UM – Israel Partnership for Research

The 2nd Annual D. Dan and Betty Kahn

University of Michigan – Technion

Collaborative Cardiovascular Research Symposium

"Electricity and Sugar in the Heart"

Collaboration Leaders:

Michael Aviram and David Pinsky

December 6th, 2012

Technion – Institute of Technology

Ruth Hall, Bruce and Ruth Rappaport Faculty of Medicine

Haifa, Israel

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08:00-08:30 Registration

08:30-09:20 Opening Remarks

Eliezer Shalev; Minnie and Ruben Finkelstein Academic Chair, , Professor of Obstetrics and Gynecology, Chairman of the Department of Obstetrics and Gynecology at "Ha'Emek" Medical Center in Afula and Dean of the Rappaport Faculty of Medicine, Technion.

David Pinsky; J Griswold Ruth and Margery Hopkins Ruth Professor of Internal Medicine; Professor of Molecular and Integrative Physiology; Taubman Scholar; Division Chief, Cardiovascular Medicine; Director, Cardiovascular Center, University of Michigan

Michael Aviram; Tanenbaum Chair in Preventive Medicine, Professor of Biochemistry, Head, Lipid Research Laboratory, Director, Clinical Research Institute at Rambam and Senior Vice Dean, Ruth & Bruce Rappaport Faculty of Medicine, Technion.

Announcement on the 2012 collaborative grant awardees

Ofer Binah (Technion) **+ Dan Michele** (UM): Muscular Dystrophy Patient-Specific Stem Cell Derived Cardiac Myocytes for Studying Disease Mechanisms and Therapy Development

Peleg Hasson (Technion) **+ Santhi K. Ganesh** (UM): TGF-beta and Lysyl Oxidase Interactions in Arterial Development and Remodeling

2011 Awardee Update

Marcelle Machluf (Technion) + **Jérôme Kalifa** (UM): Site-specific Ultrasound-Enabled Cardiac Anti-Fibrotic Gene Therapy

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Ami Aronheim (Technion) + **Omer Berenfeld** (UM): The Role of the ATF3 Transcription Factor in Atrial Remodeling and Atrial Fibrillation

09:20-10:30 Presentations

Chair: Jóse Jalife, MD Cyrus and Jane Farrehi Professor of Cardiovascular Research, Professor of Internal Medicine; Professor of Molecular and Integrative Physiology; Co-Director, Center for Arrhythmia Research; Director, Cardiovascular Research Center

Haim Hammerman MD, FESC, Director**,** Department of Cardiology, Rambam Medical Center, Rambam Health Care Campus. Associate Professor, Bruce & Ruth Rappaport Faculty of Medicine.

09:20-09:35 Eldad Tzahor (Weizmann Institute): Heart Development and Regeneration: Lessons from the Embryo

09:40-9:55 David Bach (UM): Mitral Valve Prolapse with Left Atrial Enlargement out of Proportion to Mitral Regurgitation

10:00-10:15 Amir Landesberg (Technion): Reverse Excitation Contraction Coupling; the Effects of the Loading Conditions on the Energy Consumption and Action Potential.

10:20-10:30 Thomas Crawford (UM): My Heart Your Heart – A Collaborative Effort to Alleviate Lack of Pacemaker Access.

10:30-11:00 Coffee Break

11:00-12:35 Presentations - <u>Diabetes Section</u>

Chair: Ohad Cohen, MD Institute of Endocrinology, Chaim Sheba Medical Center, Tel Hashomer

Naim Shehadeh, MD Department of Pediatrics A, Rambam Medical Center, Haifa

11:00-11:15 Alan Saltiel (UM): Inflammatory Links between Obesity, Diabetes and Energy Expenditure

11:20-11:35 Rodica Pop-Busui (UM): Cardiovascular Autonomic Neuropathy, Myocardial Dysfunction and Cardiovascular Risk in Diabetes

11:40-11:55 Sandeep Pandit (UM): Impaired Electrical Propagation in the Diabetic Heart

12:00-12:15 **Doron Aronson (Technion):** Mechanisms of Diabetic Cardiomyopathy

12:20-12:35 **Andrew Levy (Technion):** Pharmacogenomic Application of the Hepatoglobin Genotype in the Prevention of Diabetic Cardiovascular Disease: From the Bench to the Bedside

12:35-13:35 **Lunch Break**

13:35-15:00 **Presentations**

Chair: **Hector Valdivia**, MD, PhD, Frank Norman Wilson Professor of Cardiovascular Medicine and Professor of Internal Medicine, Cardiovascular Medicine

Moshe Flugelman, Head, Inpatient Cardiology, Carmel Medical Center, Ruth & Bruce Rappaport Faculty of Medicine, Technion.

