



First Look

The Next Wave of
Cardiovascular Breakthroughs

Monday, May 1 | 8:00AM – 11:30AM

WORLD MEDICAL INNOVATION FORUM



2016 First Look: The Next Wave of Cancer Breakthroughs

Defining Functional Protein Networks
with High-Throughput Proteomics

Wilhelm Haas, PhD

Assistant Professor of Medicine,
Massachusetts General Hospital, Harvard Medical School

Early career Harvard Medical School investigators kick-off the World Medical Innovation Forum with rapid fire presentations of their high potential new technologies. Nineteen rising stars from Brigham Health and Massachusetts General Hospital will highlight in ten minute presentations their discoveries and insights that will be the disruptive cardiovascular care of the future. This session is designed for investors, leaders, donors, entrepreneurs and investigators and others who share a passion for identifying emerging high impact technologies. The top presenter each from BWH and MGH will be awarded the Austen-Braunwald Innovation Prize on Day 2 of the Forum. The prize carries a \$10,000 award.

AUSTEN-BRAUNWALD AWARD

The inaugural Austen-Braunwald Innovation Award will be given this year to honor the First Look presenter who most embodies the innovative, entrepreneurial and forward thinking of W. Gerald Austen, MD and Eugene Braunwald, MD—two of the world's finest cardiovascular pioneers. Awards will be presented to one Brigham Health presenter and one Massachusetts General Hospital presenter. The \$10,000 award will be granted by a small selection committee for overall presentation quality, innovativeness, commercial potential, caliber of disruption, and market need.

The Award will be judged throughout the morning session with winners announced on **Tuesday, May 2 at 12:15PM–12:30PM.**



W. Gerald Austen, MD

Surgeon-in-Chief, Emeritus, MGH; Chairman, MGH Chiefs Council; Edward D. Churchill Distinguished Professor of Surgery at HMS

W. Gerald (Jerry) Austen, MD received his BS degree in mechanical engineering from the Massachusetts Institute of Technology and his MD degree from Harvard Medical School. His residencies were at the MGH and he had additional training in England. Following two years of clinical and research work at the National Heart Institute in Bethesda, Dr. Austen returned to the MGH to lead heart surgery and, at age 39, was appointed Chief of the Surgical Services at the MGH, a role he held for 29 years. Dr. Austen was a Founding Trustee of Partners HealthCare. He also was the Founding President and CEO of the Massachusetts General Physicians Organization (MGPO). Dr. Austen was the first MGH physician elected to the MGH Board of Trustees. Dr. Austen is a member of the National Academy of Medicine and a Fellow of the American Academy of Arts and Sciences.



Eugene Braunwald, MD

Physician-in-Chief, Emeritus, BWH; Founding Chair, TIMI Study Group; Distinguished Hersey Professor of Medicine at HMS

Eugene Braunwald, MD received his medical training at New York University and completed his Medical Residency at the Johns Hopkins Hospital. He became a Clinical Associate in the (then) National Heart Institute. Subsequently, he served as the first Chief of the Cardiology Branch and then as Clinical Director of the National Heart, Lung and Blood Institute. Dr. Braunwald served as the founding Chairman of the Department of Medicine at the University of California, San Diego and he was Chairman of the Department of Medicine at the BWH. He was a founding trustee and Chief Academic Officer of Partners HealthCare. Dr. Braunwald is the only cardiologist who is a member of the National Academy of Sciences.

2017 CARDIOVASCULAR INVESTIGATORS

- 6 Elena Aikawa, MD, PhD
- 7 Manu Beerens, PhD
- 8 Caroline Burns, PhD
- 9 Susan Cheng, MD
- 10 Sammy Elmariah, MD
- 11 Mark Feinberg, MD
- 12 Yick Fong, PhD
- 13 John Groarke, MD
- 14 John Higgins, MD
- 15 Jennifer Ho, MD
- 16 Amit Khera, MD
- 17 Mark Lindsay, MD, PhD
- 18 Steven Lubitz, MD
- 19 Rejeev Malhotra, MD
- 20 Bradley Maron, MD
- 21 Benjamin Olenchock, MD, PhD
- 22 Jorge Plutzky, MD
- 23 Jason Roh, MD
- 24 Paul Yu, MD, PhD

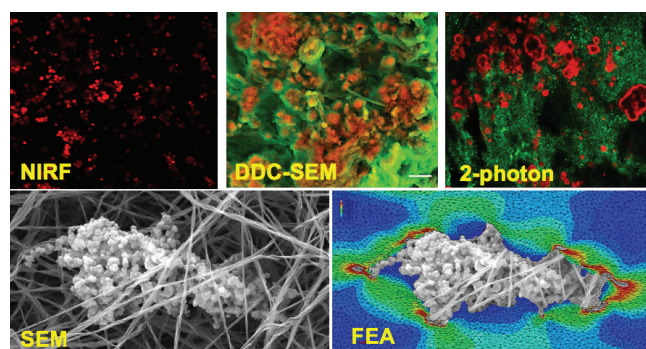


Figure 1. Visualization of subcellular microcalcifications using high-resolution microscopy.

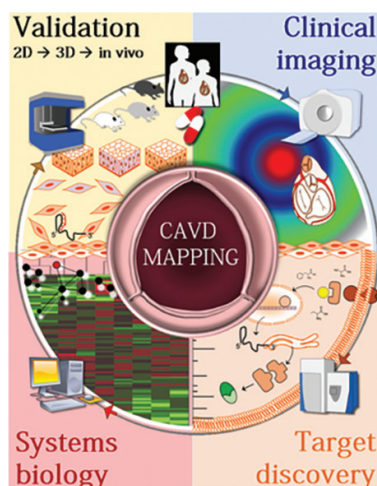


Figure 2. CAVD Discovery Pipeline.

Novel Target Discovery Pipeline for Calcific Aortic Valve Disease



Elena Aikawa, MD, PhD

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Aortic stenosis due to calcific aortic valve disease (CAVD) is the most prevalent valvular disorder and is on the rise as the population ages. Left untreated CAVD has a dismal prognosis, inevitably leading to death. Annually, in the US alone, 80,000 patients progress to severe CAVD, requiring aortic valve intervention and at a cost of over \$20 billion. Despite these clinical and economic burdens, no medical therapies are available for CAVD. The only existing treatment options are the invasive and costly surgery or transcatheter valve replacement. Further research is thus necessary to identify key molecular mechanisms and develop new drug targets for CAVD.

Calcifying extracellular vesicles (100-300 nm), released from cardiovascular cells, aggregate and nucleate microcalcifications (Nature Materials 2016; JCI 2016). This process lies below the resolution of standard clinical imaging modalities, a major barrier to overcome in this field. Our recent studies demonstrated that high-resolution microscopy and molecular imaging combined with nanoparticle tracking analysis, and a novel 3D-bioprinting technology modeling the native valve leaflet, can visualize and quantify vesicle-derived microcalcifications, providing a powerful tool for exploring this process in vivo and in vitro (Figure 1).

My current research aims at discovering novel therapeutic targets for CAVD. The cross-disciplinary collaboration among innovative clinical and basic science investigators at BWH has utilized cutting-edge techniques to establish the CAVD Discovery Pipeline (Figure 2). This project expedites the translation of basic research findings into clinic by integrating clinical parameters and PET/CT imaging obtained from patients before valve surgery, with post-operative pathology, proteomics, transcriptomics, single cell analysis, and multi-dimensional network analysis, thereby creating an integrated map of human CAVD.

Our results will provide insight into mechanisms that identify early stages of disease that will ultimately permit early therapy in patients with subclinical valve disorders and help select personalized treatment options. Moreover, our results will lead to patentable products (e.g., diagnostic databases, therapeutics, imaging and laboratory probes) that will immediately impact CAVD research, diagnosis and therapy.

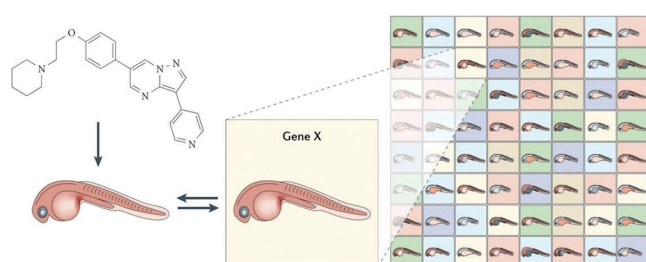


Figure 1. Drug screening in zebrafish to study phenotype-genotype correlations.

