The Clyde and Helen Wu Center For Molecular Cardiology

HEART HORIZONS

COLUMBIA UNIVERSITY MEDICAL CENTER

New Laboratories Planned for Wu Center for Molecular Cardiology

The laboratories of the Clyde and Helen Wu Center for Molecular Cardiology will be moving to newly renovated and expanded space on the fifth floor of the Berrie Medical Sciences Building this spring.

"The new laboratories will enable a dramatic expansion of the current research capabilities for molecular cardiology, stated Dr. Andrew R. Marks, the Director of the Wu Center. "We will be able to perform more detailed studies at the cellular level and will have an enhanced capacity to study drug effects in animal models of human heart diseases," Dr. Marks added.

The move will increase the total area devoted to the Wu Center by approximately 6,000 square feet. The space will include state-of-the-art imaging facilities that will be used to probe the insides of heart cells as well as a newly designed animal laboratory that will be on the seventh floor of the Berrie building. *> continued on back*

Chinese TV visits the Wu Center

On March 10th and 11th the largest TV station in China, CCTV, visited the Wu Center as part of a documentary on the life and accomplishments of Clyde and Helen Wu. With hundreds of millions of viewers, CCTV is the most heavily viewed station in the world. CCTV International (CCTV-9) is the English-language 24-hour news channel of China Central Television (CCTV), China´s largest national TV network. Launched on September 25, 2000, CCTV International reports news and information to a global audience, with a special focus on China.

Members of the Wu Center were interviewed, including Drs. Jian Shan, Xiaoping Liu and others who are learning research techniques in the Center. Dr. Clyde Wu and his wife Helen visited the laboratories and met with many of the students and fellows who benefit from their generous support.

Testimonials about the enormous impact that Clyde and Helen Wu have had on Columbia University Health Sciences were given by numerous faculty who have been supported by the Wu family.

The TV show includes a segment filmed in Detroit, where Clyde and Helen are major supporters of the Detroit Symphony Orchestra, as music, aside from medicine, is their other great love.

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A Special Message from the Director

These are exciting times for heart research – and they are challenging times!

The excitement is generated by the scientists in the Clyde and Helen Wu Center for Molecular Cardiology, who have made tremendous advances in the past year towards new understandings of and treatments for heart disease. Many of these discoveries are highlighted in this issue of Heart Horizons. One discovery is already in the clinic - Wu Center scientists have discovered a novel mechanism that causes heart failure and sudden cardiac death, the leading causes of death in the United States and the developed world. The cause is a calcium leak in heart muscle cells. The Wu Center scientists have developed a new kind of drug, called a "rycal" that fixes the leak. The new rycal drugs are being tested in patients now! It took five years from basic conception of the cause of heart failure to achieving a drug for testing in patients; this is considered very rapid progress in drug development.

The challenges include years of reduced funding from the National Institutes of Health, which has been ravaging the heart research community, driving away potential new investigators and handcuffing established scientists. Most academic heart research programs are suffering from lack of funding. Support for the N.I.H. from the stimulus package will help, but it is not going to fix the underlying the problem - a fundamental lack of consistent and substantial funding for heart research that matches the enormity of the impact of heart disease on our lives.

The Wu Center has continued to recruit new faculty, welcoming Wayne Hendrickson, a leader in figuring out the structure of proteins, which is fundamental for drug development and understanding disease mechanisms; Henry Colecraft, a leader in understanding calcium in the heart; and Filippo Mancia, an expert in the structure of membrane proteins. These three outstanding and brilliant scientists join the faculty of the Wu Center at a critical time. It is essential to unite talented investigators in order to compete successfully for scarce funds for research and form teams that can use novel and interdisciplinary approaches.

The Wu Center is the home of molecular biologists who are also members of the Cardiovascular Research Initiative (CVRI), started by Dean Lee Goldman to bring together all the heart researchers throughout Columbia.

Several of the Wu Center scientists will be moving to newly renovated laboratories in the Berrie Medical Sciences Building, affording greater synergy and access to modern technology for their research.

The Wu Center already has an unparalleled track record for bringing new discoveries into clinical application to help patients fight heart disease. If you have read this far, I know you are interested in our work and how to support it. On behalf of my colleagues, I thank you for your interest and invite you to visit our laboratories, meet the scientists in the Center and learn about the future of heart research!

Violin Family Chair Awarded to Professor Wayne Hendrickson

University Professor Wayne Hendrickson has been appointed as the Violin Family Chair in the Department of Physiology and Cellular Biophysics. This new chair in the basic sciences is the generous gift of George Violin MD, P&S '67, his wife Joan and their family. Dr. Violin graduated from Columbia University College of Physicians and Surgeons in 1967 and completed his ophthalmic residency at Massachusetts Eye and Ear Infirmary. He was one of the pioneers in small incision cataract and implant surgery in Massachusetts and has had experience in this area for almost a quarter of a century.

He is a fellow of the American College of Surgeons and a charter member of the American College of Eye Surgeons. He is affiliated with Caritas Norwood Hospital, Faulkner/Brigham and Women's Hospital, Massachusetts Eye and Ear Infirmary and New England Medical Center. He devotes most of his practice to cataract surgery, LASIK and related surgeries. He was one of the early investigators of epikeratophakia, a precursor of current LASIK technology.

