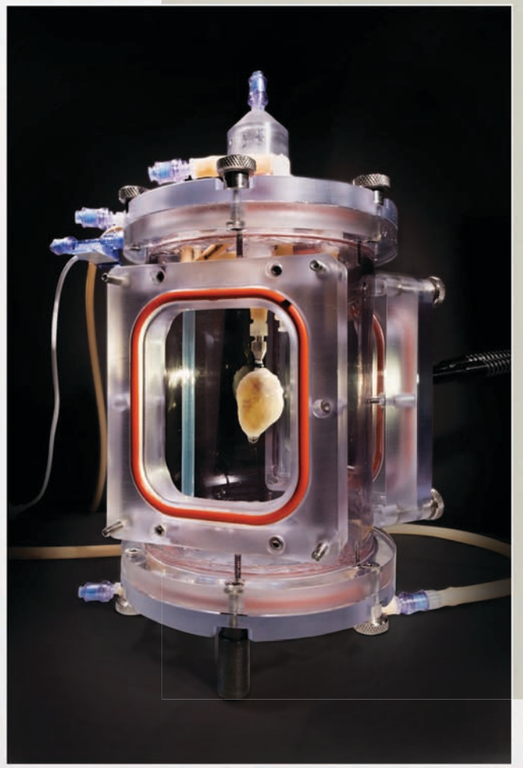
Building a BETTER HEART

Over 3,000 people in the United States are waiting for a donor heart on any given day. Tragically, availability of hearts is insufficient to meet the demand. The Cardiac Research Institute at MMRL has undertaken a project to bioengineer new hearts that someday could be available for transplantation.

Cardiac Research Institute
at MASONIC MEDICAL RESEARCH LABORATORY



On the cover – Scientists at the Cardiac Research Institute have undertaken a project to bioengineer new hearts that someday could be available for transplantation without the danger of auto immune rejection. A first step in that process is stripping the heart to its translucent white protein skeleton, seen here, before it is regenerated with induced pluripotent (non-embryonic) stems cells.

Visit mmrl.edu to learn more

Building a Better Heart

Welcome to the Future of Medicine

The Masonic Medical Research Laboratory (MMRL) – today also known as the Cardiac Research Institute (CRI) – has been performing innovative medical research since 1958. The results have advanced our understanding of the causes of heart disease and have contributed to over a 50 percent decline in deaths from heart disease since 1980.

Hearts that function better also lead to a better quality of life.

Few laboratories have been as progressive, productive or influential in the field of experimental cardiology.

Today the Institute is unique among medical research centers worldwide in its ability to study the genetic causes of lethal cardiac arrhythmias responsible for sudden cardiac death and to design gene-specific therapies.

CRI's scientific breakthroughs have helped to develop new heart medications and diagnostic procedures, as well as novel therapeutic approaches for the management of cardiac arrhythmias.

What's more, work now being performed at CRI/MMRL is endeavoring to develop hearts for transplantation that are genetically compatible and free from the risk of autoimmune rejection.

The Institute stands as a beacon of hope for all whose lives have been or will be touched by heart disease.

That hope is made possible by the thoughtful generosity and commitment of the organizations and individuals who support our research.

We are working for all of you.
Board of Directors and Staff

Every Heartbeat Counts™

Detecting Heart Problems

A Remarkable Organ

Your heart is an organ like no other. It beats 70 times a minute, 100,000 times each day, moving 4,300 gallons of blood daily through the body's intricate vascular network. Although displacement of blood is its primary function, every beat of this unique muscular pump is initiated and finely regulated by electrical impulses that originate in the heart itself.

Electrical currents in the form of positive and negative charged ions flow across the membrane of each cell causing voltage surges that set the heart in motion. Sodium ions rush into the cells, followed by potassium and chloride ions making a quick exit. The resulting voltage spike or action potential regulates the influx of calcium ions that mediate the sliding motion of filaments within each cell, causing their shortening or contraction. These electrical signals are measured by the electrocardiogram or ECG, which informs our doctor about the health of our heart.

When Things Go Wrong

Without electrical activity, the heart lies motionless and serves no useful purpose. Disorderly electrical activity – also known as cardiac arrhythmias – can render the heart inefficient or totally useless as a pump. Extreme disorganization of the electrical activity can lead to sudden death, the single most prevalent mechanism of death in the United States. It takes the lives of over 350,000 Americans each year.

