

# Lerner Research Institute

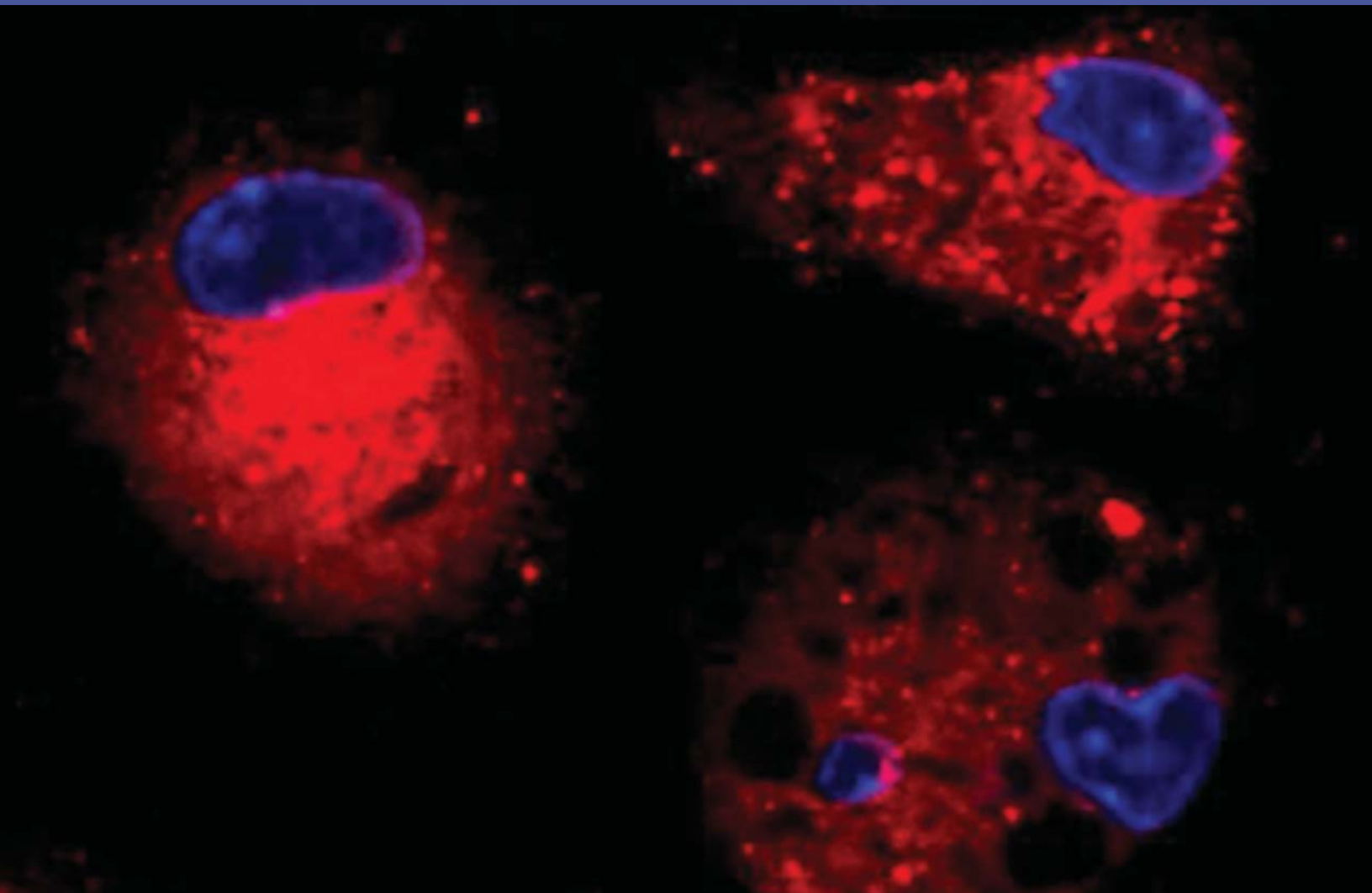
Focusing on the Patients of Tomorrow | Spring 2008

**Feature Article:**

Laboratory Research —  
The Engine Driving Exceptional Heart Care pg. 4

**Also In This Issue:**

Cardiac Research Through the Years pg. 11 | The Heart of Fundraising pg. 13  
Defining Diabetes pg. 14





## Cleveland Clinic Lerner Research Institute: World-Class Heart Care Starts Here



Paul E. DiCorleto, PhD

In 1945, when the Division of Research (now Lerner Research Institute) was created under the leadership of Irvine H. Page, MD, its exclusive focus was on cardiovascular diseases, such as heart attacks, hardening of the arteries, stroke and hypertension.

During its early years, the Institute was a leader in groundbreaking discoveries that helped to explain how cardiovascular diseases develop and how they might be treated.

Our researchers were the first to synthesize a key compound angiotensin that led to the development of multiple antihypertensive medications. Research by Helen B. Brown, PhD, led to the then-landmark theory that fat levels in the blood that contribute to hardening of the arteries could be modified by changing diet — the first effort to explain how cholesterol is deposited in blood vessel walls. Follow-up research by Lena Lewis, PhD, advanced the understanding of low- and high-density lipoproteins (LDL and HDL) and their role in cardiovascular diseases. Dr. Page, along with local Cleveland businessmen, founded the American Foundation for High Blood Pressure, later to become the Council for High Blood Pressure Research of the American Heart Association.

And the list goes on.

All of the past discoveries and the research we do today lead to one result: better care for patients with cardiovascular diseases.

In this issue, we discuss how our research environment encourages clinicians and laboratory researchers to work together on this important health issue, and we look at some of the contemporary laboratory and translational research projects under way.

We also introduce you to Jan Jensen, PhD, one of our recent recruits, whose cutting-edge research into how pancreas cells develop could lead to a cure for diabetes. Dr. Jensen was appointed to the newly created Eddie J. Brandon Endowed Chair for Diabetes Research and is Director of the Center for Diabetes Research within the Institute's recently established Department of Stem Cell Biology and Regenerative Medicine.

If you have a story idea or area of research you would like to see discussed, please drop us a note.

I hope you enjoy this issue and find the information interesting and enlightening.

Paul E. DiCorleto, PhD, Chairman  
Lerner Research Institute

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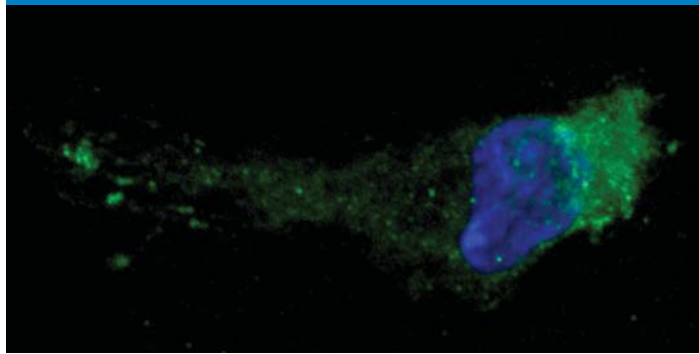
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**CONTENTS**



**COVER STORIES**

**Down to Basics** .....4  
*Laboratory-based discovery — unlocking how diseases develop and progress at the cellular, molecular and genetic levels — is the foundation of patient care. At Lerner Research Institute, the range of prestigious laboratory-based and translational research programs and Centers targeting cardiovascular disease drives development of new diagnostic tests and treatments for Cleveland Clinic's heart patients.*

**Through the Years** .....11  
*Laboratory-based and translational researchers have been at the forefront of making discoveries that explain how and why cardiovascular diseases develop and progress.*

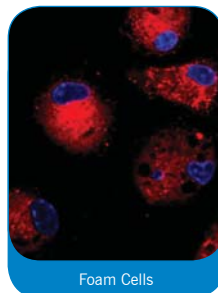
**To Market** .....12  
*Several discoveries made in Lerner Research Institute laboratories are making their way to the marketplace — improving patient care and impacting economic development in northeast Ohio.*

**FEATURES**

**The Heart of Fundraising**.....13  
*"Giving from the mind" can lead to tomorrow's cures.*

**Defining Diabetes** .....14  
*Jan Jensen, PhD, is using the independence of the newly created Eddie J. Brandon Endowed Chair in Diabetes Research to investigate ways for the human body to use its own adult stem cells to cure itself of diabetes.*

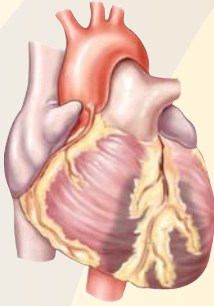
**Institute Insider** .....18  
*The latest developments and research achievements at the Lerner Research Institute.*



**ON THE COVER:**

**Foam Cells**

When a type of white blood cell called macrophages are exposed to oxidized low-density lipoproteins (LDL), they ingest it and become loaded with cholesterol and fat — and become foam cells. It is their accumulation in the blood vessel wall that leads to the formation of atherosclerotic plaque, commonly known as hardening of the arteries. (Photo: Roy Silverstein, MD, Chair, Cell Biology).



# Down to

*Supporting great medical care for heart patients is exceptional laboratory-based research — the engine that drives development of new diagnostic tests and treatments for cardiovascular diseases. For 13 consecutive years, U.S. News & World Report has ranked Cleveland Clinic’s cardiac care number one in the country. And the Lerner Research Institute’s leading basic and translational research is unlocking the keys to the number one killer in the United States.*



W.H. Wilson Tang, MD

When it comes to caring for his heart patients, W.H. Wilson Tang, MD, finds himself in a unique position to help people. He’s both a physician and a researcher.

As a clinician in the Cleveland Clinic’s Department of Cardiovascular Medicine, Dr. Tang is a member of one of the world’s leading heart centers. Here,

he sees first-hand how diseases progress and how patients respond to therapies. He’s on the front lines of cardiac care.

The other aspect to Dr. Tang’s care is the research he conducts in the Lerner Research Institute. As a laboratory-based investigator in the Department of Cell Biology, he searches for the genetic and biochemical causes of human heart failure and diseases and disorders of heart muscle.