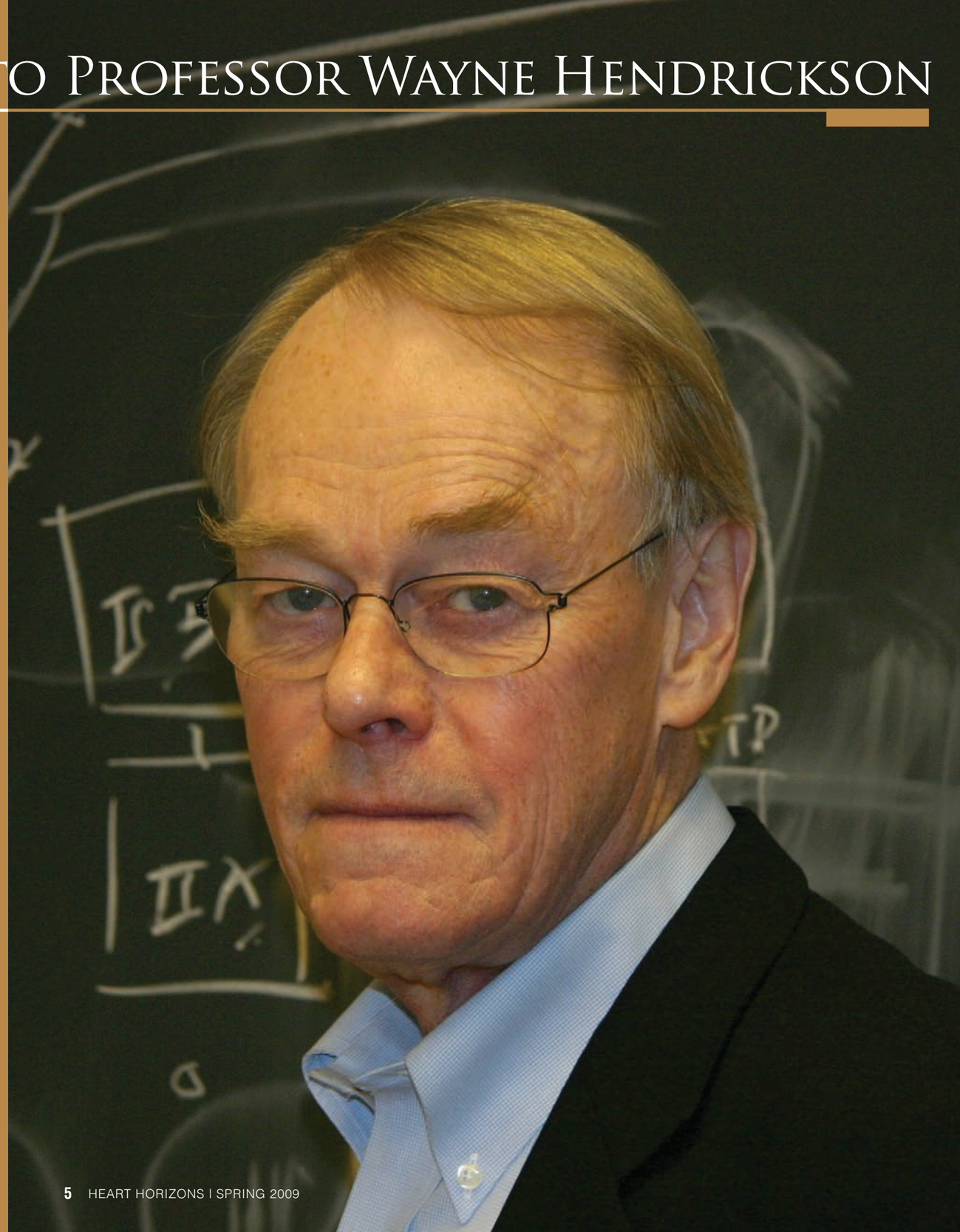
Dr. Violin has been the subject of many news articles concerning his expertise in the areas of laser vision correction and cataract surgery. He has been featured, and has appeared as a guest speaker, on numerous local television and radio broadcasts, where he has discussed state of the art technologies in both of these areas.

Wayne A. Hendrickson is a University Professor at Columbia University and an Investigator with the Howard Hughes Medical Institute. He has a BA from the University of Wisconsin at River Falls and a PhD in biophysics from Johns Hopkins University based on work with Warner Love. His postdoctoral research was with Jerome Karle at the Naval Research Laboratory (NRL). He remained at NRL as a Research Biophysicist until he joined the Department of Biochemistry and Molecular Biophysics at Columbia in 1984.

Dr. Hendrickson will head the newly established program in structural biology in the Department of Physiology and Cellular Biophysics that will include Dr. Ming Zhou and the newest recruit, Dr. Filippo Mancia. Work in this new program will focus on elucidation of the structure of membrane proteins that underlie fundamental processes in the cardiovascular system and are targets for drug therapies.

Research in Dr. Hendrickson's laboratory focuses on the structure and function of biological molecules. He and his colleagues use x-ray crystallography to study molecular properties in atomic detail. By analyzing x-ray beams diffracted from crystals, they are able to reconstruct images of crystallized molecules. Their advances in diffraction methods (notably stereochemically restrained refinement, the multiwavelength-anomalous-diffraction (MAD) method, selenomethionyl proteins, and synchrotron instrumentation) have been instrumental in the emergence of structural biology as a major force in modern biology and molecular medicine. They use this technology themselves in investigations on membrane receptors and cellular signaling; on viral proteins and HIV infection; and on molecular chaperones and protein folding.

