risk of having several types of cancer, including breast and thyroid cancer. Women with the \textit{PTEN} mutation have an 85 percent chance of developing breast cancer in their lifetime. “The \textit{KILLIN} mutation appears to carry an even higher risk of breast cancer than the \textit{PTEN} mutation,” Dr. Eng says. “But we are still trying to figure that out.”

Dr. Eng applies this science to her clinical work with patients in the Center for Personalized Genetic Healthcare, the clinical arm of the Genomic Medicine Institute. She helps patients determine their risk of having certain diseases and to develop plans for preventing them. The center employs physicians and genetic counselors who offer services in adult, pediatric and prenatal genetic testing.

Because she is passionate about improving patient care through research, Dr. Eng says she is in the right place. “Cleveland Clinic is a melting pot of modern medicine,” Dr. Eng says. “We have top physicians and top scientists working together and a large patient population. It is a recipe for success.”

\textbf{Pictured: Charis Eng, MD, PhD}
# Red Flags for Genetic Counseling

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<td><strong>1. You have a family history of breast and/or other cancers.</strong></td>
<td>If cancer runs in your family, talk to your doctor about genetic counseling. Certain family factors — including the other red flags outlined below — may put you at greater risk.</td>
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<td><strong>2. You get breast cancer before age 50.</strong></td>
<td>Breast cancer is more common in women after age 55 or 60. Being diagnosed at a young age means you may have a higher risk of getting breast cancer again later in life.</td>
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<td><strong>3. Your breast cancer is a specific type.</strong></td>
<td>For example, “triple-negative” breast cancer is associated with the BRCA genes. “When we see a patient with a triple-negative breast cancer, we often recommend genetic counseling. We know those cancers have a higher likelihood of being hereditary, even if there’s not a big family history,” Halle Moore, MD, says. A different type of breast cancer, lobular, is associated with stomach cancer and is caused by the CDH1 gene.</td>
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<td><strong>4. You develop cancer in both breasts.</strong></td>
<td>Getting cancer in one breast is common enough, but having it in both breasts is a sign of extremely high risk, Dr. Eng says.</td>
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| **5. You get breast cancer at any age but have one other risk factor, such as:** | • Having a close relative who had breast cancer before age 50  
  • Having a close male relative who had breast cancer  
  • Having a close relative who had ovarian or other types of cancer  
  • Being of Ashkenazi Jewish descent  
  For example, breast and ovarian cancers often are linked, especially in people with BRCA mutations. Dr. Eng says that having breast cancer with additional types of cancer can be a red flag, too. For example, having both breast and thyroid cancers may mean that you have a PTEN mutation. |
| **6. You have both breast cancer and another type of cancer.** | If a family member has a mutation that increases cancer risk, you should be tested, too. This does not mean that you will inherit the family mutation. You have an equal chance that it will be negative — in which case your risk is the same as for the general population. |
| **7. One of your family members has a gene mutation.** | (Courtesy of Cleveland Clinic Health Hub) |
Most chronic diseases arise during adulthood. But what if there were a way to prevent them, starting in the womb?
Giovanni Piedimonte, MD, Chair of Cleveland Clinic’s Pediatric Institute and staff member in Lerner Research Institute’s Department of Pathobiology, is conducting research aimed at understanding how respiratory diseases develop in the lungs of children. For many years, he says, physicians assumed that babies are born with fully developed lungs. “This was an essential error,” he says. In fact, the brains and lungs of children do not fully develop for several years after birth. Moreover, the fetal and newborn periods are critical for developing lifelong health. Conversely, the damaging effects of smoking or poor nutrition during pregnancy can last a lifetime.

Dr. Piedimonte’s research team recently demonstrated, for the first time, that a common childhood virus, respiratory syncytial virus (RSV), crosses the placenta from mother to fetus. RSV is the leading cause of lower respiratory infections in infants and young children, and most children are infected by their second birthday. The virus infects the lungs and breathing passages and, although symptoms are mild for healthy adults and older children, poses a serious risk to infants, young children and older adults.

Dr. Piedimonte’s team showed in the lab that once the virus is contracted in the womb, it remains in the lungs of the fetus and profoundly influences lung development. Reinfection in the first year of life could lead to chronic coughing, wheezing, shortness of breath or asthma. “The only way to prevent this from occurring is to control the infection in mothers,” Dr. Piedimonte says. Until a vaccine is available, however, we must rely on educating mothers about staying healthy through nutrition, hand washing, and not smoking.

