ISSUE HIGHLIGHTS

HEART HORIZONS
COLUMBIA UNIVERSITY MEDICAL CENTER

How You Can Become Part of the Revolution in Heart Care

Private support is crucial to the ongoing research at the Center for Molecular Cardiology. As our extraordinary research facility grows, we need to perpetually renovate and improve our laboratories, recruit new researchers, and provide fellowships for young scientists, among many other things.

Contributions in any amount help us continue our work, whether a small personal contribution, a memorial gift, or a significant grant. Opportunities for naming are still available.

Some 64 million Americans with cardiovascular disease stand to benefit from the groundbreaking discoveries you can read about in this newsletter. It may seem a long way from the laboratory bench to the bedside, but the intent of translational medicine is to shorten that distance. Every successful step we make in heart research today could very well benefit you or someone you love tomorrow.

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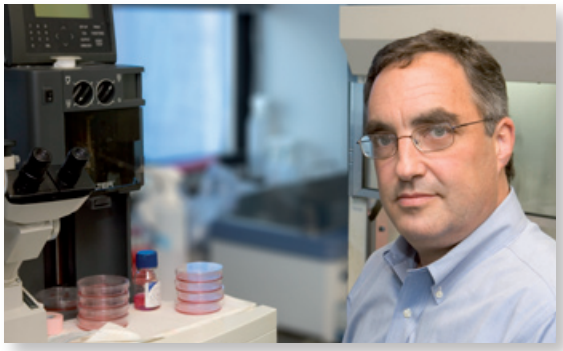
A Special Message from the Director



Here at Columbia University Medical Center, we've begun a revolution in the treatment of heart disease, the number one killer in the United States and Europe. Like every revolution, ours started with ideas. One idea is that we can address the root causes of cardiovascular disorders through sophisticated bench science created by new insights from the human genome. Another is that working together, rather than in isolation, our top-ranked scientists can make greater progress faster. And a third is that if we marry the most advanced research to the best in clinical treatments, our patients can benefit sooner from our laboratory findings. We call this medicine, founded on the bedrock of bench science, translational.

Thanks to the generous beyond measure gift of Clyde Wu, M.D., and his wife, Helen, we have established the Wu Center of Molecular Cardiology at Columbia and are beginning to attract impressive new talent. In this issue of Heart Horizons, you can read about our recent recruit, Henry Colecraft, Ph.D., an outstanding biophysicist who studies calcium and potassium channels in the heart.

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$10 Million Gift from Clyde & Helen Wu Endows World-Class Research Center

Columbia Trustee and cardiopulmonary specialist Clyde Wu, M.D., a 1956 graduate of Columbia Medical School, and his wife, Helen, have given $10 million to permanently endow the Clyde and Helen Wu Center for Molecular Cardiology. This extraordinary gift allows the Center to move forward aggressively in the search for a cure for diseases of the heart.

"I've always believed that to advance clinical medicine you must dig a little deeper into basic science," Dr. Wu says. "I hope that by increasing our involvement and commitment to basic science other people will see the logic and follow suit."

As a practicing physician since the "Dark Ages" of cardiology, Dr. Wu has witnessed a revolution in the treatment of heart disease. "When I first started my internship, the only thing we had for heart attack survivors was morphine for the pain, and they had a high rate of mortality," Dr. Wu recalls. "Now advances such as clot-busting drugs, angioplasties, and stents have reduced mortality to around 5 percent to 7 percent. Those advances came from basic science."

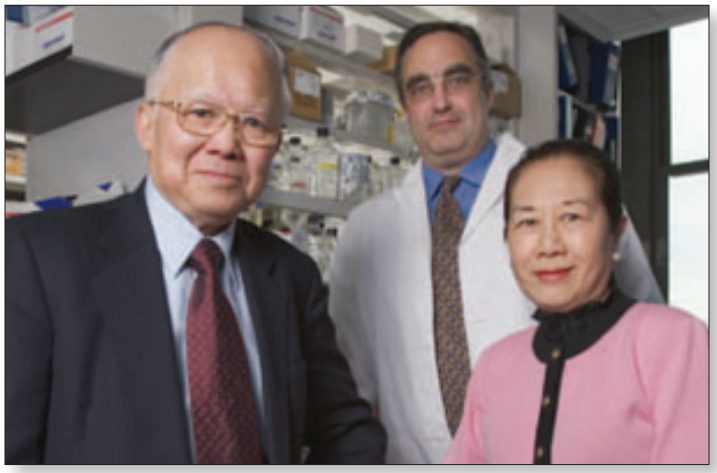
But despite the great strides made in cardiology in the past 50 years, cardiovascular disease is still the nation's leading cause of death.