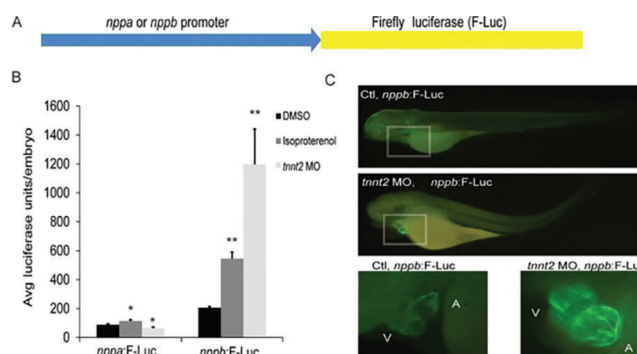


Figure 2. Generation of transgenic reporter lines to score for heart failure.

A Zebrafish Pipeline for Cardiovascular Precision Medicine



Manu Beerens, PhD

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Cardiomyopathies and their consequences heart failure, arrhythmia and sudden death remain difficult to treat. Current treatments have met with limited clinical success due to the heterogeneous nature of the underlying disorders. Hence, there is an unmet clinical need for more efficient development of etiology specific therapies with higher efficacy.

Gaining more insight into the molecular mechanisms that cause distinct forms of cardiomyopathy will be a vital step to rapidly identify novel drugs with high therapeutic potential and minimal side effects. While mammalian models are not readily adaptable for such high-throughput chemical or genetic screens, cell-based studies lack the complexity to faithfully reproduce all aspects of heart failure. The rapid cardiovascular development of zebrafish embryos, their optical transparency and low maintenance costs have led to the widespread use of zebrafish in cardiovascular sciences.

We have created a platform to rapidly and reliably define the cardiac performance of mutants for multiple forms of cardiomyopathy. In addition, we combined these automatically generated parameters with luciferase-based reporters of clinically relevant biomarkers for heart failure. Altogether, this enables highly automated phenotype-driven screens in zebrafish disease models.

In summary, our data identify high-throughput screening in zebrafish as an exquisite platform to rapidly identify small molecule compounds with higher therapeutic potential than conventional drugs to treat cardiomyopathy. The reproducible success of this strategy paves the way for co-clinical modeling of genetic forms of cardiac and vascular disease.

Using Zebrafish to Understand and Harness Cardiac Regeneration



Caroline Burns, PhD

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The adult mammalian heart lacks any appreciable capacity to regenerate ischemia-damaged muscle. By comparison, injured zebrafish hearts mount an impressive regenerative response driven by robust myocardial proliferation. My laboratory's research program is driven by the simple assumption that a complete understanding of cardiomyocyte proliferation regulatory mechanisms in zebrafish could be leveraged to promote heart regeneration in humans. Here, I will discuss recent advances in our understanding of zebrafish heart regeneration by focusing on our efforts to characterize the influences of epigenetic mechanisms, the Notch signaling pathway, and myocardial ploidy on regulating cardiomyocyte proliferation. In addition, I will discuss how the zebrafish might be utilized to identify pharmacological drivers of myocardial proliferation that could be employed for clinical benefit.

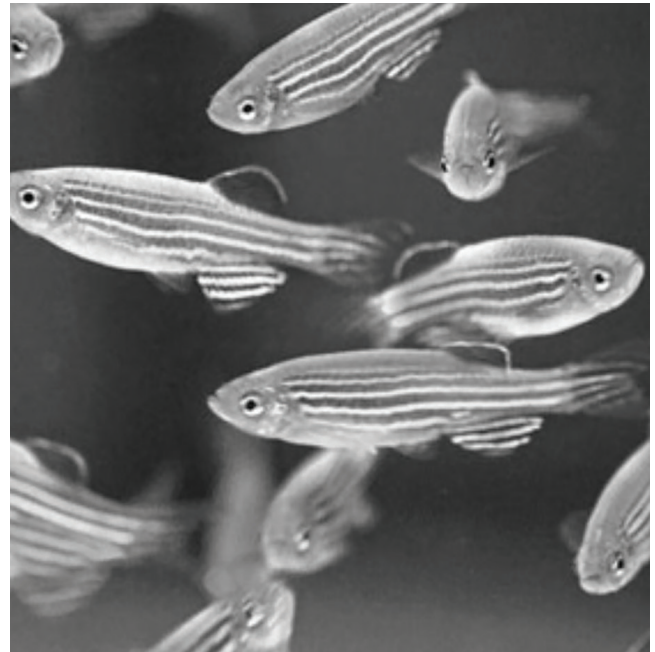


Figure 1. Zebrafish is a genetically tractable model organism that can efficiently regenerate their hearts following injury.

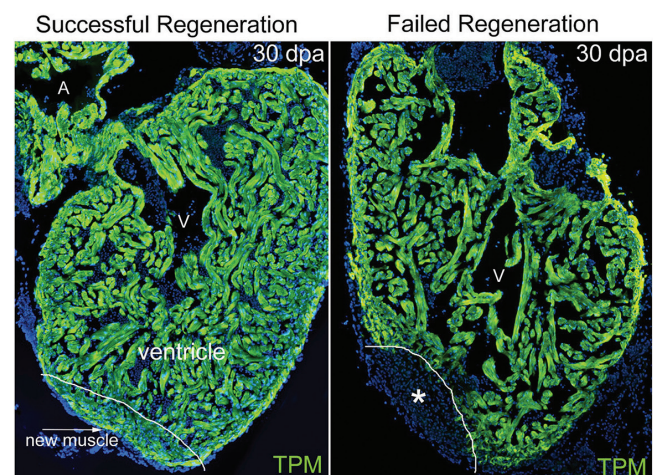


Figure 2. Cardiac sections from an adult zebrafish heart that consists of a single atrium (A) and ventricle (V) immunostained for heart muscle Tropomyosin (TPM) and DAPI. Left section: New muscle is observed within 30 days post-amputation (dpa). Right section: A Notch pathway mutant that lacks the capacity to regenerate new muscle at 30 dpa. Instead, these hearts form a collagen-rich scar (not shown) like those after infarct in humans.

Bioactive Lipid Profiling Can Identify Potential Targets for Altering Life Course Trajectories Toward Cardiometabolic Disease



Susan Cheng, MD

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We use data and biosamples collected serially from well-phenotyped population-based cohorts to derive life course trajectories that mark individuals who are more or less likely to develop cardiometabolic disease outcomes in their lifetime. In analyses of age-based trends, we use models that account for secular time trends. In turn, in analyses of time trends, we use models that account for the effects of aging. By taking both approaches, in parallel, we can begin to delineate longitudinal patterns of change in risk that are related to aging from those related to secular trends in the prescribing of medications commonly used to modify risk.

Our analyses to date indicate that hypertension and diabetes remain the leading contributors to cardiovascular disease and death, both with aging and over time. Importantly, not all persons who develop hypertension over the life course are the same, and not all persons who develop diabetes over the life course are the same. Interestingly, there is wide variability in the trajectories of individuals who develop either overt or precursor forms of these major risk factors and, in turn, their lifetime risk for cardiovascular disease. We can begin to differentiate between persons tracking along distinct life course trajectories by performing small molecule profiling at various time points over a longitudinal study.

In early work, we have found that certain subsets of bioactive lipids are especially informative for distinguishing between persons on different life course trajectories. Termed eicosanoids, these small lipid species represent the broad diversity of upstream mediators of systemic inflammation. We have observed that a number of previously unidentified eicosanoid mediators (of more than 500 eicosanoids measured) are not only associated with cardiometabolic risk factors and new-onset cardiovascular disease, but also are modulated by existing FDA-approved agents, including aspirin, statins, and ACE inhibitors. Taken together, these findings highlight the potential to precisely identify specific mediators of life course disease trajectories as well as potential new molecular targets for altering these trajectories (i.e., to achieve course corrections).

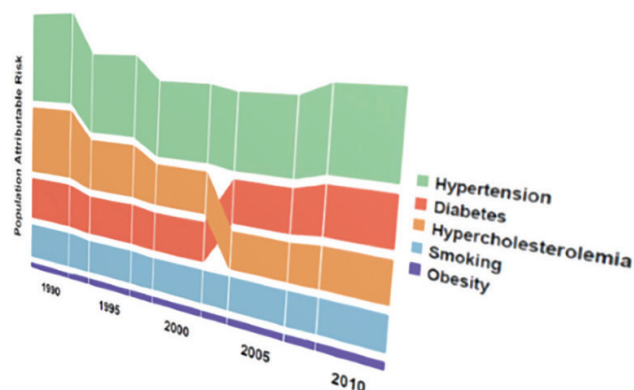


Figure 1. Age- and time-trends can be derived from population-based longitudinal data.