Dr. Hendrickson has published numerous research articles and related reviews and serves on advisory bodies for several scientific organizations. He is a founding editor of *Current Opinion in Structural Biology and of Structure*, and he is a founder of SGX Pharmaceuticals. His honors include the Aminoff Prize of the Royal Swedish Academy of Sciences, the Gairdner International Award and the Harvey Prize of the Technion – Israel Institute of Technology. He is a fellow of the American Academy of Arts and Sciences and a member of the National Academy of Sciences.



Professor Helen Hobbs Delivers Second Annual Clyde and Helen Wu Distinguished Visiting Professor Lecture

December 1, 2008 – "A person's risk of heart disease can't be blamed solely on eating too many cheeseburgers and other foods high in saturated fat. Genetic makeup also plays a powerful role," states the Howard Hughes Medical Institute web site introducing the work of Dr. Helen Hobbs, who presented the second annual Helen and Clyde Wu Distinguished Visiting Professor Lecture, entitled "Genetic Protection from Diseases of Plenty," to a standing room only crowd at P&S in the Berrie Building Auditorium. Dr. Hobbs, a member of the US National Academy of Sciences, is a Howard Hughes Medical Institute Investigator, a Professor of Internal Medicine and Molecular Genetics, and Director of the Eugene McDermott Center for Human Growth and Development at the University of Texas Southwestern Medical Center at Dallas, and Director of the Donald W. Reynolds Cardiovascular Clinical Research Center, also in Dallas.

The Clyde and Helen Wu Distinguished Visiting Professor Lecture is supported by a generous donation from Helen and Clyde Wu, P&S '56. Last year's inaugural speaker was Professor Robert Lefkowitz from Duke University, who spoke about his pioneering work on seven transmembrane receptors that govern the heart's response to stress. On December 7, 2009 Professor Shaun Coughlin, Director, Cardiovascular Research Institute (CVRI) at UCSF and Professor of Medicine and Cellular and Molecular Pharmacology, will deliver the third annual Clyde and Helen Wu Distinguished Visiting Professor Lecture and will describe his work on factors regulating thrombosis in the cardiovascular system.

The following excerpt from the HHMI web site describes Professor Hobbs' research and career development:

"Helen Hobbs has discovered new genes and variations within genes that account for individual differences in blood levels of low-density lipoprotein, the "bad" cholesterol. High LDL cholesterol is a major risk factor for heart disease and heart attack because it contributes to the buildup of plaque that can clog artery walls. By identifying the genes that influence cholesterol levels and exploring their function, Hobbs's studies are laying the groundwork for the development of new cholesterol-lowering drugs.

Hobbs was chief resident at UT Southwestern Medical Center in Dallas and well on her way to becoming a practicing endocrinologist when she decided to give research a try. Her mentor, Donald Seldin, then the school's head of medicine, was convinced that Hobbs possessed the natural curiosity and the drive to flourish in a research environment, even though she had no experience at the bench, and that she would not be fulfilled in her work without the challenge of new discovery. "He knew all my strengths, but more importantly, he knew all my weaknesses, and he felt strongly that I should do this," Hobbs recalls. Seldin arranged for her to work as a postdoctoral fellow in the laboratory of two well-established investigators—Michael Brown and Joseph Goldstein—who later won a Nobel Prize for discovering the cell-surface receptor for LDL cholesterol and demonstrating its role in cholesterol metabolism.

Hobbs initially struggled in the laboratory. She much preferred the faster pace of clinical medicine and was easily frustrated by her own technical mistakes. "Patience is not my virtue. It took me a long time to adjust to the slow pace of laboratory science," Hobbs says. But once she started to get results, Hobbs relished the thrill of scientific discovery. When she joined the Brown-Goldstein laboratory, the pair was trying to understand how mutations in the LDL-receptor gene affect the receptor's function. One of Hobbs's first research successes was finding a mutation in this gene that alters its ability to bind LDL cholesterol. Today, she admits, "I am able to delight more in the slower process of telling a scientific story with my work. Ironically, the observations I have made with the greatest potential for clinical impact came from studies driven by scientific curiosity rather than thoughts of developing new therapies."

Since setting up her own laboratory at UT Southwestern in the late 1980s, Hobbs has discovered genetic defects that cause very high and very low blood levels of cholesterol and has studied the faulty proteins that underlie these disorders. This information may help determine how the body normally regulates cholesterol by removing it from the bloodstream and shuttling it to the liver, where it is broken down in the bile. In 2001, she identified a genetic defect that causes a rare type of high-cholesterol disorder, autosomal-recessive hypercholesterolemia. People with the disease have normal-functioning LDL receptors but can't remove LDL cholesterol from the bloodstream. She and her colleagues also discovered two genes, ABCG5 and ABCG8, that play key roles in maintaining the proper balance of sterols in the body, including plant-based sitosterol and animal-based cholesterol. Mutations in either gene can lead to a buildup of cholesterol in the blood.

In addition to her laboratory work, Hobbs runs the Dallas Heart Study, aimed at uncovering the risk factors for heart disease and at finding new treatments. Initiated in 1999, the study includes taking blood samples and performing detailed heart imaging studies in 3,000 Dallas County residents (about half of them African American). Based on data already collected, Hobbs recently identified two beneficial genetic mutations linked to low levels of LDL cholesterol. The gene alterations were found almost exclusively among African Americans, even though as a group they have a higher risk of heart disease. One out of 50 African Americans in the study had either of the mutations, which increase the amount of cholesterol the liver removes from the body.

