CARDIOLOGY DIVISION PUBLICATIONS 2009
G. William Dec, MD; Chief
Kenneth Chien, MD, PhD, Associate Chief
Stathis Antoniades, MPH, Senior Administrative Director
Adrienne Sisco, Administrative Director for Research

Cardiology Clinical/Translational /Basic Research Publications:

Total publications: 357
Original articles: 257
Reviews/Chapters: 99
Textbooks 1

Key Scientific Achievements

Cardiovascular Research Center

Kenneth R. Chien, MD, PhD
This paper was recognized as one of the top advances in heart disease and stroke research for 2009 by the American Heart Association:


Quoted from the AHA press release: “In this study, scientists grew a piece of spontaneously beating heart muscle using stem cells from a mouse embryo. This is a major advancement toward one day repairing damage caused to the heart muscle by a heart attack.”

Antonis A. Armoundas, PhD
The implantable cardioverter defibrillator (ICD) is the most effective means of treating lethal ventricular arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF). However, despite its rapid acceptance and growth, the main limitation of current ICD technology is that it is only able to detect and treat an arrhythmia after the arrhythmia has started. However, many ventricular arrhythmias lead to rapid hemodynamic instability and may quickly become fatal, leaving a very narrow time window for the arrhythmia detection and delivery of therapy. Additionally, there is considerable evidence to suggest that ICD shocks may be detrimental, and in some cases increased non-arrhythmic mortality. Therefore, the design of novel ICD technology capable of delivering preventive, patient-customized therapy, prior to the actual on-set of an arrhythmia, will be a paradigm shift in improving the efficacy of ICD therapy and reducing the morbidity associated with ICD shocks.

A key component of our work in 2009 involved to investigate the hypothesis that one may develop a method for preventing potentially lethal heart rhythm disturbances,
VT/VF, by recording cardiac electrical activity from within the heart, measuring beat-to-beat variability in the morphology of electrocardiographic waveforms, namely repolarization alternans (RA), and using the measured beat-to-beat variability to control the delivery of electrical therapy to the heart. We have developed a novel pacemaker which we can use to suppress RA in-vivo, and recently we have shown that suppression of RA resulted to decreased arrhythmia susceptibility.

This paradigm shift in ICD technology is expected to (i) reduce the morbidity and mortality resulting from failure, delay or false detection of VT/VF, (ii) reduce the frequency of the ICD discharges, (iii), reduce the pain and complications associated with high-energy ICD therapy (iv) reduce collateral damage to the myocardium during high output electrical shocks, (v) prolong ICD battery life span and potentially reduce health care costs.

Dmitriy Atochin, PhD

We examine the importance of endothelial nitric oxide synthase (eNOS) as an Akt1 substrate by generating Akt1-deficient mice (Akt1(-/-) mice) carrying knock-in mutations (serine to aspartate or serine to alanine substitutions) of the critical Akt1 phosphorylation site on eNOS (serine 1176) that render the enzyme "constitutively active" or "less active." The defective postnatal angiogenesis characteristic of Akt1(-/-) mice was rescued by crossing the Akt1(-/-) mice with mice carrying the constitutively active form of eNOS, but not by crossing with mice carrying the less active eNOS mutant. This genetic rescue resulted in the stabilization of hypoxia-inducible factor 1alpha (HIF-1alpha) and increased production of HIF-1alpha-responsive genes in vivo and in vitro. Thus, Akt1 regulates angiogenesis largely through phosphorylation of eNOS and NO-dependent signaling.

C. Geoff Burns, PhD
Discovery of the zebrafish secondary heart field.
Defects in secondary heart field stem cells are important causes of cono-truncal congenital cardiovascular malformations. Through the characterization of a protein required for TGFbeta signaling and cre/lox based lineage tracing, the Burns Lab has discovered that zebrafish cardiogenesis relies on a stem cell population analogous to the mammalian secondary heart field. As a result of this discovery, the zebrafish model system now becomes a highly relevant and useful model organism for discovering novel genetic and environmental causes of cono-truncal defects in humans.

Patrick T. Ellinor, MD, PhD


In this manuscript we identified a novel genetic locus for atrial fibrillation by performing a meta-analysis of five genome wide studies in community based cohorts. This study
confirms that even more typical forms of atrial fibrillation observed in the community has a genetic basis.

Chris Newton Cheh, MD

We established for the first time the in vivo relevance of the natriuretic peptide system in blood pressure regulation in humans. These findings have direct implications for the role of natriuretic peptide mimetics (including recombinant BNP, sildenafil, BAY41-2272 a direct sGC stimulator) as antihypertensive therapies. We are currently using genetic stratification in human physiologic experiments to establish the interaction of natriuretic peptide genetic variation with acute and chronic responses to salt exposure (R01 PI: Newton-Cheh, Wang). This work was selected among 256 abstracts for an award as Best Translational Research at the MGH Clinical Research Day.


