Research Programs & Scientific Achievements

www.mmrl.edu

Mission Statement

The Masonic Medical Research Laboratory is a not-for-profit institute dedicated to improving the health and quality of life for all. The Laboratory's primary mission is to conduct high quality basic and clinical research aimed at generating knowledge and information necessary for development of the medical cures and treatments of tomorrow. The Laboratory is also committed to providing education and training to basic scientists, clinical researchers and students who will perpetuate and extend the fight against disease.

Vision Statement

To be regarded as a world leader in medical research, dedicated to generating the knowledge necessary to develop innovative solutions to medical challenges facing society and providing a creative environment for the education and training of the innovators of tomorrow.

Exciting Discoveries Lie Just Beyond the Horizon...

Cardiac arrhythmias or irregular heart rhythms claim more lives than any other mechanism of heart disease. Over the past four decades, Masonic Medical Research Laboratory (MMRL) investigators have been credited with either discovering or unraveling the mechanisms of the majority of known cardiac arrhythmias. As a result of our scientific achievements, the practice of medicine has been revolutionized and mortality from heart disease has been greatly reduced. The MMRL's scientific record has earned it international prominence as a leading research center in the fight against heart disease.

The ability to understand the electrocardiogram (ECG) is critical in the diagnosis and treatment of a heart attack and a wide variety of inherited cardiac diseases. Electrical instability of the heart that develops under these conditions can lead to cardiac arrhythmias and thus to sudden cardiac death. Our legacy of scientific breakthroughs has helped to generate new heart medications and develop diagnostic procedures for the management of cardiac arrhythmias, and has aided in the advancement of life-saving technologies.

Our Laboratory is also committed to providing education and training to basic scientists, clinical researchers and students who would perpetuate and extend the fight against disease. I am honored to work with a Board of Directors and staff dedicated to remaining at the cutting edge of discovery in the fight against heart disease. However, our ability to tackle new frontiers is critically dependent on the generosity of foundations, corporations and individuals who understand the value of medical research and realize that the best that science and medicine have to offer is yet to come.

Our *Campaign for Discovery* is geared to building on our scientific legacy and perpetuating as well as advancing our mission by increasing our endowments to a level of $50 million by our 50th Golden Anniversary. In the pages that follow, you will learn in more detail of our past scientific accomplishments, current research efforts and our vision of the future. The impressive progress that we have made in this field of medicine in recent years is encouraging and with appropriate commitment of resources, we can look forward to important advances in the months and years ahead.

We are deeply indebted to all who have supported us in these efforts in the past and invite you to join our growing family of friends and to partner with us as we forge ahead in our fight against the debilitating diseases that plague our society and diminish our quality of life.

Exciting discoveries lie just beyond the horizon and it is my hope that together we can bring them within reach.

Dr. Charles Antzelevitch
Executive Director
Director of Research
Masonic Medical Research Laboratory

Research at the MMRL… Past, Present and Future

Since its founding in 1958, the Masonic Medical Research Laboratory (MMRL) has been committed to basic medical research aimed at finding solutions to diverse medical problems facing our society. Basic research is focused on fundamental mechanisms of cell function needed to sustain life in any living system. Unlike basic investigations, clinical research is patient-oriented, conducted on human subjects or on material of human origin such as blood or tissues in which the investigator interacts with human patients. This area of research delves more directly into mechanisms of human disease with a focus on the development of therapeutic interventions. With the introduction of a Molecular Genetics program, the MMRL is now integrally involved in clinical research specifically designed to identify the genetic basis for human disease responsible for abnormal rhythms of the heart. These arrhythmias include ventricular tachycardia and fibrillation, which can lead to sudden cardiac death, as well as atrial fibrillation, which can reduce quality of life and dramatically increase the risk of stroke.