Dr. Tang is a “physician-scientist,” a role that bridges the gap between traditional laboratory-based research and clinical cardiac care. It’s an example of the cycle of cardiac care at Cleveland Clinic – leading cardiovascular research improves care for heart patients, and those clinical experiences feed back into laboratory investigations.

“I pursue laboratory-based research in addition to my clinical work because it provides a level of understanding of the processes in cardiovascular diseases and treatment beyond what can be learned at the patient’s bedside,” Dr. Tang said. “Quality research is an extremely important contributor to the level of care we can provide to cardiovascular patients.

“I strongly believe there are fewer and fewer physician-scientists who balance clinical practice with laboratory-based research,” Dr. Tang said. “But there is a need to apply basic science findings to patient care. Likewise, questions are raised at the patient’s bedside that can be tested in the laboratory.”

The presence of cardiac research facilities also provides essential training opportunities and can help to recruit talented professionals, said Dr. Tang, himself recruited from Stanford University Medical Center in 2004.

“The proximity and availability of research facilities is important, as well as the availability of Institute researchers who are willing to be mentors and collaborators with physician-scientists,” he said. “Careers are built upon existing infrastructure and expertise. The collaborative research programs that you find at Cleveland Clinic and the Institute are key to the success for young faculty, especially those who have primarily clinical training.”

## **An ‘Engine’ For Care**

“Research is the engine that drives the clinical mission in cardiovascular care,” said Roy Silverstein, MD, Chair, Cell Biology. “We’re among the top institutions for cardiac research, and without research, there would be less recognition for our world-class patient care. The advances we’ve made in the laboratory during the past several decades impact the level of care and prognosis for many people with cardiovascular disease.

“There’s been a drastic decrease in cardiovascular disease deaths in the last generation,” Dr. Silverstein said. For example, according to the National Heart, Lung, and Blood Institute’s Framingham Heart Study in 2004, the risks of sudden cardiac death and

# Basics

coronary heart disease decreased by 49% to 64% from 1950 to 1999, a decrease attributed largely to a better understanding of cardiac diseases and prevention.

Additionally, in December 2007 the American Heart Association released a study that showed death rates from heart disease and stroke are falling in the United States, though heart and artery disease remains the leading cause of death. The AHA reported an estimated 869,724 people died from heart disease in 2004, compared to 911,163 in 2003. The group predicts that in 2008, 770,000 people in the United States will have a heart attack and 430,000 will have a recurrent attack, and another 175,000 will have a silent first heart attack.

"In the 1950s, heart attacks among men in their 50s and 60s were more common than today. When President [Dwight] Eisenhower had his heart attack, the common treatment was several weeks or months of bed rest," Dr. Silverstein said.

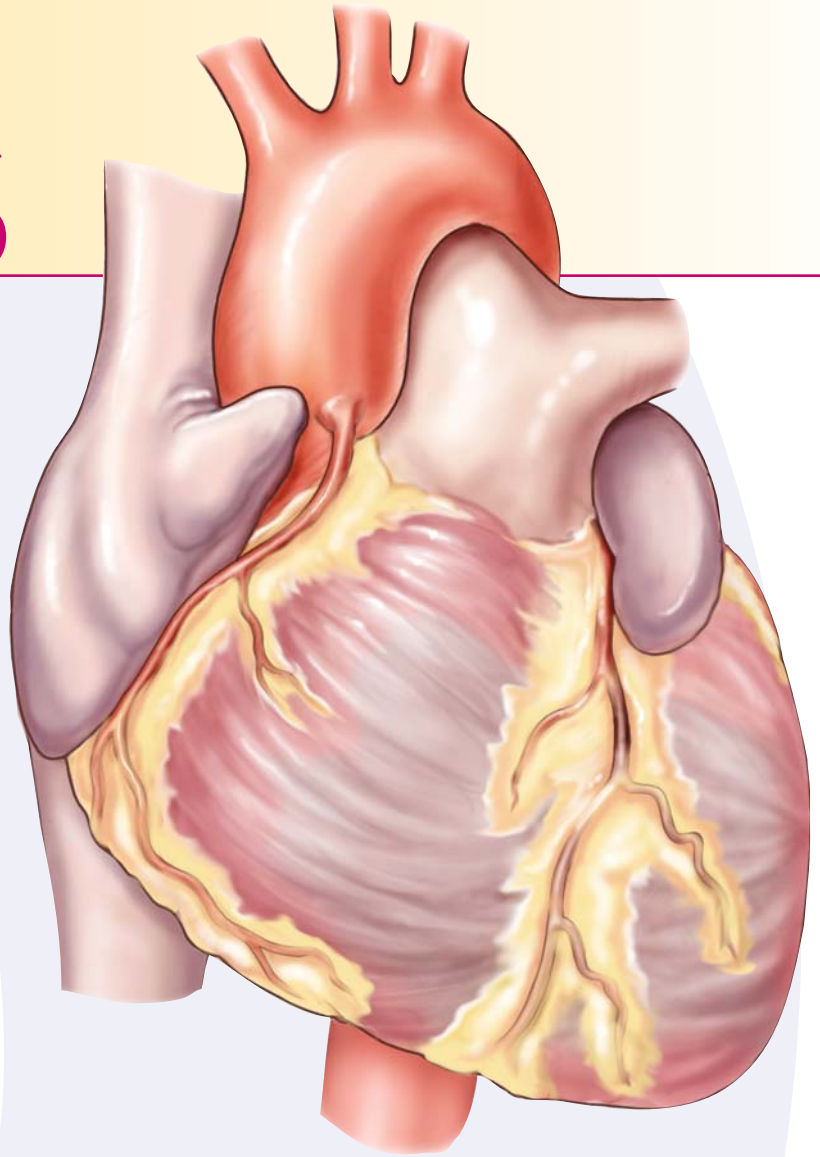


Roy Silverstein, MD

"Today, most people who have heart attacks can expect to live long lives. Discoveries made in laboratories about statins [a class of drugs that reduce serum cholesterol], aspirin, stents and drugs called beta-blockers that treat angina and hypertension, among other conditions, have contributed to that success," he said.

Among the Institute's laboratory-based research are projects to understand the growth of blood vessels, unlock how and why plaque deposits form on blood vessel walls, identify new diagnostic tools to predict cardiac events, and find ways to use the body's own stem cells to repair damaged heart tissues. There are even multi-investigator projects in the Department of Biomedical Engineering to develop miniature heart-assist pumps and a total artificial heart.

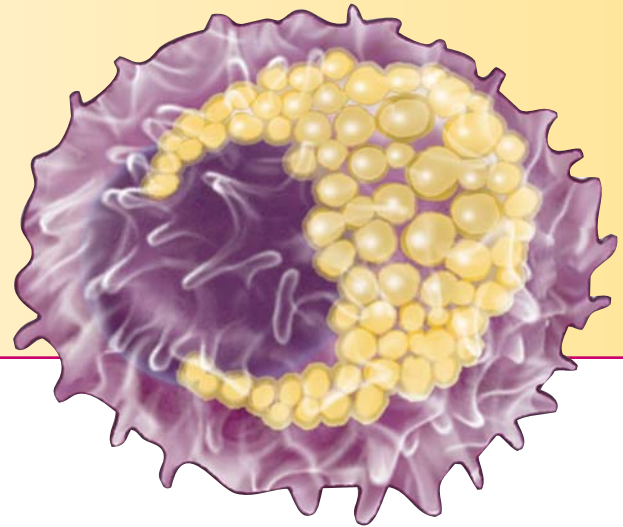
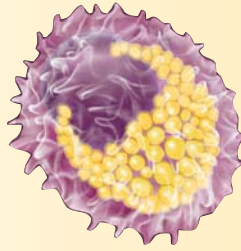
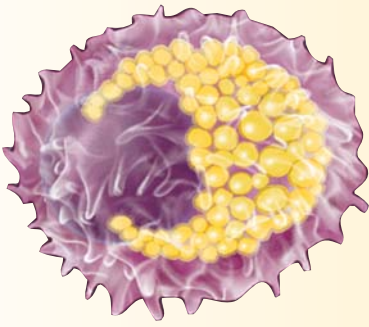
"Coronary arterial disease is a lifelong accumulation of causes, and curing coronary diseases is a complex task," Dr. Silverstein



said. "Clearly our goal is to cure disease. But we also want to be able to slow its pace, make it chronic and, therefore, manageable. The more we can unravel the causes of coronary diseases, the more options will be available to clinicians who treat cardiac patients."

One significant measure of the Institute's status is its prestigious grants and centers devoted to cardiovascular diseases.

"We have a large and successful group of investigators with a sense of collaboration," said Dr. Silverstein, who is the Principal Investigator for two such research projects. "We've seen the growth of multi-investigator programs. Once you have one successful program, it attracts interest and it's easier to establish more."



### SCCOR One — or Two — for the Institute

As the name implies, Specialized Center for Clinically Oriented Research (SCCOR) grants, awarded by the National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health, require clinical and laboratory-based scientists with a broad range of skills to work together on a unified theme. The focus is on clinically relevant research, and at least 50% of funded projects are related directly to patients.

The Institute has received two major SCCOR grants in recent years, one of the few cardiovascular research centers to attract multiple SCCOR grants.



Edward Plow, PhD

In 2004, the NHLBI awarded a \$17.5 million, five-year SCCOR grant to study coronary artery disease (CAD) at the molecular and genetic levels, and how it leads to heart attacks. The Principal Investigator is Edward Plow, PhD, Chair, Molecular Cardiology. He and his team study a family of proteins called thrombospondins, which are

secreted by cells and incorporated into the extracellular matrix, to explain their role in heart attacks.

Other project leaders are Jonathan Smith, PhD, Cell Biology, who identifies genes that contribute to the development of lesions on the inside of blood vessel walls caused by plaque deposits; Stanley Hazen, MD, PhD, Cell Biology and Head of the Section of Preventive Cardiology and Rehabilitation, who looks at how altered lipids (fatty compounds such as low-density and high-density lipoproteins) link to CAD; and Qing Wang, PhD, Molecular Cardiology, who hunts for genes that lead to CAD or heart attacks.

