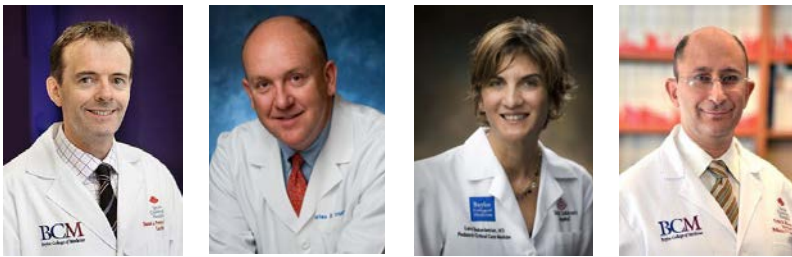


# CARDIOVASCULAR RESEARCH INSTITUTE

Spring Quarterly 2017

## Texas Children’s ranked No. 1 in heart care

Texas Children’s hospital ascended to the top of the charts ranking #1 in cardiology and #4 overall in the most recent US News & World Report. Texas Children’s received the no. 1 ranking because of its excellence in multiple areas including patient safety, death rates, and case complexity. This is a notable achievement for the Texas Medical Center, which is historically known for the surgical procedures pioneered by cardiac surgeons Dr. Michael E. DeBakey and Dr. Denton A. Cooley. Houston’s legacy is perpetuated by current leadership at Texas Children’s who have helped to achieve this successful rise to the top in the cardiovascular field. Of note, several Texas Children’s leaders are CVRI members. They include Daniel Penny, MD PhD, chief of cardiology; Charles Fraser, MD, chief of congenital heart surgery; Lara Shekerdeman, MD, chief of critical care; and Emad Mossad, MD, chief of anesthesiology (pictured below in order from left to right).



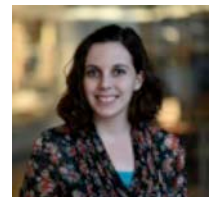
Follow the link below to read the full story featured in the Houston Chronicle.

<http://www.chron.com/news/health/article/Texas-Children-s-ranked-No-1-in-heart-care-11248983.php>

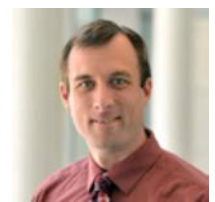
## Kelsey Jarrett, Dr. William Lagor, and colleagues develop a CRISPR-based strategy for the generation of a mouse model of atherosclerosis and its treatment

Researchers at Baylor College of Medicine have published findings on the identification of a mechanism by which they can manipulate blood cholesterol levels and atherosclerosis in a mouse model using a novel CRISPR-based strategy.

The research was led by Kelsey Jarrett, a graduate student in the William Lagor lab, and supervised by William Lagor, Ph.D., Assistant Professor of Molecular Physiology & Biophysics, at Baylor College of Medicine. The team developed an elegant new model for atherosclerosis and examined potential therapeutic interventions for this condition. Using CRISPR/Cas9 technology, they found that disrupting the low-density lipoprotein receptor gene in livers of mice led to increased blood cholesterol and atherosclerosis. In contrast, simultaneous disruption of Apolipoprotein B – a key component of low-density lipoprotein cholesterol – prevented disease. The paper entitled “Somatic genome editing with CRISPR/ Cas9 generates and corrects a metabolic disease” was published in Scientific Reports in March 2017. Research team members are from Baylor College of Medicine Cardiovascular Research Institute and the Molecular Physiology & Biophysics department.



Kelsey Jarrett



Dr. Lagor

The Lagor lab focuses on the study of molecular mechanisms controlling atherosclerosis, which contributes to a range of cardiovascular complications. The lab is currently working on developing methods to treat atherosclerosis using gene-editing techniques that involve the CRISPR technology. Dr. Lagor recently gave a CVRI seminar on CRISPR-mediated gene editing. More information about the Lagor lab can be found at <https://www.bcm.edu/research/labs/william-lagor>.