Dr. Piedimonte cites Cleveland Clinic’s “Healthy Expectations,” an innovative, proactive approach to preventing maternal obesity. The goal of this program is to improve pregnancy outcomes through weight management and nutritional guidance of women before, during and after pregnancy. Once the child is born, the new “Be Well Kids” program continues the work by providing comprehensive services for the prevention and management of obesity and related chronic diseases from infancy to adolescence. “Reducing chronic diseases is key to our nation’s survival,” Dr. Piedimonte urges. “And the clock starts before birth.”
Breast Milk Component Could Save Lives

We’ve all heard the saying, “breast is best,” but what exactly is so magical about breast milk? Researcher Carol de la Motte, PhD, of the Department of Pathobiology, has uncovered the science behind one of its special powers.

Dr. de la Motte studies inflammatory bowel disease (IBD), a group of disorders characterized by inflammation and pain in the digestive tract. In her studies of colitis, or inflammation of the lining of the colon that is sometimes caused by bacterial infection, she found a unique characteristic of hyaluronic acid (HA), a sugar molecule found in human breast milk. Expecting it to aggravate colitis because of its pro-inflammatory properties, she instead found that HA improved the symptoms.

After collecting hundreds of samples of breast milk from generous donors, Dr. de la Motte isolated HA and tested it against *Salmonella* bacteria infection, a common source of foodborne illness that can be deadly in infants and the elderly. HA acted like an antibiotic, preventing the bacteria from surviving in cells of the intestine.

“When a newborn infant first ingests breast milk,” Dr. de la Motte says, “the introduction of HA turns on a cascade of events in the baby’s digestive tract that defend against infection.” Part of that cascade involves proteins called “defensins” that kill bacteria that try to infect cells. Another way HA may inhibit infection is by blocking the attachment of bacteria to cell surfaces. With nothing to hold onto, the bacteria are swept away through the digestive tract.

Dr. de la Motte recently received a generous award from Cleveland Clinic’s International Leadership Board (ILB) to continue her groundbreaking research. Established in 2011, the ILB’s International Research and Innovations Fund supports research projects with potential for success and global impact on health care. Dr. de la Motte is grateful for this support because it will enable her to test HA’s antibiotic effects against other types of bacteria. These include *Clostridium difficile* (“C. diff.”), a common cause of hospital-acquired infections that leads to many deaths each year, and enterotoxigenic *E. coli*, the cause of traveler’s diarrhea. Because HA is a natural substance, side effects are unlikely, and patients will not develop resistance that is common with pharmaceutical antibiotics.

“HA would not act directly on bacteria like drugs but would heighten several of the body’s defenses against invading bacteria,” Dr. de la Motte says. “Interestingly, more than 50 percent of babies normally carry the *C. diff.* bacteria but do not get sick from it. We are investigating whether milk HA mediates that protection.”

*C. diff.* has become a major worldwide health problem — and it is getting worse. Because infection occurs frequently in people receiving long-term antibiotic treatment and in the elderly, treating it has created a financial burden for the healthcare system.

Dr. de la Motte will collaborate with Belinda Yen-Lieberman, PhD, Director of Clinical Virology, Serology and Cellular Immunology in the Department of Clinical Pathology, and Kyle Brizendine, MD, Department of Infectious Disease, on the *C. diff.* project.
The International Leadership Board, established in 2010, comprises Cleveland Clinic’s closest and most dedicated international friends from 15 countries. This group of global ambassadors provides counsel to Cleveland Clinic CEO and President Delos “Toby” Cosgrove, MD, and philanthropic support for high-priority initiatives. In 2011, the board established the International Research and Innovations Fund to support research with high potential for success and impact on global health.

In 2013, three research groups received funding through this program for innovative projects affecting a range of disease areas. They are led by Carol de la Motte, PhD, Department of Pathobiology; Bruce Lamb, PhD, Department of Neurosciences; Tatiana Byzova, PhD, Department of Molecular Cardiology, holder of the Robert Canova Endowed Chair in Angiogenesis Research, and Eric Klein, MD, Chair, Glickman Urological & Kidney Institute, and holder of the Andrew C. Novick, MD, Distinguished Chair in Urology.