The centerpiece of this SCCOR is Cleveland Clinic's GeneBank, a database and collection of 10,000 DNA samples from people who have been treated at the Cleveland Clinic Heart and Vascular Institute. These samples play a key role in the genetic studies that are part of understanding CAD.

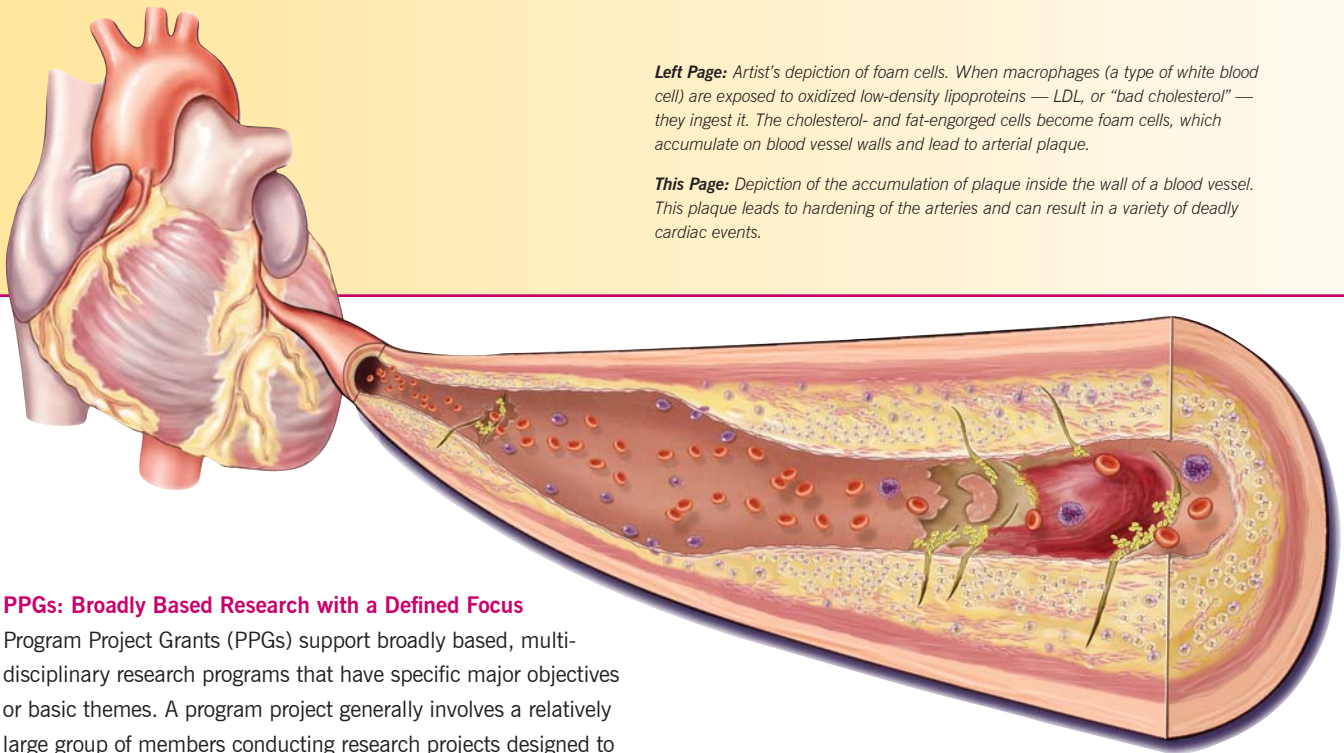
"An important goal of research is not necessarily how to treat one person, but how to treat a thousand patients. Basic understanding of diseases leads to the cures of tomorrow," Dr. Plow said. "Understanding the genes that increase a person's risk of cardiac events is the first step to diagnosing individuals at high risk and identifying targets for new therapies."

In 2006, the NHLBI awarded a five-year, \$13.5 million SCCOR grant for the Center for Thrombosis Research. Arterial thrombosis, or blood clots, is a major cause of most heart attacks and strokes.

"During the last 30 years, we've learned a lot about thrombosis and how blood platelets function and proteins assemble to form clots," said Dr. Silverstein, the Center's Principal Investigator. "But there is a clear need for more research to understand the root causes of blood clots and to improve links between laboratory and clinical research. We excel at translational research — moving discoveries from the laboratory into clinical applications — and I think this is one reason why this was one of only three such grants awarded by the NIH at the time.

"At the end of five years, we hope to have identified new genetic or molecular markers that can help predict a patient's risk of coronary disease," Dr. Silverstein said.

Cleveland Clinic investigators collaborate with researchers at Case Western Reserve University and University Hospitals in Cleveland. The grant funds five separate research projects within the overall program. Additionally, the grant supports the Institute's Research Core Services that provide centralized services for genetics, statistics, cell and molecular analysis, and clinical research. In addition to Dr. Silverstein, the other project leaders are Dr. Plow; Thomas McIntyre, PhD, Cell Biology; Kandice Marchant, MD, PhD, Chair, Cleveland Clinic Pathology and Laboratory Medicine; and Keith McCrae, MD, a physician-scientist in the Division of Hematology and Oncology at University Hospitals who is an Associate Professor of Medicine at the Case School of Medicine.



**Left Page:** Artist's depiction of foam cells. When macrophages (a type of white blood cell) are exposed to oxidized low-density lipoproteins — LDL, or “bad cholesterol” — they ingest it. The cholesterol- and fat-engorged cells become foam cells, which accumulate on blood vessel walls and lead to arterial plaque.

**This Page:** Depiction of the accumulation of plaque inside the wall of a blood vessel. This plaque leads to hardening of the arteries and can result in a variety of deadly cardiac events.

**PPGs: Broadly Based Research with a Defined Focus**

Program Project Grants (PPGs) support broadly based, multi-disciplinary research programs that have specific major objectives or basic themes. A program project generally involves a relatively large group of members conducting research projects designed to explain the various aspects or components of the objective.

The patriarch of the Institute’s PPGs is “Vascular Cell Function and Atherosclerosis,” under the direction of Paul E. DiCorleto, PhD, Institute Chair — a 25-year study that has attracted about \$32.5 million from the NIH. Originally awarded in 1983, the grant has been renewed four times.



Paul E. DiCorleto, PhD

“The longevity of the project is a result of the insights we gain and the good ideas and new directions that develop over the years,” Dr. DiCorleto said. “Some of our seminal observations include understanding and explaining the role of oxidation [the effect oxygen has on other molecules] in plaque formation on blood vessel walls [atherosclerosis] and the role of the cells that line blood vessels in causing diseases when the body is under stress or is injured.”

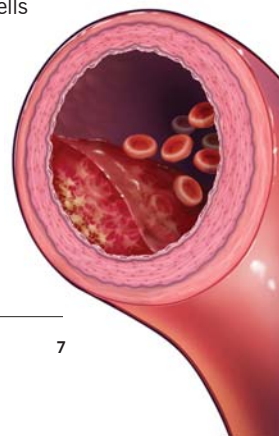
The long-term goal has been to understand how blood-borne and cell-derived factors produce or contribute to deposition of plaque on the inside of artery walls. “We’ve really been able to push further into understanding the biology and pathology of atherosclerosis,” he said.

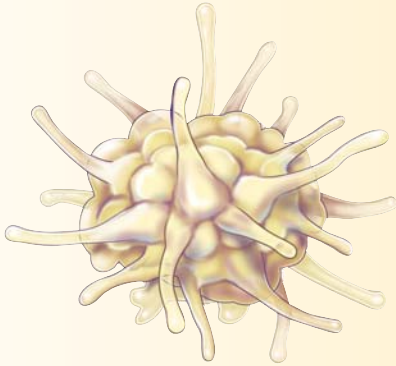
Dr. DiCorleto’s focus is the signaling pathways that encourage the cells lining artery walls (or endothelial cells) to increase production of platelets, which is a major cause of blood clots that lead to heart attacks and strokes.

Other project leaders are Guy M. Chisolm, III, PhD, Cell Biology, who investigates how oxidized fatty compounds called lipoproteins cause injury to the cells that are part of the artery wall; Donna Driscoll, PhD, Cell Biology, who focuses on how the trace element selenium is used by proteins that protect vascular calls against oxidation; and Paul Fox, PhD, Cell Biology, who studies how inflammatory antibodies called cytokines regulate a copper-containing protein called ceruloplasmin that has a role in the progression of arterial lesions.

Dr. Plow leads an \$8 million, five-year PPG that investigates the role of integrins in vascular biology. Integrins are receptors on the surface of cells that are important in the communication between cells and their extracellular environment, in defining cellular shape and mobility, and in regulating the cell cycle. Integrins mediate these responses by controlling the attachment of cells to other cells and the attachment of a cell to components in its immediate environment.

The PPG focuses on the Beta3 integrin, which is essential to clot formation by controlling how platelets work and to the formation of blood vessels (or angiogenesis). Dr. Plow specifically researches the structure and function of platelet integrins.





Among the other program investigators, from Molecular Cardiology, are Jun Qin, PhD, who studies the structural basis of integrin function and interaction and how they are regulated by other molecules; Joan Fox, PhD, who tracks how events within cells regulate how cells move and adhere; and Tatiana Byzova, PhD, who explains integrin involvement in blood vessel formation.

Last year, the NHLBI announced a new \$11.6 million, five-year PPG for a team of researchers in the Department of Cell Biology. They are studying how oxidation affects the behavior of low-density lipoproteins (LDLs) in the artery wall, leading to heart attacks and strokes.

Oxidation is the chemical reaction that causes iron to rust and copper to turn green. Human cells and tissues are generally protected from oxidation by the oxygen in air; but within the human body, oxygen can interact with certain molecules to become extremely reactive. In turn, this reactive oxygen can change the chemical nature of still other molecules — making them function in ways they're not supposed to.

The researchers examine the “A to Z” of phospholipid oxidation, including how LDL becomes oxidized, the structural features of oxidized LDL that influences its biological activity, the fate of oxidized phospholipids after they are formed in the body, and how oxidized phospholipids interact with cells and tissues of the cardiovascular system.