Hobbs still sees patients in the clinic on a weekly basis who have very high or low levels of cholesterol, and sometimes their symptoms lead to the identification of a new disorder that becomes the focus of her work in the laboratory. Recently, Hobbs saw a patient whose LDL cholesterol level skyrocketed after he went on the low-carb Atkins diet. She found abnormalities not only in the patient's cholesterol metabolism but also in the metabolism of other family members, and she is now trying to pinpoint this defect."

Professor Shaun Coughlin to Deliver Third Annual Clyde and Helen Wu Distinguished Professor Lecture

Professor Shaun Coughlin, Director, Cardiovascular Research Institute and Professor of Medicine and Cellular and Molecular Pharmacology, University of California at San Francisco, will deliver the Third Annual Clyde and Helen Wu Distinguished Professor Lecture on December 7, 2009.

Dr. Coughlin's cardiovascular research discovered how thrombin, an enzyme that causes blood to clot, works on the cellular level. In the process, he identified a new family of receptors that are broadly involved in a number of biological processes and have important implications for the development of novel treatments for diseases and pathologic events in which thrombosis plays an important role, including heart attacks and many strokes. His discoveries led to a greater understanding of platelets and clot formation.

Dr. Coughlin received his BS and MS degrees in 1976, and his PhD in 1981, from the Massachusetts Institute of Technology, and was awarded an MD from Harvard Medical School and the Harvard-MIT Division of Health Sciences and Technology in 1982. He joined the Cardiovascular Research Institute at the University of California, San Francisco in 1984 as a postdoctoral fellow and joined the faculty in 1986. He was named Professor of Medicine in 1996 and was appointed Professor of Cellular and Molecular Pharmacology, as well as Director of the Cardiovascular Research Institute in 1997.

Dr. Coughlin is the recipient of numerous honors and awards. In 2004 he won the Bristol Myers Squibb Cardiovascular Research Award and he was elected to the National Academy of Science.

The Clyde and Helen Wu Distinguished Professor Lecture is supported by a generous gift from Clyde P&S '56 and Helen Wu. The inaugural Clyde and Helen Wu Distinguished Professor Lecture was given by Robert Lefkowitz in 2007 and the second by Helen Hobbs in 2008.

Department of Physiology Latest Recruit

Filippo Mancia

We are interested in the structure and function of membrane proteins. Proteins that reside within the plasma membrane are responsible for how a cell detects and responds to extra-cellular stimuli of biological, chemical and physical nature. High-resolution snapshots of such molecules offer invaluable insight into the function of a given protein and provide the framework to test structure-based mechanistic hypotheses. We primarily use X-ray diffraction of protein crystals to obtain structural information to atomic detail, while we employ multiple biophysical and biochemical techniques, as well as cell-based assays, for functional studies. Our efforts are currently devoted to three main areas of research:

1. G-protein coupled receptors (GPCRs): GPCRs represent the largest family of genes in the human genome. Ligand-binding to a GPCR leads to the initiation of an intracellular signaling cascade through G-protein activation. The mechanism of activation, likely shared by all GPCRs, remains elusive to date. We are investigating the function of GPCRs, with a particular focus on serotonin receptors, by means of functional and structural studies.

2. Intramembrane Proteases (IMPs): Polypeptide chains are cleaved within the membrane in a wide variety of regulatory cellular processes. The aspartyl-IMPs presenilins are the catalytic core of g-secretase, an enzyme thought to be involved in the onset of Alzheimer's disease. We are studying prokaryotic homologs of presenilins and related IMPs.

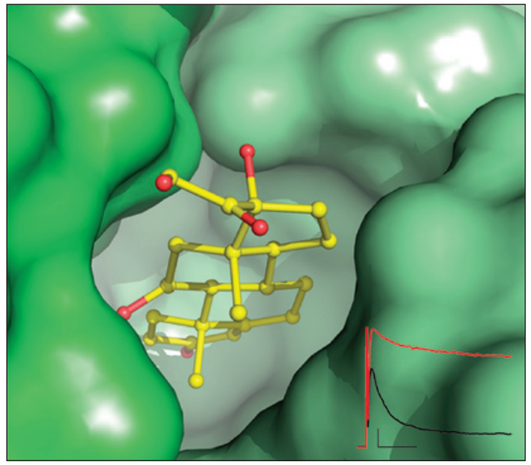
3. Structural Genomics of Membrane Proteins: We interact closely with the New York Consortium of Membrane Protein Structure (NYCOMPS) center and have contributed to implementing a high-throughput platform for expression, screening and purification of membrane proteins.

Research Advances from WU Center Faculty: Insights into Arrhythmias, Atherosclerosis, Stent Restenosis and Muscular Dystrophy

Novel Regulation of Potassium Channels by Steroids

Ming Zhou

The Shaker family voltage-dependent potassium channels (Kv1) are expressed in a wide variety of cells and are essential for cellular excitability. In humans, loss-of-function mutations of Kv1 channels lead to hyperexcitability and are directly linked to episodic ataxia and atrial fibrillation. All Kv1 channels assemble with beta subunits (Kvb), and certain Kvbs, for example Kvb1, have an N-terminal segment that closes a channel by the N-type inactivation mechanism. In principle, dissociation of Kvb1, although never reported, should eliminate inactivation and thus potentiate Kv1 current. We found that cortisone increases mammalian Kv1 channel activity by binding to Kvb1. A crystal structure of the Kvb-cortisone complex was solved to 1.82 A resolution and revealed novel cortisone binding sites. Further studies demonstrated that cortisone promotes dissociation of Kvb. The new mode of channel modulation may be explored by native or synthetic ligands to fine tune cellular excitability. Cortisone dissociates voltage-dependent K+ channel from its beta subunit. Published in *Nature Chemical Biology* in November 2008.