Dr. de la Motte’s group is studying the antibacterial effects of a component of human breast milk (see page 16 for story), which may lead to novel treatments for deadly, antibiotic-resistant infections. Dr. Lamb is studying the relationship between traumatic brain injury and Alzheimer’s disease, a devastating illness for which there is no cure. Dr. Byzova and Dr. Klein are searching for biomarkers of aggressive prostate tumors that may lead to a simple blood test for prostate cancer screening and staging.

“These research projects could change the way we practice medicine,” says Paul E. DiCorleto, PhD, Sherwin-Page Chair of the Lerner Research Institute. “The International Research and Innovations Fund helps ensure that these innovative ideas are not shelved due to lack of funding.”
Research Offers Hope for Infertility

For couples facing infertility, in vitro fertilization (IVF) often is the best option for having a biological child. However, despite significant strides in IVF technology, treatment success is not guaranteed. Some women undergo multiple unsuccessful rounds of IVF, with no scientific explanation. To improve the odds of pregnancy for these women, a research team at Cleveland Clinic’s Lerner Research Institute and the OBGYN & Women’s Health Institute are actively investigating what factors are involved in the success or failure of an IVF cycle.

During a woman’s menstrual cycle, new blood vessels are formed to deliver blood to reproductive tissues in preparation for pregnancy. Adequate blood flow is essential for the proper formation of follicles, or cysts, that protect eggs released from the ovaries and the development of the endometrium, or lining of the uterus, where the embryo implants.

One area of IVF research focuses on angiogenesis, the formation of new blood vessels. This process is thought to be controlled by a type of stem cell, called proangiogenic hematopoietic stem cells, which are released from the bone marrow and signal other cells to proliferate and form new blood vessels. The Cleveland Clinic research team is led by Jeffrey M. Goldberg, MD, Section Head of Reproductive Endocrinology and Infertility, and Serpil C. Erzurum, MD, Chair of the Department of Pathobiology and holder of the Alfred Lerner Memorial Chair in Innovative Biomedical Research. The team is collaborating in exploring the role of angiogenic stem cells in the physiology of menstruation and, eventually, IVF success rates.

Key team members Rebecca L. Flyckt, MD, a staff physician in Reproductive Endocrinology and Infertility, and Kewal Asosingh, PhD, a staff scientist in the Department of Pathobiology, examined patients’ blood samples, looking for the presence of a subset of angiogenic stem cells at several points in the IVF treatment cycle. They discovered that these cells, also associated with estrogen levels, fluctuate in response to ovarian stimulation. The finding opens the possibility that angiogenic stem cell levels may vary according to the individual, offering a possible explanation for why IVF does not always work.

Dr. Flyckt and Dr. Asosingh say they hope to continue these studies with a larger patient population to determine whether levels of angiogenic stem cells can help predict who will achieve a viable pregnancy with IVF. Eventually, their research could lead to a treatment that would increase blood vessel formation and enhance success rates. For the many couples who undergo expensive and invasive rounds of IVF without success, this research may provide them with some much-needed answers and, even more importantly, hope.
Harboring Hope Fund

About one in six couples has difficulty conceiving a child without medical interventions such as in vitro fertilization (IVF). IVF is costly, however, and insurance covers treatments for only 20 percent of patients. Even couples with the best chance of success may require more than one cycle of treatment.

Cleveland Clinic’s Harboring HopeSM fund offers grants to assist childless couples who have failed one cycle of IVF at Cleveland Clinic. The program seeks support from those who understand the richness that completing a family can bring to a couple’s life. For more information about supporting this program, please visit giving.ccf.org/harboringhope.
“We’re seeing things we’ve never seen before,” says Nina Desai, PhD, of the OBGYN & Women’s Health Institute and Department of Biomedical Engineering in the Lerner Research Institute. “This could change everything.”

There’s still a hint of wonder and disbelief in her voice.

Dr. Desai, Director of the Cleveland Clinic In Vitro Fertilization Lab, is talking about the embryoscope. This new technology revolutionizes the in vitro fertilization process, monitoring fertilized embryos’ development moment by moment — without disturbing their environment. New information from an embryoscope makes it much easier for IVF specialists to choose the best, most viable embryos to implant — increasing the chances of successful pregnancy and births.

An embryoscope is a high-tech incubator with a time-lapse camera that allows researchers to see continuous imaging of embryos developing. Most fertilized embryos today are kept in traditional incubators and researchers can only check on them once or twice a day. They can only be examined for minutes at a time, and researchers must be careful not to disturb the embryo’s environment. That’s not a worry with an embryoscope. IVF researchers touch a screen and watch in detail an embryo’s development moment by moment. They can better check for abnormalities and developmental milestones such as cell division, which can make a difference in the embryo’s ability to implant.

