The Fourth Cardiff Cardiovascular Genetics Symposium

“Current Trends in Diagnosis and Therapies”

List of Speakers

Professor Robert Hinton

Dr. Hinton graduated from Bucknell University with degrees in Art History and Philosophy. He earned his medical degree from the Medical University of South Carolina in Charleston SC. He completed his pediatric residency training at Memorial Health University Medical Center in Savannah GA and his pediatric cardiology fellowship at Cincinnati Children's Hospital Medical Center. Dr. Hinton went on to pursue a postdoctoral fellowship in Cardiovascular Genetics and Molecular Cardiology at Cincinnati Children's Hospital. He has been an attending staff member of the Division of Cardiology since 2006.

Dr. Hinton's clinical interests relate to cardiovascular genetics and echocardiography. He is a member of the cardiovascular genetics service, and staffs the echocardiography laboratory. Dr Hinton's academic interests focus on translational research efforts using mouse models of human disease to identify new therapeutic targets. Dr. Hinton is a member of the American Academy of Pediatrics, the American Heart Association, the American Society of Bioethics and Humanities, and the American Society of Matrix Biology. He was elected to the Society for Pediatric Research in 2007.

Abstract

Translational research in pediatric heart disease: lessons from development

Pediatric heart disease (PHD) is a significant source of early morbidity and mortality. PHD includes cardiovascular malformation, cardiomyopathy, arrhythmia and aortopathy, and the causes of isolated PHD are increasingly understood to be genetic. Genetic abnormalities underlying PHD often impact developmental programs. Mouse models of human disease provide important insight into pathogenesis and define specific pathways involved in disease initiation and progression. Preclinical animal studies are necessary to advance new diagnostic and therapeutic approaches, as well as management guidelines.

Professor Judith Goodship

Judith Goodship is Professor of Medical Genetics at Newcastle University. With Tim Goodship she led the research that implicated complement factor H in haemolytic syndrome (HUS) which in turn led on to research of other components of the complement system In HUS. In addition to her university role she is an NHS consultant in the Northern Genetic Service which is based at the Newcastle Upon Tyne Hospitals NHS Foundation Trust but sees families with genetic disorders throughout the north of England

Abstract

Molecular diagnosis for congenital heart disease

For most cases of congenital heart disease (CHD) there is no previous family history and the cause is not clear. However, chromosomal abnormalities have been known to cause CHD since the identification of Down's, Edward's and Patau's syndromes and Turner's syndrome. Smaller trisomic and monosomic chromosomal segments were also detected in CHD cases by karyotyping; the introduction of comparative genome hybridisation to arrays in recent years has led to a higher detection rate for pathogenic copy number variants though CNVs of unknown significance are also detected.

There are over a thousand recognised syndromes in which CHD features, the majority very rare but Noonan syndrome which has an incidence between 1:1000 and 1:2500 live births is a condition about which all cardiologists need to know. Examples of conditions such as Noonan syndrome in which making a molecular diagnosis is important for patient management will be discussed. As is the case with Noonan syndrome, there are a number of genes that when mutated can present with a structural malformation or cardiomyopathy.

Making a molecular diagnosis for CHD gives information about natural history, informs management and provides accurate recurrence risks and offspring risks.

Dr Helen Wallis

Dr Wallis began her training in cardiology in the Wessex deanery (Swindon /Bath / Southampton) before moving to Wales. She developed her interest in ACHD whilst a registrar in Cardiff and then trained in the ACHD Unit at the Queen Elizabeth Hospital in Birmingham with Dr Sara Thorne and Dr Paul Clift.

Dr Wallis became a consultant in 2007 and since then has been striving to develop the ACHD Service in Wales in her role as 'ACHD Lead for Wales', together with her colleagues Dr Dirk Wilson and Dr Nav Masani. She helps care for the ACHD population of South Wales with Cardiff as the 'tertiary ACHD centre', with specialist outpatient clinics held across South Wales.