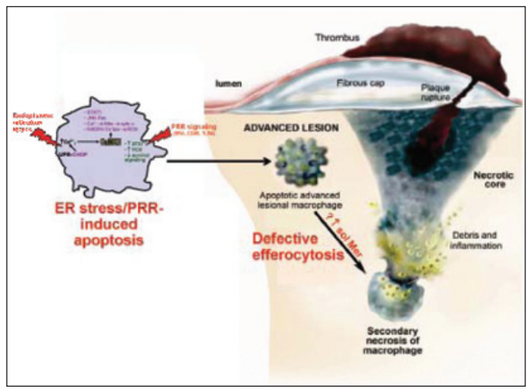
Cortisone potentiates potassium current. Cortisone, a common drug treating inflammation, was found to interact with beta subunit of voltage-dependent potassium channels. A high resolution crystal structure of cortisone in complex with the beta subunit reveals a novel regulation site. The beta subunit is shown as surface representation in green, and cortisone is shown as ball-and-stick, with carbon in yellow and oxygen in red. Potassium currents recorded before (black) and after (red) cortisone application are shown in the lower right corner. Ongoing research in Dr. Zhou's lab is aimed at understanding the physiological functions and pharmacological regulations of potassium channels.

Atherosclerosis and the Causes of Sudden Cardiac Death

Ira Tabas

The Tabas laboratory is studying the cell biological mechanisms responsible for transformation of benign atherosclerotic lesions into those that are likely to cause acute coronary syndromes, including unstable angina, myocardial infarction, and sudden cardiac death. The combination of macrophage death in advanced lesions plus defective phagocytic clearance of the dead macrophages is a critical linked process that promotes plaque vulnerability.

In 2008, the Tabas laboratory made several important discoveries related to each component of the linked process. For years, Tabas and others have implicated the endoplasmic reticulum stress effector CHOP in the process of advanced lesional macrophage death. Using genetically targeted mice in two separate atherosclerotic backgrounds, the laboratory provided direct molecular genetic causation data to support the role of CHOP in macrophage death and plaque vulnerability in advanced plaques. Moreover, in collaboration with the Marks laboratory, the laboratory found that CHOP functions in apoptosis by stimulating release of calcium from ER stores via activation of inositol 1,4,5-triphosphate receptors (IP3Rs). With regard to phagocytic clearance of dead macrophages, the laboratory used another set of genetically altered mice to show a definitive role for the receptor Mertk in the uptake of apoptotic macrophages in atheromata. Most importantly, a genetic mutation in this receptor resulted in a marked increase in vulnerable plaque progression. Recent data from the laboratory indicate that a defect in Mertk caused by cell-surface proteolytic cleavage is associated with vulnerable plaques in human arteries.



Atherosclerosis and the Causes of Sudden Cardiac Death (con't)

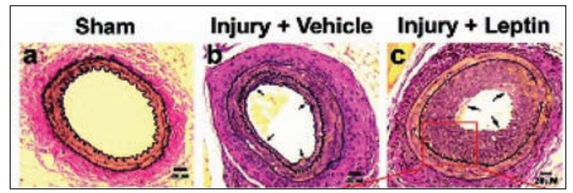
New Research May Improve Cardiac Stents for Patients with Diabetes

Andrew Marks

The naturally high levels of leptin in diabetic patients may reduce the effectiveness of drug-eluting stents used to treat heart blockages, but using a chemical that differs from the one commonly used to coat stents could counteract this effect.

The work by researchers in the Clyde and Helen Wu Center for Molecular Cardiology at Columbia University Medical Center could potentially improve outcomes in diabetics who get stents, they say. Though drug-eluting stents reduce the chance coronary arteries will become blocked again, clogged stents are still more common in diabetic patients than in the general population.

A hormone commonly associated with obesity – leptin – may be partly responsible, according to recently published research in the *Proceedings of the National Academy of Sciences* by Andrew Marks, MD, Chair of Physiology & Cellular Biophysics and Clyde and Helen Wu Professor of Molecular Cardiology, and Steven Marx, MD, Associate Professor of Medicine and Pharmacology.



Leptin-induced neointimal hyperplasia after arterial injury in mice is resistant to sirolimus. Femoral artery injury. Micrographs of neointimal formation (arrows) in representative injured femoral arteries in the presence or absence of leptin.

The study found that leptin, at the elevated concentrations frequently found in patients with diabetes, stimulates the growth of cells responsible for clogging the stents in mice, even in the presence of sirolimus, a drug used in many stents to prevent cell growth.

The same mouse study also identified a drug – a PI3 kinase inhibitor – that counteracts the effect of leptin on cell growth. If added to current drug-eluting stents, such a drug may further reduce reclogging rates in patients with diabetes to the single digit rates seen in other patients.

About 250,000 Americans with diabetes receive drug-eluting stents every year. An improved stent would significantly reduce the numbers who eventually need coronary bypass surgery after their stents become severely obstructed. The research was supported by the NIH and the American Heart Association.