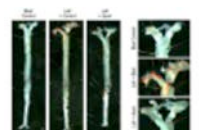


Fig 4 of article

## 5<sup>th</sup> Annual CVRI Symposium

This year's CVRI symposium was held on April 4, 2017 at Baylor College of Medicine. The symposium showcased a full day of speakers accented by midday rapid-fire poster sessions. The day culminated in an awards ceremony and networking reception.

The CVRI symposium created opportunities for clinicians and scientists from all career levels to share their cardiovascular-related work with colleagues from around the Texas Medical Center. The symposium emphasized the diversity of cardiovascular research around the medical center, and aimed to promote new collaborations between basic, translational, and clinical researchers. This day went a long way toward fulfilling the CVRI mission to "enhance collaborative opportunities for research in cardiovascular science."

### Abstract and Poster Winners

The 5<sup>th</sup> annual CVRI symposium featured researchers from all stages of their career. Moreover, this collaborative event showcased cardiovascular studies from academic and clinical realms giving clinicians and scientists the opportunity to learn from one another. Students, postdoctoral associates, and clinical fellows alike presented their work through talks and posters at this year's symposium.

All abstract submitted for presentation were reviewed and ranked by a team of expert judges. The top ranked abstracts were invited for a presentation during this year's CVRI Symposium. Jenny Sun, Paul Pang, Dr. Jennifer Karmouch, and Dr. Alexis Frazier-Wood were selected to present their work alongside invited faculty members who spoke at the 5<sup>th</sup> annual CVRI symposium. These graduate students, postdoctoral associates, and young investigators presented riveting talks to inform the CVRI membership of their research findings.

Jenny Sun is a graduate student from Dr. Russell Ray's lab. She presented a talk on sudden unexplained death in epilepsy (SUDEP). During her talk, Jenny presented evidence supporting the hypothesis that disruption of electrical signals in the brain stem causes cardiac and respiratory arrest in SUDEP.

Paul Pang, graduate student in Dr. Tom Cooper's lab introduced his work on deadly arrhythmias in patients with myotonic dystrophy type 1 (DM1). He found that adult mice bearing the fetal version of a cardiac sodium channel often found in DM1 patients developed abnormal heart rhythms.

Jennifer Karmouch, PhD postdoctoral fellow at the University of Texas Houston in Dr. A.J. Marian's lab, presented her findings on an inherited heart defect associated with cardiac arrhythmias. She showed that non-muscle cardiac cells contribute to the pathogenesis of this disease known as arrhythmogenic cardiomyopathy.

Alexis Frazier-Wood, PhD, Assistant Professor in the Children's Nutrition Research Center at Baylor College of Medicine presented her findings on a metabolomic study investigating the connection between the Mediterranean-style diet and cardiovascular health.



CVRI abstract-winning selected speakers are pictured to the left alongside CVRI directors, from left to right: CVRI director Dr. Xander Wehrens, Paul Pang, Jenny Sun, Jennifer Karmouch, and CVRI associate director Dr. Biykem Bozkurt.

A total of 67 posters were presented during three poster sessions during the CVRI symposium. All posters were judged by expert reviewers. After a brief presentation and question and answer session, the posters were ranked. One winner was selected from each of the following categories: students, postdoctoral fellows, clinical fellows, and junior faculty. The winners were Ann Quick, student in the Wehrens lab, Dr. Nanbing Li, postdoctoral fellow in Dr. Mary Dickenson's lab, Dr. Andrew Landstrom, fellow in pediatric cardiology – who was featured in the Fall 2016 CVRI newsletter – took home the prize for best clinical fellow poster presentation, and Dr. Vivek Singh, Assistant Professor in Surgery at Baylor College of Medicine, won the best junior faculty poster award.

Ann Quick presented her work on a kinase and structural protein known as SPEG, the expression of which is decreased in human heart failure. SPEG is required for normal cardiac structure and function. She found that SPEG works by modulating key components of the calcium signaling system in cardiac muscle cells that helps these cells maintain their shape and beat efficiently.