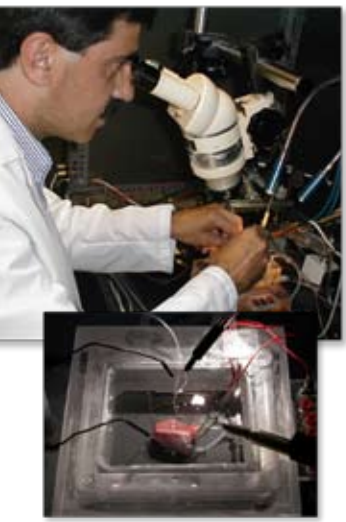
Genetic and genomic research is quickly transitioning us from a society in which treatment is empiric to one in which therapy is based on the specific cause of the disease, tailored to the individual patient. This knowledge is ushering in a new era that will change the face of medicine as we know it today. It has been three decades since scientists first harnessed the power of DNA by placing it into bacteria to direct the production of human insulin and growth hormone. In the late 1980's, we witnessed the identification of the structures of genes, which permitted for the first time the delineation of the genetic basis for inherited diseases. By the start of the 1990's, genes that increase the risk for breast and colon cancer were identified. In 1998, MMRL scientists in collaboration with investigators nationwide identified for the first time a gene responsible for sudden cardiac death due to ventricular fibrillation. The turn of the century witnessed the crowning achievement of decades of painstaking work with the completion of the Human Genome Project, which identified every gene in the human body. Surprisingly, there proved

to be only 30,000-35,000 functional genes, although the various isoforms and combinations of these genes are believed to give rise to over 100,000 different proteins, responsible for normal function of the human body. This milestone shifted the spotlight from genetics to genomics, the study of the human genome represented by the entire set of human genes. Genomic analysis is today used to identify the cause of disease as well as to develop better diagnostic tests and treatments. The melding of genomics with drug therapy has given way to pharmacogenomics, a field of study that holds promise for identifying which medication at what dose is best for each individual patient afflicted with a given disease and which drug is likely to lead to life-threatening adverse reactions. Standard dosing of first line medications for disease in all individuals will soon be relegated to the footnotes of history, as the gene-directed therapy takes hold with the genetic make-up of an individual dictating the specific approach to treatment. The MMRL is involved in each of these exciting new disciplines.

The MMRL is currently one of a handful of medical research institutes worldwide capable of studying the genetic causes of the lethal cardiac arrhythmias responsible for sudden cardiac death in young adults, children and infants and designing gene-specific therapy. Although MMRL investigators do not interact with patients directly, through collaborations with physicians worldwide, we are provided blood from patients suffering from abnormal rhythms of the heart. Following extraction of the DNA, genetic sequencing is performed to identify errors in the genetic code, known as mutations. The mutant gene is then cloned and expressed in a human cell line so as to identify the nature of the cellular defect. The characteristics of the defect provide specific direction for the design of novel drugs and other innovative approaches to therapy. Thus, starting and ending with patients in the clinic, we are able to bring the research full circle by delving into the cause of disease at the genetic level, its root basis.

Our research is divided into three disciplines that work closely together: molecular genetics, molecular biology and electrophysiology. Our goal is to correlate basic mechanisms of arrhythmia with the signs and symptoms of disease in patients so as to formulate more precise diagnostic criteria and more specific treatments and cures.

Electrophysiology, Molecular Biology and Molecular Genetics



Using molecular genetic techniques, our scientists are unraveling the basis for a number of inherited diseases including three forms of sudden cardiac death: the Long QT, Short QT and Brugada syndromes. One such study provided the first definitive data linking genetic mutations of the Long QT syndrome to Sudden Infant Death syndrome or (SIDS). Another, revealed mutations that can dramatically increase the risk for sudden death in patients suffering a heart attack. Using genetic and pharmacogenomic methodologies, the MMRL is leading the way in the development of innovative and effective pharmacologic treatment for Atrial Fibrillation, one of the greatest unmet medical needs in our society today.