Researchers Discover New Tactic Against Fatal Muscular Dystrophy

Andrew Marks

Columbia Drugs Similar to One in Trials for Heart Disease May Slow Muscle Loss in Muscular Dystrophy Patients

Based on a striking similarity between heart disease and Duchenne muscular dystrophy, researchers at Columbia University Medical Center have discovered that a new class of experimental drugs for heart failure may also help boys with the fatal muscular disorder.

At first glance, heart failure and muscle-wasting Duchenne couldn't appear more different. Duchenne affects young boys before they begin kindergarten, destroying their muscle cells. The boys become progressively weaker through their teens and usually die in their twenties. In people without Duchenne, heart failure typically starts much later in life, robbing the heart's pumping ability in the 7th, 8th or 9th decade of life.

But the new study found that the muscle cells affected in both diseases have sprung the same microscopic leak that ultimately weakens skeletal muscle in Duchenne and heart muscle in heart failure. The leak lets calcium slowly seep into the skeletal muscle cells, which are damaged from the excess calcium in Duchenne.

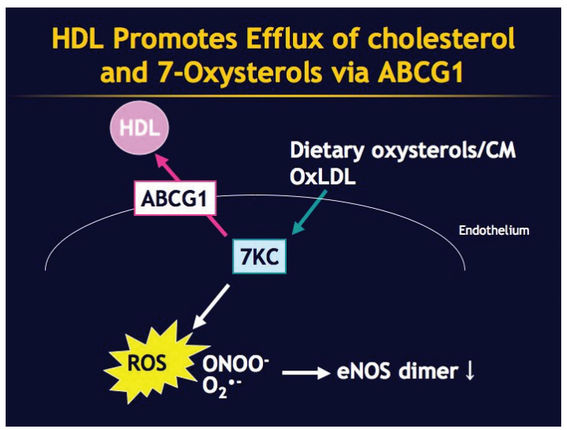
Andrew Marks, MD, the study's leader, hypothesized that a new class of experimental drugs developed at CUMC – which he had designed to plug the leak in the heart – could also work for Duchenne. The drugs, when given to mice with Duchenne, dramatically improved muscle strength and reduced the number of damaged muscle cells. "This was extremely exciting to us," says Dr. Marks, chair of the Department of Physiology & Cellular Biophysics and Clyde and Helen Wu Professor of Molecular Cardiology. "If it works in people, our drug won't be a cure, but it could slow the pace of muscle degeneration and extend the lives of people with Duchenne."

The study was published online Feb. 8 in *Nature Medicine*. Though the new drugs are not FDA-approved or currently available for Duchenne patients, one similar to that used in the Duchenne study is undergoing Phase I safety trials, and later this year trials will begin for heart failure.

New Ways that Raising HDL May Prevent Heart Disease

Alan Tall

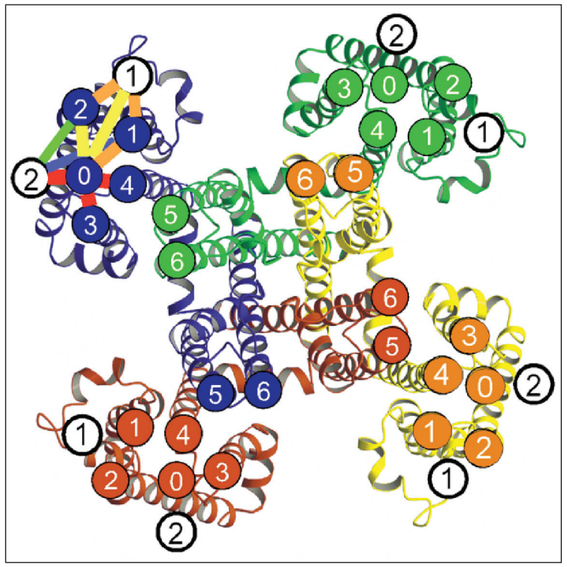
There is reasonable human data suggesting that HDL levels are associated with improvements in endothelial function involving eNOS. We found that ABCG1 is highly expressed in mouse and human endothelial cells, where it promotes efflux of cholesterol and 7-oxysterols (in your diet) to HDL. In mice with single or combined deficiencies of ABCA1 and ABCG1, it appears that ABCG1 has the predominant role in preserving endothelial eNOS activity on a high cholesterol diet. We have defined two underlying mechanisms: 1) efflux of 7-oxysterols reduces ROS-mediated reduction of the active, dimeric form of eNOS, and 2) efflux of cholesterol relieves the inhibitory interaction between eNOS and Cav-1. Therefore therapies that raise HDL may have atheroprotective properties via effects on endothelial ABCG1.