13:35-13:50 **Lior Gepstein (Technion):** Electrophysiological Implications of Pluripotent Stem Cell

13:55-14:10 **Daniel Michele (UM):** Mechanisms of Cardiomyopathy in Inherited Muscular Dystrophies.

14:15-14:30 **Michael Eldar (Sheba Medical Center):** Asymptomatic Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) – Risk Stratification and Therapeutic Options

14:35-14:45 **David Sherman (UM):** Drug Discovery and Development Efforts Employing Unique Chemical Diversity Resources against Cardiovascular Targets

14:50-15:00 **Adam Stein (UM):** Epigenetic Regulation of Cardiomyocyte Phenotypes

15:00-15:25 **Coffee Break**

15:25-16:40 Presentations

Chair: Uri Rosenchein, Head, Department of Cardiology, Bnai Zion Medical Center, Associate Professor Ruth & Bruce Rappaport Faculty of Medicine, Technion.

Basil S. Lewis, Louis Edelstein Professor of Medicine and Medical Research, Bruce & Ruth Rappaport Faculty of Medicine and Director, Department of Cardiovascular Medicine, Lady Davis Carmel Medical Center.

15:25-15:40 **Santhi Ganesh (UM):** Genetic Approaches to Understanding Arterial Dysplasia

15:45-16:00 **Monther Boulus (Technion):** Unmet Need in Mapping and Ablation in Atrial Fibrillation

16:05-16:20 **Yoram Etzion (Ben Gurion University):** Arterial Tachycardia-Remodeling in Rats, Applications for Genetic and Molecular Studies of Arterial Fibrillation

16:25-16:40 **Uri Yaron (J&J):** Innovation in the Mapping and Ablation of Atrial Fibrilation.

20:00 Reception - Dan Panorama Hotel

20:30 Dinner

Closing Remarks:

Lawrence Jackier
Chairman of the Board of Governors of the Technion

Peretz Lavie
President, Technion Institute of Technology

Eliezer Shalev
Dean, Ruth & Bruce Rappaport Faculty of Medicine

Alan Saltiel
University of Michigan

David Pinsky and Michael Aviram - Thank you and "Charge for the future"

Eldad Tzhaor, PhD

Heart Development and Regeneration: Lessons from the Embryo

Over the past few years we have focused on the developmental programs of the heart and skeletal muscles of the head. In contrast to our understanding of how skeletal muscle is formed in the trunk, much less is known about the tissues and molecules that induce the formation of the head musculature. Our studies over the last decade have addressed the origins, signaling, and genetics of distinct head muscles. Considerable cellular and genetic variations exist among the different craniofacial muscle groups, and their associated satellite cells. Cellular and molecular parallels are drawn between cardiac and pharyngeal muscle developmental programs, and argue for the tissues' common evolutionary origins. During embryogenesis, parts of the heart and craniofacial muscles arise from common origins within the pharyngeal mesoderm (PM). I will present unpublished data revealing a hierarchical gene regulatory network of transcription factors expressed in PM progenitors that initiates heart and craniofacial organogenesis. Genetic ablation experiments that perturbed this network in mice resulted in severe heart and craniofacial muscle defects. We identified Lhx2, a LIM domain transcription factor, as a novel player during cardiac and pharyngeal muscle development. Lhx2 and the bHLH transcription factor Tcf21 genetically interact with Tbx1; furthermore knockout of these genes recapitulates specific features of DiGeorge/velo-cardio-facial/22q11.2 deletion syndrome. We suggest that PM-derived cardiogenesis and myogenesis are network properties, rather than properties specific to individual PM members. These findings shed new light on the developmental underpinnings of congenital heart and craniofacial defects.

