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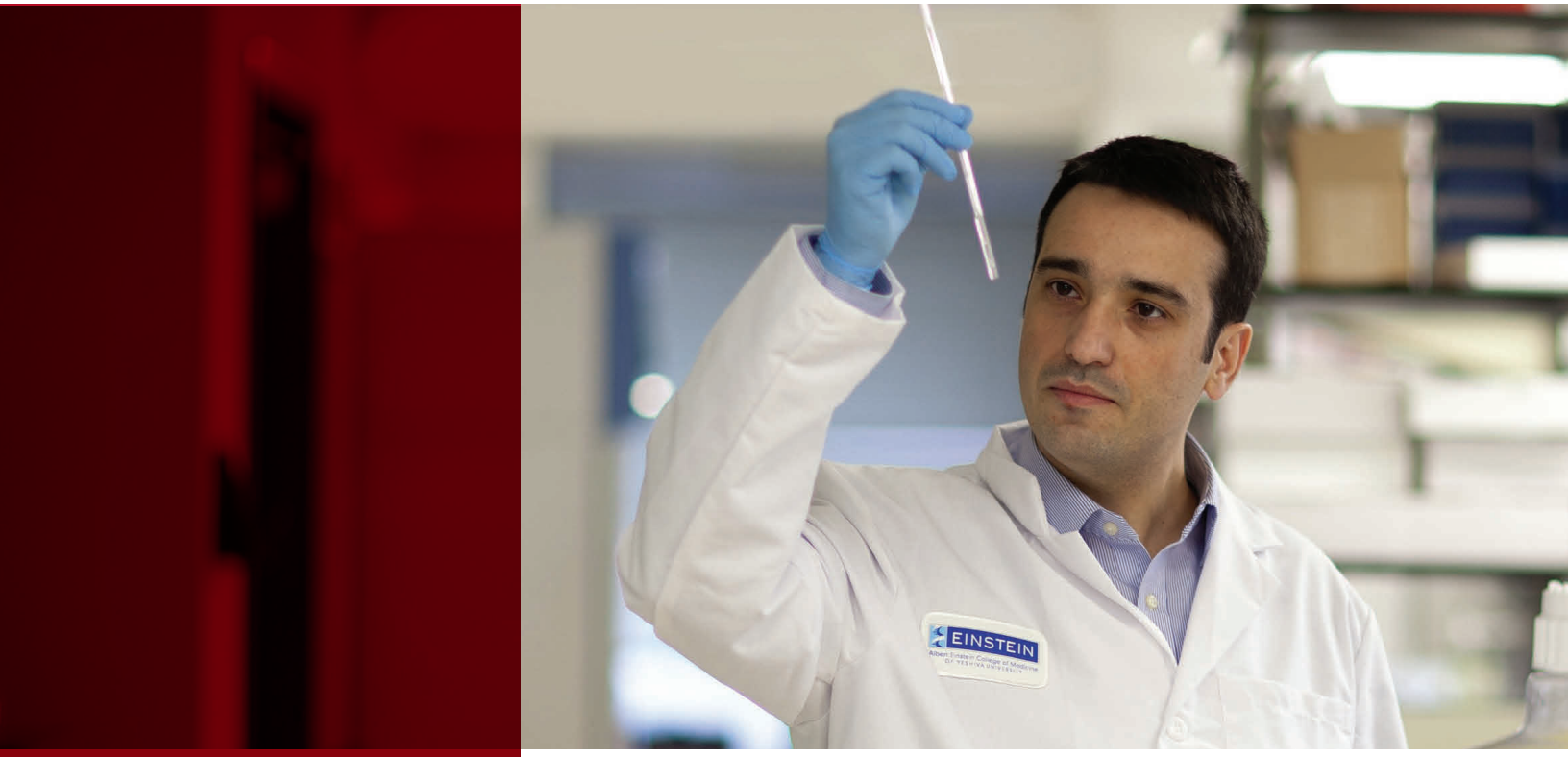
Science at the heart of medicine

IN THIS ISSUE

The genetics of sudden death, page 3

NEWS

The Wilf Family Cardiovascular Research Institute



Escaping the Executioner Protein

"When it comes to life-and-death decisions in a cell, a protein called BAX has the last word," says Evripidis Gavathiotis, Ph.D., an assistant professor of biochemistry and of medicine. BAX does its deadly work following heart attacks, by orchestrating the killing of heart muscle.

"This 'executioner protein' attaches to a cell's mitochondria, the energy 'power plants' contained in cells," explains Dr. Gavathiotis. "BAX then creates holes in the membranes of mitochondria, draining cells of their energy supply." The cells never have a chance to heal. Heart failure may follow—the result of the heart-muscle damage caused by BAX.

But what if the death sentence could be commuted?

Richard N. Kitsis, M.D., director of the Wilf Family Cardiovascular Research Institute, met Dr. Gavathiotis at a professional meeting in 2010, and their conversation soon revealed a shared passion for cell-death pathways in general and BAX in particular.