Gaining Insight into Hypertension, In-Stent Restensosis, and Arrhythmias

Steven Marx

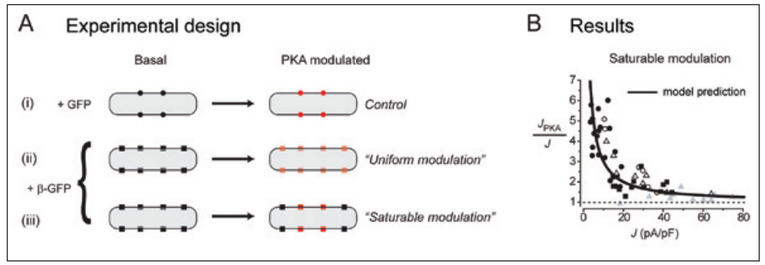
Steven Marx's research focuses on two major areas: **(1)** Cardiac: studying the regulation of ion channels in normal and pathological conditions in the heart. Altered cardiac ion channel function is associated with heart failure and arrhythmias. **(2)** Vasculature: understanding molecular mechanisms leading to vascular smooth muscle proliferation, migration and contractility. BK channels, as well as other vascular smooth muscle cell K+ channels, serve as regulators of $Ca2^{+}$ entry into the cell and thus are required for effective smooth muscle cell relaxation. Defects in BK channel function have been associated with increased incidence of seizures and disorders of smooth muscle contraction such as hypertension, asthma and urinary incontinence. The BK channel accessory subunit, called the beta1 subunit, is also critically important for its regulation. For instance, in hypertension and in asthma, down-regulation or mutations in the beta1 subunit are associated with disease. We believe that BK channel will represent a unique target for drug therapy to treat these disorders. We have recently identified a unique and potent small-molecule modulator of BK channels. Our goals are to understand how the beta1 subunit regulates the alpha subunit. In collaboration with Professor Arthur Karlin (Department of Physiology & Cellular Biophysics), we are exploring the contacts between the alpha and beta1 subunits by determining the extent of endogenous disulfide bond formation between cysteines substituted just extracellular to the two beta1 transmembrane (TM) helices, TM1 and TM2, and to the seven alpha TM helices, consisting of S1 – S6, conserved in all voltage-dependent potassium channels, and the unique S0 helix (Figure 1). We postulate that the TM1 and TM2 act as pincers on the voltage-sensor domain to modulate channel function.



We have taken a model of the structure of Kv1.2 in the closed state [1] as a model for the structure of BK alpha S1 through S6. The circles (white, black lettering) representing the extracellular ends of beta1 TM1 and TM2 are placed according to the means of the top three extents of crosslinking to the beta TM helices. The circles are connected by color-coded lines, shown only in the blue beta subunit, representing the binned extents of crosslinking: light blue, 5-19%; green, 20-39%; yellow, 40-59%; orange, 60-79%; red, 80-100%.
(From Liu et al, Proc Natl Acad Sci U S A. 2008 Aug 5;105(31):10727-32)

The Response to Stress – Insights into Heart Failure

Henry Colecraft



Protein kinase A (PKA) mediated up-regulation of L-type calcium currents in heart is essential to the fright-and-flight response. Loss of this channel modulation is a harmful hallmark of heart failure.

An important step towards understanding how this loss of modulation occurs in heart failure is to define the surplus capacity, or functional reserve, of the regulation under normal conditions. To achieve this, we titrated the number of calcium channels in heart by over-expressing an auxiliary beta subunit using recombinant adenovirus. Our results indicate that there is essentially no functional reserve for PKA-mediated increase in L-type calcium channels in heart. Therefore, this channel modulation would be expected to be highly sensitive to even subtle derangements of the PKA activation pathway, as is known to occur in heart failure.

Understanding the Regulation of Electrical Currents in the Heart

Robert Kass

The cardiac-delayed rectifier K+ current (IKS) is carried by a complex of KCNQ1 (Q1) subunits, containing the voltage-sensor domains and the pore, and auxiliary KCNE1 (E1) subunits, required for the characteristic IKS voltage dependence and kinetics. Inherited mutations in either subunit can cause heritable arrhythmias, and, most notably, mutations in the first transmembrane Q1 helix which cause gain of IKS function underlie two forms of congenital atrial fibrillation (AF). The functional consequences of the inherited AF mutations require interactions between the E1 and Q1 subunits, but the structural basis for this requirement demands insight into the intersubunit location which has not previously been known. In this study, we located the transmembrane (TM) helix of E1 (E1-TM) relative to the Q1 TM helices (S1–S6) using disulfide cross-linking of substituted cysteines. Our experiments indicate that the beta subunit of this channel (E1) is located between two TM

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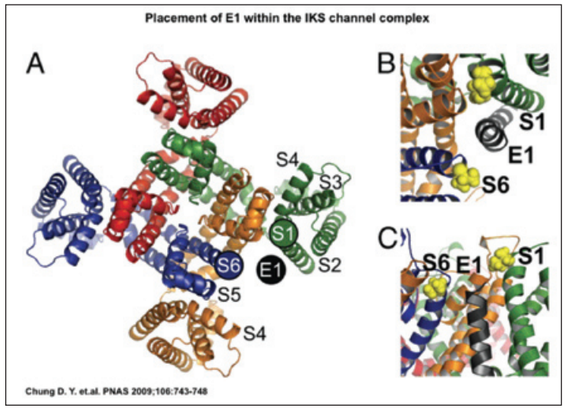

Figure 1. Placement of E1 within the IKS channel complex. (A) Extracellular view of a tetramer of Q1 with superimposed E1-TM. The extracellular ends of the S1 and S6 helices of two different Q1 subunits are indicated by filled circles, color-coded like the underlying model. Our proposed location of the extracellular end of one E1-TM is shown as a black circle. (B) Extracellular view of E1 docked in the open state model of IKS from Kang et al. (C) Side view of Kang et al. open mode