David S. Bach, MD

Mitral Valve Prolapse with Left Atrial Enlargement out of Proportion to Mitral Regurgitation

Accurate quantitation of mitral regurgitation (MR) severity is challenging, and best performed using an integrative approach. Because left atrial (LA) and left ventricular (LV) dilation are compensatory mechanisms expected to accompany chronic severe MR, their presence can be used to support or establish a diagnosis of severe MR. A series of 9 patients (3 women and 6 men, age 45 to 78 years, followed for 4.8 ± 2.2 [range 1.9 to 8.5] years) were identified with mitral valve prolapse (MVP) and trace or mild MR, but with severe (7 of 9 [LA volume index ≥ 40 mL/m^2]) or moderate (2 of 9 [LA volume index 30-40 mL/m^2]) LA enlargement. 2 of 9 patients also had evidence of mild LV enlargement (LV volume index 76 – 86 mL/m^2). No patient had LV hypertrophy, significant LV diastolic dysfunction, or atrial fibrillation. It is possible that the connective tissue abnormality responsible for MVP also can result in LA or LV enlargement out of proportion to MR, with potential clinical implications leading to over-estimation of MR severity.

Amir Landesberg, PhD

Reverse Excitation Contraction Coupling; the Effects of the Loading Conditions on the Energy Consumption and Action Potential.

Frank-Starling's Law and the well-known end-systolic pressure volume relationship of the left ventricle reflect the effects of the mechanical loading conditions (preload and afterload) on cardiac contraction and energy consumption. We have studied the underlying mechanisms at the whole heart level and isolated fiber level. The studies strongly suggest that there is a dominant feedback of the number of force generating actomyosin cross-bridges to cardiac troponin calcium affinity.

The above concept, denoted as the cross-bridge calcium cooperativity, predicts that an increase in the generated force shortens the action potential duration, and this prediction was validated in isolated trabeculae. Moreover, it suggests that rapid decline in the force by sarcomeres in the border zone of a weak (ischemic) myocardium during the late relaxation phase causes calcium release from troponin. This late calcium surge can initiate calcium waves by calcium induced calcium release from the sarcoplasmic reticulum, and produce delay after depolarization. These changes in the free-calcium and the associated delayed after depolarization were validated experimentally by inducing reversible inhomogenous excitation contraction coupling in a segment of isolated trabeculae. Modulation of cytosolic calcium concentration by the loading conditions also affects mitochondrial calcium and regulates ATP production. The rate of ATP production by the mitochondria is coupled to the rate of ATP consumption by the sarcomere through changes in the nucleotide and calcium concentrations. The effect of changes in the loading conditions on the cytosolic calcium transient can explain the empirical observation that significant changes in the metabolic fluxes can occur without significant changes in the key nucleotide (ATP and ADP) concentrations. Thus, the reverse excitation contraction coupling through the effect of the loading condition on the cytosolic calcium has important repercussions for development of triggered arrhythmias and the modulation of the failing heart mechanics and energetics.

Quantitative investigations of the mechanisms underlying the cardiac control of the excitation contraction coupling and biochemical to mechanical energy conversion are important for understanding disease mechanisms and may lead to development of novel drugs and therapeutic modalities.

Thomas C. Crawford, MD

My Heart Your Heart – A Collaborative Effort to Alleviate Lack of Pacemaker Access

Globally, one million people die annually due to lack of access to pacemaker therapy. Small retrospective studies show pacemaker reuse is associated with similar rates of infection to that of new implants. We collected 1,100 devices with >75% of the original battery life and developed a validated sterilization protocol. Technion's biomedical engineering expertise may lead to the development of advanced device testing protocols to assure proper mechanical function of all pacemaker components. Other potential avenues for collaboration would include expansion of device collection and tracking.

Alan Saltiel, PhD

Inflammatory links between obesity, diabetes and energy expenditure

Obesity is associated with chronic low-grade inflammation that negatively impacts insulin sensitivity. High fat diet can increase NFκB activation in mice, which leads to a sustained elevation in levels of the non-canonical IKKs, IκB kinase ε (IKKε) and TBK1, in liver, adipocytes and adipose tissue macrophages. We explore the role of these enzymes by gene knockout and inhibitor studies. These data suggest that IKKε and TBK1 play an important role in chronic inflammation in liver and fat, hepatic steatosis and whole-body insulin resistance. Blockade of the activity of these two kinases produces increased energy expenditure and thermogenesis, along with improved insulin resistance and fatty liver. We will discuss the role of inflammation and the NFkB pathway in the generation of insulin resistance and persistent obesity in metabolic disease.