By explaining how oxidation changes the chemical nature of phospholipids, and how those changes affect their function, the researchers hope to gain a better understanding of such common diseases as atherosclerosis and diabetes and to develop new tools for diagnosis and treatment of these disorders.

“LDL is particularly susceptible to oxidation, which occurs during inflammation. We're looking at what makes LDL go bad. What makes our approach to studying oxidation and LDL unique is how the program will combine advanced chemical and biochemical studies, state-of-the-art cell biology, and genetic mouse models within a coordinated research effort. I think the NIH saw added value to that approach,” Dr. Silverstein said. He is joined by project leaders Martha Cathcart, PhD, Dr. Hazen, and Dr. McIntyre.



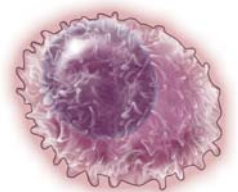
Stanley Hazen, MD, PhD

### Center for Cardiovascular Diagnostics and Prevention

Created in 2003 and chaired by Stanley Hazen, MD, PhD, Cell Biology, the Center for Cardiovascular Diagnostics and Prevention, a joint effort of Preventive Cardiology, Molecular Genetics, and the Cleveland Clinic Cardiovascular Coordinating Center, is part of Cleveland Clinic's

Heart and Vascular Institute. This multidisciplinary Center hosts research programs with the goal of extending laboratory-based investigations into clinical studies in the general areas of inflammation and treatments used to prevent cardiovascular diseases. Studies within Dr. Hazen's laboratory aim at identifying how inflammation contributes to cardiovascular disease, and how that understanding can be used to assess risk, monitor responses to therapies, and develop novel therapies. Additional studies focus on how high-density lipoprotein (HDL) protects against plaque build-up and also how HDL can be rendered “dysfunctional” within plaque that forms on the inside of blood vessel walls (called atherosclerotic plaque).

Joseph DiDonato, PhD, Cell Biology, who is Laboratory Director of the Center, examines how a protein complex called NF-kappa B contributes to chronic inflammatory diseases like atherosclerosis (or hardening of the arteries). Ariel Feldstein, MD, Cell Biology and Pediatric Gastroenterology, oversees research on explaining development of fibrous tissues and disease progression in fatty liver disease, a common complication of elevated lipids. A team led by Thomas McIntyre, PhD, Cell Biology, focuses on how and why blood platelets are activated and how that increased platelet activity contributes to the formation of blood clots (or thrombosis), the triggering process in heart attack and stroke. Stephen Nicholls, MBBS, PhD, Cell Biology and Cardiovascular Medicine, Medical Director of the Center, does research aimed at developing imaging methods to evaluate how well novel therapies affect plaque formation in blood vessel walls that supply the heart.





**Left Page:** An image of an activated platelet (far left). Normally used to clot blood, platelets can also provide an early warning of inflammatory diseases such as accumulation of plaque on the inside of blood vessel walls.

As cell membranes and lipoproteins age and deteriorate, they apparently “sprout whiskers” composed of an assortment of protruding oxidized fatty acids of varied structures. The image illustrates a macrophage probing the surface of a cell that has “sprouted whiskers.”

**This Page:** An artist’s rendering of macrophages that have entered an artery wall.

Research studies by several investigators also center on either genetic and molecular processes or nutritional factors involved in plaque progression and regression, as well as the influence of plasma lipoproteins on molecular events in atherosclerosis. Ephraim Sehayek, MD, Cell Biology, focuses on discovery of genes that modify absorption of fat by the intestine and their involvement in atherosclerosis, cardiovascular disease and obesity. Finally, W.H. Wilson Tang, MD, investigates the genetic and biochemical causes of human heart failure and disorders of heart muscle function.

One of the Center’s goals is to develop and validate novel diagnostic tests for cardiovascular and other inflammatory diseases. These tests are then made available for clinical trials through the Preventive Research Laboratory, a certified reference laboratory that supports clinical research studies both within Cleveland Clinic as well as numerous large multicenter clinical trials.

“Cardiovascular disease is a major killer of adults,” Dr. Plow said. “It’s an area that includes a wide array of different diseases and conditions, and different grants enable us to study different aspects. The more components you look at, the greater overall understanding you get of an important and deadly disease process.”

### Global Cardiovascular Innovation Center

You have a diagnostic test or new medical device that could potentially improve care for heart patients. Now what?

The Global Cardiovascular Innovation Center (GCIC) can help to commercialize those innovations, accelerating them to market to speed their use in patient settings.

The GCIC’s charter is to develop and acquire new technologies for the treatment of cardiovascular disease, spawn new companies, and recruit experienced leaders and emerging companies to establish an internationally recognized cluster of cardiovascular expertise locally and in the region. The GCIC is a \$250 million research and product development consortium and has received \$60 million from the State of Ohio as the largest-ever grant made under Ohio’s Third Frontier Project, the state’s billion-dollar effort to expand Ohio’s high-tech research capabilities, promote innovation and create high-paying jobs.



Steven Nissen, MD

“The leading cause of death in the United States is heart disease, and the creation of an internationally recognized center will help Cleveland Clinic to continue to develop life-saving technologies and treatments,” said Steven Nissen, MD, Principal Investigator and Chairman of Cleveland Clinic’s Heart and Vascular Institute.



Mark Low

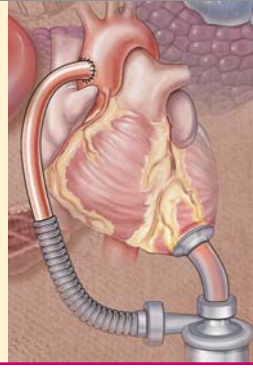
“The Center creates in Ohio an environment to create and attract new cardiovascular-oriented businesses,” said Mark Low, Managing Director. A significant portion of the funds from the Third Frontier grant will be used to provide start-up funding for new commercial enterprises in Ohio. In addition, the Center will build a new

65,000-square-foot building to house selected GCIC member companies in their early stages. Located close to the heart of the Cleveland Clinic research and clinical operations, the Center will provide the proximity and links to ensure that translational research moves rapidly from preclinical studies to early- and late-phase clinical trials, and on into clinical practice.

“Together with the other academic, clinical, corporate, and economic development partners in the consortium, the GCIC is striving to establish Cleveland and Ohio as one of the premier locations for locating cardiovascular businesses,” says Low. “We aim to establish an environment that provides unparalleled access to researchers, mentors and development expertise, low-cost and flexible incubator space, core facilities for rapid prototyping and development, and world-class preclinical and clinical testing and to leverage a strong supply and manufacturing infrastructure — the complete array of factors that businesses need to grow.”

Peter R. Cavanagh, PhD, DSc, Chair, Biomedical Engineering, said the magnitude of the investment and the potential to create a world-class cardiovascular innovation center is impressive.

Researchers in the Department of Biomedical Engineering are developing a ventricular assist device (left) that can aid a patient with heart failure. The proposed Global Cardiovascular Innovation Center will help to commercialize this and other discoveries, accelerating them to market to speed their availability to patients.



Peter R. Cavanagh,  
PhD, DSc

“By comparison, the country of Portugal is spending \$40 million nationwide to upgrade its biomedical engineering capability. We have a \$60 million investment right here,” he said. “There are many places that deliver standard-of-care treatment, but what distinguishes us is that we also have an active research and commercialization infrastructure.

It does differentiate us, and this Innovation Center provides yet another unique advantage both for businesses and patients.”

Several initiatives at the Institute are already under way in conjunction with the GCIC.

Medical Device Solutions (MDS), under the direction of Brian L. Davis, PhD, Biomedical Engineering, focuses on transforming ideas into new functional prototype medical devices. These prototypes demonstrate the technical feasibility and clinical use of the concepts. MDS has added two engineers who are dedicated to cardiovascular projects and will have a presence in the new Center. MDS coordinates several research support services: mechanical prototyping (which manufactures the prototypes of the devices); engineering (which supports the mechanical engineering needs); electronics (which designs and fabricates the electronic components); and polymer research (which supports development of polymer and biologic materials that might be required).

ZIN Medical, jointly owned by ZIN Technologies and Cleveland Clinic, and a recipient of a grant from GCIC, uses technology partly developed by Dr. Cavanagh to provide wireless remote monitoring of patients from their homes, offices or any other place outside of a hospital. Patients' vital signs are recorded and transmitted in real time to physician's offices and can be automatically downloaded into patient's records, reducing the cost and frequency of office visits. The technology can monitor sleep disorders, as well as cardiac, neurological, obstetric, and orthopedic metrics.

Just as important, the GCIC is a major community development investment in the Fairfax neighborhood that borders the Cleveland Clinic. Fairfax Renaissance Development Corporation (FRDC), a nonprofit community development corporation serving the area, is the developer and owner of the building in which GCIC-funded start-up companies will be located. Cleveland Clinic will master-lease the building from the FRDC, which represents a significant partnership between Cleveland Clinic and the neighborhood.

“We're confident that the Center will be the catalyst for the revitalization on the south side of Cedar Avenue, which is shared by the neighborhood and the Cleveland Clinic. The Fairfax neighborhood is our home, and we will all benefit from this partnership,” said Vickie Eaton Johnson, FRDC Executive Director.

“Yes, it's about science,” said Dr. Cavanagh, “but it's also about science linking with the community. With this Center, we can create jobs, invest in our community, and be a leader in developing innovative cardiac devices and taking them to patients quickly and efficiently.”

## Heart Disease Statistics

- Heart disease is the leading cause of death for both women and men in the United States.
- In 2002, 696,947 people died of heart disease (51% of them women). This was 29% of all U.S. deaths.
- Heart disease is the leading cause of death for American Indians and Alaska Natives, African-Americans, Hispanics, and whites.
- In 2002, age-adjusted death rates for diseases of the heart were 30% higher among African-Americans than among whites.
- Coronary heart disease is the principal type of heart disease. There were 494,392 people who died from coronary heart disease in 2002. That is about 71% of all heart disease deaths.
- In 2006, heart disease was projected to cost more than \$258 billion, including health care services, medications and lost productivity.
- Worldwide, coronary heart disease kills more than 7 million people each year.