Nanbing Li, PhD displayed elegant and insightful images of developing mouse embryos resulting from her work on cardiovascular development. She found that a gene known as *Ascc2* – identified in the Knockout Mouse Project unbiased genome screen – is required for cardiac development and embryonic viability.

Andrew Landstrom, MD, PhD, presented his clinical research findings during the poster session. He showed the importance of mutation location in genes with known catecholaminergic polymorphic ventricular tachycardia (CPVT) association.

Vivek Singh, PhD, junior faculty in the surgery department at Baylor College of medicine, presented a poster on his efforts to reprogram cardiac fibroblasts into heart muscle cells. Dr. Singh demonstrated that a combination of transcription factors and micro RNAs could be used to successfully transform cardiac non-muscle cells into muscle cells which may be important for future regenerative medicine studies.

CVRI poster winners are pictured to the right alongside CVRI leadership from left to right Dr. Wehrens, Ann Quick, Dr. Nanbing Li, Dr. Andrew Landstrom, Dr. Vivek Singh, and Dr. Biykem Bozkurt.



## Keynote Speakers

The Cardiovascular Research Institute was honored to host Dr. Christine Seidman and Dr. Richard Gibbs as keynote speakers for 5<sup>th</sup> annual CVRI symposium. Both are internationally recognized pioneers in cardiovascular research and have made immense contributions toward advancing our knowledge in this field. They enlightened us with their cutting edge work spanning from basic to clinical research on cardiomyopathy and heart failure.

Dr. Christine Seidman is a Howard Hughes Medical Institute Investigator and the Thomas W. Smith Professor of Medicine and Genetics at Harvard Medical School and Brigham and Women's Hospital. She is a leading scientist in the field of familial cardiomyopathy, who has provided new insights into mechanisms by which deleterious human mutations cause cardiomyopathy. Dr. Seidman discovered the first dominant mutations in cardiac transcription factors (TBX5 and NKX2.5) causing congenital heart disorders. Throughout the last decade, she defined multiple disease-causing roles for mutations in critical cardiac genes.

The title of Dr. Seidman's lecture at the CVRI symposium was "Genetics of Cardiomyopathy: Getting to the Heart of the Matter". Her talk enlightened us with an array of topics covering role of Titin truncation variants in cardiomyopathy, the involvement of myosin in ATP turnover, and the effects of Titin mutations on sarcomere integrity of induced pluripotent stem cells (iPSCs). Dr. Seidman discussed genetic backgrounds of both hypertrophic and dilated cardiomyopathy and highlighted how different genetic mutations can predict individuals at high risk for either of these diseases. She explained how different truncations of the Titin gene are related to pediatric and adult cardiomyopathies. She also shared breakthrough research from her group demonstrating the effect of Titin truncation variants. They found that they could engineer cardiac cells from human iPSCs with Titin mutations that mimicked cells from hearts with dilated cardiomyopathy. Dr. Seidman's talk highlighted many of the important advancements she and her colleagues have contributed to the cardiomyopathy field. However, she also shed light on the gray areas of cardiomyopathy research as she raised an interesting question about the definitive causal factor of hypertrophic cardiomyopathy being increased cardiac contraction or decreased relaxation.

Dr. Richard Gibbs is the founder and director of the Human Genome Sequencing Center at Baylor College of Medicine. He led the group who presented the first diploid sequence of a human. He is a pioneer of developing breakthrough whole-exome capture methods in whole genome sequencing of several diseases including heart failure, cancer and autism.

The title of Dr. Gibbs' talk was "Adult Genomics in the Clinic: The 'Mars Program' ". Dr. Gibbs gave us an overview of the advancement of whole genome sequencing and how much research needs to be done to make it more efficient and economical for using in disease prediction and treatment. He highlighted the difficulties his group along with other research groups from all over the world had to overcome by comparing this project as the current 'Mars Project'. Dr. Gibbs inspired us through his insightful talk to be more involved in solving this puzzle linking genetic signatures to different diseases.