Dr. Desai says, “Embryos do amazing things when we’re not looking. With an embryoscope I might see one that developed more erratically than the other. It gives us extra information that could provide an edge in choosing the most viable embryos.” This extra information may also lead to new perceptions of what “good” embryos are in relation to the IVF process.

Because fewer embryos will be transferred through a more efficient selection, the number of higher risk multiple pregnancies will decrease. Of the 70 patients Dr. Desai or her team have treated using an embryoscope, 49 have gotten pregnant.

This technology could revolutionize the way in vitro fertilization procedure is done, says Dr. Desai. “One day soon, no one will be doing IVF the way it’s done now. IVF is constantly evolving,” she says. “In the near future we may see embryo selection being made by computer imaging systems that constantly monitor embryo progression past critical endpoints.”
Science Outside the Box

It is well-known that scientists rely heavily on federal money to support their research. Because of this, a stagnant National Institutes of Health budget has intensified an already competitive funding climate in which, as a consequence, many innovative research questions are left unanswered. To keep their labs running, investigators often are forced to focus on tried-and-true experiments that have a higher chance of being funded than more unusual ideas might.

The Chairman’s Innovative Research Fund was established in 2011 to help overcome this challenge. **Paul E. DiCorleto, PhD**, Sherwin-Page Chair, designed the program to encourage investigators to pursue creative research. By providing up to $50,000 for one year (renewable for a second year), the fund offers researchers an opportunity to gather enough preliminary data to submit a competitive federal grant proposal.

Forty-nine investigators applied for Innovative Research funding in 2013, of which two projects were chosen. **Bruce D. Trapp, PhD**, Chair of the Department of Neurosciences, will use the funds to study neurological deficits resulting from open heart surgery, and **Patrick C. Ma, MD, MS**, Department of Translational Hematology and Oncology Research, will analyze how cancer treatment leads to genetic changes in tumor cells.

For more information about the Chairman’s Innovative Research Fund and supporting disease-oriented research, please contact Shawna Hofstetter, Senior Director of Development, at 216.445.8523 or hofstes@ccf.org.
Jane and Lee Seidman Support Alzheimer’s Research

This summer, Cleveland philanthropists Jane and Lee Seidman visited the Lerner Research Institute, touring several labs and talking with researchers about their work in Alzheimer’s disease. In 2012, a research team including Bruce Lamb, PhD, Richard Ransohoff, MD, and Sanjay Pimplikar, PhD, of the Department of Neurosciences and Gary Landreth, PhD, of Case Western Reserve University, received the first Multi-Center Program Grant ever awarded by the Alzheimer’s Association, made possible by a partnership with Mr. and Mrs. Seidman. The team will study overactive or dysfunctional immune cells and inflammation associated with Alzheimer’s disease.

“Due to the tight funding climate, this project did not initially receive funding, although our proposal was reviewed favorably,” Dr. Lamb says. “Fortunately, our colleagues in the Neurological Institute (Jeffrey Cummings, MD, and Richard Rudick, MD) connected us with Mr. and Mrs. Seidman, who were able to provide considerable financial support to form this unique partnership with the Alzheimer’s Association.”

Alzheimer’s disease is one of the top 10 leading causes of death in the United States, and its prevalence is increasing. Understanding the disease progression is critical to developing new treatments.

Longtime supporters of Cleveland Clinic, Mr. and Mrs. Seidman also established the Jane and Lee Seidman Endowed Chair for Advanced Neurological Education in 2005 with Alexander Durat Rae-Grant, MD, of the Neurological Institute as the first chair holder.

For more information about supporting or touring Lerner Research Institute labs, please contact Shawna Hofstetter, Senior Director of Development at 216.445.8523 or hofstes@ccf.org.