# Through the Years

Laboratory-based and translational researchers at Cleveland Clinic have made a number of landmark discoveries that explain how cardiovascular diseases develop. These insights led to new preventive strategies, diagnostic and assessment tools, and treatments. The following are just a few of the advances since Cleveland Clinic was created:

- In 1930, work by D. Roy McCullagh, PhD, on inhibin was among the earliest on the well-known family of statins, a class of drugs that reduce serum cholesterol levels.
- The first chemical synthesis of the compound angiotensin contributed greatly to the development of antihypertensive medications used today.
- The “Mosaic Theory” of hypertension was developed by Irvine H. Page, MD. The theory states hypertension rarely has one cause; rather, it results from shifts among many conditions.
- Researchers first showed the effectiveness of various antihypertensive drugs in reversing enlargement of the heart.
- Research into how and why plaque deposits form on blood vessel walls (or atherosclerosis) led to the then-landmark theory by Helen B. Brown, PhD, that fat levels could be modified by changing diet; the first effort to explain how cholesterol is deposited in blood vessel walls; proof that the brain regulates blood pressure; and the discovery of clot-like deposits caused by a protein in the blood called fibrinogen.
- Dr. Page, the first Chair of the Division of Research (now Lerner Research Institute), along with local Cleveland businessmen, founded the American Foundation for High Blood Pressure. It later became the Council for High Blood Pressure Research of the American Heart Association.
- Lena Lewis, PhD, advanced the understanding of lipoproteins and their role in cardiovascular diseases, the effects of diet on serum lipids, cholesterol dynamics and the accumulation of fatty deposits on the inside of artery walls.
- F. Merlin Bumpus, PhD, joined the Division and would be a leader in synthesizing angiotensin — a major breakthrough that helped to spur development of antihypertensive drugs. Dr. Bumpus would succeed Dr. Page as Division chair.
- In the early 1980s, Cleveland Clinic scientists were among the first to formulate the theory of how oxygen affects fatty proteins called lipoproteins, which leads to atherosclerosis. Examples are low-density lipoprotein (LDL, or “bad cholesterol”) and high-density lipoproteins (HDL, or “good cholesterol”).
- Discovered the novel enzyme human chymase that helps regulate blood pressure.
- Started work on a total artificial heart and a series of ventricular assist devices to help people with heart failure — progress that continues today.
- Discovered that an increase in an enzyme called myeloperoxidase in blood plasma can increase the likelihood of coronary artery disease — a discovery that led to a simple blood test that accurately predicts the likelihood that a patient will suffer a heart attack.
- Discovered a “heart attack gene” that links a genetic mutation and heart attacks.
- Developed new imaging software to evaluate heart disease.
- Unlocked how your body can use its own stem cells to regenerate heart tissue damaged during a heart attack.
- Explained exactly how smoking increases the risk of coronary artery disease — providing new diagnostic tools.

## Risk factors for heart disease among adults (for years 1999–2002 unless noted)

- 30.2%: Percentage of persons aged 20 years and older with hypertension or taking hypertension medications
- 17.3%: Percentage of persons aged 20 years and older with high blood cholesterol
- 6.5%: Percentage of persons aged 20 years and older with physician-diagnosed diabetes
- 30.5%: Percentage of persons aged 20 years and older who are obese
- 21.6%: Percentage of adults aged 18 years and older who are current cigarette smokers (2003)
- 37.6%: Percentage of adults aged 18 years and older who engage in no leisure-time physical activity (2003)

Source: Centers for Disease Control and Prevention

# To Market

*Today's laboratory discoveries can be tomorrow's cures. Commercialization can make those cures available more quickly.*

Discoveries made in Lerner Research Institute laboratories can provide a twofold benefit. Biomedical innovations lead to new diagnostic tests and treatments that improve patient care. And new spin-off companies that commercialize such discoveries take them to market quickly and efficiently and create jobs that bolster economic development in northeast Ohio.

In recent years, several new companies have been formed from the cardiovascular research undertaken at the Institute. With the help of CCF Innovations, these companies are among the vanguard of emerging biotechnology companies that affect patients' lives. The following are three companies translating Institute achievements into improved care for heart patients.



Marc Penn, MD, PhD

## **AcelleRX Therapeutics**

After a person suffers a heart attack, the body sends out a distress signal directing the patient's own as-yet-undefined stem cells to go to the heart. There they "differentiate" into heart tissue cells and start to repair the damage. The trouble is, after a short period of time, this homing

signal ends and the body stops repairing itself.

Is there a way to keep that signal on — or even to turn it back on later — so a patient's heart heals more naturally, efficiently and quickly?

AcelleRX develops technologies discovered by Marc Penn, MD PhD, Stem Cell Biology and Regenerative Medicine and Cleveland Clinic's Department of Cardiovascular Medicine, to influence a patient's own stem cells to travel to the site of the injured heart tissue. The stem cells then continue the tissue healing.

The company has secured grants, a strategic partner and financial investors to support further development of its technologies and intellectual property, hire management, and build its initial operational capabilities. It is building its team in the next 18 months to support a Phase I clinical trial to treat chronic heart failure patients.



Andrei Gudkov, PhD, DSci

## **Cleveland BioLabs, Inc.**

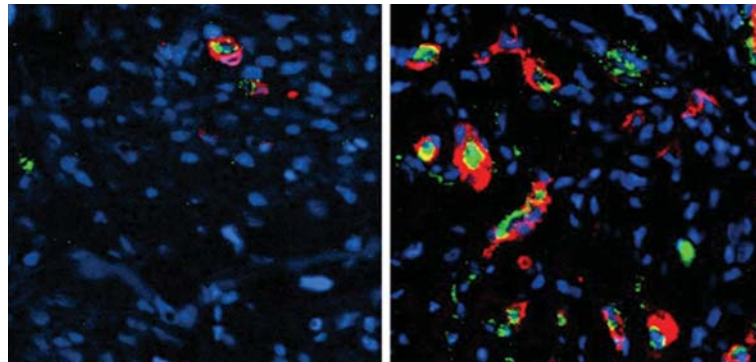
All cells go through a regular cycle of life and death called apoptosis. When it goes normally, apoptosis keeps a person's cell population in balance — not too many or too few of any particular type of cell.

But exposure to radiation, whether intentionally from cancer therapy or unintentionally from a terrorist attack or nuclear accident, can disrupt the genes that guide apoptosis. This disrupted or "unregulated" apoptosis can lead to cancers or other illnesses.

Started by Andrei Gudkov, PhD, DSci, former Chair of the Institute's Department of Molecular Genetics, Cleveland BioLabs (Nasdaq: CBLI; Boston Stock Exchange: CFB) is developing drugs to offer protection from radiation and to treat cancer. These drugs could be administered to first responders such as firefighters, police officers or members of the military prior to entering an area subjected to radiation. Or they could be given to cancer patients before starting radiation to lessen possible genetic damage. These drugs also show promise in helping to protect the heart from damage caused by a decrease in blood to heart tissue.

## **Cleveland BioLabs has two prospective drugs in clinical trials:**

- Protectan CBLB502 protects cells from apoptosis and has a broad spectrum of potential applications, including protection from exposure to radiation.
- Curaxin CBLC102 is designed to kill tumor cells by simultaneously targeting two regulators of apoptosis. It can be effective against a number of malignancies, including renal cell carcinoma, soft-tissue sarcoma and hormone refractory prostate cancer.



# The Heart of Fundraising



## PrognostiX

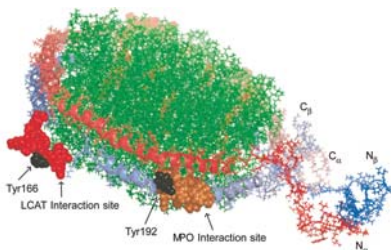
Imagine a simple blood test that, when combined with a patient's clinical history and an electrocardiogram, can predict with a high degree of certainty the likelihood of a heart attack.

That test is here.

Developed by PrognostiX and approved for use by the U.S. Food and Drug Administration, the CardioMPO™ test is sold and is being used by hospitals around the world to measure levels of the enzyme myeloperoxidase (MPO) in human plasma. The enzyme was identified as a reliable predictor of future near-term cardiac events by a research team headed by Stanley Hazen, MD, PhD, Cell Biology and Section Head of Preventive Cardiology and Rehabilitation.

MPO is part of the body's immunity system and is released when the body responds to infection or inflammation. Hardening of the arteries caused by plaque build-up in blood vessels is a type of chronic inflammation. Inflammation causes the release of MPO. Dr Hazen's research team within the Institute has been a world leader for more than a decade in studies showing at both basic and clinical levels how MPO is a major player in vascular inflammation and development of hardening of the arteries. The CardioMPO test was a "spinoff" of this work. With this single blood test, physicians can assess a patient's potential for cardiac events by detecting high levels of MPO in their blood plasma — weeks or even months before a heart attack.

PrognostiX is using its innovation in identifying biomarkers in urine to develop a non-invasive test to assist physicians in diagnosing and monitoring asthma. In addition, tests that can help to diagnose and monitor the effectiveness of treatments are being developed for other types of cardiovascular and inflammatory diseases and neurodegenerative disorders.



Dear Friends,

It's human nature to be touched by individual tales of suffering and to donate our dollars when there's an emergency such as a natural disaster. It allows us to help victims now by providing an immediate sense that we are able to do something. Oftentimes we call it

"crisis giving" — essentially it's giving from the heart.

When donating to charity, your heart may be in the right place, but your mind may not be. For example, when we see a child dying from cancer, we think "I have to help!" That comes from the heart. But we can extend our concern for this child or the fate of other children like her by asking how our donations could have prevented the illness, or what type of medical research could have occurred providing earlier detection or more effective treatment options. That's giving from your mind.

Every day at the Lerner Research Institute, friends such as you donate money not only because there is an emotional connection, but because you have engaged your minds. You understand that behind every illness, every disease, there are research questions that must be asked and explored before a cure can be found. It's only at that point that true medical progress can occur.

Please join us at the upcoming Friends of the Lerner Research Institute event scheduled for June 17 (you can register to attend and get details and updates at <http://www.lerner.ccf.org/giving>).