We identified common genetic variants at ten loci that modulate myocardial repolarization, as represented by the electrocardiographic QT interval, in humans, 5 previously recognized and 5 novel. These variants collectively identify 20% of the population with 10msec higher QT interval, equal to the QT prolongation associated with drugs pulled from the market for association with ventricular arrhythmias. We are currently studying these variants in human physiologic experiments, in which individuals stratified by genotype group are administered moxifloxacin, a mild QT-prolonging therapy (Harvard Catalyst Pilot).


This large-scale international genome-wide association study identified 8 genetic loci, 6 of which had never previously been implicated in blood pressure regulation in humans. This work was selected as one of the top ten findings in 2009 in cardiovascular research (http://americanheart.mediaroom.com/index.php?s=43&item=914 ITEM #8). We are undertaking large-scale resequencing of these loci in 400 individuals from the Framingham Heart Study (NIH Intramural funds).


Here, in the largest genetic study conducted to date for myocardial infarction, we mapped nine gene regions associated with early-onset myocardial infarction. Several of
these gene regions do not relate to known risk factors and thus, point to new pathways to atherosclerosis that do not seem to work through known risk factors.

**Randall T. Peterson, PhD**


This manuscript describes a screen for small molecules that reverse the disease phenotype in a zebrafish model of acute myeloid leukemia. The molecules discovered point to a role for Wnt signaling in AML and suggest a novel therapeutic approach for its treatment.

**Jesse D. Roberts, MD**


In this publication, we examined the novel hypothesis that an elastin modifying enzyme, lysyl oxidase, plays an important role in the pathogenesis of bronchopulmonary dysplasia. My laboratory utilized neutralizing antibodies to assess the role of excessive TGF-β activity plays in disrupting elastin formation and contributes to decreased alveologenesis in the injured newborn lung. These studies refine the mechanisms involved with the formation of chronic lung disease.

**Stanley Shaw, MD, PhD**


Together, these two papers establish a novel, generalizable platform for the synthesis, screening and characterization of chemically-modified nanoparticles for molecular imaging. Paper #1 describes a new method to screen a library of imaging nanoparticles for those with targeting specificity against a desired cell type, and its application to visualization of blood vessels in vivo. Paper #2 describes a new method to quantitate the affinity and kinetics of imaging nanoparticles binding to their targets, and identifies new complexity in conventional wisdom.

**Sean M. Wu, MD, PhD**

The Wu laboratory has continued its work on the biology of Nkx2.5+ cardiac progenitor cells in 2008. Based on the finding from its publication in Cell in 2006, Dr. Wu has described the potential use of multipotent cardiac progenitor cells derived from embryonic stem cells (ESC) and induced pluripotent stem cells (iPSC) to understand cardiac development, disease, and regeneration in an essay published in Cell in early
2008 (#1). Related to this, Dr. Wu has also compared the regenerative potential of adult versus embryonic stem cells for cardiac therapy (#2). In a collaborative effort with Dr. William Pu at Boston Children’s Hospital, Dr. Wu has shown in an article in Nature that an epicardial progenitor cell population marked by the expression of WT1 can undergo cardiomyogenic differentiation, express Nkx2.5, and form cardiomyocytes during fetal development (#3). To address the lineage precursors and descendents of embryonic cardiac progenitor cells, Dr. Wu has published a preview article in Cell Stem Cell evaluating the role of mesoderm posterior 1 as a master regulator of cardiogenesis in the developing heart (#4) and characterized the postnatal descendents of embryonic Nkx2.5+ progenitor cells (#5). Given the tremendous therapeutic potential for cardiac stem cells to treat cardiovascular diseases, Dr. Wu was invited to publish an expert opinion article in Drug Discovery Today: Therapeutic Strategies on the clinical readiness of cardiac stem cell-based therapy (#6) and have collaborated with Drs. Domian and Chien on the derivation of engineered cardiomyocytes using ESC-derived committed ventricular cardiomyogenic progenitor cells (#7).

The Wu laboratory has also introduced a new line of research on the exciting and emerging topic of iPSC and nuclear reprogramming in 2008. With the assistance from Dr. Hochedlinger’s lab at the MGH Center for Regenerative Medicine, Dr. Wu has derived multiple lines of iPSC carrying the Nkx2.5-eGFP transgenic reporter and show that despite their described capacity to undergo cardiomyogenic differentiation, iPSC-derived cardiomyocytes exhibit impaired maturation compared with ESC-derived cardiomyocytes (#8, #9). This work is currently under journal review and revision. To further characterize such difference, Dr. Wu has received a seed grant from the Harvard Stem Cell Institute to examine the functional capacity of iPSC-derived heart and skeleton during embryonic development. With the anticipated role of iPSC to transform stem cell biology and perhaps clinical therapy in the future, Dr. Wu is currently using developmental approaches to examine ways to generate functional organs from iPSC in a project funded by the NIH Director’s New Innovator Award that specifically encourages high risk/high impact scientific endeavors.