Pictured (left to right): Bruce Lamb, PhD, Jane Seidman, Lee Seidman, Paul DiCorleto, PhD
New Endowed Chairs

The Lerner Research Institute is pleased to announce the naming of two endowed chairs — the Betsy B. de Windt Endowed Chair in Cancer Biology and the Kendrick Family Endowed Chair for Prostate Cancer Research. Thanks to the generosity of the de Windt and Kendrick families, these chair holders, who also are new to Cleveland Clinic, will receive funding to begin innovative projects, purchase equipment, and hire research personnel.
Qing Yi, MD, PhD, holder of the Betsy B. de Windt Endowed Chair in Cancer Biology, is also the newest department chair of the Lerner Research Institute, leading the Department of Cancer Biology. For the past 20 years, Dr. Yi has strived to develop new cancer treatments by harnessing patients’ own immune systems. Called immunotherapy, this innovative area of study holds great promise, he says, because of its low risk for toxicity and specificity in killing cancer cells instead of healthy cells. He now focuses on one particular type of cancer, multiple myeloma, a white blood cell cancer that causes widespread damage to the body. Dr. Yi’s team recently discovered through laboratory research that disease-fighting proteins called monoclonal antibodies can kill myeloma cells.

Dr. Yi came to Cleveland Clinic from the University of Texas (UT) MD Anderson Cancer Center, where he was a professor of medicine in the Department of Lymphoma/Myeloma, Division of Cancer Medicine, and Center for Cancer Immunology Research. He earned his medical degree at Jiangxi Medical College in Nanchang, China, and his PhD in immunology at Karolinska Institute, Stockholm, Sweden.

Nima Sharifi, MD, is an associate staff member in the Department of Cancer Biology and holds the Kendrick Family Endowed Chair for Prostate Cancer Research. He came to the Lerner Research Institute from the University of Texas (UT) Southwestern Medical Center, where he was an assistant professor in the Division of Hematology/Oncology since 2008.

Dr. Sharifi earned a bachelor’s degree in biology (summa cum laude) from Virginia Polytechnic Institute and State University. During medical school at the University of Pittsburgh, he was awarded a Howard Hughes Medical Institute fellowship to work in the laboratory of George Stark, PhD, FRS, former Lerner Research Institute Chair. Dr. Sharifi completed an internship and residency at Yale-New Haven Hospital and medical oncology and postdoctoral fellowships at the National Cancer Institute.

Dr. Sharifi, whose research focuses on advanced prostate cancer, recently discovered that a genetic mutation enables castration-resistant prostate cancer, the deadliest form of the disease, to escape treatment. Dr. Sharifi holds joint appointments in the Department of Solid Tumor Oncology, Taussig Cancer Institute, and the Glickman Urological & Kidney Institute.
New Staff

The Lerner Research Institute welcomes seven new staff members, each of whom offers unique skills and expertise to enhance our disease-focused research programs.

J. Mark Brown, PhD, a former Assistant Professor at Wake Forest School of Medicine, recently joined the Department of Cellular and Molecular Medicine. Dr. Brown earned his doctorate in cellular and molecular nutrition at the University of North Carolina at Greensboro in 2004 and completed his postdoctoral training in animal models of atherosclerosis and lipoprotein metabolism at Wake Forest University in 2009. His research focuses on the interrelationship between nutrient metabolism and the development of chronic metabolic diseases. Dr. Brown recently discovered that blocking the action of a specific protein prevents diseases related to a high-fat diet, including obesity, diabetes and liver disease.

Gregory T. Clement, PhD, joined the Department of Biomedical Engineering from Harvard University, where he was an Associate Professor in the Department of Radiology at Brigham and Women’s Hospital and Harvard Medical School. He earned a bachelor’s degree in physics at The Ohio State University and a master’s degree and doctorate in physics at the University of Rhode Island. Dr. Clement has served on many national and international committees and grant review sections and is a member of the advisory board for *Physics in Medicine and Biology* and the editorial board for *Ultrasound in Medicine and Biology*. Dr. Clement’s research focuses on improving ultrasound resolution, especially in the brain.

Emina Huang, MD, joined the department of Stem Cell Biology and Regenerative Medicine and holds a joint appointment in Colorectal Surgery in Cleveland Clinic’s Digestive Disease Institute. She comes to Lerner Research Institute from the University of Florida, Gainesville, where she was a professor of surgery. Dr. Huang’s research focuses on “colitis-associated cancer,” specifically, the relationship between inflammation and initiation of cancer, as well as the transition of colitis to cancer. A graduate of Oberlin College (with high honors) with a medical degree from Stanford University, Dr. Huang completed residencies in general and colorectal surgery at the Grant Medical Center and The Ohio State University.

