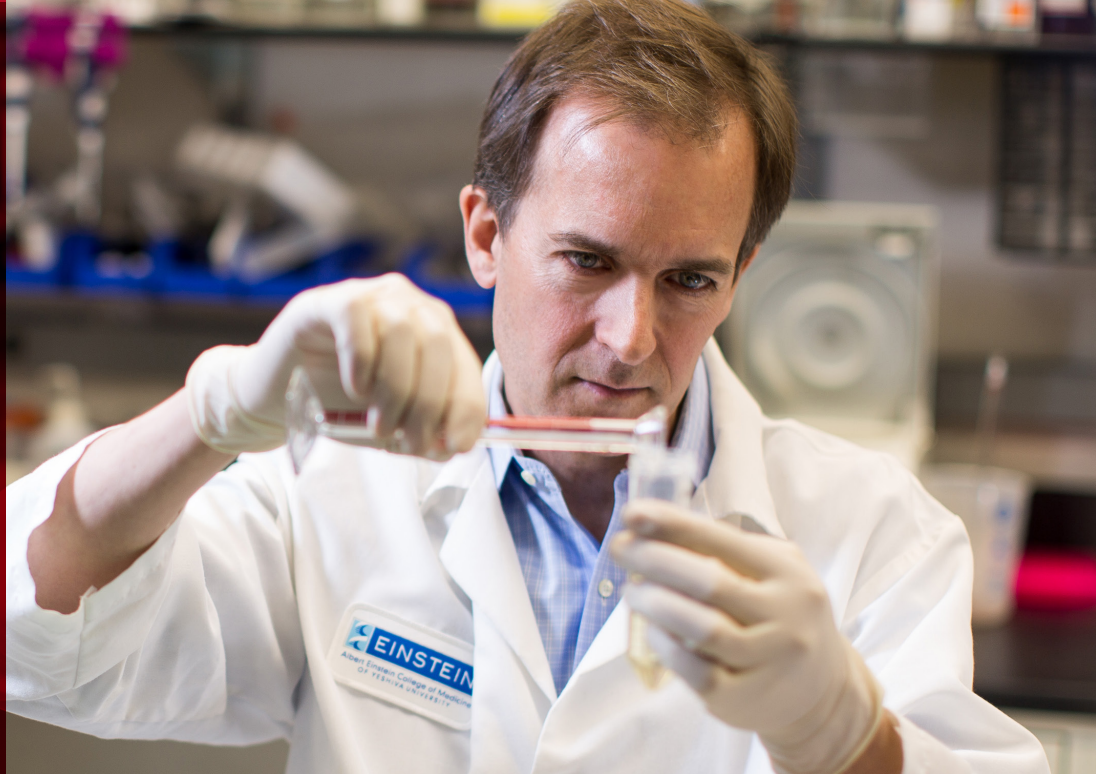


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## The Wilf Family Cardiovascular Research Institute



### Journey to the Center of a Blood Vessel

**N**icholas E. S. Sibinga, M.D., above, wants to prevent two of America's leading killers: heart attacks and strokes. Key risk factors for both are high blood pressure and high blood cholesterol, and Dr. Sibinga's strategy is to minimize the blood vessel damage they cause.

Dr. Sibinga, an associate professor of medicine (cardiology) and of developmental and molecular biology, studies the earliest effects of high blood pressure and high cholesterol at the molecular level.

High blood pressure and high blood cholesterol affect arteries differently. The damage from high blood pressure starts as inflammation that can lead to hardened, thickened, inflexible arteries (arteriosclerosis); high blood cholesterol leads to artery-clogging fat buildup (atherosclerosis).

Dr. Sibinga focuses on proteins involved in repairing cells that are in the early stages of damage from high blood pressure and cholesterol. "By the time arteries are blocked, you already have a serious problem," says Dr. Sibinga. His findings could lead to new therapies that would save many lives.

## MESSAGE FROM THE DIRECTOR



RICHARD N. KITSIS, M.D.  
Director, Wilf Family  
Cardiovascular Research  
Institute  
Dr. Gerald and Myra Dorros  
Professor of Cardiovascular  
Disease

**T**his issue focuses on Dr. Nicholas Sibinga's research on the heart's all-important coronary arteries.

The coronary arteries run along the surface of the heart. They have the crucial task of keeping heart muscle healthy by providing it with blood rich in oxygen and nutrients. But when coronary arteries become narrowed or clogged, areas of heart muscle become starved for oxygen and die—and a heart attack (sometimes called a “coronary”) results.

The main underlying problem is atherosclerosis, a disease process that causes cholesterol and other substances to accumulate within the coronary arteries. Dr. Sibinga studies why atherosclerosis develops and how it can be stopped.

Previous research has yielded lifesaving drugs called statins, which lower blood cholesterol levels, slowing atherosclerosis. But better treatments are needed. Our hope is that new drugs that target atherosclerosis in additional ways may work in concert with statins to halt atherosclerosis and prevent heart attacks.