Long QT Syndrome

Among the many syndromes associated with abnormal rhythms of the heart is the Long QT syndrome (LQTS). Like other arrhythmic diseases, LQTS is an abnormality of the heart's electrical system caused by defects in heart muscle cell structures known as 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 derives from the distinctive electrocardiographic (ECG) signature, which takes the form of an unusually long interval between the Q and T waves. The QT interval is a measure of the time it takes the heart to return to its resting state after contracting to pump blood to the rest of the body. The syndrome can be inherited or acquired. The acquired form of the disease is often caused by drugs used to treat arrhythmias, depression, migraine, and schizophrenia. The Experimental Cardiology team at the MMRL has remained at the cutting edge in the generation of new knowledge relative to the identification of drugs that may prove to be life-threatening. The MMRL has become a referral center for pharmaceutical and biotechnology companies and is working with a number of pharmaceuticals worldwide to evaluate the safety of their drugs and assist with the approach to FDA.

Congenital LQTS is one of the most tragic circumstances in which arrhythmias strike. Individuals born with this syndrome usually lead a perfectly normal childhood. After puberty or in their late teens, they

start to develop dizzy spells, if not caught in time and treated, one of these dizzy spells could result in sudden death, tragically taking them away in the prime of their lives. MMRL investigators are actively involved in the identification of gene mutations that lead to the development of congenital Long QT syndrome and thus are able to assist physicians in the administration of gene-specific therapy for this syndrome.

Short QT Syndrome

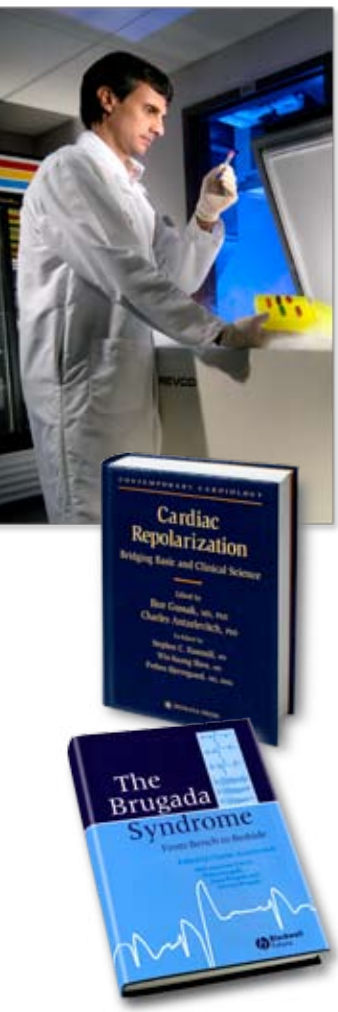
Over the past year, our scientists succeeded in identifying the gene responsible for a relatively new clinical entity responsible for sudden death in infants, children and young adults and a pharmacologic approach to therapy that can be used as an adjunct to implantable cardioverter defibrillators. Over the past three years, in reports co-authored by colleagues from throughout the world, we and others reported a new clinical entity known as the Short QT syndrome.

Members of these families display a very short QT interval on their ECG and suffer from life-threatening abnormal rhythms of the heart. In a study published in the leading clinical journal of the American Heart Association, *Circulation*, we developed an experimental model of the Short QT syndrome which reproduces the electrocardiographic and arrhythmic features of the syndrome. Studies involving expression of a clone of the mutant gene helped us identify a drug (quinidine) to correct the genetically-mediated electrical malfunction. This drug proved to be effective in reversing the ECG defect in patients with the Short QT syndrome. Thus, once again starting and ending with the patient in the clinic, we have brought the research full circle by delving into the cause of disease at the genetic level. We continue to search for the genes responsible for this syndrome and are on the track of new genes for the Short QT syndrome.

Catecholaminergic Polymorphic Ventricular Tachycardia

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) is an inherited disorder predominantly affecting children or adolescents. Affected children 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,* we presented a new experimental model for this syndrome. The report provided new insights into the cause of arrhythmias associated with the disease and in particular the cause of sudden death, which proved to be different from that generally presumed. New treatment strategies suggested on the basis of this finding will be pursued.