Stay of Execution

Dr. Gavathiotis had succeeded where many had failed: he had identified key spots on BAX where the protein can be turned off. "We found three different spots on

(continued on page 2)

Newsletter of the Wilf Family Cardiovascular Research Institute

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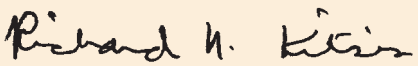
MESSAGE FROM THE DIRECTOR

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

In the last six months, some prized recruits have arrived at the Wilf Family Cardiovascular Research Institute. Among them is Dr. Evripidis Gavathiotis, a stellar chemical and structural biologist and inventor of new drugs for heart disease and cancer. This newsletter describes Dr. Gavathiotis' ongoing effort to create new drugs to limit damage during a heart attack.

In addition, in the "Discoveries" section, we describe the work of current Wilf Family Cardiovascular Research Institute scientists Drs. Tom McDonald (genetics of sudden death), Daphne Hsu (heart transplantation in children) and Daniel Spevack (fixing leaky heart valves). We are proud of our broad spectrum of research, ranging from basic science to bedside clinical cardiology. We believe that this combined approach will help us discover truly novel therapies for cardiac patients—today and in the future.

This newsletter also reports on some recent grants that the National Institutes of Health (NIH)—the federal agency that finances most of the high-level research in the United States—has awarded to Wilf Family Cardiovascular Research Institute scientists. (See "Our Supporters," page 4.) NIH funds have become severely limited in the current economy, and it is a testament to our scientists that they have successfully attracted NIH support. But even in the best of times, NIH financing covers only a portion of the actual costs of discovery. For this reason, we encourage everyone interested in new cures for heart disease to consider aiding our efforts.



Escaping the Executioner Protein *(continued from page 1)*

the structure of the BAX protein that we can target to inactivate BAX," says Dr. Gavathiotis. "You can think of them as BAX's Achilles' heels."

Having made the move from the Dana Farber Cancer Institute/Harvard Medical School to Einstein in 2011, Dr. Gavathiotis is now looking for drugs that will target BAX and turn it off—thereby preventing the heart failure that all too often follows heart attacks. Like many Einstein researchers, he uses a computer as well as a microscope in his search.

"On the computer, we can screen thousands of molecules that potentially will bind to our target," he says. Once the computer's mathematical algorithms and functions reveal molecules with BAX-binding potential, the next task is to confirm in the laboratory that the molecules do indeed bind to BAX. "If so, we'll test those molecules in cells and in rodents to see if they can prevent death of heart-muscle cells and, more important, protect the heart's function," he says. The most promising of those molecules might become drugs that could save the lives of some of the more than 400,000 Americans who die of heart failure each year.

Bad Guy's Good Side

Curiously, the protein that's such a threat following heart attacks may actually be a hero under other circumstances. "Cancer cells have found a way to *prevent* BAX from doing its job of inducing cell death," says Dr. Gavathiotis. "The cells survive and proliferate, driving tumor growth. Since we had discovered the places on BAX that we could target to turn it off, we then started seeking a molecule that can turn BAX on and induce cancer-cell death. We'd have to do it specifically to cancer cells while sparing the normal cells," he says.

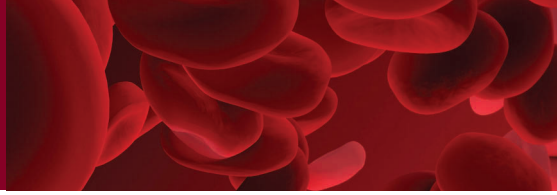
Dr. Gavathiotis and his colleagues recently made a significant advance in their search for a BAX turn-on: They reported in *Nature Chemical Biology* that a small molecule called BAM7 can activate BAX. BAM7 is currently undergoing extensive tests in blood and solid-tumor cancers and will, the researchers hope, become the first of a new class of targeted medicines that can kill cancer cells.

cardiovascular Q&A

Q: What's the difference between a heart attack and heart failure?

A: In a **heart attack,** blood flow to the heart muscle is suddenly cut off. The cause is usually a disease process called atherosclerosis, in which fat, cholesterol and other substances accumulate in the coronary arteries that provide oxygenated blood to the heart. When this "plaque" ruptures, a blood clot may form around it, clogging the arteries and depriving heart muscle of oxygen. Symptoms include discomfort in the chest, arms or other areas of the upper body; shortness of breath; cold sweat; nausea; and lightheadedness.

Heart failure, contrary to the way it sounds, is typically a chronic condition resulting from the heart-muscle damage caused by a heart attack. As it struggles to pump, the damaged heart compensates by enlarging or pumping faster. Symptoms include shortness of breath; coughing or wheezing; swollen feet, ankles, legs or abdomen; and fatigue.



The Genetics of Sudden Death

Thomas V. McDonald, M.D.
Professor of Medicine (Cardiology)
Professor of Molecular Pharmacology
Albert Einstein College of Medicine
Attending Cardiologist
Department of Medicine
Montefiore Medical Center
Co-director, Einstein-Montefiore Cardiogenetics Clinic

Potassium is a key heart-rhythm regulator: it creates the right environment for the electrical "spark" that triggers the heartbeat. In a cocaine user who died suddenly, Dr. McDonald and his colleagues discovered a genetic mutation (called KCNQ1-S277L) that disrupted the heart's potassium balance and thus its ability to carry electrical current. In another sudden-death victim, an obese patient who had undergone stomach banding and was having trouble keeping liquids and solids down, they found a different genetic mutation (called G816V HERG). Both mutations caused a dangerous condition called Long QT Syndrome (LQTS), in which the heartbeat's QT interval is delayed.