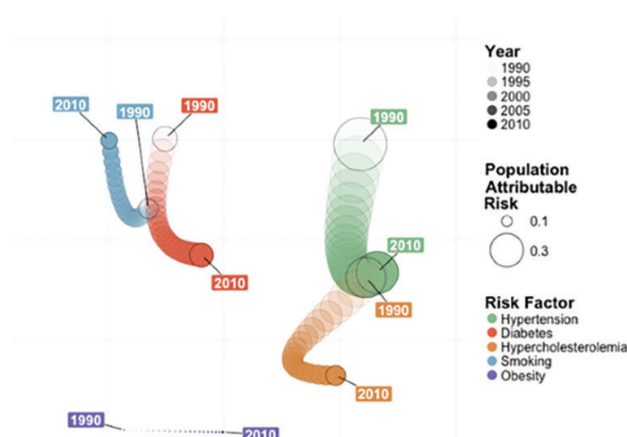


Figure 2. Contributors to risk over time, and their key components, can be identified.

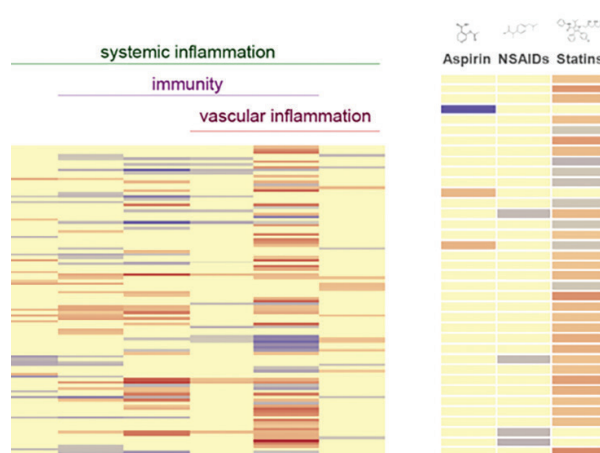


Figure 3. Eicosanoids segregate across lifetime risk profiles and are influenced by medications.

Small Molecule Predictors of Outcome After Cardiac Interventions



Sammy Elmariah, MD

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SUMMARY

Aortic stenosis (AS) is present in >20% of older adults, and the prevalence and socioeconomic burden of AS continues to grow as our population ages.¹ The development of symptoms drives the decision for aortic valve replacement (AVR); however, symptom onset identifies a late-stage cohort that frequently exhibit irreversible left ventricular (LV) maladaptive remodeling that are associated with morbidity and mortality after AVR.^{2, 3} There is an unmet clinical need for objective measures to identify early, reversible stages of maladaptive LV remodeling in AS patients (Figure 1).

We are identifying circulating small molecules that predict LV reverse remodeling and clinical outcomes after transcatheter AVR (TAVR). Using metabolomic profiling techniques, we identified circulating blood metabolites that predict acute kidney injury after TAVR (Figure 2).⁴ We have also discovered that in patients with severe AS, circulating metabolite levels associate with measures of LV structure and function, the acute alleviation of LV pressure overload, and risk of death after TAVR (Figure 3). Together, these findings demonstrate the promise of small molecule profiling in enhancing biologic insights and personalizing the delivery of transcatheter valve interventions.

SPECIFIC AIMS

Aim 1. Characterize circulating metabolites and proteins that associate with the extent of maladaptive LV remodeling. We are examining circulating small molecules that reflect the extent of maladaptive remodeling quantified by cardiac magnetic resonance imaging and echocardiography.

Aim 2. Identify circulating metabolites predictive of diminished LV reverse remodeling after alleviation of LV pressure load, stratified by the presence of LV systolic dysfunction. We are investigating the value of pre-TAVR metabolic profiles in predicting the 1-year post-TAVR %-reduction in LV mass in patients with normal and reduced LVEF, respectively, and the %-improvement in LVEF in patients with reduced LVEF.

Aim 3. Determine the prognostic value of circulating metabolites in predicting symptom onset and AVR in patients with asymptomatic moderate to severe AS. We are identifying metabolites that predict symptom onset and/or AVR within asymptomatic patients with moderate to severe AS and preserved LVEF.

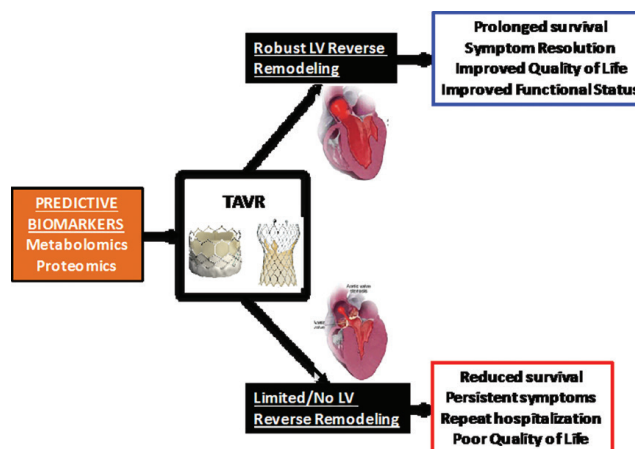


Figure 1. Schematic depicting biomarker use to predict outcomes after TAVR.

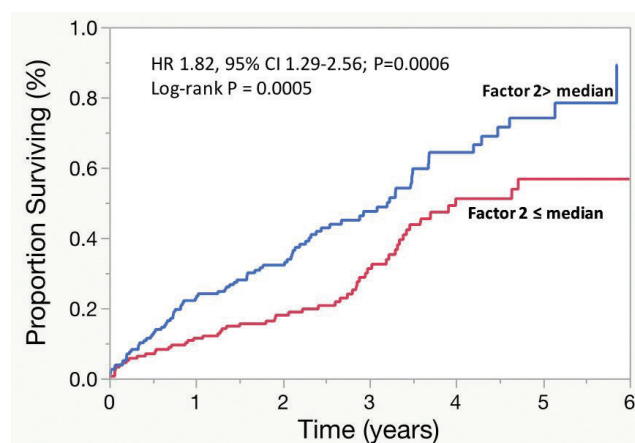


Figure 2. Circulating metabolites predict acute kidney injury (AKI) after TAVR.

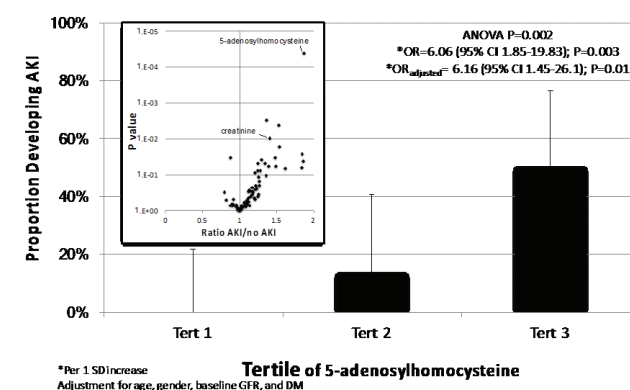


Figure 3. Circulating metabolites predict acute kidney injury (AKI) after TAVR.

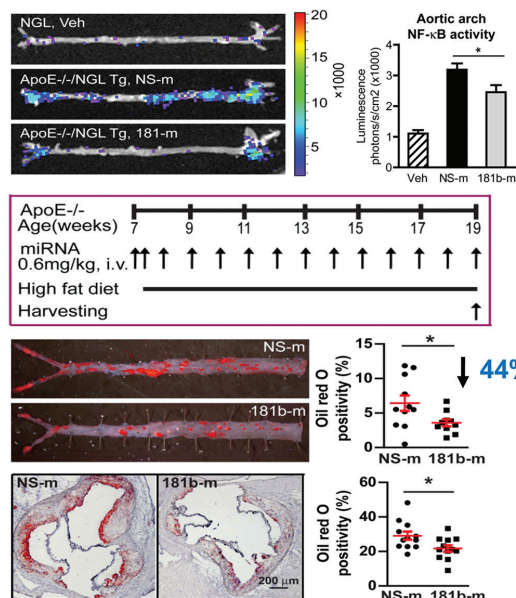


Figure 1. miR-181b delivery inhibits vessel wall inflammation and atherosclerosis

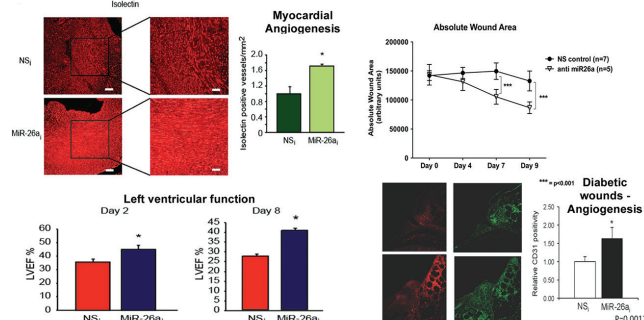


Figure 2. miR-26a inhibitors improve angiogenesis and repair in hearts and diabetic wounds.