Brugada Syndrome

Our scientists take pride in having discovered the first gene 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 life. Some are individuals who have not been sick a day in their lives. Others are athletes who have endured strenuous training without any medical problems, until one day, they die suddenly in their sleep, often without warning. This syndrome has confounded doctors for decades and has left many families devastated. Our scientists demonstrated for the first time that a faulty gene that encodes the sodium channel in the heart contributes to the development of this syndrome. Using experimental models of the disease developed at the MMRL, 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. Because of these advances, individuals with this disease can be identified genetically as well as clinically and appropriate therapy can be administered before a tragic outcome ensues.

MMRL investigators have been invited to write reviews on the Brugada syndrome and inherited arrhythmic diseases for prominent journals and textbooks. We were recently honored with an invitation to write a review on drug therapy for the Brugada syndrome in the *Handbook of Experimental Pharmacology.* In 2003, the MMRL hosted an International Consensus Conference on the Brugada syndrome, co-chaired by Drs. Antzelevitch and Pedro Brugada. The consensus document highlighting diagnostic criteria and approaches to therapy appeared in *Circulation* and *Heart Rhythm.* A book edited by Dr. Antzelevitch entitled, *The Brugada Syndrome: From Bench to Bedside* was published soon after.


Dr Alejandra Guerchicoff
RYAN'S PLATE

Working with colleagues in Korea, our scientists have identified a new treatment for the Brugada syndrome. In many cases of congenital Brugada syndrome, the genetic defect causes a loss of function of the sodium current. This drug, a derivative of a Chinese herbal medicine known as Danshen, slows the inactivation of the sodium channel, thus leading to a gain of function that reverses the effect of the genetic defect.

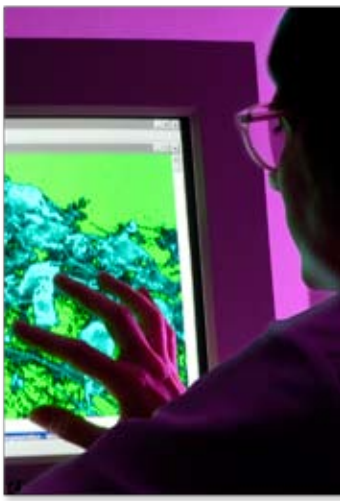
These models have provided us the capability of developing and testing new therapeutic modalities to combat sudden death.

Sudden Infant Death Syndrome (SIDS)

Sudden Infant Death syndrome (SIDS) has been attributed to numerous diverse and poorly defined mechanisms. Cardiovascular, respiratory and infectious diseases have been implicated. The first direct evidence linking SIDS to a congenital heart defect, the Long QT syndrome (LQTS), was published in *The New England Journal of Medicine* in 2000 based on work done by our 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 of 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% of SIDS cases are due to disorders of heart rhythm.

In recent years our scientists have developed experimental models of life-threatening cardiac arrhythmias, including the Long QT, Short QT, and Brugada syndromes, as well as Catecholaminergic Polymorphic Ventricular Tachycardia. These models have provided us the capability of developing and testing new therapeutic modalities to combat sudden death in infants, children and young adults afflicted with these congenital syndromes. Part of our focus over the past couple of years has been to define when and how

regional distinctions in electrical function of the heart develop as a function of age. This information will guide us in understanding better the basis for fatal arrhythmias that develop in infants and children and the contribution of cardiac arrhythmias to SIDS. This area of study is the basis for one of our National Institutes of Health (NIH) grants. The recently approved renewal of this NIH grant also focused on mechanical heterogeneity within the ventricles of the heart and how this changes with development. Electrical heterogeneity within the atria (upper chambers) of the heart and its contribution to the development of arrhythmias like Atrial Fibrillation is an additional focus of the grant.



