

Molecular biology of heart disease

Robert Roberts

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Abstract

Dr. Robert Roberts is currently Professor of Medicine and Director of the Ruddy Canadian Cardiovascular Genetics Centre along with being President and CEO of the University of Ottawa Heart Institute. Prior to this appointment, he was Chief of Cardiology for 23 years at Baylor College of Medicine, Houston, Texas. His original research was in cardiac enzymology which led to the development of the MBCK test which was the standard diagnostic assay for myocardial infarction for more than 3 decades. In the late 1970s, his research interests switched to molecular biology and the genetics of cardiomyopathies. He is regarded as one of the founders of molecular cardiology and has identified and sequenced more than 20 genes responsible for cardiovascular disorders. In the past 6 years, he has pursued genome-wide association studies to identify genes predisposing to coronary artery disease (CAD) and myocardial infarction. The first genetic variant for CAD, 9p21, was identified by Dr. Robert's laboratory and, in collaboration with the international consortium, CARDIoGRAM, has identified 13 novel genes for CAD.

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INTRODUCTION AND EDUCATIONAL EXPERIENCE

Robert Roberts (Figure 1) received his MD from Dalhousie University and completed his residency in Internal Medicine and Fellowship in Cardiology at the University of Toronto. Funded by a Canadian Heart Foundation Scholarship he pursued research in enzymology and cardiac metabolism at the University of California, San Diego, following which he was Director of the Cardiac Care Unit at Barnes Hospital and Associate Professor of Medicine, Washington University. In 1982, he accepted a position as

Chief of Cardiology at Baylor College of Medicine and became Professor of Medicine with joint appointments in the departments of Cell Biology and Molecular Physiology and Biophysics. On April 1, 2004, Dr. Roberts was appointed President and CEO of the University of Ottawa Heart Institute and Director of The Ruddy Canadian Cardiovascular Genetics Centre. He is also an adjunct Professor of Medicine at Baylor College of Medicine.

ACADEMIC STRATEGIES AND GOALS

Dr. Roberts, in addition to his role as clinician, educator and academic leader has been a very productive scientist. His early research focused on quantification and diagnosis of ischemic heart disease. He developed the first quantitative assay for the plasma MB isoenzyme of creatine kinase (MBCK) in 1974^[1,2] and the first radioimmunoassay (RIA) for MBCK^[3], based on an antibody to the B-subunit in 1976, which was also the first RIA for an isoenzyme. MBCK remained the standard for the diagnosis of myocardial infarction throughout the world for more than three decades^[4-12]. He was the first to purify mitochondrial CK^[13,14] and clone the cytosolic CK genes^[7,15]. Today all markers for myocardial infarction, including the troponins, are antibody-based. He isolated and purified the plasma MM and MB CK subforms^[8,16], elucidated the mechanism responsible for their generation, and utilized them to develop an assay for the early diagnosis of infarction^[8]. His laboratory played a pivotal role in the quantification of the extent of damage associated with myocardial infarction^[4,6,14] and the effect of therapies on experimental infarction^[17-19] in clinical trials, including β blockers^[20] and thrombolytic therapy^[20-27]. Notably, the Diltiazem on Non-Q-wave Infarction Study was directed by Dr. Roberts and showed diltiazem to be an effective therapy for non-Q-wave infarction which remains the mainstay of therapy 25 years later^[28].

On moving to Baylor, Dr. Robert's basic research effort focused on the application of the techniques of recombinant DNA to cardiac growth^[19,29-32] and molecular genetics. These efforts would subsequently earn him the title of one of the founders of molecular cardiology. He edited and co-authored the first textbook on Molecular Basis of Cardiology in 1993^[33], and continues to author the section on Molecular Cardiology in numerous text books including Hurst's The Heart for the past two decades^[34-36]. In the early 1980s, he cloned the genes for all three human creatine kinases^[7]. His achievements were sufficiently recognized by the mid-1980s, that he was chosen by the American Heart Association to direct one of the three initial Bugher Training Programs for molecular biology of the cardiovascular system. Dr. Roberts' research has since been devoted to molecular genetics of cardiovascular disease.

ACADEMIC ACHIEVEMENTS

He has made many contributions in the field of molecular genetics on hypertrophic cardiomyopathy^[37-48], familial di-

lated cardiomyopathy^[49,50], muscular dystrophies^[51,52], atrial fibrillation^[45,53-56], Wolf Parkinson White Syndrome^[57,58], Human eHAND^[59], and arrhythmogenic right ventricular cardiomyopathy^[60-62], and accomplished the following: (1) mapped the first locus for familial dilated cardiomyopathy; (2) mapped the first locus for atrial fibrillation; (3) mapped the first locus for arrhythmogenic right ventricular dysplasia in North America; (4) cloned and sequenced the desmin gene responsible for familial dilated cardiomyopathy; (5) identified the first gene for Wolff-Parkinson-White syndrome; (6) identified the troponin T mutation responsible for dilated cardiomyopathy; and (7) identified a novel family of proteins that bind specifically to triplet repeats and are responsible for myotonin mRNA nucleocytoplasmic transport^[51,63-65]. He developed the only transgenic rabbit^[66] with a phenotype of hypertrophic cardiomyopathy and together with transgenic mice has elucidated the pathogenesis of familial hypertrophic cardiomyopathy. Utilizing these transgenic animal models, he and his colleagues identified that statins, angiotensin II blockers and aldosterone inhibitors could reverse the phenotype^[44,67,68]. In 2005, he showed that the hypertrophic cardiomyopathy phenotype in the transgenic rabbit could be prevented with atorvastatin therapy^[36]. The pioneering application of genetics in research and clinical management of cardiomyopathies developed Baylor Cardiology into a major referral center for inherited cardiovascular disease.