Translational Trials in non-coding RNAs

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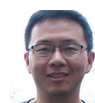
While current therapeutics for cardiovascular disease target protein-encoding genes derived from <2% of the genome, accumulating studies reveal that a large portion of the non-coding genome is actively transcribed, and ~50% of these transcripts are microRNAs and long non-coding RNAs. Emerging studies from our laboratory and others have begun to identify non-coding RNAs as critical mediators of key pro-inflammatory and angiogenic signaling pathways relevant to a range of cardiovascular disease states including atherosclerosis, diabetes, and myocardial injury and repair.

Despite current therapies and prevention, atherosclerotic cardiovascular disease (ASCVD) and its attendant complications such as myocardial infarction, stroke, and peripheral artery disease accounts for the majority of all deaths from cardiovascular disease. Current paradigms suggest that endothelial cell inflammation is a critical pathophysiological event that contributes to disease development and progression. Identification of novel non-coding RNAs that reduce endothelial inflammation may serve as the foundation for controlling vascular inflammation and ASCVD.

Our recent studies in mice and human subjects highlight an important cell-specific role for miR-181b as a suppressor of endothelial inflammatory responses in the vessel wall for both acute (e.g., sepsis) and chronic vascular disease states (e.g., atherosclerosis, insulin resistance, and obesity). Current studies have identified FDA-approved compounds that can target this microRNA in endothelial cells, which may provide additional therapeutic opportunities for regulating cardiometabolic disease. Similar approaches have revealed novel roles for lncRNAs in atherosclerosis.

We have also discovered roles of miRNAs involved in ischemic cardiovascular disease where tissues have insufficient blood supply. For example, delivery of inhibitors to miR-26a potentially increased angiogenesis and protected the heart in response to myocardial infarction, and skin in response to diabetic wound healing. Current efforts have established a platform for identifying small molecules that target these miRNAs, which may provide novel therapeutic approaches to improve blood supply to cardiovascular tissues.

Collectively, an understanding of the role of miRNAs and lncRNAs in the vascular endothelium may provide novel therapeutic opportunities for controlling a range of ischemic cardiovascular diseases.



New Approaches to Controlling Stem Cell Fate

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Embryonic stem cells and induced pluripotent stem cells, which can be propagated indefinitely in culture in an undifferentiated state or induced to differentiate into every cell type in the adult body, holds promise for regenerative medicine. Proper execution of these distinct but developmentally relevant programs requires precise tuning of gene expression by transcription factors. Indeed, aberrant transcriptional regulation is the root cause of many human diseases including developmental disorders, cancers, and degenerative diseases.

We have devised various biochemical strategies to isolate and characterize critical cellular machinery responsible for transcription in stem cells, and to reconstruct the complex process of gene expression in vitro. This technique, in combination with genetic and computational methods, provides powerful tools to understand the function of these gene regulatory factors in healthy cells and the fundamental mechanism by which their misregulation can lead to human diseases and disorders.

Controlling Stem Cell Fate by Transcription Factors

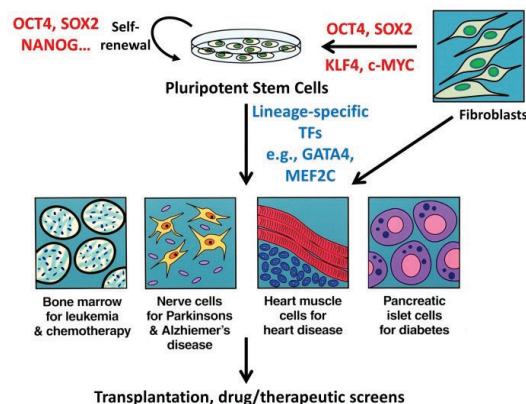


Figure 1. Controlling stem cell fate by understanding transcription factor functions.

In Vitro Reconstitution of Cell Type-specific Transcription

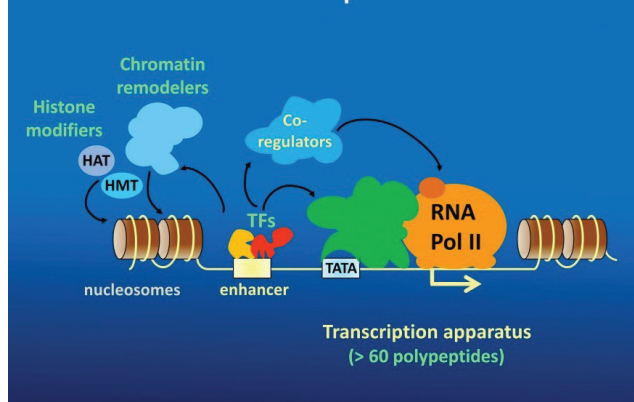


Figure 2. Understanding fundamental mechanism of gene transcription by in vitro reconstitution.

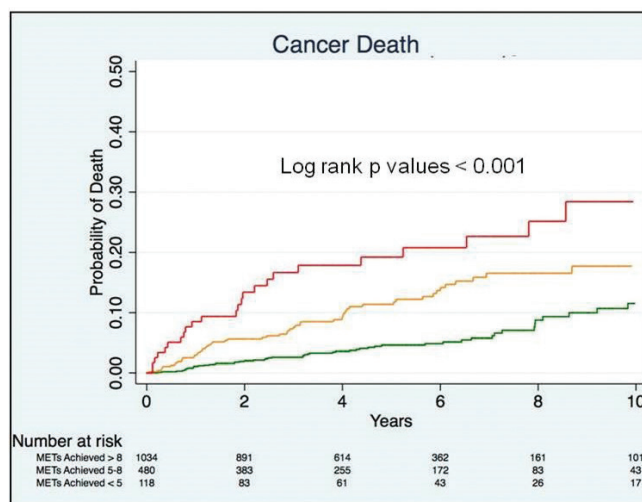


Figure 1. Probability of cancer death in cancer survivors achieving > 8 METs (green), 5-8 METs (orange), and < 5 METs (red) during exercise treadmill testing.

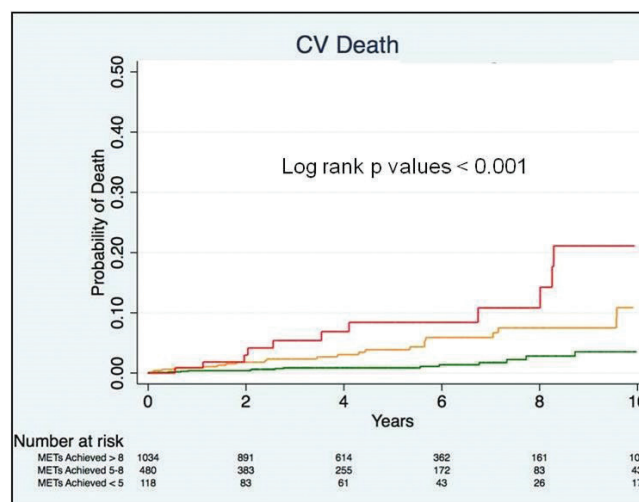


Figure 2. Probability of cardiovascular (CV) death in cancer survivors achieving > 8 METs (green), 5-8 METs (orange), and < 5 METs (red) during exercise treadmill testing.

Exercise Prescription to Improve Cardiovascular and Cancer Outcomes in Cancer Survivors



John Groarke, MD

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SUMMARY

Exercise prescription upon completion of cancer therapies could improve fitness, as well as cardiovascular and cancer outcomes for select cancer survivors. Given the growing population of cancer survivors, exercise prescription has tremendous clinical and commercial potential.