Atrial Fibrillation

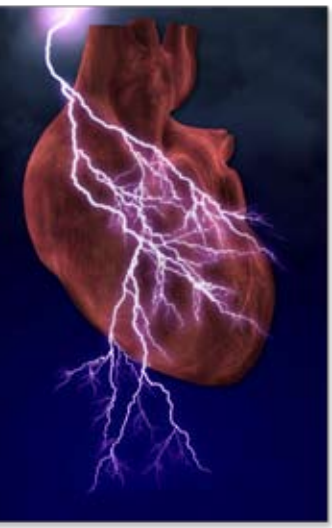
Atrial Fibrillation (AF) is the most common arrhythmia encountered in the clinic. AF afflicts nearly 1 in 20 individuals at age 65, 1 in 5 individuals at age 80 and is increasing in prevalence as Americans age. Over the past year, we have uncovered a new mechanism responsible for initiating AF, known as late phase 3 early afterdepolarizations. Effective pharmacological treatment of AF is one of the largest unmet medical needs facing our society today; most available drugs have low efficacy and those with high efficacy, have high toxicity. We are working with a biotechnology company to develop a novel drug for the treatment of Atrial Fibrillation. This agent has high efficacy in experimental models, but unlike other drugs in this category, it has very low toxicity. Clinical trials to assess its effectiveness in the management of AF are expected to begin soon.

The MMRL is also leading the way in the detection of gene defects that can predispose to the development of AF in relatively young indivduals. Working with colleagues in Denmark, we have found a mutation in a subsidiary subunit of a potassium channel to be associated with an inherited form of AF.

Recent Landmark Discoveries

A New Clinical Entity Responsible For Sudden Cardiac Arrest

The MMRL recently uncovered the genetic basis for a new clinical entity responsible for sudden cardiac arrest. The landmark discovery was reported in the January 30, 2007 issue of *Circulation*.



Dr. Charles Antzelevitch and a team of investigators and collaborators from Canada, Germany, France and Italy described a new clinical entity characterized by an elevated ST segment and abbreviated QT interval in the electrocardiogram (ECG) in three families with a history of sudden cardiac death. Affected family members were all found to have mutations in the genes that encode the cardiac calcium channels, which permit the flow of calcium ions into the cells of the heart. The defective genes called CACNA1C and CACNB2b were found to generate a smaller than normal electrical current and thus to be responsible for creating an electrical imbalance that results in potentially fatal arrhythmias. The MMRL's ability to link calcium channel loss of function mutations to sudden cardiac death opens exciting new avenues for better diagnosis and treatment of inherited sudden death syndromes that affect young adults, children and infants.

These studies hold promise for improved genetic identification of individuals at high risk for sudden death during or after a heart attack.

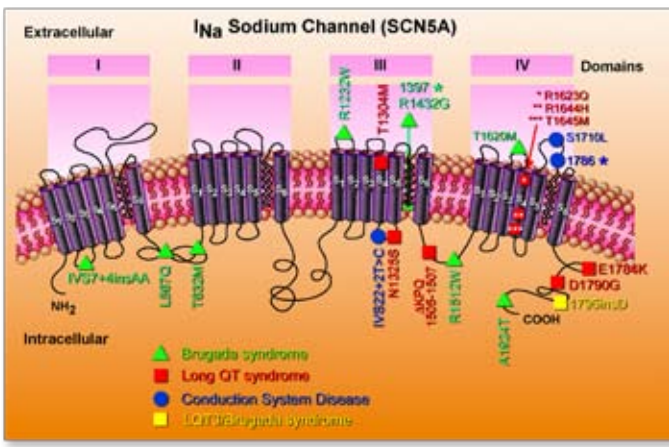
Electrical Storm Developing During A Heart Attack

Each year, nearly 1 million individuals in the United States suffer an Acute Myocardial Infarction (AMI) or heart attack. Approximately 20% to 25% experience sudden cardiac death soon after due to the development of Ventricular Tachycardia and Fibrillation (VT/VF). Although identification of patients at risk for primary VF during AMI remains rather poor, recent reports have highlighted the importance of family history, pointing to the possibility of a genetic predisposition. We recently conducted a study designed to examine the contribution of genetic mutations to arrhythmogenesis in a cohort of patients who developed one

or more episodes of VT/VF during Acute Myocardial Infarction (AMI). We identified a mutation in the gene that encodes the alpha-subunit of the human cardiac sodium channel in a patient with multiple episodes of VT/VF, termed an electrical storm.