A New Paradigm

"Most state-of-the-art treatments for heart disease target symptoms," says the Center's director, Andrew Marks, M.D., the Wu Professor of Molecular Cardiology and chairman of the Department of Physiology. "The Clyde and Helen Wu Center for Molecular Cardiology is devoted to an entirely new treatment paradigm that targets the underlying cause of the illness. Dr. Wu has been a great supporter of the center in the past and with this generous gift we will be able to turn what we've learned in the past few years into better therapies."

Eventually, the Center hopes to develop treatments that will end the need for heart transplants and invasive devices, such as pacemakers. One such drug developed by Dr. Marks is in clinical trials now.

"I have all the confidence in Andy and his staff and



I'm sure they will open new doors in understanding cardiology," Dr. Wu says. "Their work is classic translational research, in which you enter an area for knowledge's sake and then you see the possibility for applications. This is what great centers do."

A History of Giving

Dr. Wu's gift to the Center is the latest example of a long history of philanthropy. In the 1980s, he and his wife, a former concert pianist, presented a gift to construct a piano practice room in Bard Hall, a Medical School residence. They later established an interest-free student loan endowment fund, to ease the burden of education and training on worthy students. .

Over the years, the Wus have made gifts to establish four Clyde and Helen Wu Professorships in Clinical Oncology, Immunology, Molecular Cardiology (currently held by Dr. Marks), Chemical Biology (held by Dr. James Rothman, Professor of Physiology).

Dr. Wu is the chairman of the Health Sciences Committee and serves on CUMC's new Board of Visitors. He is a cardiopulmonary specialist and serves on the clinical faculty of Wayne State University College of Medicine in Detroit.

"Wu Endowment Puts Columbia in Cardiology's Forefront"

HENRY COLECRAFT, Ph.D.

Targeting Excitable Cells

Biophysicist Henry Colecraft, Ph.D., recently arrived from Johns Hopkins University to set up the Calcium Channel Physiology Lab, where he will continue his work on the heart's calcium channels. He is the Wu Center's first new recruit.

"He comes highly recommended by international scientists," says Dr. Andy Marks. "I decided to recruit him after hearing his lecture at a Gordon Conference a year ago."

The Gordon Conferences have been held since the 1920s to promote discussions and the free exchange of ideas at the research frontiers of the biological, chemical and physical sciences. Interdisciplinary cross-fertilization is integral to Columbia's new Cardiovascular Research Initiative as well.

While being interviewed for Heart Horizons, Dr. Colecraft had to stop to direct the telephone installer where to put a phone in his new Columbia lab. He's used to relocating, but this is the first time he's moved his lab. Born in Ghana, he lived in Boston while his father attended Harvard, went to London for his undergrad degree in Physiology, followed by a doctorate from the University of Rochester (New York) and post doctoral studies at Hopkins where he became an Assistant Professor of Biomedical Engineering.

No Ordinary Gimmick

Calcium channels are a popular target for drugs treating diseases such as hypertension, arrhythmias, and pain, but Dr. Colecraft has a new gimmick. Make that a GEMIICC, an acronym for Genetically Encoded Molecules for Inducibly Inhibiting Calcium Channels.

GEMIICCs are proteins that can be acutely activated with a chemical agent to turn off calcium channels and have both research and therapeutic applications in the cardiovascular system and beyond. The combination of chemical and genetic regulation built into the GEMIICCs potentially makes them more selective calcium channel blockers than traditional drugs. Right now Dr. Colecraft's lab is seeking to move the GEMIICC technology beyond the proof-of-concept stage to applications in animals.