Alan Tall: Personal Research and Update on the CVRI

Despite major gains due to the use of statins to lower LDL, atherosclerotic cardiovascular disease remains the number one killer in the US and Europe and is also a threat to the people of the emerging economies. Alan Tall, head of the Molecular Medicine Division within the Department of Medicine, is carrying out research on plasma high density lipoproteins (HDL), which act as a protective factor in the development of atherosclerotic disease independent of LDL. Dr. Tall discovered the first human genetic deficiency state resulting in dramatically elevated HDL levels, caused by mutations in the cholesteryl ester transfer protein (CETP) gene. This discovery spurred the development of drugs to inhibit CETP that are being evaluated in advanced human clinical trials. Although the first drug in this class (torcetrapib) failed in human studies, subsequent research has revealed that this was likely due to off-target toxicity, and several other compounds without this toxicity are in phase 3 studies. In the meantime, Dr. Tall has continued basic research on HDL and with colleague Nan Wang has discovered a novel ATP binding cassette transporter, ABCG1, which along with ABCA1 is responsible for most of the efflux of cholesterol from macrophage foam cells to HDL. This has led to recent studies in which Tall and colleagues have discovered that HDL and the ABC transporters act in the bone marrow to suppress the proliferation of hematopoietic stem cells and myeloid progenitor cells, leading to suppression of monocytosis in animals fed high cholesterol diets, with consequent reductions in atherosclerosis. This is a new concept for the atheroprotective effect of HDL and points to the hematopoietic stem cell as a potential key player in atherogenesis.

Dr. Tall is also the head of the Cardiovascular Research Initiative (CVRI) of Columbia University. This is a broad, multi-disciplinary effort to foster both basic and clinical cardiovascular research. Dr. Tall, with Associate Director Robert Kass, leads an Executive Committee consisting of the basic science and clinical leadership and meets monthly to discuss and coordinate faculty recruitment and retention, visiting professorships, research funding opportunities and fund-raising. The mission statement, membership and current news items are available at http://www.cvri.columbia.edu/. The CVRI interfaces with the Wu Center in Molecular Cardiology headed by Dr. Marks, and Dr. Marks is an active member of the Executive Committee of the CVRI. The CVRI Executive Committee also advises on the selection of Wu Visiting Professors, as well as on the selection process for the Katz prize in Cardiology. The CVRI organizes bi-annual Research Symposia, featuring outstanding talks by CV researchers in different departments and disciplines. This provides a unique opportunity for interdisciplinary insights and collaborations. A major goal for this year is the recruitment of faculty in cardiovascular science. Priority areas for recruitment are cardiovascular genetics, vascular biology and cardiac development. Joint searches with Medicine, Pediatrics and Physiology are currently underway. Potential faculty are screened by the CVRI Executive Committee as well as by their potential host departments. During this academic year five different individuals have been hosted at Columbia as part of this recruitment effort. A long-term goal of the CVRI is to raise funds for a new building devoted in part to Cardiovascular Research.

Understanding the Regulation of Electrical Currents in the Heart

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this channel (E1) is located between two TM helicies (S1 and S6) on different subunits of Q1 (Figure 1), and furthermore provide insight into a role of E1 rotational movement in the control of channel gating. This work, for the first time, allows an understanding of the structural basis of mutations in this key potassium channel that cause atrial fibrillation in humans. Because the work provides a structural framework to understand the basis for AF in patients carrying these mutations, it also provides the salient functional effects of selected cross-links as follows: A disulfide from E1 K41C to S1 I145C strongly slowed deactivation, and one from E1 L42C to S6 V324C eliminated deactivation. Given that E1-TM is between S1 and S6 and that K41C and L42C are likely to point approximately oppositely, these two cross-links are likely to favor similar axial rotations of E1-TM. In the opposite orientation, a disulfide from E1 K41C to S6 V324C slightly slowed activation, and one from E1 L42C to S1 I145C slightly speeded deactivation. Thus, the first E1 orientation strongly favors the open state, while the approximately opposite orientation favors the closed state.

New Laboratories Planned for Wu Center for Molecular Cardiology, including a New Logo

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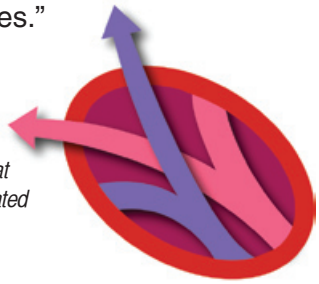
"The relocation of the Wu Center for Molecular Cardiology will place our scientists near others working in the related fields of diabetes and obesity, both of which play major roles in contributing to heart disease, so this will increase synergy at Columbia. In addition, we anticipate that the next new research building will be adjacent to the Berrie building and will include several floors for new heart researchers, so being right next to that effort will create a focus on campus for all of basic heart investigations," Dr. Marks noted.

In addition to the laboratory of Dr. Marks, others on the floor will include Professor Henry Colecraft, who works on calcium channels in the heart, and Dr. Filippo Mancia who works on the structure of membrane proteins, including calcium channels. "Setting up these new labs offers the opportunity for collaborations and should really help advance efforts in molecular cardiology at Columbia," according to Professor Henry Colecraft. "It is going to be great to work together and train new scientists to follow in our footsteps. The environment for molecular cardiology is terrific here at Columbia and the support from the Wu's has really helped bring together a lot of talented scientists who are working hard together to conquer heart diseases."



A new logo, designed by Brian Soda and Marnie Foster-Marks, has been developed to represent the Clyde and Helen Wu Center for Molecular Cardiology. The "W" in the logo represents both the "Wu" support for the Center and the flow of deoxygenated (blue) blood that returns from the body to the right side of the heart while the oxygenated (red) blood is pumped out of the left side of the heart to the organs.