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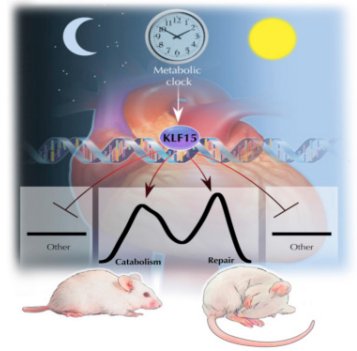
## CVRI Member Profile

### Lilei Zhang, MD, PhD



Lilei Zhang, M.D., Ph.D. is an Assistant Professor in the Molecular and Human Genetics department at Baylor College of Medicine. Dr. Zhang completed her medical training at the Peking University Health Science Center and her graduate research training at John Hopkins University. She completed additional medical and research fellowships at Case Medical Center in Ohio before coming to Baylor College of Medicine in 2016.

As a physician-scientist, Dr. Zhang's research focuses on uncovering the genetic and epigenetic regulation of the heart in health and disease. This goes hand-in-hand with Dr. Zhang's work in the clinic, which focuses on providing precision diagnostics to adults with genetic predisposition to cardiovascular disease.



The Zhang lab uses rodent models in addition to human induced pluripotent stem cell-derived cardiomyocytes in order to study genetic regulation of the heart in cardiomyopathies and heart failure. Much of Dr. Zhang's work focuses on circadian rhythms of molecules in the heart. Dr. Zhang's theorizes that disruption of these natural rhythms among cardiac molecules can lead to loss of genetic regulation and detrimental remodeling leading to heart failure. In a recent publication in Cell Reports (2016), Dr. Zhang demonstrated that a molecule known as Kruppel-like factor 15 (KLF15) controls the genes governing active versus repair phases of the heart on a daily basis (represented by the image on the right). Dr. Zhang also gave a lecture at the 5<sup>th</sup> annual CVRI symposium where she spoke about the role of REV-ERB $\alpha$  in this process, which gets recruited by KLF15 to promote cardiac quiescence. Overall, Dr. Zhang's work highlights the importance of circadian rhythms on genetic regulation of the heart for normal cardiac function.

As a physician scientist Dr. Zhang is uniquely suited to research the genetic regulation of cardiovascular disease and apply that knowledge to provide her patients with precision medicine. Ultimately, Dr. Zhang would like to develop cardiovascular therapeutics targeting cardiac gene regulation.

For more information about Dr. Lilei Zhang's research, please visit her BCM webpage at:  
<https://www.bcm.edu/people/view/lilei-zhang-m-d-ph-d/659fb688-2da6-11e6-a974-005056b104be>

## CVRI Seminar Series 2017-18

Each fall and spring semester, CVRI presents a series of lunch time seminars designed to inform cardiovascular physicians, scientists and clinical and research trainees of recent discoveries in cardiovascular research. These seminars are presented by distinguished physicians and researchers from noted institutions around the country and within the Texas Medical Center who have recently published and are actively involved in research. Seminars take place one Wednesday per month, from noon to 1:00 pm, and lunch is provided. Seminars are open to all faculty, staff, and students who are interested. For more information about the CVRI Seminar Series, please visit [www.bcm.edu/research/cardiovascular-research-institute/seminars](http://www.bcm.edu/research/cardiovascular-research-institute/seminars).

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The Cardiovascular Research Institute at Baylor College of Medicine was established in 2012 as a key strategic initiative to enhance collaborative opportunities for research in cardiovascular sciences. CVRI aims to provide administrative and research support to promote collaborative and interdisciplinary basic, translational, and clinical research. In the near future, the CVRI aims to develop educational tracks for students, residents, fellows, and junior faculty to train future leaders in basic, translational and clinical cardiovascular medicine and research. The Institute is led by Director Xander Wehrens, MD, PhD, and Associate Director Biykem Bozkurt, MD, PhD.