In other news, we are delighted to announce a new member of the Wilf Family Cardiovascular Research Institute, Dr. Jorge Kizer, who joins us from Cornell. A future newsletter will highlight Dr. Kizer's exciting research on bioactive factors—molecules secreted by fat, skeletal muscle and heart muscle cells—that lead to cardiovascular disease.

We deeply appreciate the support we have received from the greater Einstein community in our efforts to eradicate heart disease and its impact on individuals and families.

*Richard N. Kitsis*

## Journey to the Center of a Blood Vessel *(continued from page 1)*

### Meet the Proteins

Dr. Sibinga is especially interested in proteins that are potent helpers and healers of the smooth muscle cells in the blood vessel walls:

- **Fat1 cadherin.** Levels of Fat1 cadherin, found in cell membranes, increase significantly after vascular injury. The protein receives chemical signals from nearby cells injured by the chronic inflammation of atherosclerosis. It then controls the growth and movement of individual cells to orchestrate vascular repair.
- **Atrophins.** Levels of atrophin proteins also rise significantly after vascular injury. Atrophins bind to Fat1 cadherin to steer just the right number of newly made smooth muscle cells to weak or damaged areas of the vessel wall. Mouse studies show that when smooth muscle cells produce too little Fat1, the repair process goes haywire and too many smooth muscle cells are laid down in the injured area of the blood vessel wall—leading to a dangerous thickening.
- **Beta-catenin.** This protein, which also binds to Fat1, helps injured smooth muscle cells survive during repair by turning on specific survival genes that help the cells cope with vascular damage.

These proteins may be especially useful in treating restenosis and post-transplant arteriosclerosis.

**Restenosis.** Balloon angioplasty and stenting are used to widen coronary arteries narrowed by heart

disease. But up to 40 percent of the time, these widened arteries renarrow—a process known as restenosis. “Once we understand the signals by which Fat1 promotes migration of cells to the site of a vascular injury, it could lead to a new generation of stents coated with the protein, which will directly contact smooth muscle cells and speed the body's natural healing process,” says Dr. Sibinga, also an attending physician in the division of cardiology at the Montefiore Einstein Center for Heart and Vascular Care. Mobilizing atrophins and beta-catenin also could help the repair effort.

**Post-transplant arteriosclerosis:** Within 10 years of receiving a heart transplant, about half of the patients experience thickening of the coronary artery walls. This artery thickening reduces blood supply to the heart and can lead to heart failure. We already know that Fat1 is turned on in transplant arteries as well as in other vascular injury settings and could be a potential therapy. Dr. Sibinga is studying another protein, colony stimulating factor 1 (CSF-1), which causes inflammation in blood vessel walls. In experiments, mice that can't produce CSF-1 don't develop transplant arteriosclerosis. This finding suggests a new prevention strategy in humans: several investigational cancer drugs that inhibit CSF-1 may also prevent transplant arteriosclerosis. (Less is known about atrophins' and beta-catenin's role in transplant arteriosclerosis.)

Meanwhile, when Dr. Sibinga counsels patients about heart health, he emphasizes the role of inflammation and the importance of taking statins. (See Q&A below.)

## cardiovascular



**Q:** Statins counteract the fat buildup that can lead to heart attacks and strokes. Do they also fight inflammation?

**A:** Statins lower LDL cholesterol (low-density lipoprotein cholesterol, sometimes called “bad cholesterol”) effectively, but they also have beneficial anti-inflammatory effects. “This combination of cholesterol lowering and inflammation quenching makes statins particularly useful medications,” says Dr. Sibinga.

## Visualizing Success in Cardiac Revascularization

**Mario J. Garcia, M.D.**

Professor of Medicine (Cardiology)  
Professor of Radiology  
Pauline A. Levitt Chair in Medicine  
Chief, Division of Cardiology  
Albert Einstein College of Medicine  
Co-director, Montefiore Einstein Center  
for Heart and Vascular Care



Heart failure results from the abnormal function of any portion of the heart. When the dysfunction occurs in the left ventricle, poor blood flow in the ves-

sels that nourish it is often the cause. Restoring the blood supply is imperative—and cardiologists generally recommend invasive catheterization or surgical revascularization procedures.

Although revascularization is successful in many patients, its risks may outweigh its benefits in others. A new study led by Dr. Garcia and cardiology fellow Jorge Romero, M.D., found that certain imaging techniques work best in predicting whether a patient will respond well to these invasive treatments.

Their analysis, published in the May 2012 issue of *JACC Cardiovascular Imaging*, endorsed the imaging techniques known as contrast-delayed enhancement and low-dose dobutamine MRI. These methods enable physicians to see whether a patient's heart can handle the invasive procedure and will respond well to it. Combining the two techniques can be particularly useful in predicting whether revascularization surgery will succeed.

## Modulating the Immune Response

**Nikolaos G. Frangogiannis, M.D.**

Professor of Medicine (Cardiology)  
Edmond J. Safra/Republic National  
Bank of New York Chair in  
Cardiovascular Medicine  
Albert Einstein College of Medicine



If a region of the body is deprived of blood for long enough, the cells there will die. When this happens in heart muscle, the immune system launches

a response that serves to heal the injury but, if prolonged or dysregulated, can also damage the heart, causing cardiac enlargement and, ultimately, heart failure. Mammals naturally express molecules that keep the immune system in check. A study led by Dr. Frangogiannis showed that IRAK-M, a molecule produced after injury as a “stop” signal that restrains the immune response, decreases cardiac damage after an acute infarction.