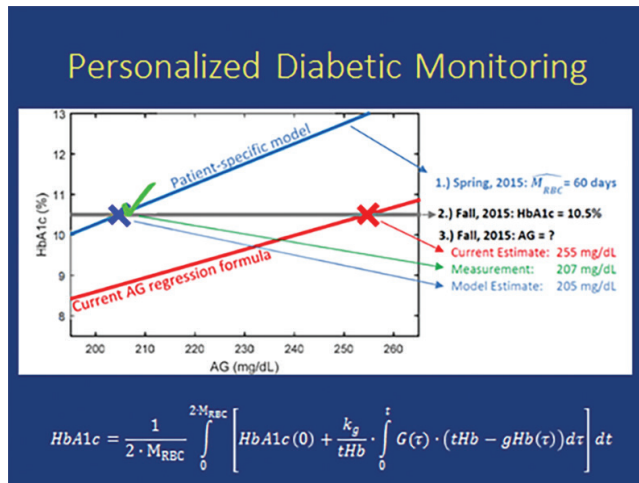
PROPOSAL

Advances in cancer care have achieved significant improvements in cancer survival, such that the population of cancer survivors in the United States now exceeds 14 million. Many cancer therapies are associated with adverse cardiovascular outcomes in survivors. In addition, prevalent deconditioning and impaired cardiopulmonary fitness undermine quality of life among survivors of adult and pediatric cancers.

Studies have demonstrated improvements in cardiopulmonary fitness in cancer survivors achieved through exercise interventions. Cardiac rehabilitation is a lifestyle program that has established benefits in a range of cardiovascular diseases. This proposal suggests that specifically tailored, exercise-based cardiac rehabilitation should also be considered for select survivors following completion of cancer therapies. This program would promote physical fitness, tackle deconditioning, facilitate

education regarding increased cardiovascular risk conferred by cancer therapies, and empower patients with risk reduction strategies. The author's research has shown that every 1 metabolic equivalent (MET) increase in exercise capacity is associated with 25%, 26%, and 17% respective reductions in adjusted risk of all-cause death, cancer death, and cardiovascular death, in a large cohort of cancer survivors (Figures). These data highlight potential prognostic gains that may be achieved by exercise prescription in cancer survivors. Furthermore, this research has identified predictors of impaired exercise capacity in cancer patients that would direct patient selection for this intervention.

Given the growing 'at risk' population of cancer survivors who would potentially benefit, exercise prescription has significant commercial potential. There is a strong case to achieve insurance coverage for this program for select patients, which would offer an additional source of revenue for hospitals. Moreover, many cancer patients motivated to regain their fitness following cancer therapies would appreciate the opportunity to pay out-of-pocket for physician-directed tailored rehabilitation programs offered either through hospitals or private gyms.



Personalized diabetic monitoring reduces errors by more than 50%.

Personalizing Diabetic Management with Hemoglobin A1c



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People with diabetes need to control their blood glucose (sugar) level to reduce their long-term risks of heart attack, kidney failure, vision loss, and more. Treatments are adjusted according to each patient's recent average blood glucose. The current standard measurement of average glucose is significantly inaccurate for about 1 in 3 patients and highly inaccurate for about 1 in 12. We have developed a personalized measurement of blood glucose that reduces errors by more than 50%. We adjust for each patient's unique physiology and rely only on existing routine clinical assays.

The amount of glycated hemoglobin (HbA1c) in a patient's blood provides the best estimate of average glucose. HbA1c is the gold standard for managing patients with diabetes and is now recommended for diagnosis as well. HbA1c is far more accurate than the random instantaneous glucose measurements that were previously used. Nevertheless, substantial unexplained glucose-independent variation makes HbA1c inaccurate, limiting the precision of medical care for hundreds of millions of diabetics. These errors can make a patient with poorly controlled diabetes appear not to have diabetes at all. Conversely, patients working hard and achieving good glucose control may be told that their disease is poorly controlled and that more intense interventions are required.

We combined knowledge of the dynamics of hemoglobin glycation and red blood cell kinetics with glucose measurements to derive a mechanistic mathematical model enabling patient-specific adjustment of HbA1c, yielding a more accurate average glucose. We found that inter-patient variation in derived mean red blood cell age explains all glucose-independent variation in HbA1c. We tested our method by personalizing estimates of average glucose for four independent groups of more than 200 patients and reduced errors by more than 50%. The current standard of care provided had errors >30 mg/dl for one in 12 patients. The patient-specific method reduced this error rate to less than 1 in 220. Our personalized approach should improve medical care for diabetes using existing clinical measurements.

Characterizing an Early HFpEF Phenotype: Cardiometabolic Disease and Pulmonary Hypertension



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Heart failure (HF) remains a major public health problem worldwide. Half of patients with HF have HF with preserved ejection fraction (HFpEF), a highly heterogeneous and complex entity, with no approved therapies to date. We have recently shown that obesity and associated metabolic dysfunction (1) increase the risk of future HFpEF, and (2) are associated with pulmonary hypertension (PH), a distinct HFpEF subphenotype. In our study, pulmonary artery pressures (PAP) were 10 mmHg higher in obese individuals with versus without metabolic disease. Notably, elevated PAP occurred in the absence of elevations in pulmonary capillary wedge pressure, suggesting intrinsic PH. Similar elevations in PASP have previously been associated with a 2.7-fold increased risk of mortality in individuals without known cardiopulmonary disease, highlighting the importance of PH in preclinical populations.

In animal models, multiple obesity-related pathways lead to PH, including insulin resistance, inflammation, oxidative stress, and adipokine signaling. Characterizing these pathways in humans may elucidate how cardiometabolic dysfunction can lead to cardiac and pulmonary vascular remodeling and progress to overt HFpEF. In this context, we are actively pursuing two related lines of investigation:

1. The role of adipokines in obesity-related PH: We are investigating the role of insulin resistance and circulating adipose-derived hormones in pulmonary vascular dysfunction. A unique aspect of this research is the use cardiopulmonary exercise testing with hemodynamic monitoring to evaluate dynamic responses in pulmonary vascular function to exercise.
2. Pulmonary artery endothelial cell phenotype (PAEC) and obesity-related PH: In collaboration with other groups, we have developed a novel protocol to isolate and phenotype fresh human pulmonary artery endothelial cells (PAECs) during right heart catheterization. We are examining specific molecular mechanisms underlying PAEC dysfunction in obesity-related PH, including endothelial insulin signaling.

These studies have the potential to provide important insights into mechanisms driving PH in metabolic disease, and will lay the foundation for future studies focused on disease prevention and optimal therapies in obesity-related cardiovascular diseases like HFpEF.

Genetic Risk, Adherence to a Healthy Lifestyle, and Coronary Disease



Amit Khera, MD

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Both genetic and lifestyle factors are key drivers of coronary artery disease, a complex disorder that is the leading cause of death worldwide. Long recognized to be heritable, genomewide association analyses have identified more than 50 independent variants robustly associated with risk of coronary disease. These risk alleles, when aggregated into a polygenic risk score, are predictive of incident coronary events and provide a continuous and quantitative measure of genetic susceptibility. Here, we determined the extent to which increased genetic risk can be offset by a healthy lifestyle.

The relationship between genetic and lifestyle factors and incident coronary events was explored in more than 50,000 individuals of prospective cohort studies (Khera AV et al; *N Eng J Med*; 2016). The relative risk of incident coronary events was 91% higher among participants at high genetic risk (top quintile of polygenic scores) than among those at low genetic risk (bottom quintile of polygenic scores). A favorable lifestyle (defined as at least three of the four healthy lifestyle factors – no current smoking, no obesity, regular physical activity, and a healthy diet) was associated with a substantially lower risk of coronary events than an unfavorable lifestyle (defined as no or only one healthy lifestyle factor), regardless of the genetic risk category. Among participants at high genetic risk, a favorable lifestyle was associated with $\approx 50\%$ reduction in coronary risk as compared to an unfavorable lifestyle.

Patients may equate DNA-based risk estimates with determinism, a perceived lack of control over the ability to improve outcomes.³² However, our results provide evidence that life-style factors may powerfully modify risk regardless of the patient's genetic risk profile.

Ongoing work seeks to refine the polygenic score to improve its ability to discriminate genetic risk in multiethnic populations. Moving forward, genomic medicine may facilitate identification of a small subset of individuals with significantly increased risk of coronary disease and application of a targeted intervention to mitigate this predisposition.