On moving to the University of Ottawa Heart Institute, he founded The Ruddy Canadian Cardiovascular Genetics Centre. This was initiated by a \$5 million donation from John and Jennifer Ruddy followed by two endowed Fellowships of \$1 million each by Doug Arand and Michael Potter and Family. While his research up to this time had been on single gene disorders he now focused on genetics of common cardiovascular disorders, namely coronary artery disease (CAD). The Ottawa Heart Genomics Study was initiated in 2004 in pursuit of genes responsible for CAD and myocardial infarction. It was the first genome-wide association study (GWAS) to utilize the 500 000 DNA chip to genotype for CAD. This led to the mapping of the first locus 9p21 for CAD^[69]. The risk imparted by this locus is independent of known risk factors for CAD and was published in Science on May 3, 2007^[70]. The Ruddy Canadian Cardiovascular Genetics Centre, under the direction of Dr. Roberts, rapidly acquired an international reputation and the capacity to perform high throughput genotyping (> 300 million genotypes per day) and DNA sequencing. In recognition of his scientific contributions he became a member of the International Consortium, CARDIoGRAM^[71], which subsequently led to the discovery of over 95 genetic risk variants regulating lipids^[72], and most recently a landmark study of over 23 genetic variants with increased risk for CAD and myocardial infarction^[73]. These studies have led to numerous investigations regarding the mechanism of action of 9p21, including studies in Dr. Roberts' laboratory^[74-77]. Utilizing the 9p21 gene, studies were performed which showed it could predict the severity and progression of CAD^[77-79]. In a collaborative genome-wide study,

his lab recently identified the first gene in the ABO group that predisposes to myocardial infarction, and ADAMTS7 which predisposes to coronary atherosclerosis without infarction^[80]. He is currently involved with a GWAS to map genes predisposing to hypertension^[81]. In recognition of this effort, Dr. Roberts as Principal Investigator along with his co-investigators were awarded a \$12 million grant for genetic research by the Canadian Foundation for Innovation in 2006 and another 5-year grant from the Canadian Institutes of Health Research.

Dr. Roberts is world renowned as an educator, particularly in bringing the techniques of molecular biology and genetics to the cardiovascular community. He has supported this mission through several venues including national and international academic and government committees. Dr. Roberts is currently a member of the Medical Advisory Committee to the Leducq Foundation (2010-2013) and the Gairdner Foundation (2010-2013). He is also on the Board of Directors for Fields Institute. He serves on the Grant Review Committees for the Canadian Institute for Health Research (CIHR), Genome Canada, Genome Quebec, the National Heart, Lung and Blood Institute (NHLBI) and the Heart and Stroke Foundation of Ontario. Dr. Roberts chairs the Safety Monitoring of the RAMICAT clinical trial. He is the editor of *Current Opinion in Cardiology* and is on the editorial board of several journals. Dr. Roberts served on the Cardiovascular Study Section of the National Institutes of Health (1979-1982), the Cardiology Advisory Committee of the NHLBI (1984-1988) and subsequently the Advisory Council of the NHLBI (2000-2001). He was Chairman of the Study Section for the Cardiovascular Physiology and Pathophysiology Committee of the American Heart Association (1990-1993) and a member of the Central Research Review Committee (1990-1995). He served on the American Heart Association (AHA) Scientific Sessions Committee from 1986-1990. He became a member of the Research Planning Evaluation Committee for the AHA (1994-2001), and served as Vice-Chairman (1997-1999) and Chairman (1999-2001), and during this time, he also served on the Board of Directors for the AHA. He served as Vice President of the AHA (2001-2002). In 1991, he served as Chairman of the Scientific Sessions for the American College of Cardiology (ACC) and served on the Board of Trustees (1996-2001), Young Investigators' Awards Committee (1988-1990), Member of Budget, Finance and Investment Committee (1997-2003), Nominating Committee (1998-2000) and Chairman of the Advisory Committee for Merck/Pfizer/ACC Foundation (2000-2006), and Member, CIHR Team Grant A (2007-Present). Dr. Roberts has lectured throughout the world and has been the plenary speaker at many national meetings including the American College of Chest Physicians Simon Rodbard Lecturer, 61st Annual Scientific Meeting of the Japanese Circulation Society, Mikamo Lecturer, Tokyo, Japan 1997, opening Plenary Speaker for the Japanese College of Cardiology 1995, Japanese Cardiology, the Secondary International Symposium on Heart Failure in Geneva,

Switzerland, Simon Dack Presidential Address at the ACC Scientific Sessions (2002) and the State-of-the-Art Lecture, Canadian Cardiovascular Society (2005).

In recognition of his contributions, he has received several national and international awards. Dr. Roberts received the Distinguished Scientist Award from the ACC in 1998, the Award of Meritorious Achievement from The American Heart Association (2001), Master of the ACC (2007), and recently was awarded the McLaughlin Award from the Royal Society of Canada (2008). He was awarded the Robert Beamish Leadership Award in 2005. He has over 800 publications including Associate Editor of *Hurst's The Heart*, (1989-present) and was awarded the Most Highly Cited Researcher (2002).

CONCLUSION

Dr. Roberts is a major national and international educator for molecular genetics throughout the cardiac community. He chaired and participated in a core curriculum course of molecular biology for the clinician at the AHA and ACC Annual Scientific Sessions each year for over 15 years. He has participated in the fellowship program sponsored by AHA, ACC and NHLBI annually for over 20 years. As the Director of the Bugher and NHLBI training programs, he trained more than 40 molecular cardiologists, held leadership positions in the AHA and ACC and has been recognized as an important leader in the research and practice of cardiology worldwide. Several of his fellows are Chiefs of Cardiology in the USA, Canada, Japan and several other countries.

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