Abstract

Managing an Adult with Congenital Heart Disease - National Guidelines for ACHD/GUCH

The Adult Congenital Heart Disease (ACHD) population is increasing exponentially and is expected to do so for the next 10-15 years. The estimated ACHD population in the UK is now in excess of 250,000 with more adults then children living with congenital heart disease. There is an increasing recognition that this population requires specialist care by experts trained in ACHD with care co-ordinated through specialist adult congenital surgical and cardiac centres. The aim is to present the current published guidelines on ACHD management and give a cardiologist's perspective on the importance of genetics in this complex area.

Professor Catherine Nelson-Piercy

Catherine Nelson-Piercy is a Consultant Obstetric Physician at Guy's and St. Thomas' Hospitals Trust and Queen Charlotte's and Chelsea Hospital in London. Her undergraduate studies were at King's College, Cambridge University and St Bartholomew's Hospital. She trained as a physician, and was taught Obstetric Medicine by Professor Michael de Swiet. She specialises in the care of women with medical problems in pregnancy. Professor Nelson-Piercy runs special joint clinics for women with renal disease, cardiac and rheumatic disorders, hypertension and epilepsy in pregnancy. She offers pre-pregnancy counselling for women with pre-existing medical problems and those with problems in previous pregnancies.

Professor Nelson-Piercy has been involved in the development of several evidence-based National Guidelines notably for "Contraception in Women with Heart Disease", BTS / SIGN "Asthma in Pregnancy" and RCOG Green top guideline on "Reducing the risk of thromboembolism during pregnancy, birth & the puerperium". She has over 200 publications and has edited five books and written the successful *Handbook of Obstetric Medicine*, now in its fourth edition. She was also one of the central assessors for maternal deaths and chapter author for Heart Disease in 'Saving Mothers Lives', CEMACH (Confidential Enquiry into Maternal and Child Health) 2000-02, 2003-5 and 2006-8.

Professor Nelson-Piercy is the President of the International Society of Obstetric Medicine (ISOM), sat on the Education Committee and Executive Committee of the British Maternal and Fetal Medicine Society (BMFMS) and was the first Flexible Working Officer for the Royal College of Physicians of London, with responsibility for flexible / part-time training and working. She is editor in chief of a new journal *'Obstetric Medicine: the medicine of pregnancy.'* Professor Nelson-Piercy was awarded the FRCOG *ad eundum* in 2007 and is the youngest ever recipient of this honour. In 2010 she was awarded the title of Professor of Obstetric Medicine at King's College London.

Abstract

High risk pregnancy with inherited cardiac diseases

Cardiac disease is the leading cause of maternal death in the UK, and most deaths are from acquired rather than congenital heart disease. The commonest cardiac causes of death are aortic dissection, cardiomyopathy (mainly peripartum rather than familial dilated), myocardial infarction and SADS (Sudden Adult / Arrhythmic Death Syndrome). Many deaths are associated with substandard care. Sometimes this relates to the lack of appropriate pre-pregnancy counselling in women with inherited cardiac disease. The underlying cardiac disease may not be recognized (eg. Marfan syndrome or Ehlers

Danlos type 4.) or the symptoms and signs of heart failure and other presentations of cardiac disease are not recognized.

Pre-pregnancy counselling allows for stratification of high, intermediate and low risk cardiac conditions with an appropriate plan for multidisciplinary care in pregnancy. It is imperative that such counselling and care in pregnancy is delivered by clinicians with expertise in the management of heart disease in pregnancy. For some women delivery in a tertiary centre is appropriate where such expertise is concentrated. The team caring for such women should include obstetricians, cardiologists, obstetric anaesthetists, fetal medicine specialists, geneticists and midwives.

Most drugs used to treat cardiac disease are safe in pregnancy but errors of omission are common. CXRs, cardiac MRIs and chest CTs are safe in pregnancy. Pacemakers and Implantable Cardiac Defibrillators (ICD) do not cause problems and there are very few cardiac indications for delivery by caesarean section.