Coronary Disease Caused by Complex Interplay of Genetic and Environmental Factors

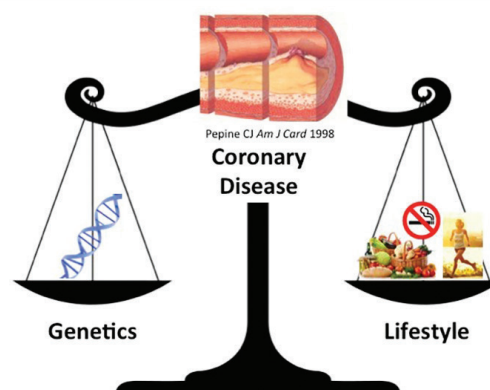
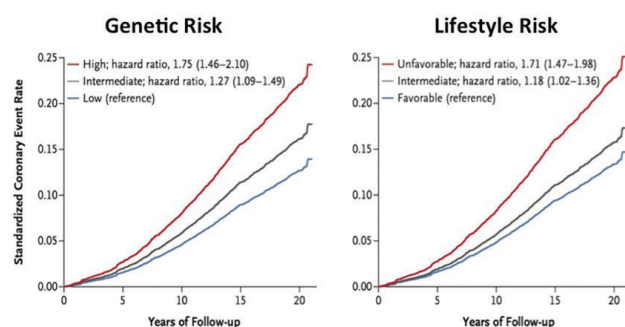


Figure 1. Genetic and lifestyle drivers of coronary risk.

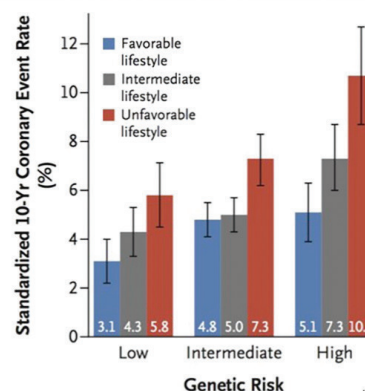
Both Genetics and Lifestyle Factors Strongly Associated with Coronary Risk



Khera AV, *N Eng J Med*, 2016

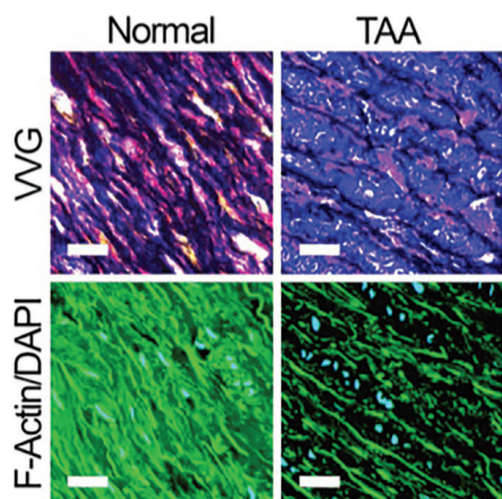
Figure 2. Both genetic and lifestyle risk predict coronary events.

Favorable Lifestyle Associated With a $\approx 50\%$ Reduction in Coronary Events Regardless of Genetic Risk Profile



Khera AV, *N Eng J Med*, 2016

Figure 3. Favorable lifestyle can offset genetic predisposition for coronary disease.



Isselbacher et al., *Circulation*, 2016

Aortic tissue from patients shows loss of cytoskeleton.

A Novel Epigenetic Complex Implicated in Thoracic Aortic Aneurysm (TAA)



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The Lindsay laboratory focuses on the clinical expression and molecular etiology of human thoracic aortic aneurysm (TAA). Aneurysm represents the anatomic expression of aortic organ failure with dilation and eventual tear; an event termed “dissection” associated with high mortality. In our research we use human and murine genetics as well as animal modeling to investigate the etiology and pathologic progression of inherited and sporadic aortic disease.

In our work we take advantage of genetic changes (mutations) that cause aortic disease in humans to create cellular models of aortic dysfunction. Through the examination of these cellular models we have discovered novel cell signaling pathways that are specifically activated in the pathologic state. We are primarily interested in how transcriptional regulatory events cause vascular smooth muscle cells (VSMC) to modify phenotype with resultant failure of extracellular matrix homeostasis. Genetic discovery in TAA has identified families of alteration, however mechanistic interconnections amongst groups have remained

obscure. A common pathologic feature of TAA tissue involves VSMC phenotypic change with contractile protein deficiency. Using comparative gene expression in human VSMCs we identified activation of a chromatin remodeling complex that mediates deleterious phenotypes of VSMCs across TAA gene families including cytoskeletal disruption and down regulation of contractile protein elements. Genetic or pharmacologic inhibition of the complex slows aortic growth and improves aortic performance in experimental models of TAA.

Dr. Lindsay is a member of the Cardiology Division faculty and the MGH Heart Center. He attended the University of Virginia School of Medicine where he completed the Medical Scientist Training Program, obtaining M.D. and Ph.D. degrees. He completed residency training in pediatrics as well as fellowship training in pediatric and congenital cardiology at the Johns Hopkins Hospital. He is member of the Thoracic Aortic Center and the Cardiovascular Genetics Program at MGH.



Atrial fibrillation may be episodic and asymptomatic, making diagnosis challenging.

Atrial Fibrillation: Causal Basis and Personalized Risk Assessment



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Cardiac arrhythmias are a leading cause of morbidity and sudden death, and collectively constitute a substantial public health problem. We are focused on understanding the causes of cardiac arrhythmias and applying discoveries to improve outcomes in patients with these conditions. Our research spans disciplines involving human genetics, mobile health technology, and clinical trials.

A major area of our work is focused on atrial fibrillation, which develops in about one in four individuals over the course of their lifetimes. Atrial fibrillation is associated with increased risks of stroke, heart failure, dementia, and mortality, and accounts for about \$26 billion in excess health care costs annually in the United States. Despite the public health importance of atrial fibrillation, its biological mechanisms remain poorly understood.

Our efforts are motivated by two critical observations. First, current treatments for atrial fibrillation are suboptimal – collectively, they have limited effectiveness, cause substantial morbidity, and are costly. Second, most individuals at risk for atrial fibrillation and related morbidity, including strokes, remain hard to identify.

Together with collaborating investigators, we have helped lead the AFGen Consortium (www.afgen.org), an international network of investigators examining the genetic basis of atrial fibrillation. We have identified over 20 genomic loci associated with atrial fibrillation, and in doing so have identified previously unrecognized pathways involved in the development of atrial fibrillation. In ongoing work, we are studying the causal basis of atrial fibrillation, applying discoveries to estimate risk of disease in a personalized manner, leveraging the power of electronic health records to improve management of patients with atrial fibrillation, and implementing cost efficient mobile cardiac rhythm monitoring technologies to test interventions that may minimize morbidity in patients with atrial fibrillation.

Targeting Vascular Calcification to Prevent Cardiovascular Disease



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Vascular calcification is the abnormal deposition of calcium phosphate crystals within the blood vessel wall, is one of the strongest risk factors for cardiovascular disease, and predicts clinical events such as myocardial infarction and stroke. The following approaches are being utilized in our laboratory to target vascular calcification:

Human Genetics: Approximately 50% of cardiovascular disease is driven by genetic causes. We have identified novel genes associated with vascular calcification by performing a multi-center genome-wide association study in >9000 individuals, as part of the Framingham Heart Study.

Cell-based Assays: Vascular smooth muscle cells (VSMC) and endothelial cells (EC) reside in the vessel wall and play critical roles in the development of vascular calcification. These cells first undergo a process of transdifferentiation, changing to a different cell phenotype, before calcification occurs. Our laboratory has optimized assays to model vascular calcification in vitro. Using this technique, we have discovered novel inhibitors of VSMC and EC transdifferentiation and calcification.

In vivo Imaging: Our laboratory utilizes near-infrared fluorescent imaging probes that specifically target calcium phosphate crystals and macrophages, to precisely characterize the temporal and spatial relationships between vascular calcification and vascular inflammation in models of atherosclerosis. These tools provide mechanistic insights into the development of vascular calcification in vivo and allow for the assessment of potential new drug therapies.

Biomarkers and Clinical Trials: Our laboratory has created a prospective registry of patients who suffer from a severe form of diffuse vascular calcification known as calciphylaxis. We have identified abnormal serum matrix Gla protein (MGP) levels as a hallmark for this disease. MGP is an endogenous inhibitor of vascular calcification that requires vitamin K-dependent carboxylation for activation. We have determined that the majority of patients with calciphylaxis have vitamin K deficiency and are enrolling calciphylaxis patients in a randomized trial to determine if vitamin K therapy improves disease outcomes.