For more information about CVRI, please visit [www.bcm.edu/cvri](http://www.bcm.edu/cvri), or contact Administrative Assistant Yvonne Arceneaux at [yvonne.arceneaux@bcm.edu](mailto:yvonne.arceneaux@bcm.edu) or 713-798-6951.

## From the Director



### **Xander Wehrens, MD, PhD**

*Director, Cardiovascular Research Institute  
Juanita P. Quigley Endowed Chair in Cardiology  
Professor, Department of Molecular Physiology &  
Biophysics, Medicine (in Cardiology), Pediatrics, and Center  
for Space Medicine  
Co-Director, Medical Scientist Training Program*

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One of the Cardiovascular Research Institute's (CVRI) core missions is to promote innovative research by facilitating new collaborations across affiliated departments and hospitals. With the goal of encouraging additional collaborative projects, we are introducing a quarterly newsletter to inform CVRI members of ongoing research and recent notable achievements.

Collaborative research was highlighted extensively during our 5<sup>th</sup> Annual Symposium of the Baylor College of Medicine CVRI. It was encouraging to see how many collaborations formed during the past 5 years have cumulated

Together, CVRI institutions and scientists form a repository of medical knowledge that has few equals in medical research. Membership in CVRI offers an extraordinary opportunity to create partnerships with scientists who can provide transformative insights into ongoing research. The Institute's goal is to provide a platform to share this knowledge in order to more quickly translate scientific discoveries into effective, innovative clinical therapies.

I hope you will feel free to reach out to me to share your projects and discoveries to ensure that the dialogue continues.

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## Awards

Dr. Xander Wehrens, Director of the Cardiovascular Research Institute, Professor in the Departments of Molecular Physiology & Biophysics, Medicine, and Pediatrics, and Center for Space Medicine, received the 2017 Outstanding Investigator Award from the International Society for Heart Research. On June 2, he delivered a keynote lecture at the annual ISRH meeting entitled "Calcium Release Unit Defects—Source of Many Cardiac Evils?"

This annual award recognizes an outstanding scientist who (i) is making major and independent contributions to the advancement of cardiovascular science, and (ii) is leading a growing research program likely to play a major role in the future. The main criteria for selecting awardees are scientific excellence, independence, and potential for future research contributions. Awardees are chosen from nominations across all international sections of the International Society for Heart Research.

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## Funding Opportunities

The American Heart Association has several upcoming research awards (see the timeline below). Monitor the [AHA Application Information](#) webpage for updates.

### 2017-18 AHA Funding Opportunities Timeline\*

Award Program	Letter of Intent Deadline	Application Deadline	Award Start Date
SFRN Vascular Disease	Aug 1	Sept 26	April 1
AIREA	X	Oct 3	April 1
Institutional Undergraduate	X	Oct 4	April 1
Established Investigator	Aug 1	Oct 23	Jan 1
Predocctoral Fellowship	X	Nov 1	July 1
Postdoctoral Fellowship	X	Nov 2	July 1
Merit Award	Aug 15	Nov 6	April 1
Career Development	X	Dec 4	July 1
Innovative Project	X	Dec 11	July 1
Transformational Project	X	Jan 16	July 1
Collaborative Sciences	Nov 1	Feb 5	July 1
SFRN Atrial Fibrillation	TBA	TBA	July 1
Institute - Data Grants & Methods Validation	X	June 29	Oct 1
Institute - Uncovering Patterns	X	Aug 24	Nov 1

\* Dates are subject to change

## Not a member?

If you have received this newsletter and are not currently a member of CVRI, we invite you to submit an application for membership in one of Baylor College of Medicine's strongest strategic initiatives, the Cardiovascular Research Institute.

Please fill out the [online membership form](#) on CVRI's membership page at [www.bcm.edu/research/centers/cardiovascular-research-institute/membership](http://www.bcm.edu/research/centers/cardiovascular-research-institute/membership).