Dr. Colecraft reminds the interviewer that millions of cells must be coordinated to make the heart beat. This is achieved through the use of electrical signals which are one of the fastest communication modes in biology. The calcium channels reside on the heart cells and open in response to the electrical messages. This allows calcium to flow into the cells to trigger the heart's contraction.

Microscopic Manipulations

Dr. Colecraft says the lab is looking for new tools to manipulate calcium channels, and he is delighted to be at the Wu Center. "It has a nice vision," he says, "and it's exciting to be part of that. The history of cardiology has been continual progress," he points out. "New technologies are applied as they develop, and we hope that GEMIICCs may one day have some applications in the treatment of cardiovascular diseases."

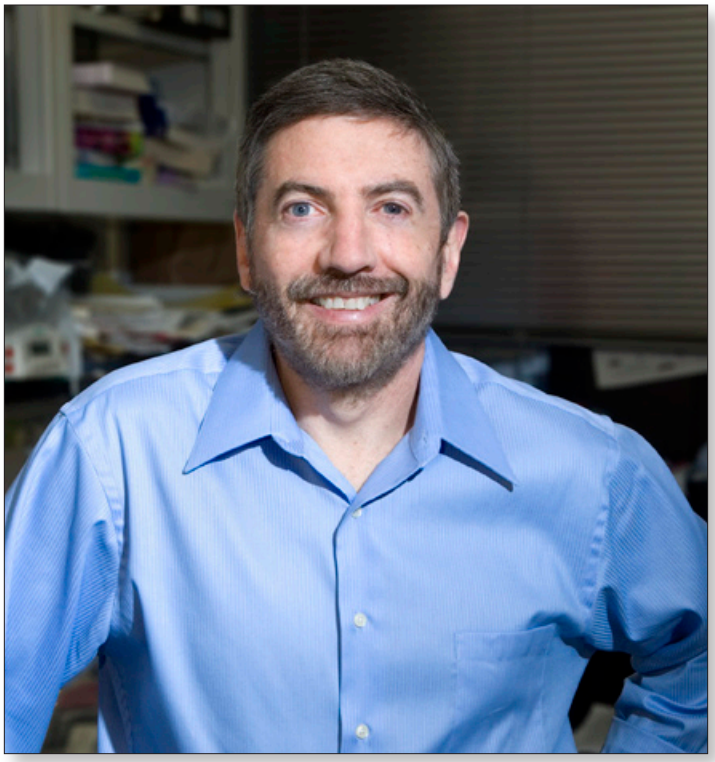
While Dr. Colecraft is the Columbia Medical Center's first African-American basic science faculty member, a summer internship program for students under-represented in medicine founded by Dr. Marks will help to ensure that future Henry Colecrafts can pursue their dreams.

"with the advent of stem cell research, we have the potential of regenerating a broken heart."

Closing in on Plaques

"Almost everybody in the industrialized world has a legion of atherosclerotic plaques in their arteries," says Dr. Ira Tabas, Vice-President of Research at Columbia University's Department of Medicine. This isn't as bad as it sounds. In fact, for mystery lovers, it's the start of a puzzle as exciting as Sherlock Holmes' deductions from the fact that a dog did not bark. If everybody has these plaques in such quantities, why don't we all suffer heart disease as a result?

"Only a few of the plaques are dangerous," Dr. Tabas explains. "Most are asymptomatic. It's those that progress to become what we call vulnerable plaques that cause problems." While the majority of plaques remain safely attached to the arterial walls, vulnerable plaques may rupture or erode, letting materials loose in the bloodstream that can clog up vessels. Heart attack, stroke, and angina can be the result.



From this perspective, the challenge is not so much to try to prevent atherosclerotic plaques, but rather to stop them from progressing to the dangerous vulnerable stage. This is Dr. Tabas's goal, and recent discoveries in his lab make it seem closer than ever before.

Dr. Tabas's research focuses on two of the most important factors in the formation of vulnerable plaques: necrosis, or cell death, and inflammation. "The cells that die are white blood cells that normally fight infections, but here they're getting involved in the plaques," he says.