Dr. Frangogiannis and his team used genetic methods to ablate (remove) IRAK-M in mice and observed a more damaging response—and heart enlargement—after cardiac injury. Applied to humans, these results suggest that patients who have heart enlargement and develop heart failure after a heart attack may not properly activate signals that suppress inflammation. The researchers' findings were published in a 2012 issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*.

## HIV and Atherosclerosis

**Robert C. Kaplan, Ph.D.**

Professor of Epidemiology &  
Population Health  
Albert Einstein College of Medicine



HIV antiretroviral therapy has lengthened the lives of people infected with HIV—but survivors often go on to develop cardiovascular disease (CVD), setting the stage

for heart attack and stroke.

Dr. Kaplan and his colleagues recently examined how well blood cholesterol levels in HIV-positive women predict their risk for atherosclerosis, which occurs when fatty substances are deposited in the arteries and can lead to CVD.

The researchers carried out ultrasound scans of the carotid arteries of the HIV-positive women to assess atherosclerosis severity, and they also measured the women's blood cholesterol levels. Higher cholesterol levels were strongly associated with atherosclerosis severity among HIV-positive women on antiretroviral therapy. But the link was less clear for the HIV-positive women not receiving such therapy.

These results suggest that standard blood cholesterol levels may not be an adequate indicator of CVD risk in untreated HIV-infected women.

The study appeared in a 2012 issue of *Atherosclerosis* with Dr. Kaplan as senior author.



### ON THE WEB

To learn more about the Wilf Family Cardiovascular Research Institute, please visit the institute's website at [www.einstein.yu.edu/centers/cardiovascular-research](http://www.einstein.yu.edu/centers/cardiovascular-research).

### EASY AS ABC

Cardiovascular disease is the number-one cause of death in the United States, and stroke is number four. Avoiding them is as easy as ABC:

- Avoid tobacco**
- Become more active**
- Choose good nutrition**





# our supporters

## NOTABLE GIFTS AND GRANTS

*The Wilf Family Cardiovascular Research Institute gratefully acknowledges the generosity of the individuals and organizations whose support is critical to advancing our mission.*

### Congratulations!

**Dr. Richard N. Kitsis**, director of the Wilf Family Cardiovascular Research Institute and the Dr. Gerald and Myra Dorros Chair in Cardiovascular Disease, has received a Scholar Innovator Grant of \$100,000 per year for two years from the Harrington Discovery Institute at University Hospitals Case Medical Center in Cleveland. The grant program supports the nation's best physician-scientists in their efforts to accelerate promising drug discoveries into novel treatments for patients. In addition to the grant, the Scholar Innovators have access to a newly formed, world-class Innovation Support Center, where industry experts provide critical commercialization assistance and financial resources to help the discoveries progress into products.

Dr. Kitsis is in august company; nine other winners hail from such institutions as the University of Pennsylvania, Johns Hopkins University, Stanford University and the University of California, San Francisco. He was the only investigator to receive a grant for heart research.

Dr. Kitsis will direct the grant funds toward his joint effort with Evipidis Gavathiotis, Ph.D., assistant professor of biochemistry and of medicine, to create the first-in-class drug to reduce heart cell damage from acute myocardial infarction.

Dr. Kitsis is also a professor of medicine (cardiology) and of cell biology.

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The International Society of Heart Research has selected Dr. Kitsis to deliver the 2013 President's Distinguished Lecture at its world congress in July in San Diego.

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**Dr. Mario J. Garcia**, a professor of medicine (cardiology) and of radiology and the Pauline A. Levitt Chair in Medicine, has received the 2012 Outstanding Dominican American in Medicine Award from the American Chamber of Commerce of the Dominican Republic. Luis Heredia Bonetti, founder of Dominican Week and past president of the American Chamber of Commerce of the Dominican Republic, presented the award to Dr. Garcia at a ceremony in Washington, DC, last fall. Dr. Garcia was honored for his contributions in advancing cardiovascular care through clinical excellence and research.

Dr. Garcia is also chief of the Einstein/Montefiore division of cardiology and co-director of the Montefiore Einstein Center for Heart and Vascular Care.

## FOR MORE INFORMATION

To learn more about supporting the work of the Wilf Family Cardiovascular Research Institute at Albert Einstein College of Medicine, please contact Glenn Miller, associate dean for institutional advancement, at 718.430.2411 or [glenn.miller@einstein.yu.edu](mailto:glenn.miller@einstein.yu.edu).

THE WILF FAMILY  
CARDIOVASCULAR  
RESEARCH INSTITUTE

### OUR MISSION:

- To better understand cardiovascular disease—the world's number-one killer
- To translate this knowledge into novel treatments to relieve suffering and improve human health

### ADMINISTRATION

Director  
Richard N. Kitsis, M.D.