Never before has giving to medical research been more necessary and valued. For your past, current and future philanthropic support, I thank you!

*Alicia Hoose*

**Alicia Hoose, MPA**  
Director of Development

# Defining Diabetes

*Can the body cure itself of diabetes? Jan Jensen, PhD, leads cutting-edge genetic research that could find a way for the body to make functioning islet cells – the key to a patient's ability to make insulin.*



Jan Jensen, PhD

In the few days after conception, the human embryo is a microscopic bundle of undefined cells. Each cell is alike, with no unique form, characteristic or purpose other than to continue to divide and grow.

But within a short period, a transformation takes place. These cells differentiate. Genetic signals tell them

where they're supposed to be in relation to other cells and the type of tissue they are to become. Some will become heart tissue. Some will form the nervous system. Others will develop into bone or other organs.

And some receive signals to become pancreatic beta cells — the specialized cells with the single purpose of producing insulin so the body can process, store and use sugar (glucose).

What genes are responsible for sending these signals that start pancreatic beta-cell development? And can understanding and harnessing the signaling process lead to new therapies for people whose pancreatic beta cells no longer exist or have become deficient in regulating blood glucose, thus causing diabetes?

This genetic signaling is the focus of Jan Jensen, PhD, who was recently recruited from the University of Colorado to the Lerner Research Institute for the newly created Eddie J. Brandon Endowed Chair in Diabetes Research. Dr. Jensen is also Director of the Center for Diabetes Research within the Institute's new Department of Stem Cell Biology and Regenerative Medicine.

As a developmental biologist, Dr. Jensen studies embryogenesis — specifically, the genes involved in the development of mammalian embryos. “Previously, almost all we knew was from working with flies and worms, because it was too difficult to study genes in mammals. Those organisms, however, fail to provide a reasonable framework for understanding human pancreatic development. But with new technology, we can now apply our work to understanding ourselves,” he said.

“When do these cells normally develop and can we explain that? If we can explain that process, perhaps we can apply it to develop methods to cure diabetes,” Dr. Jensen said. “All forms of diabetes are related to a loss of the capacity to control blood glucose, and we now know that this is related to either a loss of beta cells or a loss of the function of beta cells. Therefore, renewing this cell

type may represent a possible treatment for all types of diabetes. With more than 300 million people worldwide suffering from the disease, the need is there.”

Ideally, one may imagine a therapy in which the early undefined (or undifferentiated) embryonic cells would be given genetic marching orders to become beta cells of the pancreas, also called islet cells, uniquely tasked to manage the body's glucose. Alternatively, one may imagine a therapy in which non-islet cells of the adult pancreas could be converted to beta cells. There is growing evidence that cells of the adult pancreas may be able to generate new beta cells, but it is also known that this process is a rare event. More knowledge is needed to be able to convert a diabetic patient's pancreatic cells into new beta cells.

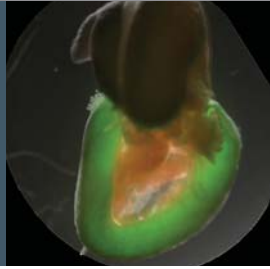
There are several therapies under investigation, all of which are justified by the fact that it is possible to transplant existing islet cells from donors, which essentially cures the disease. But there are far too few donors to meet the demand, not all diabetes patients are candidates, and as in any other transplantation, patients' immune systems must be suppressed, with all the attendant health risks such suppression carries.

One particular approach favored by some is to use a benign virus or other medium to introduce a portion of a gene to the patient's cells in the hopes of “correcting” a gene or providing a “cue for differentiation.” This approach, however, is difficult and involves using a foreign body as a carrier for the desired section of the gene. Furthermore, it is becoming clear that single “master genes” rarely exist and may not be able to fully do the trick of inducing a single cell type.

Then there's Dr. Jensen's approach — cell replacement therapy that relies on learning which genes to “turn on” and “turn off” to regulate the development of a cell using the signals that are used during embryogenesis, when these cells normally develop. “We want to create a pattern or patterns capable of generating tissue, in this case islet cells, which are uniquely identified. The embryo knows how to do it; we still do not. But we don't want to introduce new cells or genetic materials; we only want to generate new cells, using guidance molecules that the cells can respond to,” he said.

“It's like driving a car to get to a destination. As you drive, you look for road signs or signals to tell you which way to turn, how fast to go, and which lane to stay in. If you don't get the right input at the right time and place, you get lost,” Dr. Jensen said.

The red area in the image on the right is an embryonic mouse pancreas. Pancreatic beta cells, which are essential to producing insulin so the body can process sugars, is the focus of diabetes research by Jan Jensen, PhD. Islets of Langerhans (artist's illustration) are groups of specialized cells known as the insulin-producing tissue that also make and secrete hormones.



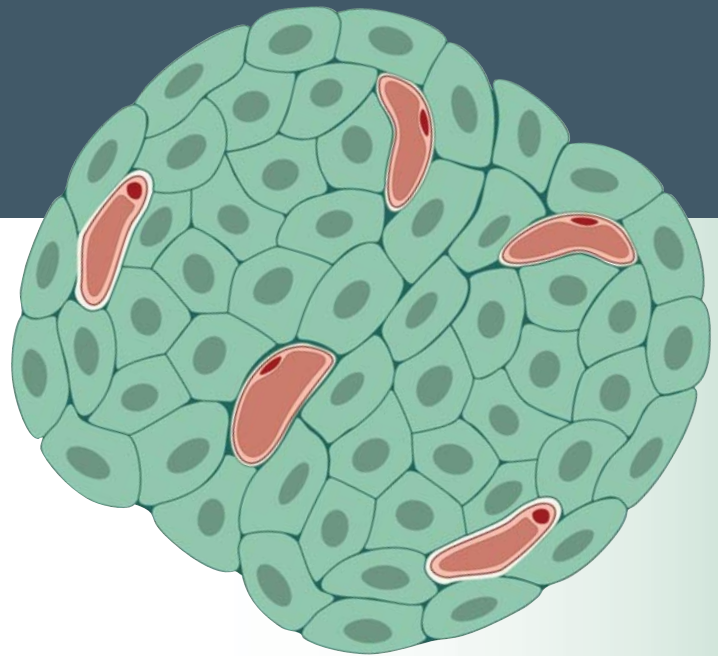
"Cells encounter choices, and they need to get the right input at the right time and place. We simply don't know enough about those 'road signs' for islet cells."

And there have been a lot of road signs to consider. Of the 25,000 genes that comprise the human genome, about 300 belong to "road sign instructive genes." By whittling those down further using bioinformatics, Dr. Jensen and other researchers have identified about 30 genes that are prime targets for study, as all of these operate in the developing pancreas. Any of those genes in any combination could be the key to signaling the creation of islet cells.

Assuming the correct genetic signaling is identified, what do you use as the basis for the future islet cells? Dr. Jensen thinks the answer is immature or undifferentiated cells in the pancreas called pancreatic progenitor cells. These cells have the potential to be "defined" and become islets cells if they receive the proper genetic signaling. But he also strongly believes that human embryonic stem cells represent a valuable option to consider.

Considering the use of adult pancreatic cells, Dr. Jensen said there are two possible sources: cells from people who sign organ donor cards stating they wish pancreatic progenitor cells to be harvested along with other organs and tissues; or a diabetic patient's own pancreatic progenitor cells. "The latter is highly interesting to consider, as beta cells generated from the diabetic pancreas are genetically identical to the patient, and the immunosuppression may be much easier to perform, as compared to the situation in which the patient receives cells from a non-identical donor," he said. "But there are practical limitations to developing such a strategy, even if the proper guiding signals were known. We would need to be able to administer such signals locally in the pancreas of a patient, or be able to expand a limited number of pancreatic cells from a biopsy. None of those issues are trivial."

How does the endowed chair support his research? "It provides more freedom for my approach to understand the complexity of genetic signaling. Typically, researchers who focus on only one gene or pathway have better chances for support from the National Institutes of Health. The endowed chair enables me to pursue what's called a 'systems biology' approach — investigating an array of genes and their interactions," Dr. Jensen said.



Dr. Jensen, who received his PhD from the University of Copenhagen, didn't start out to be a developmental biologist. His initial interest was physics, but a research career in that discipline is difficult to come by, and Dr. Jensen wanted to perform research. Instead, he opted to become a biochemist and molecular biologist. By chance, the native of Denmark was hired as a researcher in the Department of Developmental Biology at the Hagedorn Research Institute, an independent basic research component within Novo Nordisk A/S devoted to finding a cure for diabetes and its complications. "I got completely immersed in the subject," he said. A few years later, he was convinced that the U.S. research environment would be ideal for "doing more," and he accepted a position as Faculty at the University of Colorado in the Barbara Davis Center for Childhood Diabetes, where he established his independent research group.

Diabetes, although treatable, is a formidable disease, currently not curable for life. It affects the patient gradually, shortening lifespan, and is associated with a devastating set of complications, reducing the quality of life, even with the best available treatment. Dr. Jensen believes that the solution to treating patients with new islet cells is essentially a simple one, but he emphasizes that it is also one that requires a much better understanding of the genetic complexity underlying how a cell develops, and this research is not done by a single individual.

As for what he would like to see 20 years from now? "I hope that the method of obtaining a 'universal beta-cell source' is fully developed, and that such cells are practically available for all. In that light, I hope that I can find some part of my research as an integral piece," Dr. Jensen said. "And if so, I'll be very happy, and tremendously satisfied. Can a researcher ask for more?"

## Diabetes' Reach

- 20.8 million people — 7% of the population — have diabetes, including diagnosed (14.6 million people) and undiagnosed (6.2 million people) cases.
- Younger than age 20: About 176,500 people have diabetes.
- Age 20 years or older: 20.6 million; 9.6% of all people in this age group have diabetes.
- Age 60 years or older: 10.3 million; 20.9% of all people in this age group have diabetes.
- Men: 10.9 million; 10.5% of all men aged 20 years or older have diabetes.
- Women: 9.7 million; 8.8% of all women aged 20 years or older have diabetes
- 1.5 million new cases of diabetes were diagnosed in people aged 20 years or older in 2005.
- Diabetes was the sixth leading cause of death listed on U.S. death certificates in 2002. According to death certificate reports, diabetes contributed to a total of 224,092 deaths.