Feng Lin, PhD, came to Lerner Research Institute’s Department of Immunology from Case Western Reserve University, where he was an Associate Professor in the Department of Pathology and in the National Center for Regenerative Medicine. Dr. Lin earned a bachelor’s degree from Nankai University, China, and his doctorate from Sichuan University, China. His research focuses on the role of the complement system, an important part of natural immunity, in the pathogenesis of autoimmune diseases. Dr. Lin will also apply his research to the study of transplantation immunology, with the goal of developing new strategies for preventing transplant rejection.
Paul D. Marasco, PhD, an expert in providing a sense of touch to advanced prosthetic limbs, joined the Department of Biomedical Engineering as a dual appointee — he also is an investigator at the Advanced Platform Technology (APT) Center of Excellence and Director of Amputee Research in the Department of Physical Medicine and Rehabilitation at the Louis Stokes Cleveland Department of Veterans Affairs Medical Center (VAMC). Dr. Marasco works with patients who have had amputations to learn more about brain organization, cognition and how to “close the loop” so prosthetic limbs can improve function and quality of life with touch and limb-movement feedback. He earned a doctorate in neuroscience from Vanderbilt University’s Brain Institute and completed a postdoctoral fellowship at the Center for Bionic Medicine of the Rehabilitation Institute of Chicago.

Sujata Rao, PhD, came to the Department of Ophthalmic Research from Cincinnati Children’s Hospital Medical Center, where she was a research associate in the Department of Developmental Biology. Dr. Rao studies developmental biology of the eye and recently published data in Nature demonstrating that a light response pathway regulates eye development in utero. Dr. Rao earned her doctorate at Cornell University’s Department of Neurobiology and Behavior and completed a fellowship at Cincinnati Children’s. She holds a bachelor’s degree from the University of Bombay (India) and a master’s degree from Tata Institute of Fundamental Research, also in Bombay.

Yuankai (Kenny) Tao, PhD, is the newest member of the Department of Ophthalmic Research. Dr. Tao came to LRI from the Massachusetts Institute of Technology, where he was a postdoctoral fellow in the Laser Medicine and Medical Imaging Group of the Research Laboratory of Electronics, Department of Electrical Engineering and Computer Science. Dr. Tao earned dual bachelor degrees in electrical and biomedical engineering at Duke University and his doctorate in biomedical engineering at Duke in 2010. His research interests are in developing novel eye biopsy techniques, specifically for applications in assessing cancer margins, endoscopic screening and treatment tracking and ophthalmic diagnostics and surgical guidance.
Bernadine P. Healy, MD (1944-2011), was the first woman to chair the Lerner Research Institute and also to direct the National Institutes of Health (NIH). She envisioned a centralized research facility on Cleveland Clinic’s main campus, which was realized with the opening of the John Sherwin Research Building in 1991. Sadly, Dr. Healy succumbed to brain cancer in 2011, but her legacy continues with the Bernadine Healy Memorial Lectureship, honoring prominent women in science.

The 2013 lecturer will be Alice S. Huang, PhD, Senior Faculty Associate in Biology at the California Institute of Technology, previously Professor of Microbiology and Molecular Genetics at Harvard Medical School and Dean for Science at the New York University. In addition to a successful career in virology, she advocates for women in science and policy issues related to science and education.

The Healy lectureship was launched through a generous gift by Paul E. DiCorleto, PhD, Sherwin-Page Chair of the Lerner Research Institute.

For information on supporting future lectures, please contact Shawna Hofstetter, Senior Director of Development, at 216.445.8523 or hofstes@ccf.org.
Healy Scholarship Winner

The first annual winner of the Bernadine Healy Scholarship is Camila Odio, a Cleveland Clinic Lerner College of Medicine first-year medical student who says she hopes to emulate Dr. Healy in her own career.

Ms. Odio has a deep interest in internal medicine and infectious diseases, sparked by a research and shadowing experience when she was an undergraduate and the chemistry and biology courses she took. “One summer, I was fortunate enough to work in the lab of a doctor where I did research and shadowed him and his fellows in the hospital. That experience was a turning point because I realized that medicine lies at the interface of science and the human experience, which was the perfect mix for me.”

She recalls her excitement on winning the scholarship, “It was quite unexpected. I usually don’t get anything in my mailbox.”

Ms. Odio also says she was humbled by her selection, particularly because of what she has learned about the life and career of Bernadine Healy. “I am very inspired by her trail-blazing accomplishments, her focus on women’s equality in medicine and her unprecedented leadership roles in women’s health issues. I hope to dedicate my career to the pursuit of scientific knowledge and social justice, as Dr. Healy did.”