Rodica Pop-Busui, MD, PhD

Cardiovascular Autonomic Neuropathy, Myocardial Dysfunction and Cardiovascular Risk in Diabetes

Cardiovascular autonomic neuropathy (CAN) is associated with high-risk of life-threatening arrhythmias and is a strong independent predictor of mortality in patients with diabetes. Recent data also suggest that, in diabetes, CAN promotes left ventricle dysfunction in the absence of ischemic, hypertensive, or significant valvular diseases. This presentation will review data from large, prospective cohorts of patients with type 1 and type 2 diabetes supporting the role of CAN as independent predictor of mortality, and will discuss recent evidence regarding the arrhythmogenic substrate and natural history of myocardial dysfunction in diabetes.

Sandeep V. Pandit, PhD

Impaired Electrical Propagation in the Diabetic Heart

Diabetes increases the risk of sudden cardiac death, but the mechanisms remain unclear. We have investigated the electrophysiological alterations occurring in diabetic rabbit hearts. Optical mapping in Langendorff-perfused hearts showed that the action potential duration was unchanged, but the conduction velocity was reduced in diabetes. The Na^+ current (I_{Na}) density was reduced in diabetic myocytes. Staining showed a lateralization of connexins (Cx43) in diabetic hearts, but unchanged fibrosis levels. The mRNA levels of Nav1.5/Cx43 were unaltered. Computer simulations attributed the slower conduction in diabetic heart to reduced I_{Na}. An impaired "propagation reserve" may have important implications for arrhythmogenesis in diabetes.

Doron Aronson, PhD

Mechanisms of Diabetic Cardiomyopathy

Compared with the general population, the relative risk of heart failure for men and women with diabetes is approximately 2- and 5-fold greater, respectively independent of coexisting hypertension or ischemic heart disease. Echocardiographic studies in patients with diabetes demonstrated abnormal diastolic function using conventional Doppler techniques as well as with more sensitive methods such as strain, strain rate, and myocardial tissue velocity. These studies also show increased left ventricular absolute and relative wall thicknesses and left ventricular mass with diabetes. These observations led to the concept of "diabetic cardiomyopathy" as a district complication independent of comorbid conditions.

Although this entity remains controversial, I will present evidence that diabetes is associated with distinct pathophysiological mechanisms that alter the mechanical properties of the myocardium.

Collagen cross-linking is a major mechanism that diabetes-associated reduction in cardiac compliance. The formation of advanced glycosylation end products on myocardial and vascular wall and collagen causes cross-linking of collagen molecules to each other. This leads to the loss of collagen elasticity, and subsequently a reduction in myocardial and arterial compliance.

I will also discuss lipotoxicity as a contributing mechanism to cardiac dysfunction in diabetes. Obesity and insulin resistance are associated with excessive free fatty acid delivery. Fatty acid uptake by cardiac myocytes exceeds mitochondrial oxidative capacity. The resultant lipid overstorage (also known as cardiac steatosis) produces lipotoxic intermediates such as ceramide that increase production of reactive oxygen species and cause apoptosis.

Andrew Levy, MD PhD

Pharmacogenomic Application of the Hepatoglobin Genotype in the Prevention of Diabetic Cardiovascular Disease: From the Bench to the Bedside