In summary, our work combines these investigational strategies in the hopes of defining novel mechanisms and developing new treatments for vascular calcification and cardiovascular disease.



Stratifying Exercise Dysfunction

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Exercise dysfunction is highly prevalent across the global spectrum of medical diseases, and is a principal cause of morbidity and increased healthcare cost burden. Abnormalities in multiple organ systems often underlie exercise dysfunction. However, current methods for analyzing exercise test results often rely on a narrow subset of variables involving a single organ system. This reductionist approach has, in turn, hampered consensus on the parameters that define different forms of exercise dysfunction and the development of patient-specific treatments.

To address this dilemma, data were assembled from a large cohort of patients (N=738) referred to BWH (2011-2015) for invasive cardiopulmonary exercise testing (iCPET), which provides comprehensive measurements of pulmonary function, cardiopulmonary hemodynamics, and skeletal muscle oxygen extraction at rest and peak exercise (Figure 1). A correlation network of functionally distinct iCPET variables was assembled that contained 98 pairwise correlations, 39 nodes, and 101 edges (Figure 2). We focused on a 10-variable subnetwork to group patients into 4 distinct clusters. Clustering depended on contributions from all 10 variables in the subnetwork, but was independent of traditional exercise diagnoses (e.g., heart failure). The clusters were associated with distinct clinical profiles, variable exercise performance, and significant differences in hard clinical end-points (Figure 3). This systems-based method for classifying exercise dysfunction has important implications on point of care risk stratification in patients, and the development of exercise subtype-specific therapies. There is substantial opportunity for repurposing this approach to other complex clinical phenotypes for which enhanced diagnosis, prognosis, and patient-specific treatments are needed.

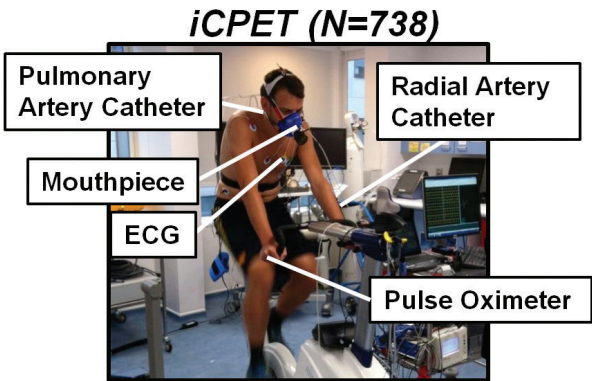


Figure 1. Invasive cardiopulmonary exercise testing (iCPET) was performed in exercise dysfunction patients.

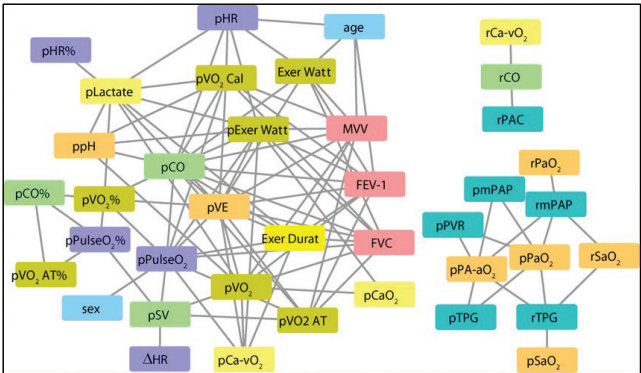


Figure 2. An exercise network was assembled based on iCPET variables.

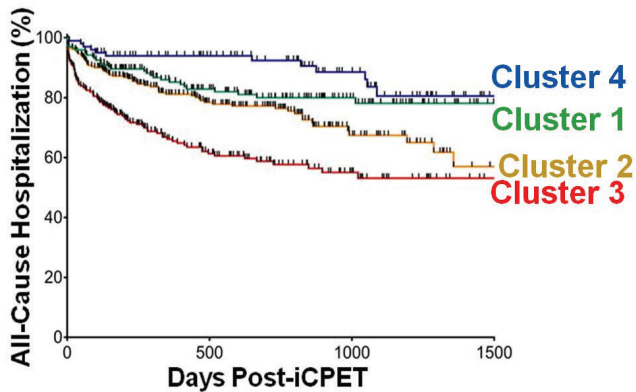
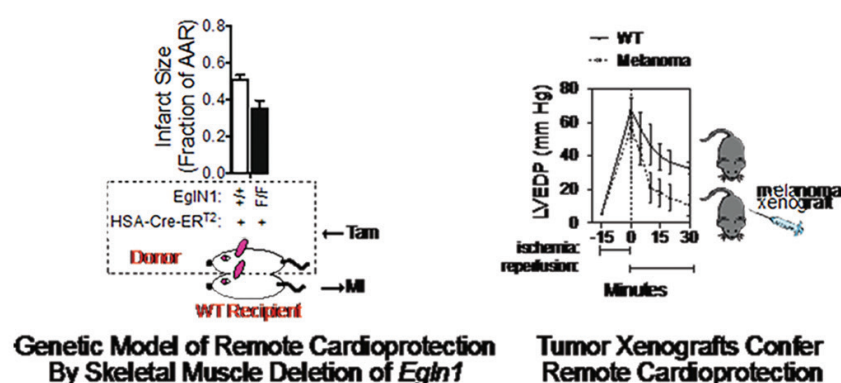


Figure 3. Patient cluster determined from the exercise network and clinical outcome.



Novel Mouse Models of Remote Cardioprotection

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Ischemic preconditioning is the phenomenon whereby brief periods of sublethal ischemia protect the heart against a subsequent, more prolonged, ischemic insult. In remote ischemic preconditioning (RIPC), ischemia to an organ remote from the heart can provide remote cardioprotection.

The alpha-ketoglutarate (α KG)-dependent dioxygenase EGLN1 senses oxygen and regulates the HIF transcription factor. We asked whether remote deletion of *EglN1*, which creates a condition of 'pseudohypoxia', could suffice to mediate remote cardioprotection. Using somatic gene deletion, we found that inhibiting *EglN1* in skeletal muscles protects mice against myocardial ischemia-reperfusion (I/R) injury.

Parabiosis experiments (Left Panel) confirmed that remote cardioprotection in this model was mediated by a secreted factor.

EglN1 deletion in the skeletal muscle, or pharmacologic EGLN1 inhibition, both cause elevated levels of the EGLN cosubstrate α KG. Elevated α KG drives hepatic production and secretion of kynurenic acid (KYNA), which is necessary and sufficient for cardiac ischemic protection in this model. Future studies will evaluate the efficacy of KYNA in a large animal model of cardiac I/R injury.

Our genetic model of remote cardioprotection suggests that remote hypoxia might be sufficient for cardioprotection. Tumors can outgrow their blood supply and become hypoxic. Indeed, hearts from mice bearing a melanoma xenograft demonstrated significant protection from global I/R injury (Right Panel).

These are tractable mouse models of RIPC that can be used to identify novel cardioprotective factors.

Harnessing Endogenous Mechanisms of Programmed Gene Expression for Therapeutic Benefit In Cardiometabolic Disorders



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Proximal mechanisms for programmatic control of gene expression exist that underlie the complex, distinct and at times disparate components of cardiometabolic health and dysfunction. Identifying such pathways offers new insights into physiologic and pathologic states, novel treatment strategies and a more rational basis for therapies based on endogenous biology. Through this focus, we identified how modulating key nuclear receptors limits inflammation or decreases visceral obesity, under pursuit as novel therapies. Epigenetics offers a completely distinct way to control complex transcriptional programs via histone modifications. While most efforts have focused on the placing ('writers', e.g. HATs) or removal ('erasers', e.g. HDACs) of histone marks, less attention has been directed to epigenetic proteins that bind to these marks ('readers') and allow transcription to proceed. The bromodomain and extra-terminal (BET)-containing family, including BRD2, BRD3 and BRD4, which bind to acetylated histones, are epigenetic reader proteins strongly implicated as therapeutic targets in cancer but previously unexplored in cardiovascular and metabolic disorders. In endothelial cells (ECs), we found BRD4 to be essential in transducing the inflammatory NF-kappa B signal to chromatin. In response to TNF α , endothelial BRD4 undergoes massive redeployment to a defined set of de novo super enhancers that drives the resulting pro-inflammatory, pro-atherosclerotic program, as seen in global ChIP-Seq studies. In vivo, BET inhibition decreases inflammation and atherosclerosis. Of note, TNF α stimulation decommissions BRD4 already active in running an endothelial gene expression program under basal conditions. BET modulation offers several novel therapeutic approaches. Selective BET inhibition, via distinct chemical structures and drug delivery, allows for potent disruption of a coordinated program involved in the pathogenesis of specific diseases while BET biology provides unique targets for manipulation. Separately, BET localization across the genome provides a new way of identifying previously unrecognized players in the inflammation and atherosclerosis as well as the maintenance of normal endothelial function. Such efforts are further supported by additional work extending BET action to other vascular and metabolic settings.