Dr Julie De Backer

Julie De Backer graduated as a doctor from the University of Ghent in 1995. She trained in cardiology at the University Hospital Ghent and the Canisius Wilhelmina Hospital in Nijmegen (NL) and has worked as a cardiologist since 2001.

Afterwards she took additional training in Medical Genetics at the University Hospital Ghent and attended further training in adult congenital cardiology at Erasmus Hospital Rotterdam.

In 2007 Dr De Backer obtained her PhD at the University of Ghent and in 2010 she was appointed as head of the cardiology clinic and medical genetics of the Ghent University Hospital and also has a Fundamental Clinical Fellow at the FWO. In October 2011 she was appointed as part-time professor at Ghent University.

Abstract

Managing aortic disease in pregnancy

In patients with known aortic disease, pregnancy entails a risk for aortic dissection/rupture, which is related to both hemodynamic and hormonal changes. The risk for pregnancy-related complications is determined by several factors, including (1) the underlying disease, (2) the aortic diameter, (3) previous surgical interventions. The risk stratification depends on these factors and may vary from low-risk to very high-risk where pregnancy may even be contra-indicated.

Management of women with known aortic disease should be initiated prior to pregnancy with adequate counselling regarding the risk of the pregnancy for the mother and fetus as well as the inheritance risk. Prophylactic surgery may be indicated in certain instances and medical treatment to decrease the rate of aortic growth is mandatory in all cases. Careful monitoring of aortic diameter and blood pressure throughout pregnancy is necessary and the mode of delivery is also dictated by the history and actual size of the aorta.

In this presentation, underlying diseases, counselling and management throughout pregnancy will be systematically addressed.

Dr Julie McGaughran

Dr Julie McGaughran ia a clinical geneticist with an interest in dysmorphology, cardiac genetics and ethical and legal challenges in clinical genetics. She is Director of Genetic Health Queensland which is a statewide superspecialty service in Queensland and also Immediate Past President of the Human Genetics of Australasia. She is also a recent member of the Board of the Royal Australasian College of Physicians.

Dr McGaughrran has a personal interest in service delivery and funding across Australia and in raising the profile of clinical genetics services, developing telehealth and EMR for clinical genetics and is also interested in developing international collaborations in clinical genetics.

Abstract

Pregnancy complicated with Cardiomyopathy

The Cardiac Genetics clinic in Brisbane was established in 2007 and sees a broad range of conditions. A cardiac obstetric clinic was established at the same. A brief over view of the clinic will be shown.

The commonest reason for referral to the clinic is cardiomyopathy and a review of cardiomyopathies in pregnancy as well as the outcomes of pregnancies from the cardiac obstetric clinic will be presented

Dr McGaughran will briefly discuss the cardiac genetics service in Queensland. She will then give an overview of cardiomyopathy in pregnancy and provide a review of the experience of the cardiac obstetric clinic at the Royal Brisbane and Women's Hospital in managing women with cardiac issues.

Dr Elijah R Behr

Dr Behr is a Senior Lecturer and Honorary Consultant Cardiologist specialising in Electrophysiology at St George's University of London and St George's Hospital, London. His research and clinical interests include the genetics, epidemiology, pathology and clinical evaluation of: unexplained sudden deaths (the Sudden Arrhythmic Death Syndrome (SADS)) and their families; drug-induced arrhythmia; ion channel diseases including the long QT and Brugada syndromes; and cardiomyopathies including ARVC. These interests extend to the study of the genetic contribution to the risk of sudden death and arrhythmia in the general population and acquired cardiac disease

Abstract (1)

Inherited arrhythmia syndromes during pregnancy

The arrhythmia syndromes are a heterogeneous group of genetic disorders that place affected individuals at risk of sudden death. During pregnancy there are altered haemodynamic demands placed upon the heart as well as a different hormonal environment that may alter that risk. While these do not necessarily imply greatly increased risk it is essential that therapy is maintained during the antepartum and postpartum periods. Most data are available for the long QT syndrome where the postpartum period is of greatest risk, although mainly related to the LQT2 sub-type of the disorder. The talk will review these and other data related to this important issue.