A Different Kind of ER

Further investigation implicated signaling pathways within the endoplasmic reticulum, or ER, of the white blood cells. However, knowing this wasn't enough to start the search for a treatment. "One wouldn't want to block ER signaling altogether, because it usually has beneficial effects," Dr. Tabas says. "Normally, these pathways help build new proteins, or help repair cells in which there is a problem with protein construction."

The key insight was that unusual amounts of cholesterol were present in the white blood cells that were involved in vulnerable plaque formation. Following up on this clue led to a vital discovery.

"When cholesterol builds up, it triggers a cascade of events," Dr. Tabas says. "Excess cholesterol enters the ER and activates a signaling pathway that leads to the death of the white blood cell. And, before they die, they're stimulated by cholesterol to produce inflammatory molecules." In other words, too much cholesterol in the ER turns out to be critical in both of the factors of vulnerable plaque formation that Dr. Tabas set out to understand.

Blocking Inflammation

In the laboratory, Dr. Tabas has been able to show that blocking cholesterol from entering the ER blocks the death of the white blood cells. Work is currently underway to demonstrate that it can stop the inflammatory response that is also implicated in vulnerable plaques.

"The trick of finding a therapy is to be as specific as possible," Dr. Tabas says. A problem that's in the arteries of everyone in the industrialized world is too big to tackle. And a treatment that interferes with the healthy functioning of the body's self-repair systems is doomed to fail. Finding the one key element that causes normal white blood cells to become part of dangerous plaques represents a feat of investigation worthy of Sherlock Holmes.

> *"The trick of finding a therapy is to be as specific as possible"*

In Search of Good Mutations

In comic books and movies like The X-Men, mutations give fantastic superpowers to a select few. In truth, we're all mutants. Naturally occurring mutations are caused by errors in the copying of DNA. The error rate in mammals is amazingly low, but because the volume of genetic information is so enormous, some estimates suggest that every human baby is born with more than 100 new mutations. These copying errors almost always have no effect, and that's a good thing—when they do, it's usually harmful.

But there are some seeds of truth in the comic books. Some mutations are beneficial, and like the X-Men, these mutants can help humanity as a whole. One such mutation causes a benign form of low blood pressure. As superpowers go, it's not much. But it could still save the planet from a menace that threatens millions of lives.

Dr. Steven Marx, a researcher with the Center for Molecular Cardiology and an Assistant Professor in the Department of Medicine, describes how. "It's still unclear why people get hypertension," he says. "But one of the standard therapies are drugs that block one ion channel, the L-type calcium channel. People who have a mutation in a different channel, called BK, have 'good' low blood pressure. A drug that activates the BK channel could be the future of treatment for hypertension."

Targeting Hypertension

Naturally occurring mutations can point scientists toward the genetic basis of a disorder. Once this clue has opened an avenue for investigation, experimentally created mutations can also provide a tool for focused study. Dr. Marx's lab can test the role of a protein involved with an ion channel by expressing a mutant form of the protein in an artificial system, and then observing how the system behaves.

Using these tools, Dr. Marx has identified a specific target associated with the BK channel that holds promise in treating hypertension, and is investigating a drug that would act on that target. There is no guarantee that this candidate drug will prove effective and safe in humans. The nature of drug discovery is that many are tested, but few succeed. Nevertheless, the discovery of a therapeutic target is valuable in itself—finding the lock is the first step in opening the door, and other groups are testing different drugs that might work on the BK "lock".

A Good Track Record

And Dr. Marx has a good track record of basic research that led to real clinical results. During his cardiology fellowship, he worked in the lab of Dr. Andy Marks studying the effects of rapamycin on smooth muscle cells. This proved to be the solution to the complications that were dogging a new form of surgery. Patients with constricted arteries benefited greatly from a procedure that inserted a stent to keep the artery open, but the stents tended to become clogged with platelets. Coating the stents with rapamycin dramatically cut down on this problem, improving the long-term success rate of the surgery and saving lives.