Diabetes Mellitus (DM) currently afflicts nearly 300 million individuals worldwide and the risk of an individual born today is one in three of developing diabetes. DM results in a dramatic reduction in the duration and quality of life due to the development of vascular complications developing 10-15 years after its onset affecting the heart, kidney and eyes. Over 75% of all individuals with DM die due to heart attacks directly as a result of DM. In addition about one-third of all DM individuals lose their kidney function and require expensive and burdensome dialysis treatment and over 10% of DM individuals lose part or all of their vision. The public health cost of DM is also staggering-principally due to management of the complications. World-wide costs of treating DM and its complications exceed $500 billion per year. Finally, there is a tremendous disparity world-wide and by socioeconomic class in the treatment that is affordable to the individual with DM. Many of the medications currently considered to be standard of care to prevent DM induced complications are too expensive for individuals of lower socioeconomic class or in the developing world. In this presentation we will present a personalized treatment approach to the management of DM based on the identification of a genetic polymorphism that predicts which individuals with DM are at greatest risk of complications and which individuals will receive benefit from a very cheap treatment ($10/year) that can reduce the incidence of heart attack, stroke and death by over 50%. This pharmacogenomic approach to disease prevention for individuals with DM represents the first application of personalized medicine to a major disease.

There exists two common alleles at the haptoglobin (Hp) locus at chromosomal coordinates 16q22 denoted allele 1 and allele 2. A given individual's Hp genotype can therefore be described as being Hp 1-1, Hp 2-1 or Hp 2-2. The prevalence of the three Hp types worldwide is approximately Hp 1-1 (15%), Hp 2-1 (50%) and Hp 2-2 (35%) making this a very common polymorphism. We have demonstrated in multiple independent longitudinal studies that individuals with the Hp 2-2 genotype and DM have an approximately 3-5 fold increased risk of developing cardiovascular disease (heart attack, stroke and cardiovascular death). This association between the Hp genotype and DM complications has been strengthened by transgenic mice and mechanistic studies.

In our studies of the function of the Hp protein particularly in the setting of MD we have shown: (1) that the Hp 2 protein is deficient in the antioxidant protection which it provides against the protein hemoglobin (Hb); (2) that the complex formed by the Hp protein and Hb is inefficiently cleared in Hp 2-2 individuals due to an impaired ability of the macrophage CD163 scavenger receptor to internalize the Hp 2-2-Hb complex-this results in an increased amount of circulating Hb in Hp 2-2 individuals in the plasma and an impaired clearance of Hb at sites of hemorrhage – including intraplaque hemorrhage which is very common in DM; (3) the Hp 2-2-Hb complex binds to High Density Lipoprotein (HDL) and transforms HDL from being a anti-atherogenic protective molecule to a pro-atherogenic molecule due to the ability of the Hp 2-2-Hb complex to mediate the oxidation transformation of HDL .

Based on these mechanistic studies we proposed that antioxidant therapy may be beneficial to Hp 2-2 DM individuals. Over the past 10-15 years multiple antioxidant studies done in man have been failures-not only failing to demonstrate benefit but actually showing net harm (over increase in mortality of 5%) from indiscriminate antioxidant therapy (principally with vitamin E). We proposed that this failure was due a lack of proper patient selection. We hypothesized that Hp 2-2 DM individuals would receive benefit from antioxidants. We first tested this hypothesis by retrospectively analyzing stored blood samples from the HOPE study and found that whereas no benefit was found from vitamin E in HOPE overall in the Hp 2-2 DM cohort CVD death and MI were reduced by over 50%. We then went on to prospectively test this hypothesis in collaboration with Clalit Health Services in a prospective double blind placebo controlled study in 47 primary health care clinics in Northern Israel and demonstrated that vitamin E reduced the incidence of MI and stroke and CV death by over 50%- recapitulating the results of HOPE.

Our goal is that governing bodies such as the WHO (World Health Organization), AHA (American Heart Association) and ADA (American Diabetes Association) will include the pharmacogenomic algorithm we are proposing in the standard treatment guidelines for DM care. Simply put all DM individuals would be Hp typed and those found to be Hp 2-2 would be given vitamin E. The public health implications and potential economic advantages of the adoption of this paradigm are clear. However, we recognize that in order for the WHO, AHA and ADA and the medical community to adopt this paradigm and issue it as a universal treatment guideline an additional placebo controlled study will need to be performed and we are currently attempting to recruit centers and raise funding in the public sector for such a study.