Nearly every minute of every day someone in this country dies of sudden cardiac death. Not all arrhythmias are life-threatening; some, like Atrioventricular Nodal Reentrant Tachycardia, although not lethal, may be incapacitating. Still others, like atrial fibrillation, are less ominous, but can lead to a stroke.

Disorderly electrical activity can render the heart inefficient or totally useless as a pump.

Uncovering Answers

Using sophisticated techniques, CRI/MMRL's experimental cardiologists are able to measure voltage signals and ion currents from preparations as small as a patch of membrane of a single cell to the heart, as a whole, and examine the effects of drugs on the function of the heart.

Our studies have helped to define the cellular basis for the different waves found in the electrocardiogram (ECG), giving the clinician a better road map and understanding of the heart. This has led to better use of diagnostic tools such as the ECG and has aided in the development of pharmacological treatments.

Prevention, diagnosis and treatment have advanced at a steady pace, offering a better quality of life for some and a new lease on life for many afflicted with heart disease.

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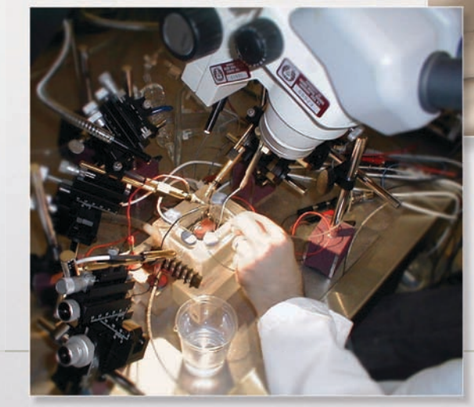


Every Heartbeat Counts™

Deepening Our Understanding

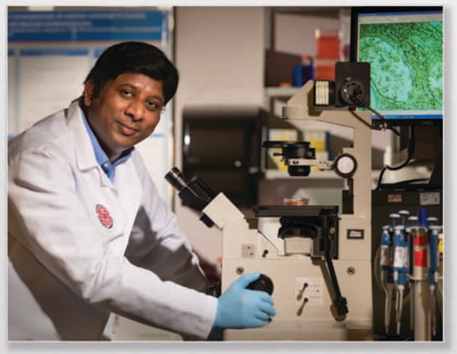
Looking Closely at Life-Threatening Arrhythmias

Our scientists have developed several experimental models of life-threatening cardiac arrhythmias, including the Long QT, Short QT and Brugada Syndromes, and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). These models have enabled the Institute to develop and test new therapeutic modalities for combating sudden death in infants, children and young adults afflicted with these congenital syndromes. Part of our focus has been to define when and how regional differences in electrical function of the heart develop with age. This information will lead to a better understanding of the basis for fatal arrhythmias and guide our understanding of how cardiac arrhythmias contribute to Sudden Infant Death Syndrome (SIDS) and atrial fibrillation, a leading cause of stroke.

Molecular Genetics

Our Molecular Genetics program identifies the genetic basis for life-threatening cardiac arrhythmia syndromes.

Inherited Syndromes like Long QT, Short QT and Brugada Syndromes cause a malfunction in the electrical activity of the heart, tragically taking the lives of infants, children and young adults with little or no warning. Our studies have shown that genetic variations, sometimes very subtle, can also predispose a person to the development of life-threatening arrhythmias following a heart attack or following the ingestion of some medications. A CRI study, showing that a common genetic variation - known as a polymorphism - predisposes patients suffering a heart attack to the development of life-threatening arrhythmias, was recognized as one of the top papers published in *Heart Rhythm* in 2012.



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Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in the clinic. It is reaching epidemic proportions in the United States, with over 2.7 million Americans affected – including nearly one in 10 individuals 80 years of age and older. As the population ages, projections indicate that its prevalence will increase to 15 million by 2050.

Because of the rapid progression of the disease and its socioeconomic impact, safe and effective pharmacological treatment is considered to be one of the greatest unmet medical needs facing our society. Most available drugs have low effectiveness, and those with high effectiveness, have high toxicity.

Scientists at the Institute are working with a biotechnology company to develop a novel therapy for AF based on atrial-selective inhibition of sodium channel current, an approach pioneered by CRI/MMRL scientists. It has shown high efficacy in experimental models, but unlike other drugs used to treat AF, it has very low toxicity. Clinical trials are being conducted to assess the effectiveness of the combination of ranolazine (Ranexa) and dronedarone (Multaq) for the safe and effective management of AF.

