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
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.

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**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**, conversely, 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)
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.

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.

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.
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.