Cardiac Sodium Channel Gene Found In Nerve Tissue

Another exciting development that came to fruition over the past year is the identification of a cardiac gene in nerve cells located in the fat pads of the heart which house the autonomic ganglia. These findings have broad implication for our understanding of a number of inherited diseases associated with cardiac sodium channel mutations. This work was recently published in *Heart Rhythm,* the official journal of the Heart Rhythm Society.



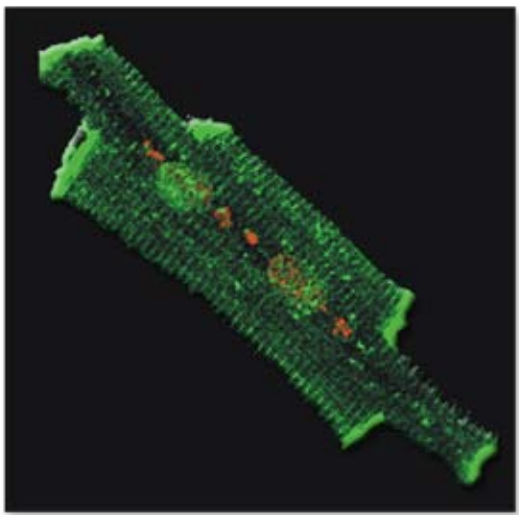
Ventricular Tachycardia After A Heart Attack

The early period after a heart attack is also associated with a vulnerable period for the development of life-threatening arrhythmias. Most patients show a slight prolongation of the QT interval in the ECG during this post-myocardial infraction (MI) period (days 2-11). In some, the post-MI electrical remodeling results in prominent prolongation of the QT interval and the development of Torsade de Pointes (TdP) arrhythmias. We have recently identified a polymorphism in the potassium channel that appears to contribute to this arrhythmic manifestation.

These studies hold promise for improved genetic identification of individuals at high risk for sudden death during or after a heart attack.

Single Most Significant Research Accomplishment

We have recently been asked to describe our single most important achievement over the past 25 years and without doubt it has been the demonstration that ventricular myocardium is not homogeneous, as previously thought, but is comprised of at least three distinct cell types that differ with respect to electrophysiological and pharmacological characteristics: epicardial, endocardial and M cells. In the 1980's, our cardiac electrophysiology team first delineated the differences between epicardium and endocardium, demonstrating that a difference in the action potential of these two cell types, namely the presence of an action potential notch in epicardium but not endocardium, is responsible for inscription of the electrocardiographic J wave. Subsequent studies showed that amplification of the J wave by exposure of the ventricular myocardium to sodium or calcium channel blockers can lead to loss of the epicardial action potential dome and thus to the development of a new mechanism for extrasystolic activity, which we termed phase 2 reentry. Thus arose the fundamentals of our understanding of the cellular basis for the Brugada syndrome and other life-threatening syndromes that arise as a consequence of J wave abnormalities.



M Cell

In the early 1990's we started to probe inside the myocardial wall, wishing to define the electrophysiologic gradation between epicardium and endocardium and to our surprise found a very unique cell type, which we named the M cell (Masonic, Midmyocardial, Moe – in memory of Dr. Gordon K. Moe). The hallmark of the M cell is the ability of its action potential to prolong out of proportion to epicardium and endocardium in response to a slowing of rate as well as in response to agents that normally prolong action potential duration (APD). These unique characteristics of the M cell permitted us to define the cellular basis for inscription of the T wave of the ECG and for the first time understand the cellular basis for bifurcation of the T wave, often seen under pathophysiologic conditions. In the presence of APD prolonging agents and bradycardia, preferential prolongation of