## Complications of Diabetes

- **Heart disease and stroke:** Heart disease and stroke account for about 65% of deaths in people with diabetes.
- **High blood pressure:** About 73% of adults with diabetes have blood pressure greater than or equal to 130/80 mm Hg or use prescription medications for hypertension.
- **Blindness:** Diabetes is the leading cause of new cases of blindness among adults aged 20 to 74 years; diabetic retinopathy causes 12,000 to 24,000 new cases of blindness each year.
- **Kidney disease:** Diabetes is the leading cause of kidney failure, accounting for 44% of new cases in 2002.
- **Nervous system disease:** About 60% to 70% of people with diabetes have mild to severe forms of nervous system damage. The results of such damage include impaired sensation or pain in the feet or hands, slowed digestion of food in the stomach, carpal tunnel syndrome, and other nerve problems.
- **Amputations:** More than 60% of nontraumatic lower-limb amputations occur among people with diabetes.
- **Complications of pregnancy:** Poorly controlled diabetes before conception and during the first trimester of pregnancy can cause major birth defects in 5% to 10% of pregnancies and spontaneous abortions in 15% to 20% of pregnancies.

*Source: The National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health*

# The Faces of Diabetes

## Type 1 Diabetes

Type 1 diabetes is an autoimmune disease. In diabetes, the immune system attacks and destroys the insulin-producing beta cells in the pancreas. The pancreas then produces little or no insulin. A person who has type 1 diabetes must take insulin daily to live. At present, scientists do not know exactly what causes the body's immune system to attack the beta cells, but they believe that autoimmune, genetic, and environmental factors, possibly viruses, are involved. Type 1 diabetes accounts for about 5% to 10% of diagnosed diabetes in the United States. It develops most often in children and young adults but can appear at any age. If not diagnosed and treated with insulin, a person with type 1 diabetes can lapse into a life-threatening diabetic coma, also known as diabetic ketoacidosis.

## Type 2 Diabetes

The most common form of diabetes is type 2 diabetes. About 90% to 95% of people with diabetes have type 2. This form of diabetes is most often associated with older age, obesity, family history of diabetes, previous history of gestational diabetes, physical inactivity, and certain ethnicities. About 80% of people with type 2 diabetes are overweight. When type 2 diabetes is diagnosed, the pancreas is usually producing enough insulin, but for unknown reasons the body cannot use the insulin effectively, a condition called insulin resistance. After several years, insulin production decreases. The result is the same as for type 1 diabetes — glucose builds up in the blood and the body cannot make efficient use of its main source of fuel.

## Gestational Diabetes

Some women develop gestational diabetes late in pregnancy. Although this form of diabetes usually disappears after the birth of the baby, women who have had gestational diabetes have a 20% to 50% chance of developing type 2 diabetes within five to 10 years. Maintaining a reasonable body weight and being physically active may help prevent development of type 2 diabetes. About 3% to 8% of pregnant women in the United States develop gestational diabetes. Gestational diabetes is caused by the hormones of pregnancy or a shortage of insulin.

*Source: National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health.*

# Institute Insider



## Uncovering Viral Weaknesses

The resilient viruses behind some of the most debilitating infectious diseases have evaded effective treatment in part because of their ability to camouflage themselves as they replicate and spread throughout a host. Institute researchers, however, have possibly uncovered a chink in the viruses' armor — and opened the possibility of new antiviral agents to combat diseases such as agents as rabies, measles (rubeola), and Marburg and Ebola viruses.

For the first time, the mystery of the genetic sequence that guides the replication of an animal virus is being unraveled by Amiya K. Banerjee, PhD, head of the Section of Virology within the Institute's Department of Molecular Genetics. The target of his research is vesicular stomatitis virus (VSV), which provides a useful prototype for the viruses mentioned above.

Replication of all cells follows the same general sequence. A cell's DNA is transcribed into messenger RNA (mRNA), which in turn codes for proteins that are the basic building blocks for new cells. As part of this sequence, a specific enzyme is needed to "cap" the initiating mRNAs to protect it from degradation and facilitate efficient translation into proteins.

In the mid 1970s, this mRNA "capping" activity was discovered first in some viral mRNAs followed by mRNAs in cells. But this capping activity remained a mystery for VSV, which belongs to the family of viruses that cause measles and Ebola, among others, because the chemical structure of the cap was slightly different from normal ones and the capping enzymes could not be identified.

"We now have solved the formation of VSV cap structure and identified the viral capping activity," Dr. Banerjee said. "This activity is distinctly different from all known capping enzymes and represents a new class of capping enzyme which clearly has evolved independently from all known cellular and viral capping

enzymes. Finding small molecules that can disrupt replication could lead to discovery of antivirals not only against VSV but other viruses belonging to this class of viruses that are highly pathogenic. The Institute has a library of more than 30,000 small molecules, and there are thousands more at other institutions and private companies. It will take time to identify the right one, but we're confident that our research will someday lead to new therapies for this class of viruses that have until now remained elusive and recalcitrant to treatment."

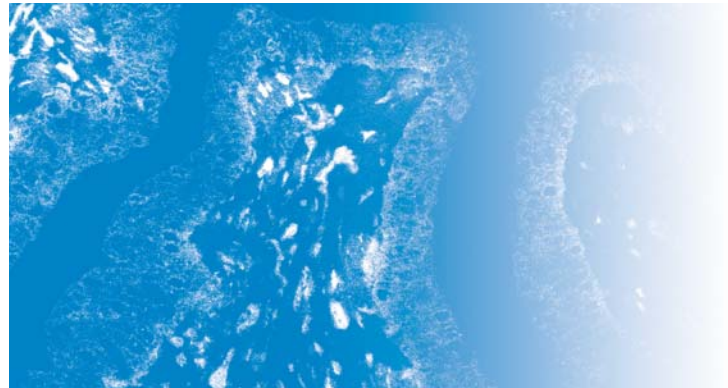
## Cell Sorting

Salvage yards use large, powerful magnets to help separate materials they want to keep from those they want to discard. Maciej Zborowski, PhD, Biomedical Engineering, and colleagues are building on the same concept, using magnets to sort and selectively save certain blood cells. The technique could be a new tool to rescue essential blood cells from the ravages of cancer chemotherapy and radiation treatments.

Dr. Zborowski uses quadrupole magnets to sort cells two ways: to collect adult progenitor (or stem) cells and to find cancer cells that have broken away from tumors and are floating in the bloodstream, posing a hazard of metastasis or resurgence of the cancer.

To sort and separate the cells, antibodies that carry magnetic nanoparticles are added to a mixture of a patient's blood. Nanoparticles are minuscule objects measured by the billionth of a meter. The antibodies adhere to their target cells, such as progenitor cells. The mixture is then pumped along a magnet, which attracts and separates the cells with the magnetic nanoparticles. The rest of the mixture continues on.

Isolating and collecting progenitor cells might help to alleviate the side effects of chemotherapy, such as hair loss, mouth sores and compromised immune systems. Additionally, the technology could



be used to count the number of any remaining cancer cells in the blood after treatment, allowing clinicians to more accurately estimate the chances for a resurgence or metastasis (an earlier diagnosis of such a spread or reappearance of cancer improves the odds of the patient's survival after any follow-up therapy).

This nanoparticle technology has been patented, and the spin-off company, IKOtech LLC, has an exclusive license to commercialize the research. The technology is in preclinical trials now, using blood samples supplied by the Cleveland Clinic Taussig Cancer Center. The next step is to gain approval by the U.S. Food and Drug Administration to start clinical trials with cancer patients.

### New Insights into New Blood Vessels

The answer to how new blood vessels grow and mature might have been found, an understanding with broad clinical importance to developing novel therapies for cancer, heart attacks, strokes and skin and tissue implantation.

Tatiana Byzova, PhD, Molecular Cardiology, said the discovery is important because blood vessel formation and growth in tumors is the major mechanism for cancer survival and spreading throughout the body.

"This knowledge is critical for developing new therapeutic approaches to treat the consequences of ischemia [a decrease in blood supply to tissues or organs]," she said. "It's critical to growing new blood vessels in the most efficient way to restore tissue viability after ischemic injury caused by myocardial infarction, stroke, trauma or by skin or tissue transplantation."

The finding centers on Akt1 kinase. Akt kinases control essential cellular functions including proliferation, apoptosis (or regulated cell death), metabolism and transcription, and they have been

promising targets for treatment of angiogenesis-dependent pathologies, such as cancer and ischemic injury.

"We found Akt1 regulates angiogenesis by several distinct mechanisms," she said. "The most critical is the direct regulation of extracellular matrix components such as thrombospondins and collagen. Overall, we describe a series of unique observations that change our understanding of angiogenesis and vascular permeability associated with human diseases."

### New Link Found in Obesity, Diabetes

Scientists have shown for the first time that a protein involved in the transfer of fat in the blood may also influence how fat cells store fat. Richard E. Morton, PhD, Cell Biology, has shown that cholesteryl ester transfer protein (CETP) is involved in the cellular storage and regulation of cholesterol and other fats and, as a result, makes previously unsuspected contributions to obesity and diabetes.

"CETP is known to shuttle different types of fat between lipoproteins — combinations of fat and protein that transport fats in the blood," Dr. Morton said. "We show that CETP also shuttles fats inside fat cells between two separate areas and that fat cells with reduced levels of CETP are unable to process fats normally.

"Cells that are deficient in CETP have unbalanced amounts of cholesterol and fats. Overall, the cells don't correctly control the amount of fats they make and store anymore. CETP deficiency disrupts storage of important fats in fat cells, which can lead to insulin resistance — a major contributor to diabetes — and the abnormal release of cytokines, proteins that stimulate the immune system. This unexpected contribution of CETP provides a new understanding of how our body stores and regulates fats and of conditions such as obesity and diabetes."

# Institute Insider *(continued)*

## Taking Guesswork Out of Healthcare Decisions

Predictions drive many healthcare decisions. A breast cancer patient, for example, may undergo a double mastectomy, since there's a chance it could prevent tumors from growing in her healthy breast. Or an epilepsy patient may begin intensive drug therapy, hoping he'll be among the percentage whose seizures can be managed.