Many benefits will be extended to you as a CVRI member, including:

- Access to a central repository of human tissue samples and core lab functions
- Collaborative opportunities for investigators, physicians, centers and institutes to foster cross-cutting opportunities and innovative translational research opportunities at BCM, the Texas Medical Center, and globally
- Opportunities for pilot grant funding for collaborative research projects in selected years
- Administrative support for submission of multi-investigator grants, program project grant proposals, and clinical trial agreements
- Listing on the BCM CVRI website and in the member database
- Participation in Institute retreats, seminars, grant workshops and other activities

For more information about CVRI membership benefits, contact Yvonne Arceneaux at [Yvonne.Arceneaux@bcm.edu](mailto:Yvonne.Arceneaux@bcm.edu), 713-798-6951.

# CVRI Member Selected

## Publications

### Dissecting the role of myeloid and mesenchymal fibroblasts in age-dependent cardiac fibrosis

Trial, J.A., Heredia, C.P., Taffet, G.E., Entman, M.L., Cieslik, K.A. **Basic Research in Cardiology**. 2017 Jul; Volume 112, Issue 4, Article number: 34.

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### Endothelial LRP1 regulates metabolic responses by acting as a co-activator of PPAR $\gamma$

Mao, H., Lockyer, P., Li, L., Ballantyne, C.M., Patterson, C., Xie, L., Pi, X. **Nature Communications**. 2017 Apr 10, Volume 8, Article number: 14960

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### Scavenger receptor B1 (SR-B1) profoundly excludes high density lipoprotein (HDL) apolipoprotein AII as it nibbles HDL-cholesteryl ester

Gillard, B.K., Bassett, G.R., Gotto, A.M., Rosales, C., Pownall, H.J., **Journal of Biological Chemistry**. 2017 Apr 3; Volume 292, Issue 21, Pages: 8864-8873.

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### Practical Approaches for Whole-Genome Sequence Analysis of Heart- and Blood-Related Trait

Morrison, A.C., Huang, Z., Yu, B., Metcalf, G., Liu, X., Ballantyne, C., Coresh, J., Yu, F., Muzny, D., Feofanova, E., Rustagi, N., Gibbs, R., Boerwinkle, E. **American Journal of Human Genetics**. 2017 Feb 2; Volume 100, Issue 2, Pages: 205-215

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### Serine/Threonine Phosphatases in Atrial Fibrillation

Heijman, J., Ghezelbash, S., Wehrens, X.H.T., Dobrev, D. **Journal of Molecular and Cellular Cardiology**. 2017 Feb, Volume 103, Pages: 110-120.

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### SPEG (Striated Muscle Preferentially Expressed Protein Kinase) is Essential for Cardiac Function by Regulating Junctional Membrane Complex Activity

Quick, A.P., Wang, Q., Philippen, L.E., Barreto-Torres, G., Chiang, D.Y., Beavers, D., Wang, G., Khalid, M., Reynolds, J.O., Campbell, H.M., Showell, J., McCauley, M.D., Scholten, A., Wehrens, X.H.T. **Circulation Research**. 2017 Jan 6; Volume 120, Issue 1, Pages: 110-119

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### High-throughput discovery of novel developmental phenotypes.

Dickinson ME, Flenniken AM, Ji X, Teboul L, Wong MD, White JK, Meehan TF, Weninger WJ, Westerberg H, Adissu H, Baker CN, Bower L, Brown JM, Caddle LB, Chiani F, et al. **Nature**. 2016 Sep 22; Volume 537, Issue 7621, Pages 508-514.