We are also conducting studies to assess the effectiveness of certain drugs and combinations of drugs on the induction of atrial fibrillation in the setting of heart failure. Heart failure affects nearly 5 million people in the United States. Each year close to 500,000 new cases are diagnosed. It is the leading cause of hospitalization in people over 65 and is often associated with atrial fibrillation, which worsens the prognosis of heart failure.

Our ongoing studies have identified a temporal window of vulnerability for the development of atrial fibrillation during the progression of heart failure. We have also shown that in our experimental models, ranolazine (Ranexa) is very potent in preventing the induction of AF in the setting of heart failure. In view of its efficacy and safety, it may be a welcome substitute to currently used drugs.

CRI/MMRL is also working to identify gene defects that can predispose young individuals to AF.

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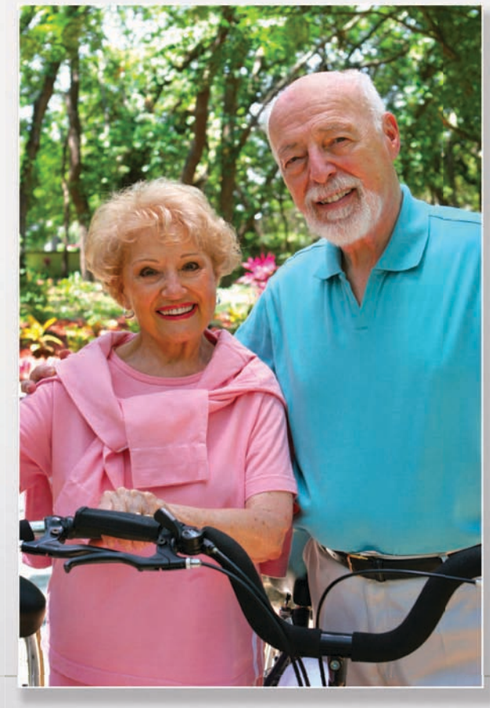

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Deepening Our Understanding

Long QT Syndrome

Like other arrhythmic diseases, Long QT Syndrome (LQTS) involves an abnormality of the heart's electrical system caused by defects in the function of ion channels. These electrical defects predispose affected individuals to a very fast heart rhythm called Torsade de Pointes, which can lead to sudden loss of consciousness (syncope) and sudden cardiac death.

The syndrome's name comes from its distinctive electrocardiographic (ECG) signature, which takes the form of an unusually long interval between the "Q" and "T" waves of the ECG. The QT interval is a measure of the time it takes the heart to return to its resting state after initially being activated. The syndrome can be inherited or acquired.

The acquired form of the disease is often caused by drugs used to treat arrhythmias, depression, infections and schizophrenia. The Experimental Cardiology team at CRI has remained at the cutting edge of finding ways to identify drugs that can be life-threatening. We have become a referral center for pharmaceutical and biotechnology companies. The CRI/MMRL works with biotechnology and pharmaceutical companies worldwide to help them evaluate the safety of drugs in their pipeline and assist with the approach to the U.S. Food and Drug Administration (FDA).

Congenital LQTS is one of the most tragic conditions under which arrhythmias strike. Individuals born with the syndrome usually lead a perfectly normal childhood. After puberty or in their late teens, they start to experience dizzy spells, which if not caught in time and treated, can result in sudden death. Our investigators are identifying gene mutations that lead to the development of congenital Long QT Syndrome and assist physicians with selection of gene-specific therapy.

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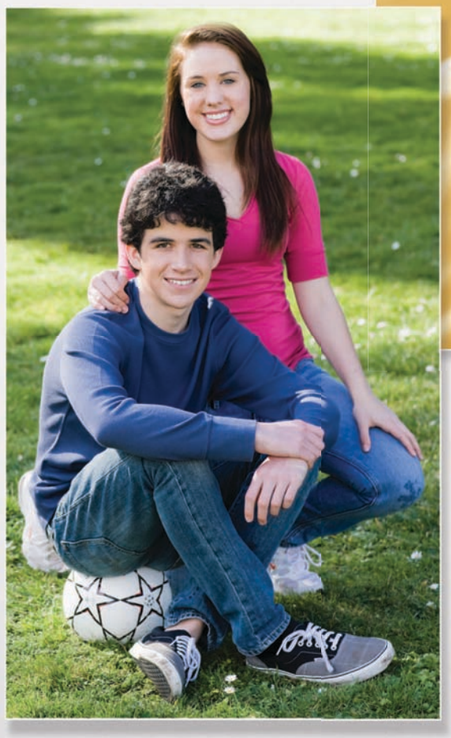


Sudden Infant Death Syndrome (SIDS)

SIDS has been attributed to numerous, often poorly defined mechanisms implicating cardiovascular, respiratory and infectious diseases. The first direct evidence linking SIDS to a congenital heart defect – the Long QT Syndrome – was published in *The New England Journal of Medicine* based on work done by the CRI/MMRL team in collaboration with clinical colleagues in Italy.