Lior Gepstein, PhD

Modeling Inherited Arrhythmogenic Syndromes with Human Induced Pluripotent Stem Cells

The study of several inherited cardiac disorders has been hampered by the lack of suitable in vitro human cardiac tissue models of disease. The advent of the groundbreaking human induced pluripotent stem cells (hiPSCs) technology may provide a possible solution to this cell-sourcing problem. This presentation will focus on the potential applications of the hiPSCs technology for basic and applied cardiac research. Initially, our efforts in establishing a cardiomyocyte differentiating system from hiPSCs will be described and the potential utilization of this differentiation system for cardiovascular developmental biology, drug testing, target validation, and regenerative medicine will be discussed. To exemplify the unique value of the hiPSCs technology for modeling inherited cardiac disorders, we will present recent work from our laboratory in studying hiPSCs-derived cardiomyocytes from patients with a number of inherited cardiac disorders. These include the congenital long QT syndrome, cathecholaminergic polymorphic ventricular tachycardia (CPVT), and Pompe glycogen storage disease. The ability of the hiPSCs approach to provide mechanistic insights into disease pathogenesis and to evaluate potential disease aggravators and novel customized treatment options will be discussed.

Daniel E. Michele, PhD

Sugar is not just fuel: mechanisms of cardiomyopathy in muscular dystrophies

Muscular dystrophies are genetic disorders characterized by severe muscle weakness, loss of ambulation and early death. Many patients with muscular dystrophy, particularly some of the most common muscular dystrophies associated with genetic disruption of the dystrophin-glycoprotein complex, suffer from clinically significant cardiomyopathy. Cardiomyopathy is the cause of death in 20-30% of patients, and an even higher percentage in those patients that live beyond the second decade. Our work is focused on understanding how disruption of the function of the DGC, specifically the function of the central protein in this complex, dystroglycan, causes cardiomyopathy. We have shown that loss of glycosylation of dystroglycan in patients and mice leads to loss of dystroglycan's function as receptor that links the cytoskeleton to the extracellular matrix. This loss of function of dystroglycan leads to a cardiomyopathy characterized my focal, acute myocellular damage leading to cumulative replacement fibrosis and cardiac dysfunction. On the cellular level, loss of dystroglycan function does not directly affect myocellular adhesion, but instead the loss of dystroglycan function results in instability of the sarcolemma during normal mechanical activity. This myocellular instability is recapitulated in other models of recessive DGC deficiency, including mouse models of Duchenne muscular dystrophy. We have recently extended our findings in recessive muscular dystrophies, to models of inherited dilated cardiomyopathies associated with dominantly inherited mutations in other members of the DGC. Together these studies indicate that sarcolemma instability during normal mechanical activity may be a common mechanism underlying the pathogenesis of cardiomyopathy in a variety of diseases associated with genetic disruption of the DGC. Therapeutic strategies to redress sarcolemma instability and/or pathogenic mechanisms initiated by loss of membrane integrity are currently being explored.

Michael Eldar, MD

Asymptomatic Catecholaminergic Polymorphic Ventricular Tavhycardia (CPVT) – Risk Stratification and Therapeutic Options

CPVT1 and CPVT2 are rare genetically transmitted diseases, causing recurrent syncope and sudden cardiac death at an early age. CPVT1 is an autosomal dominant trait, caused by mutations in RyR2, a gene encoding Sarcoplasmic Reticulum (SR) calcium release channel. CPVT2, an autosomal recessive trait, was diagnosed and characterized for the first time in a Bedouin family by a joint team from Sheba and Rambam Medical Centers. A missense mutation in the CASQ2 gene, encoding a SR calcium binding protein, was identified in affected subjects.

This presentation will focus on the difficult topics of who and when to treat (risk stratification) and on how to treat asymptomatic subjects carrying the mutations. It will be based on the literature and the experience gained by ongoing collaboration between our groups.

David Sherman, PhD

Drug Discovery and Development Efforts Employing Unique Chemical Diversity Resources against Cardiovascular Targets

The University of Michigan Center for Chemical Genomics, and the recently initiated Center for the Development of New Medicines provides state-of-the-art resources for drug discovery and development programs. These include high throughput screening, medicinal chemistry and pharmacokinetic resources. An example of an early discovery effort involving a unique natural product chemical diversity library against the PAI-1 target protein has revealed a new inhibitor with high potential for further development. This model can be readily applied to foster collaborative projects between investigators at the University of Michigan, the Technion and other academic institutions in Israel.