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### Regulating the regulator: Insights into the cardiac protein phosphatase 1 interactome

Chiang, D.Y., Heck, A.J.R., Dobrev, D., Wehrens, X.H.T. **Journal of Molecular and Cellular Cardiology** Volume 101, 2016 Sep 20, Pages: 165-172

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### Alcohol consumption and cardiac biomarkers: The atherosclerosis risk in communities (ARIC) study

Lazo, M., Chen, Y., McEvoy, J.W., Ndumele, C., Konety, S., Ballantyne, C.M., Sharrett, A.R., Selvin, E. **Clinical Chemistry**. 2016 Sep 9; Volume 62, Issue 9, Pages: 1202-1210.

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### Effects of visceral adipose tissue reduction on CVD risk factors independent of weight loss: The Look AHEAD study

Sanguaneko, A., Lazo, M., Upala, S., Brancati, F.L., Bonekamp, S., Pownall, H.J., Balasubramanyam, A., Clark, J.M. **Endocrine Research**. 2016 Jun 28; Volume 42, Issue 2, Pages: 86-95.

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### CaMKII-dependent phosphorylation of RyR2 promotes targetable pathological RyR2 conformational shift

Uchinoumi, H., Yang, Y., Oda, T., Li, N., Alsina, K.M., Puglisi, J.L., Chen-Izu, Y., Cornea, R.L., Wehrens, X.H.T., Bers, D.M. **Journal of Molecular and Cellular Cardiology**. 2016 Jun 16; Volume 98, Pages: 62-72.

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### Dysregulation of RBFOX2 Is an Early Event in Cardiac Pathogenesis of Diabetes

Nutter, C.A., Jaworski, E.A., Verma, S.K., Deshmukh, V., Wang, Q., Botvinnik, O.B., Lozano, M.J., Abass, I.J., Ijaz, T., Brasier, A.R., Garg, N.J., Wehrens, X.H.T., Yeo, G.W., Kuyumcu-Martinez, M.N. **Cell Reports**, 2016 Jun 7; Volume 15, Issue 10, Pages: 2200-2213

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### Pitx2 promotes heart repair by activating the antioxidant response after cardiac injury.

Tao G, Kahr PC, Morikawa Y, Zhang M, Rahmani M, Heallen TR, Li L, Sun Z, Olson EN, Amendt BA, Martin JF. **Nature**. 2016 May 25, Volume 534, Issue 7605, Pages: 119-23

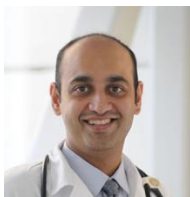
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# CVRI Themes and Leadership

## Aortopathy, Valvular Heart Disease



**Scott LeMaire, MD**  
Surgery  
Member, Executive Committee



**Vijay Nambi, MD**  
Medicine/Cardiology

## Arrhythmias, Channelopathies



**Xander Wehrens, MD, PhD**  
Physiology, Medicine  
CVRI Director



**Miguel Valderrabano, MD, FACC**  
Medicine/Cardiology

## Cardiac Regeneration, Stem Cells



**James Martin, MD, PhD**  
Physiology  
Member, Executive Committee



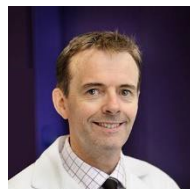
**Todd Rosengart, MD**  
Surgery  
Member, Executive Committee

[www.bcm.edu/cvri](http://www.bcm.edu/cvri)

## Congenital Developmental Heart Disease



**Mary Dickinson, PhD**  
Physiology  
Member, Executive Committee



**Daniel Penny, MD, PhD, MHA**  
Pediatrics/Cardiology  
Member, Executive Committee

## Coronary Artery Disease, Atherosclerosis, Ischemia



**Christie Ballantyne, MD**  
Medicine/Cardiology  
Member, Executive Committee



**Changyi Johnny Chen, MD, PhD**  
Surgery

## Heart Failure, Cardiomyopathy



**Biykem Bozkurt, MD**  
Medicine/Cardiology  
CVRI Associate Director



**Tom Cooper, MD**  
Pathology  
Member, Executive Committee



**Mark Entman, MD**  
Medicine, Cardiovascular Sciences  
Member, Executive Committee