A mutation in the gene known as SCN5A was shown to produce a major increase in late sodium current, providing the first unequivocal demonstration that a life-threatening event in infancy – with all the features of SIDS – may be due to a sporadic mutation causing LQTS. Support for a link between SIDS and cardiac arrhythmias has grown progressively and it is now believed that 10-15 percent of SIDS cases are due to disorders of heart rhythm.

The first direct evidence linking SIDS to a congenital heart defect – the Long QT Syndrome – was published in ***The New England Journal of Medicine*** *based on work done by the CRI/MMRL team in collaboration with clinical colleagues in Italy.*

CRI/MMRL is one of the top genetic screening centers in the world dedicated to helping families with inherited life-threatening cardiac arrhythmias.

Every Heartbeat Counts™

Deepening Our Understanding

Short QT Syndrome

Scientists at CRI/MMRL identified the first gene responsible for causing sudden death in infants, children and young adults – known as the Short QT Syndrome (SQTS) – as well as a pharmacologic approach to therapy that can be used as an adjunct to implantable cardioverter defibrillators.

Members of families in which the gene is present display very short QT intervals on their ECG and suffer from life-threatening abnormal rhythms of the heart. Our scientists have created several experimental models of the Short QT Syndrome capable of reproducing the electrocardiographic and arrhythmic features of the syndrome, which have proven useful in finding pharmacologic therapies.

CRI scientists first identified quinidine as a drug capable of reversing the effects of the genetic mutations responsible for the electrical malfunction. This drug is today used worldwide to treat patients with the Short QT Syndrome.

Starting and ending with the patient in the clinic, CRI/MMRL brought the research full circle by delving into the cause of the disease at the genetic level.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

CPVT is an inherited disorder predominantly affecting children or adolescents. Affected youngsters are in danger of sudden cardiac arrest when they exercise. This syndrome is caused by gene mutations that affect the handling of calcium in cardiac cells.

In a report published in *Circulation*, CRI presented an experimental model for this syndrome, providing new insights into the cause of arrhythmias associated with the disease – particularly the cause of sudden death – which proved to be different from that generally presumed.

Early Repolarization Syndrome

An early repolarization pattern on the ECG was long regarded as benign. In 2000, CRI scientists challenged this belief and suggested that some forms of early repolarization could result in the development of life-threatening arrhythmias. Validation of this hypothesis was provided by two studies published in *The New England Journal of Medicine* in 2008. The Cardiac Research Institute again led the way in defining the genetic and clinical aspects of the Early Repolarization Syndrome (ERS).

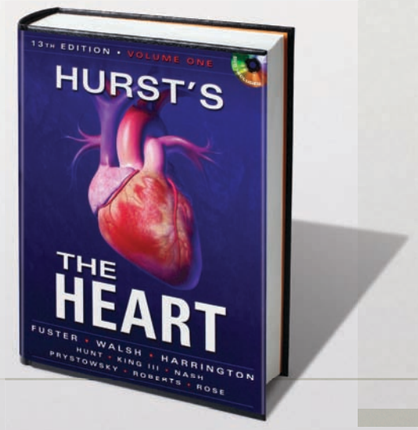
CRI scientists developed a coronary-perfused wedge model of the Early Repolarization Syndrome. With this model, we have gone on to elucidate the mechanism underlying this sudden death syndrome and have identified drugs that can be used to ameliorate the pathogenicity of the syndrome. The model has also provided insight into why early repolarization in the leads facing the inferior region of the heart are associated with a higher risk for sudden cardiac arrhythmic death.