the M cell action potential leads to amplification of spatial dispersion of repolarization, transmural dispersion of repolarization (TDR), in particular. These observations led to delineation of the mechanisms underlying a number of sudden cardiac death syndromes. Subsequent studies showed that reduction in net repolarizing current leads to a preferential prolongation of the M cell action potential, whereas an increase in net repolarizing current can lead to a preferential abbreviation of the action potential of right ventricular epicardium or left ventricular endocardium. These changes predispose to the development of potentially lethal re-entrant arrhythmias associated with the Long QT, Short QT, and Brugada syndromes as well as with catecholaminergic VT. Available data suggest that these same mechanisms are responsible for life-threatening arrhythmias associated with a variety of cardiomyopathies ranging from heart failure and hypertrophy, which involve mechanisms very similar to those operative in Long QT syndrome, to ischemia and infarction, which involve mechanisms more closely resembling those responsible for the Brugada syndrome.

Our observations led to delineation of the mechanisms underlying a number of sudden cardiac death syndromes.

Thus, our discovery of transmural electrical heterogeneity within the heart has paved the way to an understanding of the repolarization waves of the ECG and identification of the principal substrate for the development of abnormal rhythms of the heart associated with most cases of sudden cardiac death.

This finding has stimulated tens of thousand of publications in the cardiology field and has translated into better diagnosis and approaches to therapy for both congenital and acquired arrhythmic disease.

This discovery and its implications are reviewed in numerous publications such as *Circulation, Circulation Research, Journal of the American College of Cardiology, Handbook of Physiology* and the *Handbook of Experimental Pharmacology,* as well as in 4 books edited or co-edited by Dr. Antzelevitch.

Sharing Dreams for Tomorrow

Diverging from the beaten path to seek the undiscovered is the hallmark of the Masonic Medical Research Laboratory (MMRL). Medical research is about meeting head on the ever changing challenges of human health. Those challenges that confront us today are no more or less important as any in the past.

The health of Americans and citizens of the world tomorrow depends upon medical research discoveries made today. The success of our mission, and that of similar laboratories throughout the world, is critically dependent on our base of support.

Our *Campaign for Discovery* is about hopes and dreams for a better quality of life for us, our children and the generations to come. To achieve that goal, the foundation for a better tomorrow needs to be laid today. All contributions, regardless of size, help us continue to delve into the mysteries of life and discover the cures and treatments of tomorrow.

We invite you to join our growing family of friends. To make a *tax-deductible* gift to our *Campaign for Discovery,* please call our donation hotline at 1-888-888-6675 or go to www.mmrl.edu click on support and make a donation using your credit card (MasterCard or VISA) at our secure website. You may also make a check payable to the Masonic Medical Research Laboratory and mail to 2150 Bleecker Street, Utica, NY 13501.

Another way you can help ensure a healthier tomorrow for each of us as well as future generations is by including the Masonic Medical Research Laboratory in your estate planning. For more detailed information regarding planned giving and named gift opportunities, please contact the Development Office and request our brochure entitled, Ways to Give.

Every tax-deductible gift, bequest, and scientific grant received, large or small, has the potential to light the path to bright new innovations and most importantly save lives.

Sincerely,

David F. Schneeweiss
President, Board of Directors
Masonic Medical Research Laboratory

Testimonials

Research Collaboration on Cardiac Drugs Benefits Patients

By Drs. Luiz Belardinelli and Brent Blackburn

CV Therapeutics, Inc. (CVT), headquartered in Palo Alto, California, is a biopharmaceutical company focused on applying molecular cardiology to the discovery, development and commercialization of novel small molecule drugs for the treatment of cardiovascular diseases. As part of the process of developing safe and effective drugs, CVT reached out to the public scientific research sector in an effort to identify an opportunity for a joint research program. The research objective was to develop a basic understanding of the mechanisms of cardiac arrhythmias, which, in turn, would lead to the development of an assay paradigm that may be useful to assess the potential risk of new drugs to cause a certain life-threatening cardiac arrhythmia called Torsade de Pointes.