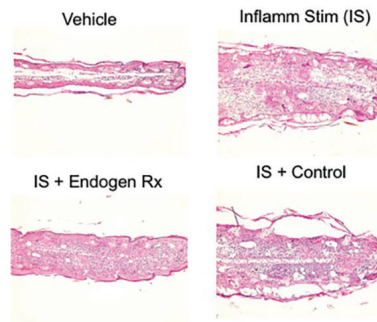


Figure 1. Mouse ear cross-sections: Activating endogenous pathways blocks dermal inflammation.

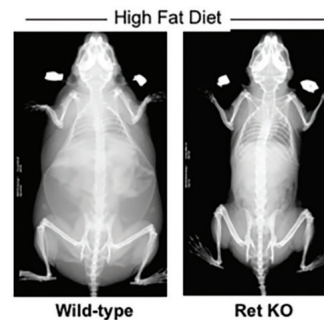


Figure 2. Manipulating endogenous ligand generation protects against diet induced obesity.

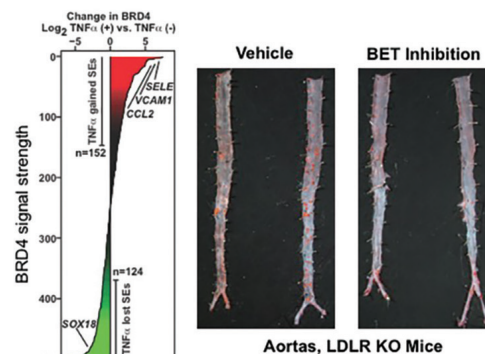


Figure 3. BRD4 controls endothelial transcriptional programs involved in inflammation and atherosclerosis.

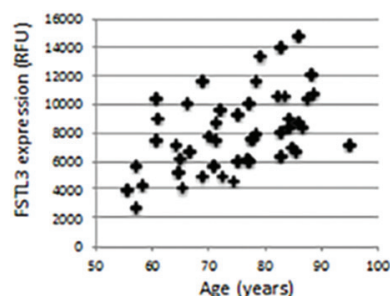


Figure 1. Activin type II receptor pathway activation increases with aging.

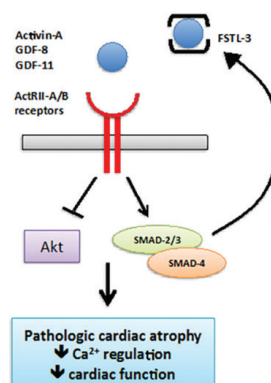


Figure 2. Activin type II receptor pathway induces pathologic cardiac atrophy.

Aging and the Activin Type II Receptor Pathway: A New Target for Heart Failure Therapy?



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Heart failure (HF) represents a leading cause of morbidity and mortality in the elderly. Despite the strong association between advanced age and HF, the underlying molecular mechanisms by which the aging process predisposes older adults to HF remain unclear. To that end, our group is exploring biological systems that potentially link aging to HF pathophysiology as an approach to identifying novel targets for HF therapy.

Using aptamer-based technology, we recently found that circulating levels of follistatin-like 3 (FSTL3), a biomarker of activin type II receptor (ActRII-A/B) pathway activation, markedly increases with aging. This finding strongly correlated with a concomitant age-related increase in circulating Activin-A levels, suggesting that Activin-A was likely a primary mediator of this phenomenon. Moreover, in a cohort of older adults with severe aortic stenosis (AS), FSTL3 levels correlated with increasing HF severity and frailty.

To elucidate the potential role of this pathway in HF pathophysiology, we have been actively investigating the effects of Activin-A and other related ActRII-A/B ligands (e.g. GDF11) on cardiac function. Current work in our laboratory suggests that ActRII-A/B pathway activation induces a pathologic form of cardiac atrophy that impairs myocardial function. This process is partially mediated through a catabolic mechanism that represses protective physiological hypertrophy pathways in the heart, resulting in impairments in calcium regulation and myocardial mechanics.

Interestingly, targeted inhibition of this pathway improves cardiac function in various murine models of HF. In a transverse aortic constriction model of AS and HF, ActRII-A/B inhibition not only prevents the development of systolic dysfunction, but can also restore the functional properties of an already failing heart. This functional effect of pathway inhibition is also seen in aging models of HF, in which ActRII-A/B inhibition improves cardiac performance and attenuates the age-related decline in exercise capacity.

In conclusion, this work identifies the ActRII-A/B pathway as a potential link between aging and HF pathophysiology that could provide a novel target for HF therapeutic development.

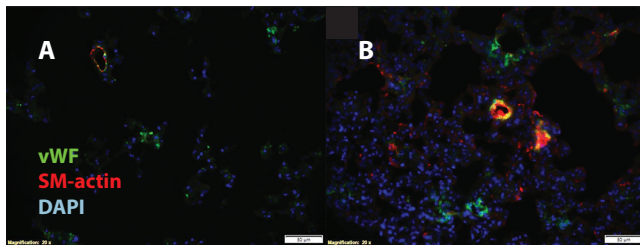


Figure 1. Mice treated with hypoxia (FIO₂=0.10 x 3wks) and BMP ligand trap exhibit more severe arteriolar remodeling (B) versus mice treated with hypoxia alone (A, bar=50uM).

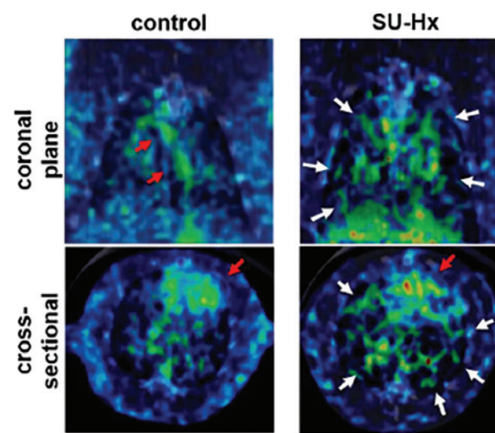


Figure 2. [89]Zr-bevacizumab PET-CT scans demonstrate increased peripheral lung uptake in rats developing severe pulmonary hypertension (SU-Hx) versus controls.



Signaling and Pulmonary Vascular Disease

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Our laboratory has investigated the role of bone morphogenetic protein (BMP) and transforming growth factor β (TGF- β) signaling pathways in the pathogenesis of vascular disease. Loss-of-function mutations involving this pathway are implicated in several congenital vascular syndromes including heritable pulmonary arterial hypertension (HPAH) and hereditary hemorrhagic telangiectasia (HHT) syndrome. A physiologic balance of BMP, Activin, Growth Differentiating Factor (GDF) and TGF- β ligand signals are essential for coordinating vasculogenesis and angiogenesis and maintaining vascular homeostasis; similarly, an imbalance in this tightly regulated network of signals can potentiate maladaptive responses to injury and inflammation.

To discern the regulation of BMP/TGF- β signaling in vascular disease, we have employed genetic models along with small molecule and recombinant probes to modify signaling. We have found that certain members of this pathway function as mechanistic biomarkers of disease, independent of the well characterized genetic syndromes: The acquired deficiency of these ligands may serve as a penetrance factor for pulmonary vascular disease following injury, whereas administering supraphysiologic levels of ligand may rescue established pulmonary hypertension. Using primary pulmonary vascular cells obtained from patients with PAH and unaffected controls, we have interrogated vascular cell functional and transcriptional responses to shear stress and BMP/TGF- β signaling to identify cellular phenotypes that may correspond to disease phenotypes. We have utilized PET-CT molecular imaging probes to determine whether a dysregulated angiogenic phenotype may be used as a sensitive and non-invasive diagnostic tool for revealing nascent pulmonary vascular disease. Finally, we have examined the propagation of BMP/TGF- β signals in cells in real time to determine the basis for functional specificity of distinct ligands in this signaling network.

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