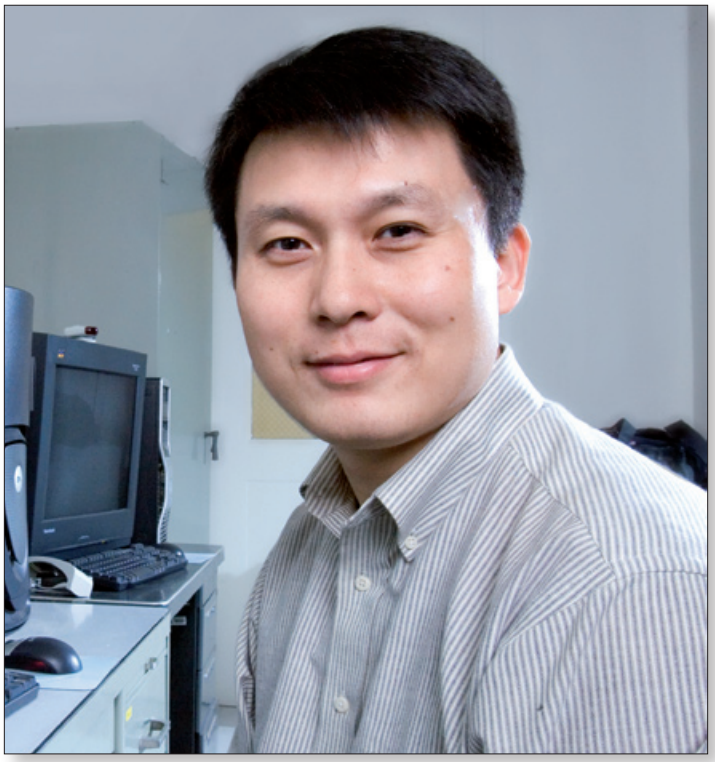
While comic book mutants fight costumed villains in the streets, Dr. Marx battles heart disorder at the lab bench. But, in the end, the motivation of this a physician-scientist is not so different from a caped crusader's. "I chose to work with patients because I wanted to face the challenges of helping people. The part of science that appeals to me is tacking difficult questions. Being able to combine these and help people through my research is what keeps me going."

The nature of drug discovery is that many are tested, but few succeed.

Zooming in on the Heart

"The modulation of voltage-dependent potassium channels is fascinating because it can be studied at so many different levels," says Dr. Ming Zhou. If you met him at a party, you'd sense his enthusiasm for his work, but without specialized training, you might have trouble following exactly what he does.

After finishing his graduate and post-doctoral training, he has begun his career in research as an Assistant Professor in the Department of Physiology and Cellular Biophysics at Columbia University Medical Center.



To help understand the object of Dr. Zhou's fascination, let's borrow a visual metaphor from Charles and Ray Eames' classic short film Powers of 10. We'll zoom in and out to survey what's happening on each level.

We'll start by focusing on a person concerned that she or he may have a heart disorder. Cardiologists listen to the patient's chest with a stethoscope and attach the electrodes of a heart monitor for an electrocardiogram, or EKG. The stethoscope reveals a steady lub-dub and the EKG machine a regular blip, blip, familiar from a million hospital scenes on TV.

Heart Close-Up

One of science's most powerful techniques is reductionism: attacking a complex problem by breaking it down into smaller pieces. "I like this approach because I want to know the details," Dr. Zhou says. So let's zoom in to the level of individual organs where we see the heart squeezing like a fist as it pumps blood through the patient's body: lub-dub.

Zooming in again takes us inside the heart, where sheets of muscle are nourished by a network of fine blood vessels and laced with silvery nerves that direct their action. Next, we zoom in to focus on a single muscle cell, contracting in a steady rhythm. Here is the source of the lub-dub: these contractions, synchronized among millions of similar muscle cells, create the beating of the heart.

Finding the Charge

But we still haven't found the origin of the blip, blip. The EKG monitors electrical activity, and to understand the electrical system of the heart, we'll need to zoom in to an individual structure within the cell's membrane, a tiny tunnel whose mouth regularly opens and closes. This is the potassium channel Dr. Zhou studies. It opens in response to a change in the voltage across the membrane, and allows positively charged potassium ions to pour out of the cell in order to equalize the voltage again.