In another series of studies using this model, we have demonstrated that the presence of an early repolarization signal in the ECG can indicate a predisposition to development of arrhythmias during hypothermia or low body temperature. Current guidelines recommend mild therapeutic hypothermia ( ) to prevent neurological damage following a cardiac arrest or heart attack. The extent to which hypothermia contributes to arrhythmogenesis and the mechanisms involved are not well defined. Recent reports point to an association between Early Repolarization pattern (ER) and the development of ventricular tachycardia/ventricular fibrillation (VT/VF) in the setting of hypothermia.

Our study demonstrated that hypothermia leads to life-threatening arrhythmias in the setting of early repolarization by exaggerating repolarization abnormalities, leading to development of phase-2-reentry.

The Institute also identified three drugs – quinidine, cilostazol and milrinone – capable of suppressing the hypothermia-induced arrhythmias.

CRI/MMRL scientists wrote the chapter on mechanisms of cardiac arrhythmias in ***Hurst's The Heart,*** *the leading reference book used by cardiologists worldwide.*

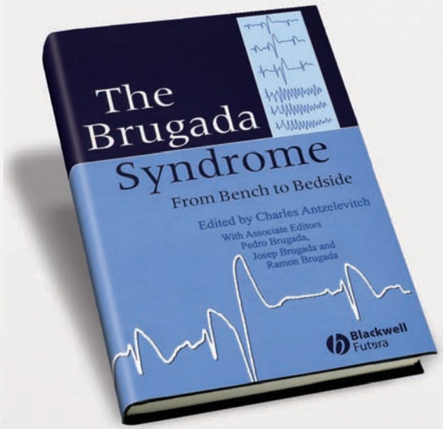


Deepening Our Understanding

Brugada Syndrome

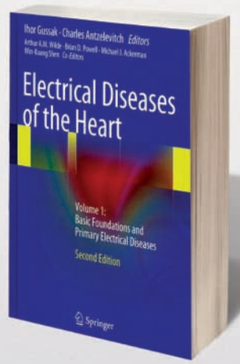
CRI/MMRL scientists also take pride in having discovered the majority of genes responsible for another form of inherited sudden cardiac death known as the Brugada Syndrome.

This disorder generally afflicts individuals as they reach the third and fourth decade of their otherwise-healthy lives. Some, in fact, are athletes who have endured strenuous training without any medical problems, until one day they die suddenly in their sleep without warning. The syndrome has confounded doctors for decades and left many families devastated.



Our scientists demonstrated that faulty genes that encode sodium, calcium and potassium channels in the heart contribute to the development of this syndrome. Using experimental models of the disease, we were able to identify a class of drugs that can be used in conjunction with implantable cardioverter defibrillators (ICDs) to protect patients from the arrhythmias that lead to sudden cardiac arrest. Thanks to these advances, individuals with this disease can be identified genetically as well as clinically, and appropriate therapy can be administered before a tragic outcome occurs.

The only book dealing exclusively with Brugada Syndrome emanated from a Consensus Conference hosted by CRI/MMRL.



Dr. Charles Antzelevitch, working with colleagues worldwide, has co-authored a two-volume second edition of ***Electrical Diseases of the Heart.*** *It is a tour de force that highlights and embraces the explosion of knowledge that captures our understanding of heart disease by researchers, scientists and clinicians.*

It Did Not Have to Happen

Hyla Molander

For Hyla, it all changed on Easter Sunday a few years ago.

Hyla was 29 and seven months pregnant with her second child. She and her 17-month-old daughter Tatiana were in the kitchen and watched her husband Erik slide down the kitchen counter and lie motionless on the floor. One minute he was laughing and talking about their future. A half-hour later, Hyla was a widow.

Erik, a victim of undetected Brugada Syndrome, did not have to die. Tatiana did not have to watch it happen. And Hyla did not have to give birth two months later holding only a photo of her deceased husband.

Today, thanks to work done at the Cardiac Research Institute at the Masonic Medical Research Laboratory, Hyla's daughters most certainly don't have to suffer their father's fate. Using molecular genetics and molecular biology, CRI/MMRL scientists were able to test family blood samples for the gene defect. With that confirmed, proper precautions were taken to minimize the girls' risk for cardiac events.

A Life Saved

Brian Shrader

When an illness presents itself in a young person, the impact is felt through the family. Such was Brian's experience in being picked up off the lacrosse field while in the grips of a mysterious cardiac arrest at age 17. Panic consumed his family and doctors were at a loss to diagnose what problem had revealed itself in an otherwise healthy and athletic person.