Paul B. Yu, MD, PhD
Our group has continued to pursue development of pharmacologic tools for the manipulation of bone morphogenetic protein (BMP) signaling in physiology and disease. Several of our publications reflect successful international collaborations applying these tools towards the elucidation of BMP function in diverse processes such as epithelial cell lineage commitment and bone mass regulation, and in diseases such as fibrodysplasia ossificans progressiva. In addition, we have continued to develop our models of vascular calcification and pulmonary arterial hypertension, using similar genetic and small molecule tools.

Jing-Ruey Joanna Yeh, PhD
We show that engineered zinc finger nucleases (ZFNs) can efficiently introduce target gene mutations in a popular model organism- zebrafish, enabling the development of human disease models in zebrafish. Furthermore, we have used a zebrafish model of acute myelogenous leukemia (AML) that we generated to identify compounds that can reverse AML-like phenotype in the zebrafish.
PUBLICATIONS

JOURNAL PUBLICATIONS


Kamiya N, Kobayashi T, Mochida Y, Paul B. Yu, Yamauchi M, Kronenberg HM, Mishina Y. Wnt inhibitors Dkk1 and Sost are downstream targets of BMP signaling through the Type Ia receptor (BMPRIA) in osteoblasts. Journal of Bone and Mineral Research. 2009; Oct 29.


Schnabel* RB, Baumert* J, Barbalic* M, Dupuis* J, Ellinor* PT, Durda P, Dehghan A, Bis JC, Illig T, Morrison AC, Jenny NS, Keaney JF Jr, Gieger C, Tilley C, Yamamoto JF,


patients with advanced heart failure and contributes to adverse ventricular remodeling after myocardial infarction in mice. *Circulation* 2009, 119:408-16.


Ponnuswamy P, Ostermeier E, Schottle A, Chen J, Huang PL, Ertl G, Nieswandt B, Kuhlencordt PJ. Oxidative stress and compartment of gene expression determine


Reviews/Chapters/Editorials


Clinical Cardiology


Heart Failure/Cardiac Transplantation


**Chapters/Reviews/Editorials**


Semigran MJ. Phosphodiesterase Type 5 Inhibition: More function with less mass. *J Am Coll Cardiol*. 2009;53:216-7


Lewis GD, Systrom DM. Normal Exercise Physiology. Up To Date, 2009


**Translational Research/Biomarkers/Epidemiology**


**Chapters/Reviews/Editorials**


Shah, RV and Januzzi JL. NT-proBNP and Heart Failure. *European Cardiovascular Disease: Clinical Insights and Practice*, 2009;1:30-34.


**Textbook**


**Nuclear Cardiology**


**Chapters/Editorials/Reviews**


Gewirtz H: “Funny Current”: If heart rate slowing is not the best answer, what might be? (Invited Editorial) – *Cardiovascular Research* 2009; 84:9-10

**Preventive Cardiology**


**Chapters/Reviews**

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See also under CVRC

**Cardiac Arrhythmia**

Singh, SM; Heist, EK; Koruth, JS; Barrett, CB; Ruskin, JN; Mansour, MC. The relationship between electrogram cycle length and Dominant Frequency in patient with persistent atrial fibrillation Persistent Atrial Fibrillation. *Journal of Cardiovascular Electrophysiology* 2009;20:1336-42.


Heist, EK, Tondo C, Blendea D, Ruskin JN, Mansour M. Mapping and ablation of atypical AVNRT from the morphologic left atrium in a patient with dextrocardia and situs inversus. PACE 2009 (in press)

**Chapters/Reviews**


**Echocardiography/Cardiac Imaging**


Senior R, Monaghan M, Main ML, Zamorano JL, Tiemann K, Agati L, Weissman NJ, Klein AL, Marwick TH, Ahmad M, DeMaria AN, Zabalgoitia M, Becher H, Kaul S,


**Reviews/chapters**


Scherrer-Crosbie M, Kurtz B. Ventricular remodeling and function: insights using murine echocardiography. *J Mol Cell Cardiol* 2009 (Epub ahead of print)


Echocardiography’s Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. J Am Soc Echocardiogr 2009;22:975-1014.


Classic images in cardiac magnetic resonance imaging: a case-based atlas highlighting current applications of cardiac magnetic resonance imaging. Francis SA, Coelho-Filho OR, O’Gara PT, Kwong RY. Curr Probl Cardiol. 2009 Jul;34(7):303-22.

**Interventional Cardiology**


Witzke C, Don CW, Cubeddu RJ, Herrero-Garibi J, Pomerantsev E, Caldera A, McCarty D, Inglessis I, Palacios IF. Impact of rapid ventricular pacing during percutaneous


**Reviews, Chapters, and Editorials**


**Vascular Medicine**


Thatipelli MR, Misra S, Sanikommu SR, Schainfeld RM, Soukas PA. Safety and short-term outcomes following controlled blunt microdissection revascularization of

**Chapters/Reviews/Editorials**


McCann A, Jaff MR. Treatment strategies in peripheral artery disease. Accepted for publication. *Expert Opin Pharmacother* 2009;10:1571-86.


Jaff MR. Editor. American College of Cardiology Focus on Vascular Disease, 2009. This is a comprehensive web-based tutorial course on vascular disease, including recorded didactic lectures, case presentations, and examination questions.