"Potassium channels are very important molecules in controlling the rhythmic beating of heart and channel malfunctioning leads to heart diseases." Dr. Zhou says. "Channel functions have been studied extensively in the last 50 years and much has been learned. In a heart cell, potassium channels do not work alone because they are assembled with other proteins. As a result, there are some problems that can't be solved by looking at the channel alone." One such problem might happen when a blockage disrupts the supply of blood to the muscle cells. Deprived of oxygen, vital electrical cycle of the muscle cell is disrupted. The culprit here may not be the channel itself, but an associated protein called the beta subunit. Dr. Zhou's research zooms in further, to the level of how beta subunit senses metabolic changes of a cell and fine tunes potassium channel activities.

Dr. Zhou is devoted to basic science, but his work has larger implications. If we could zoom out to our patient, we might find a problem that will soon be addressed in an innovative new way. We can see Dr. Zhou's work as one part of the general themes of the Wu Center for Molecular Cardiology, unraveling the riddle of how malfunctions and mutations of the heart's tiniest components lead to heart disease.

"It's a very exciting place to be," says Dr. Zhou.

"One of science's most powerful techniques is reductionism: attacking a complex problem by breaking it down into smaller pieces"

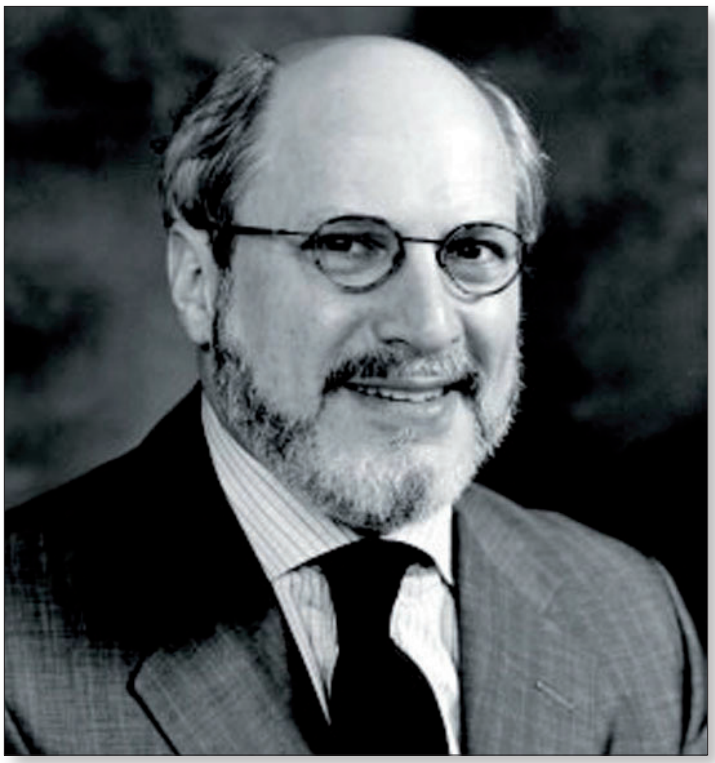
An Eye for the Promise of Interdisciplinary Research

Dr. George Violin is an eye surgeon who graduated from Columbia College of Physicians and Surgeons, but he admits he has some difficulty understanding the advanced research conducted at the Clyde and Helen Center for Molecular Cardiology.

"It's hard for a lay person to understand, but also hard for other scientists," he says. "My son (Jonathan D. Violin) is a molecular biologist, so I asked him to read some of Andy's papers."

"Wow, this is really cool stuff," was the response of the younger Violin, a Duke University researcher.

But it wasn't on their son's word alone that the George and Joan Violin Family Fund gave $2 million to the Center for Molecular Cardiology. In addition to owning and operating an ophthalmic practice that spans several offices, Dr. Violin is one of three founders of the Ambulatory Surgical Centers of America (ASCOA), which operates 21 facilities across the United States.



Organizational Genius

"I knew from ASCOA that getting an organization set up is very different from just getting the idea," he says, "One of the most promising things about the Wu Center for Molecular Cardiology is how it combines research from many disciplines. But you need exceptional leadership to be interdisciplinary—someone who can get different groups to work together and make it happen.