As his family doctor worked tirelessly to save his life, Brian was already unknowingly benefiting from research done at CRI/MMRL. He was diagnosed with Brugada Syndrome and fitted with an implanted cardioverter defibrillator at age 18. He no longer played sports, but he was grateful to be alive as a beneficiary of the Institute's research and development.

A few years later, while in law school and enjoying a lifestyle almost free from worry about his disease, Brian met the Institute's development and communications director at a CRI presentation. He was amazed to learn of the CRI/MMRL's status as the nation's leading center for the study of Brugada Syndrome. Almost immediately he found himself on the phone with the Institute's director of research, Dr. Charles Antzelevitch. "That conversation resulted in me becoming a part of the solution to my condition," Brian said.

With the CRI opening its doors to him, Brian submitted DNA for testing and received updates on the results. Already a beneficiary of the Institute's research and advancement of life-saving technologies, such as those embodied in his ICD, he looks forward to the Institute's development of further diagnostic and therapeutic strategies that will enhance medical therapy for him and all future generations.

Science and medicine are intangible until they are needed. When our quality of life is threatened or we face the loss of a loved one, we expect the surgeon, physician or medical team to administer the cure, forgetting that every cure, treatment, medication and diagnostic tool has its roots in basic science. We thank these individuals and many others for allowing us to share their personal stories.

Transforming Lives Through Science

Stem Cell Research, Tissue and Bio-Engineering

One of the most exciting areas of research at the Institute is our stem cell center, where our principal focus is on the development of human models of heart disease – particularly diseases involving inherited sudden cardiac death syndromes.

These models are advancing our understanding of the pathophysiology and helping us to design patient-specific and disease-specific treatments and cures.

In a parallel project, we are working on strategies to convert skin cells directly into heart cells without having to go through the intermediary step of forming stem cells, known as trans-differentiation.

Stem cells are cells in the human body that can change into any other cell type. Because stem cells can become blood cells, muscle, bone, cartilage and other specialized cells, they have the potential to treat a wide variety of diseases, including leukemia, Parkinson's disease, diabetes, cancer, Alzheimer's and heart disease.

This approach circumvents the need to use embryonic stem cells, and thus avoids the ethical issues involved. These induced "pluripotent" stem cells hold promise for enabling regeneration of whole organs, bringing organ transplantation medicine to new heights.

Custom-Designed Medical Therapy

The development of drugs to treat cardiac arrhythmia disease has long been hampered by the lack of suitable *in vitro* human models. The stem cell program at the Cardiac Research Institute is using induced pluripotent stem cells to create models of human disease. These *in vitro* models provide valuable new insights into the development of patient-specific medical therapy.

Cloning a Human Heart

Over 5 million Americans suffer from congestive heart failure. It is one of the most common reasons people 65 and older are hospitalized. Treatment options are limited and do not prevent the progression of the disease. In most cases, organ transplantation is the only option, yet the availability of hearts is insufficient to meet the demand. Tragically, too many Americans die every year waiting for a donor heart.

The Cardiac Research Institute has undertaken a project to bioengineer new hearts that someday could be available for transplantation. This new program will use innovative approaches designed to grow new hearts using the patient's own skin cells or bone marrow to avoid auto-immune rejection of the heart once it is transplanted. Working with Harvard Apparatus, we have designed a bioreactor that permits us to grow and mature the cloned organs.

In this approach the old hearts are first decellularized, which means that all cells are removed using a detergent called SDS. What is left behind is a collagen scaffold in the shape of a heart, which is referred to as a "ghost heart" because of its white appearance. These scaffolds are then reseeded with induced pluripotent stem cells or mesenchymal stem cells to generate a heart from the patient's own cells.

CRI scientists are using innovative approaches designed to grow new hearts using the patient's own skin cells or bone marrow to avoid auto-immune rejection of the heart once it is transplanted.

The Promise & Power of Medical Research

A Message from Dr. Charles Antzelevitch - *Executive Director, Director of Research*

We are proud to be celebrating over a half century of dedicated service to humanity in which the contributions of our talented scientists have translated into renewed hope and a better quality of life for people everywhere.

Advances are being rapidly translated into ways to prevent and treat disease. The promise of new and greater advances to treat heart and other dreaded diseases is greater than ever before. Our Institute has positioned itself to be a major player in the design of new treatments and cures.

Unfortunately, Federal funding cuts have reduced funding of biomedical research through the National Institutes of Health to historic lows, thus jeopardizing scientific discovery and the development of future therapies and cures. Scientists nationwide are closing up shop, abandoning promising research due to lack of funds.