Adam B. Stein, MD

Epigenetic regulation of cardiomyocyte phenotypes

Epigenetic mechanisms are important mechanisms for regulating gene expression profiles in developing tissues. Despite the importance of these mechanisms in defining a stable cellular identity, little is known regarding the importance of these mechanisms in regulating expression profiles in adult tissues. Using murine models, our lab has been able to show that epigenetic mechanisms do, indeed, regulate gene expression profiles in adult differentiated heart tissue. Our data demonstrate that potassium channels and calcium handling are regulated by epigenetic mechanisms. An inability to maintain the epigenome results in widened action potential duration, a decrease in the transient outward potassium current, and a predisposition to ventricular arrhythmias.

Santhi Ganesh, MD

Genetic Approaches to Understanding Arterial Dysplasia

Arterial remodeling leads to alterations in blood vessel size, shape and composition. Arterial dysplasia occurs in a variety of disorders characterized by adverse vascular remodeling in response to various inciting factors. Examples include common diseases such as in-stent restenosis and rare diseases such as fibromuscular dysplasia. Genomic approaches to understanding the mechanisms of arterial dysplasia are unbiased and offer the potential for novel discoveries. I will discuss the application of next generation sequencing and other state of the art technologies to the analysis of these vascular diseases.

Monther Boulus, MD

Unmet Need in Mapping and Ablation of Atrial Fibrillation

Catheter ablation of paroxysmal atrial fibrillation is an established treatment option with reproducible good long term success. Pulmonary vein isolation (PVI) is the accepted minimal endpoint of such an ablation procedure. My talk will focus on our experience of using a new smart touch Biosense catheter in about 40 patients. Some recent data suggest a correlation between the contact force during catheter ablation and clinical outcome. We will discuss the issue electroanatomical mapping with the Carto System integrated with CT imaging. Different techniques of achieving PVI using point by point radiofrequency, cryoablation or using multipolar ablation catheters will be also discussed.

Yoram Etzion, PhD

Atrial Tachypacing in Conscious Rodents, Application for Molecular Studies of Human Atrial Fibrillation.

My talk would review a unique model we developed, which enables long term of atrial tachypacing in conscious freely moving instrumented rodents, as a new tool for molecular studied of human atrial fibrillation (AF). AF, the most common sustained cardiac arrhythmia, is a complex, costly and progressive disease, which is fairly resistant to current antiarrhythmic modalities. AF has a self-perpetuating nature and it is known to induce changes in atrial properties, collectively defined as "atrial tachycardia-remodeling" (ATR), which increase the vulnerability of the atria to the arrhythmia. Studies in animal models have provided important insights into the pathophysiology of ATR. However, currently available models are restricted to large animals such as dogs and goats, which are expensive, not available for most laboratories and cannot be manipulated genetically. Using microarray analysis of left atrial tissue obtained from instrumented rats exposed to 48 hours of rapid atrial pacing (70 ms cycle length) vs. near normal atrial pacing (140 ms cycle length) we found 396 genes that were changed using a cutoff of 1.3 fold change and $p<0.05$ (Affymetrix Rat gene Chips; 209 upregulated and 187 downregulated). Enrichment analysis of identified molecular pathways using MetaCore™ revealed signs of cellular calcium overload and increased carbohydrate metabolism, hallmarks of human ATR. In addition, changes in pathways that are suggested to play important role in human AF such as activation of TGF-beta signaling were also noted. Comparison with a dataset of human AF revealed 44 common genes, among them some which are involved in the pathogenesis of ATR in large mammals including an upregulation of the potassium channel Kir2.1. Overall, our results indicate that atrial tachypacing in rodents may become an important new tool for molecular studies of AF-related issues. A mouse model of atrial tachypacing is currently in advanced stages of development in our laboratory, for potential use in relevant genetically-modified murine models in the near future.

Uri Yaron

Innovations in the Mapping and Ablation of Atrial Fibrillation

My talk will review the latest technologies and products developed to treat Atrial Fibrillation (AFib). AFib is the most common cardiac arrhythmia and is the leading cause of stroke. Over 150,000 patients are treated annually, utilizing mapping and ablation technologies, developed over the last 15 year.

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