"It's rare to find an organizational leader who is also a leader in science," Dr. Violin says, "But Andy Marks is a genius. He has fire in his belly, and knows how to get things done in this field. His own research is first class.

"The Wu Center for Molecular Cardiology shows great promise to become one of the leaders of the biotech revolution," Dr. Violin predicts. He suspects that Dr. Marks inherited some of his organizational genius from his father, Dr. Paul Marks, who was one of Dr. Violin's teachers in medical school and went on to become the President of Memorial Sloan-Kettering Cancer Center. "Paul was also someone who knew how to make organizations work; he set a very high standard, but Andy lives up to it."

Passing It On

Dr. Violin is modest about his own accomplishments. "Being an eye surgeon is not different from being a shoemaker," he jokes. "I'm just a simple guy. I've been successful because I was lent a hand by others, and establishing this fund is a way for me to pass it on."

Scholarships allowed him to attend Columbia University and its College of Physicians and Surgeons. More than 40 years later, he still remembers the names of the donors who set up those scholarships. With his latest endowment, in addition to the scholarship and professorship he has created at Columbia University, he has certainly added his own name to the list of those who have helped shape the future of medicine.

For Dr. Violin, the best thing about becoming a donor is that he can enjoy the progress of the Center vicariously. "Whenever something good happens through their work, I get satisfaction," he says. He feels the creation of the George and Joan Violin Family Fund for the Wu Center for Molecular Cardiology is certain to pay good dividends in satisfaction. "They're laying the groundwork for a revolution in the treatment of heart disease," he says, "You can smell it."

> *"They're laying the groundwork for a revolution in the treatment of heart disease"*

A Special Message from the Director

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Another generous grant from the George and Joan Violin Family Fund will make it possible for us to recruit an outstanding cardiovascular scientist to fill an endowed professorship.

The Wu Center is part of the Cardiovascular Research Initiative boldly envisioned by Columbia Medical School Dean Lee Goldman, M.D. This effort encompasses much of the basic and clinical research in heart disease at Columbia. Here, world-class researchers, physician-scientists and clinicians are doing critical, groundbreaking work—individually and collaboratively— to discover the underlying causes of heart disease. This initiative puts Columbia in the top tier of institutions addressing diseases of the heart.

Today's treatments, helpful as they are, address the symptoms of heart disease and not its causes. And some of them have serious side-effects. Our highest ambition is to find a cure for cardiovascular disease rather than look for better ways to treat its symptoms.

This grand ambition takes us back to the tiniest mechanisms in the human body where disease originates. We share many life processes with other animals. The best bench science illuminates these connections. For example, the fight or flight mechanism that delivers adrenaline and helped our ancestors escape approaching predators has been found in animals as small as the earthworm.

Every patient with heart failure has high levels of adrenaline, which pours out in an attempt to make the heart pump harder. One of the highlights of my research with mice was the discovery of the heart's ryanodine receptor, a channel which carries calcium. The excess adrenaline causes the receptor, or channel, to leak calcium, and this triggers arrhythmia, or irregular heartbeat. Eventually, the heart stops beating. Several years ago, we discovered a compound that stopped that leak and as a result in 2006 created a biotech venture, ARMGO Pharmaceuticals, Inc., to develop a drug based on that compound. Clinical trials are set to begin in Spring 2008.

As a physician-scientist, it's extremely rewarding to know that the hearts of thousands of patients might someday beat efficiently with this new drug. Of course, not all research leads to such dramatic results, but the hope of additional discoveries is inspiring. With the talent and cooperation of our researchers and the magnanimity of our donors, we are poised to change the practice of cardiology in the twenty-first century. In these pages you can find out about other cutting-edge research underway in our laboratories and what you can do to help advance our work. We hope you will join our revolution.

How You Can Become Part of the Revolution in Heart Care

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To discuss giving opportunities or to receive a free subscription to Heart Horizons, please contact the Center's Director of Development, Robert Thompson, by calling 212.342.0094 or by email at rt2150@columbia.edu.

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