Ms. Odio says she plans to pursue her interest in infectious diseases, research, and working with underserved populations. “I am very grateful that with this scholarship, together with a Lerner College of Medicine tuition award, I will now be able to follow my passions, rather than struggle to repay the tremendous costs of medical education.”

Ms. Odio grew up in Columbus, Ohio, and earned her undergraduate degree in molecular biology from Kenyon College in Gambier, Ohio.

Her mother is from Puerto Rico and her father from Costa Rica. “I would spend my summers visiting their countries because most of my family is still there,” she says. “Because of my Hispanic background, I am very interested in working with Latino and underserved populations. At the Lerner College of Medicine, I have pursued this interest by co-founding a partnership between Lerner College of Medicine students and a local community clinic, Neighborhood Family Practice. This involves weekly volunteering where we speak with patients (all of whom are low-income or uninsured) about nutrition and healthy habits, as well as record patient histories to help expedite the flow through a very busy office.”

She also is part of a research team examining the influence of community services on the behaviors and attitudes of adolescents in high-risk urban areas. “Through these extracurricular activities, I have been able to practice my clinical and research skills while remaining involved in the social justice issues that are extremely important to me.”

Ms. Odio also plays guitar weekly in the pediatric hematology/oncology and epilepsy units at Cleveland Clinic. “Through my conversations with patients and their families, I have been able to link the scientific and impersonal diseases I learn about in school with the human experience,” she says. “Their conversations and gratitude remind me why I am studying medicine.”

She says that her love of education also was inspired by her father, an applied scientist who connected her with research opportunities in Chile and Mexico, and her mother, a professor of Latin American literature and women and gender studies. “My mother’s influence has opened my eyes to the inequalities faced by women and minorities and our responsibility to strive for a more egalitarian community,” she says. “Lerner College of Medicine’s focus on research and its openness to new minority health volunteer initiatives will allow me to develop into the inquisitive and principled physician I hope to become.”
Thank You for Being a Friend

Ever wonder what goes on in the mind of a scientist? Lerner Research Institute’s biannual “Friends of the LRI” event gives you a chance to chat one-on-one with some of Cleveland Clinic’s most innovative researchers and learn firsthand how supporting research helps advance human health.

Our last Friends event was held in October at the historic Foundation House, adjacent to Cleveland Clinic’s main campus, and featured Stanley Hazen, MD, PhD, Chair of Cellular and Molecular Medicine and holder of the Jan Bleeksma Chair in Vascular Cell Biology and Atherosclerosis and the Leonard Krieger Chair in Preventive Cardiology. Dr. Hazen has received worldwide media attention for his research demonstrating a link between diet, intestinal bacteria and heart disease. Also speaking at the event was Qing Yi, MD, PhD, holder of the Betsy B. de Windt Endowed Chair in Cancer Biology and the newest department chair in the Lerner Research Institute.

After brief presentations and a question-and-answer session, friends and guests mingled with the speakers and research leadership. “The Friends events are a great opportunity for us to connect with the community and showcase the world-class research going on in our own backyard,” says Paul E. DiCorleto, PhD, holder of the Sherwin-Page Chair of the Lerner Research Institute.

For more information about attending or hosting a Friends event, please contact Shawna Hofstetter, Senior Director of Development, at 216.445.8523 or hofstes@ccf.org.
Pay No Taxes with a Charitable IRA Rollover

Take advantage of the chance to transfer a tax-free distribution from your IRA and make a charitable gift to Cleveland Clinic. This opportunity will end on December 31, 2013.

What are the requirements of an IRA Rollover?
• You must be 70½ or older
• You may make a gift of up to $100,000
• The distribution must be made directly to a qualified charity such as Cleveland Clinic
• Your gift is outright (tax-free rollovers to a planned gift such as a charitable gift annuity or a charitable remainder trust do not qualify)

Reminder: You have not paid taxes on your IRA contribution and will not have to pay taxes on the distribution to charity, so a charitable IRA rollover gift does not qualify for a charitable deduction. Please check with your legal or financial advisor or call Nancy McCann (216.445.8980) in Cleveland Clinic’s Philanthropy Institute to see whether a charitable IRA rollover is the best planning strategy for you.
The latest information about research achievements, educational opportunities and philanthropic options can now be delivered directly to your computer. You can now subscribe at www.lerner.ccf.org.