To help patients make treatment decisions, Cleveland Clinic physicians use software developed by the Institute's Quantitative Health Sciences (QHS) group that helps them more accurately predict outcomes, particularly for patients with common forms of cancer.

"Medical prediction is difficult," said Michael Kattan, PhD, QHS Chair. "You never go to the doctor and get a perfectly accurate prognosis. It's usually some shade of gray. Predictions are most valuable when you're looking at quantity versus quality of life."

An example is prostate cancer, which often requires patients to undergo aggressive treatment that can lead to quality-of-life tradeoffs such as impotence and incontinence.

QHS biostatisticians use Cleveland Clinic's data to analyze how certain factors affect outcomes. They typically assign a weight to each factor, and then upload the resulting equation to the software program. To check its accuracy, they pull data from the files of other patients that were not used to develop the models. Then, they check to see if their prediction matches the actual outcome in these new patients. Soon, QHS hopes to create a patient-friendly version of the software program that would be available through Cleveland Clinic's Web site.



### Could Simple Yeast Explain Human Cell Life Cycle?

For all their simplicity, yeast cells are similar to human cells in many ways. It's this similarity that might hold a key to understanding how a human cell knows when to stop dividing or to die. Kurt Runge, PhD, Molecular Genetics, uses yeast as a model to understand human cell behavior. He has found a protein in yeast that is similar to one in human cells that plays a key role in regulating cell division.

Human cells package their DNA into linear structures called chromosomes. At the ends of chromosomes are telomeres, made of specific repeated DNA sequences composed of a special enzyme called telomerase. Most cells in the human body do not make telomerase, and every time a cell divides during growth, it loses some of these specific telomere sequences. When too many telomere sequences are lost, normal cells stop dividing or die. The proteins that signal cells to stop dividing are called DNA damage checkpoint proteins.

Dr. Runge looked at yeast cells that had lost telomerase and how a specific checkpoint protein recognizes short telomeres. He found that a protein called Tel1p, the yeast equivalent of the human checkpoint protein ataxia telangiectasia mutated kinase (ATM), first recognizes and binds to short telomeres.

If cells have telomerase, Tel1p/ATM binding to telomeres causes them to be lengthened. If cells do not have telomerase, Tel1p/ATM causes the cells to stop growing for a short time. The main difference between yeast and human cells is that yeast will try to resume growth even if its telomeres are too short, whereas human cells normally do not.

"Given the striking evolutionary conservation of Tel1p and ATM, it is likely that a similar mechanism operates in human cells to limit the growth and regulate the telomere length of rapidly dividing cells," Dr. Runge said. "The lifespan of rapidly dividing human cells impacts on how our bodies degrade as we age, including reduced immune function and the ability to recover from wounds or inflammation."

### New Screening Tools for Some Cancers?

Genomic researchers at the Lerner Research Institute may have discovered a new way to assess the risk of some people developing prostate and breast cancer and head and neck tumors.

Alleles are members of a pair or series of genes that occupy specific positions on chromosomes. Researchers led by Charis Eng, MD, PhD, Director, Genomic Medicine Institute (GMI), identified 16 specific locations in the human genome where imbalances of alleles make a person more prone to breast, prostate and neck and head cancers.

The research focused on “germline” genes. These occur in every single cell of the body, are passed from generation to generation, and raise the risk of developing certain cancers. Alleles group in two ways: Different alleles can group at one or more locations on a chromosome, or sets of identical alleles can collect at one or more location.

During the study, the researchers found that having sets of identical alleles at those specific 16 locations is an important marker for prostate, breast and neck/head cancers.

Researchers also found a parallel with what are called somatic cancers. These cancers are caused by genetic mutations that occur only in cancer cells and cannot be passed on. Somatic mutations elicit gene alterations until a cell turns cancerous. In the study, cancer patients who had groups of different alleles at those 16 locations on all their germline chromosomes also had corresponding identical alleles at those same locations within their tumor cells.

“The areas of inherited cancer risk and cancers that develop somatically are generally considered two separate fields,” Dr. Eng said. “Our observations link the two cancer genetics fields and are consistent with cancer as a complex genetic trait.”

“By looking at specific locations for identical alleles, we could help to identify people who are more predisposed to developing inherited prostate, breast and head and neck cancers,” she said. “This could be another important risk assessment tool and allow us to better manage patient care even before a disease develops.”

### Mysteries of Migrating Monocytes

Inflammation can be a good thing. It's a common denominator to infection, injury and several major diseases and is critical to recovery and repair of tissues.

But you can have too much of a good thing. Unchecked, or chronic, inflammation can damage tissues and organs and lead to life-threatening disease. The complex chemical chain reactions that can control inflammation remain, to a large extent, a mystery.

Research in the laboratory of Martha K. Cathcart, PhD, Cell Biology, has possibly solved part of that mystery by uncovering a new understanding that could lead to new strategies to battle chronic inflammation that is part of diseases ranging from hardening of the arteries and multiple sclerosis to rheumatoid arthritis and Alzheimer's disease.

Researchers have known that a protein called MCP-1 directs blood monocytes to migrate from the blood into damaged or infected tissues. Monocytes are specialized white blood cells that circulate throughout the body and respond to injuries or infection.

But how does MCP-1 communicate and direct monocytes to their target? What parts of that chemical reaction are necessary to tell the monocytes where to go in the body?

Dr. Cathcart's laboratory has identified two enzymes —  $iPLA_2\beta$  and  $cPLA_2\alpha$  — that appear to play an essential role in the process. Enzymes are a type of protein involved in catalyzing, or speeding up, biochemical reactions. In this case, the enzymes act as messengers to relay information — the “call to arms” — from MCP-1 to the blood monocytes.

If the enzymes don't work properly, the information isn't relayed. It's like a broken connection during a telephone call. For example, migration and activation of blood monocytes was reduced in monocytes with deficient  $iPLA_2\beta$  and  $cPLA_2\alpha$ . Restoring the enzymes corrected this signaling both in cell culture and in mice.

And the enzymes seem to have specialized purposes:  $iPLA_2\beta$  influences both the direction and speed with which blood monocytes react, whereas  $cPLA_2\alpha$  controls only the speed of the reaction.

“Defects in these two enzymes profoundly affect the ability of blood monocytes to migrate to sites of inflammation,” said Dr. Cathcart. “As we learn how we can ‘turn on’ or ‘turn off’ these enzymes, we could control some of the inflammation associated with certain chronic diseases. The potential is for new treatments for patients with atherosclerosis, multiple sclerosis and rheumatoid arthritis, among others.”

# Institute Insider *(continued)*

## Noninvasive Liver Disease Test

Nonalcoholic fatty liver disease (NAFLD) is an “equal opportunity” disease, affecting both children and adults. It is the most common chronic liver disease and poses a tremendous public health issue to both young and old because it can kill liver cells, leading to scarring and irreversible liver damage.

One stage in the spectrum of NAFLD is nonalcoholic steatohepatitis (NASH), an accumulation of fat in the liver linked to liver damage, inflammation and various degrees of scarring and fibrosis. About 25% of NASH patients progress to cirrhosis and possibly to complications such as liver failure and liver cancer.

But the underlying chain of events at the cellular level that lead to NAFLD/NASH have been poorly understood — until now. New research has explained how the diseases progress, insight that has already led to a new technique for a noninvasive liver biopsy and could mean new strategies to prevent the diseases.

A group of researchers led by Ariel Feldstein, MD, Cell Biology and the Cleveland Clinic Department of Pediatric Gastroenterology, found key points at how NAFLD and NASH work. It starts with an accumulation of fatty acids.

A certain amount of fatty acids are normally stored in liver cells. But when the amount of fatty acids reaches a point where they cannot be contained in the cells’ usual storage places, the acids float freely within the cell and are called free fatty acids, or FFAs.

The presence of these FFAs starts a type of intracellular domino effect: FFAs cause the breakdown of lysosomes, which are structures within the cell that create enzymes that cells need to digest and process food for energy. As the lysosomes break down, they produce an enzyme called cathepsin B.

Cathepsin B, in turn, triggers dysfunction of the cells’ mitochondria — the part of the cell that contains genetic materials and enzymes needed for cell metabolism. Faulty mitochondria prevent cells from turning food into usable energy.

The end result is accelerated or uncontrolled cell death that leads to liver disease.

“Obesity and type 2 diabetes have reached epidemic proportions in most of the Western world, and both are strongly associated with nonalcoholic fatty liver diseases,” said Dr. Feldstein. “Unlocking how NAFLD and NASH progress is providing new screening and therapy options.”

For example, Dr. Feldstein and his team have developed a simple blood test that looks for signs of a certain kind of liver cell death linked to NASH. This new noninvasive test can replace traditional liver biopsies, which carry a risk of surgical complications.

Additionally, understanding the intracellular domino effect could lead to drug therapies that prevent cathepsin B from affecting a liver cell’s mitochondria. Stop the chain of events, and you could stop injuries to liver cells.

“Being able to more easily detect NASH and the prospect of a new array of drugs to interrupt the NAFLD process could provide a dramatic impact on the health and lives of countless people, especially those who are obese or have type 2 diabetes,” said Dr. Feldstein.

## Getting a “Head” start: Act now, before charitable gift annuity rates drop!

A Charitable Gift Annuity (CGA) provides donors with a fixed rate that is often higher than those available from “safe” investments. A CGA, in exchange for a gift to the Lerner Research Institute (LRI), is an effective tool for donors who seek safe and predictable returns, regular income payments for the duration of their life and, if they chose, the life of another beneficiary as well as a significant income tax deduction. Donors also get the personal

satisfaction of supporting medical research today that will lead to the cure’s of tomorrow. The American Council of Gift Annuities has announced that on July 1, 2008 CGA rates will drop and will average .5% point lower than the current rates. If you were considering utilizing a CGA in 2008 and would like to lock in the existing higher rate, please give Alicia Hoose a call at **216-444-1821**.



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ONE OF  
AMERICA'S  
TOP  
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