Private philanthropy is today more important than ever before. The success of our mission and vision, and those of laboratories like ours around the world, depends on strengthening support and building an adequate endowment to ensure that the research continues.

We invite you to join our ever-growing family of friends and become a partner in bringing the promise of major advances within reach. Your philanthropy empowers, inspires and keeps the promise of medical research alive.

About Dr. Antzelevitch

He holds the distinction of being conferred a Distinguished Scientist Award by the American College of Cardiology, Heart Rhythm Society, as well as the American Physiological Society. Under his leadership, the Cardiac Research Institute's innovative work continues to have global impact. With an h-index of 81, CRI/MMRL is ranked among the top institutes of its size anywhere in the world with respect to the frequency with which its research is cited by other scientists and physicians.

Building a Better Heart – with Your Support!

From its roots as one of Freemasonry's windows to the world, the Cardiac Research Institute at MMRL today *reaches out* to the world.

We are honored to have the support of Freemasons and Masonic organizations in a growing number of states and countries. We are also grateful for the vital support we receive from other sources such as community and private foundations, corporations and individuals.

Legacies of Innovation and Accountability

Scientific and medical research is a bridge across time, generations, continents and ethnicity. It takes vision and leadership to build that bridge and turn dreams into reality. Since its inception, CRI/MMRL has been blessed to have a dedicated group of individuals who administer its affairs. Our board of directors is selected based on their exceptional business and professional acumen. They serve without compensation.

We are equally proud to say that all who lead the Institute and carry on its work are careful stewards of the monies entrusted to them. At CRI/MMRL, 84 cents out of every dollar received directly supports life-saving and life-improving cardiac research. The CRI/MMRL has attained the highest ranking (4 star) given by Charity Navigator, America's largest independent charity evaluator. This is an achievement few not-for-profits can claim.

We practice our belief - every heartbeat does count, every gift does matter.

Cardiac Research Institute *at MMRL*

Every Heartbeat Counts™

Every Heartbeat Counts™

What Our Colleagues Say

It is with utmost pleasure that I provide this testimonial of the outstanding contributions of the Masonic Medical Research Laboratory (MMRL), also known as the Cardiac Research Institute, in advancing the cause of science and medicine.

Dr. Charles Antzelevitch is today widely regarded as one of the finest scientists and experimental cardiac electrophysiologists in the world. His leadership has propelled the CRI/MMRL into a position of international prominence in the scientific community.

CRI/MMRL investigators have made an important impact on the progress of science and medicine, particularly in areas involving the electrical function of the heart in health and disease and factors that contribute to the development of abnormal rhythms of the heart, including sudden cardiac death. In recent years they have delineated the mechanisms of a number of arrhythmic syndromes, permitting better diagnosis and approach to therapy.

Among their foremost achievements was the discovery of the M cell in the midmyocardial regions of the heart and demonstration of electrical heterogeneity within the ventricular myocardium. These seminal findings opened exciting new doors to our understanding of the electrophysiology and pharmacology of the heart and to our appreciation of the mechanisms responsible for the development of life-threatening arrhythmias.

Their ingenuity and creativity were front and center again with the development of the arterially-perfused ventricular wedge preparation, an experimental model that proved invaluable in delineation of the cellular basis for the repolarization waves of the ECG (J wave and T wave) and in the identification of the cellular basis for the development of arrhythmias under a wide variety of conditions, including those associated with congenital ion channelopathies like catecholaminergic VT, Long QT, Short QT and Brugada syndromes.

In more recent years, Dr. Antzelevitch's vision has been to harness the power of DNA in making further inroads into our understanding of arrhythmogenesis. The sophisticated team structure put together to tackle the problems of inherited arrhythmic disease and sudden death is probably unmatched anywhere in the world.

Let me close by saying that many have benefited and many more stand to benefit from the highly innovative and creative scientific achievements of CRI/MMRL and that all involved with this unique facility can take great pride in these stellar achievements.

Sincerely yours,
Douglas P. Zipes, M.D.
Professor Emeritus of Medicine, Pharmacology, and Toxicology
Director Emeritus, Division of Cardiology and the Krannert Institute of Cardiology
Editor-in-Chief, *Heart Rhythm*
Past-President of the American College of Cardiology

Cardiac Research Institute
at MASONIC MEDICAL RESEARCH LABORATORY

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