For people with LQTS, the first sign of trouble may be a fatal heart arrhythmia. But detecting the genetic defect early can alter that script. In both cases, Dr. McDonald's team found the same mutations in some family members. The team prescribed medication and counseled these people on living with their disorder. The case studies were described in 2011 and 2012 issues of *Pacing and Clinical Electrophysiology.*

Safer Transplants in the Young

Daphne T. Hsu, M.D.
Professor of Pediatrics (Cardiology)
Chief, Division of Pediatric Cardiology
Albert Einstein College of Medicine
Co-director, Pediatric Heart Center
The Children's Hospital at Montefiore

Dilated cardiomyopathy (DCM)—an enlarged and weakened heart—is the main reason that children need heart transplants. Seven out of ten children with DCM survive a decade after their transplants. But what might extend the lives of those who don't live as long?

Dr. Hsu and her colleagues analyzed the records of 261 children with DCM who received heart transplants. Using data from the Pediatric Cardiomyopathy Registry and the Pediatric Heart Transplant Study, they learned that children who had the heart-muscle inflammation called myocarditis before the operation did not survive as long.

Armed with this information, pediatric cardiology teams now know it's important to watch children who have myocarditis more carefully for rejection and other complications after transplants. The study appeared in a 2012 issue of *Circulation.*

The Value of Valve Repair

Daniel M. Spevack, M.D.
Associate Professor of Clinical Medicine (Cardiology)
Albert Einstein College of Medicine
Director of Noninvasive Cardiology
Montefiore Medical Center

When the heart's left ventricle (pumping chamber) enlarges after a heart attack, the mitral valve leading to it from the atrium (holding chamber) may no longer close tightly. Blood can leak backward, forcing the heart to pump harder and enlarging the heart further.

Surgery to correct this "mitral regurgitation" can help the heart pump more efficiently. But until now there's been no proof of positive and lasting effects on the left ventricle.

Dr. Spevack, senior author of a study in a 2012 issue of *Medical Science Monitor,* and his colleagues measured the left ventricle after surgery and found that, over time, it stopped enlarging—confirmation that the surgery helps the heart.

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.

CHOLESTEROL: WAS IT SOMETHING YOU ATE?

If you have high cholesterol, it may not be only because of what you eat. About 25 percent of the cholesterol in your blood comes from food. Your liver and other cells in your body make the remaining 75 percent.

Though eating a heart-healthy diet that's low in saturated fat, trans fats, cholesterol and overall fat (fewer than 25 to 35 percent of calories) and high in soluble fiber (found in such foods as oatmeal, barley and apples) can contribute to a better blood lipid (fat) profile, nonfood strategies can help too. Among those approaches:

- Statin drugs, which work by blocking the action of a liver enzyme essential for manufacturing cholesterol.
- Not smoking.

HEART DISEASE FACT

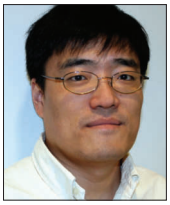
About every 34 seconds, someone in the United States has a heart attack.

our supporters

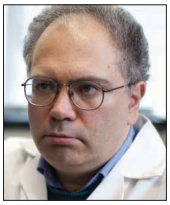
NOTABLE GIFTS AND GRANTS

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

A number of Wilf Family Cardiovascular Research Institute scientists have recently received major new grants from the **National Institutes of Health** to support their work:

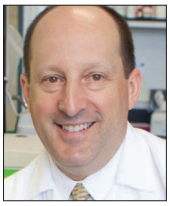


Bin Zhou, M.D., Ph.D., on the molecular and cellular mechanisms of calcification in the aorta. Dr. Zhou is an associate professor of genetics, of pediatrics and of medicine (cardiology).



Nikolaos G. Frangogiannis, M.D., on endogenous anti-inflammatory signals that play a role in resolving inflammation and healing heart muscle after a heart attack. Dr. Frangogiannis is a professor of medicine (cardiology) and the Edmond J. Safra/Republic National Bank of New York Chair in Cardiovascular Medicine.

Richard N. Kitsis, M.D., on new drugs to prevent the death of cardiac stem cells. Dr. Kitsis is a professor of medicine (cardiology) and of cell biology, the Dr. Gerald and Myra Dorros Chair in Cardiovascular Disease and director of the Wilf Family Cardiovascular Research Institute.



Dr. Kitsis and **Steven K. Libutti, M.D.,** on why mutations promote cancer in some tissues but not in others. Dr. Libutti is a professor of surgery and of genetics at Einstein, associate director for clinical services of the Albert Einstein Cancer Center, vice chair of surgery at Einstein and Montefiore and director of the Montefiore-Einstein Center for Cancer 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.