Dr. Charles Antzelevitch
Executive Director and Director of Research

This effort identified Dr. Charles Antzelevitch, Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL), as the lead expert on mechanisms of cardiac arrhythmias and action of anti-arrhythmic drugs. In particular, Dr. Antzelevitch's work on establishing the mechanism underlying congenital and drug-induced Torsade de Pointes led CVT to seek him out as an objective researcher who would apply rigorous scientific principles to characterize the potential risk of cardiac arrhythmia associated with drugs. Thus, the research collaboration between the MMRL and CVT represents an opportunity that is of interest to both institutions and ultimately of benefit to patients.

The concern about whether or not a given drug might cause Torsade de Pointes is perplexing, since there is very little one can do to confirm or refute the potential risk of a new drug. One imperfect clinical marker that has been used to alert investigators of a potential risk is prolongation of the QT interval, an electrocardiographic finding that suggests an interaction of a drug to affect cardiac repolarization. Since prolongation of the QT interval is not always associated with an increased risk of Torsade de Pointes, it is not surprising that the issue of predicting which drugs that prolong the QT interval and also have the potential to cause Torsade de Pointes has become a major focus for regulatory agencies, academia, and industry. By carefully investigating the underlying mechanisms of Torsade de Pointes, the MMRL and CVT have developed a deeper understanding of the cause of these arrhythmias and hence have developed a paradigm to assess the potential risk of new drugs. The combined efforts of MMRL and CVT have provided an opportunity to demonstrate how collaboration between academic laboratories and industry can enhance the process of well-balanced medical research while maintaining high scientific standards and objectivity, thus facilitating the process of regulatory review and approval.

Advancing the Cause of Science and Medicine

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

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

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 for better diagnosis and approach to therapy.

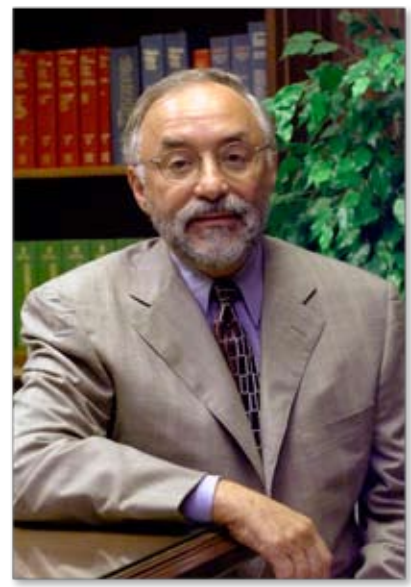
Among their foremost achievements was the discovery of the M cell in the midmyocardial regions of the heart and demonstration of electrical heterogeneity within the ventricular myocardium. These seminal findings have opened exciting new doors to our understanding of the electrophysiology and pharmacology 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. Their recent

publications dealing with the Short QT syndrome is a case in point. Within the span of several months, they found the gene defect responsible for this highly lethal disease, delineated the basis for the drug-resistance, developed an experimental model and found a pharmacological alternative to treat those affected. In a less structured environment, these discoveries might have been accomplished, but over a span of several years rather than months.

This impressive feat was repeated recently with their discovery of the genetic basis for a new clinical entity consisting of a combined Brugada and Short QT syndromes. Affected family members were found to have mutations in two subunits of the cardiac calcium channel. They accomplished what numerous teams throughout the world have been trying and have failed to do for over 8 years, find a 2nd and 3rd gene for the Brugada syndrome, as well as the 4th and 5th genes for the Short QT syndrome.



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

Sincerely yours,

Douglas P. Zipes, M.D.
Distinguished Professor

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

Scientific and medical advances are being realized at the Masonic Medical Research Laboratory thanks to caring individuals and organizations who recognize that only through an investment in medical research can we look forward to a healthier tomorrow.

MASONIC MEDICAL RESEARCH LABORATORY®

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