Abstract (2)

Recent trends in the management of inherited arrhythmia syndromes

Recent international guidelines for the management and diagnosis of arrhythmia syndromes have been produced and have proposed changes to the management of these disorders. For example the importance potential role for left cervical stellate sympathetic denervation in long QT syndrome and CPVT has been addressed forcefully as well as the role for Flecainide in CPVT and Quinidine in Brugada and early repolarisation syndromes. In general the role for ICD implantation has been minimised as much as possible while the early repolarisation syndrome represents a new challenge to the community. These guidelines and data in relation to novel therapies will be reviewed and discussed.

Dr Pier Lambiase

Dr Lambiase is Reader and Consultant Electrophysiologist at the Heart Hospital, UCL. He studied Medicine as an undergraduate at Oxford, qualifying in 1992. Cardiology specialist training was undertaken at Hammersmith Hospital and he completed a PhD at St Thomas' Hospital, KCL in 2002. This was focussed upon the adaptation of the heart to ischaemia-principally the role of progenitor cells and preconditioning. During his PhD he developed an interest in the electrophysiological mapping of heart failure patients. He was awarded the British Cardiac Society Young Investigator Award (YIA) in 2002 and was runner-up in the NASPE YIA the same year. Subsequently Dr Lambiase completed sub-specialist training in clinical electrophysiology at St Thomas'. He was appointed Lecturer at the Heart Hospital, UCL in 2004 and awarded a HEFCE Senior Lectureship in 2006 becoming a Reader in 2012. Current research interests include mapping in heart failure, the electrophysiological features of arrhythmogenic right ventricular cardiomyopathy, epicardial mapping of alternans, the molecular basis of lethal arrhythmias. Dr Lambiase undertakes a national inherited arrhythmia clinic at the Heart Hospital. This is focussed upon the identification of specific ion channel disorders in families with a history of sudden cardiac death such as long QT and Brugada syndrome. He performs radio-frequency ablation procedures, implantation of internal cardiac defibrillators and biventricular pacemaker devices. His research is funded by the MRC, BHF, Welcome Trust, Heart UK and supported by NIHR.

Abstract

Genomic basis of complex arrhythmic disorders

Genomics offers the opportunity to determine the aetiology of common arrhythmias eg.atrial fibrillation, inherited arrhythmia syndromes and mechanisms of sudden cardiac death (SCD). A wide spectrum of the rare familial rhythm disorders associated with SCD in the young is nowadays recognized. These disorders, which are typically associated with specific features on the ECG, include amongst others the LQTS, the short QT syndrome (SQTS), Brugada syndrome (BrS), cardiac conduction disease (CCD), early repolarization (ER) syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT) and familial atrial fibrillation (FAF).

As our knowledge of the field is increasing, we are moving away from the concept of simple monogenic syndromes to recognise the complexities of arrhythmogenic risk, phenotype expression and the effects of both modifiers & gene interactions. This is clearly illustrated in long QT syndrome where over 1000 mutations in 12 genes have been identified but the severity of the phenotype is also determined by the "repolarisation reserve" of the individual patient and compensatory protective mechanisms. In more complex disorders such as Brugada Syndrome the genomic approach has been rather disappointing. It is apparent that some of the originally proposed mutations may be incorrect due to lack of careful co-segregation and the

recognition that intronic sequences in the promotor region may exert powerful phenotypic effects. The situation becomes even more complex as the phenotypes become more subtle and overlap with normality-this is especially evident in the Early Repolarisation Syndrome where carriers express J point elevation also present in 10% of the population.

Many loci identified thus far by GWAS for ECG parameters unsurprisingly harbour genes encoding ion channel subunits, most already known from the rare cardiac rhythm disorders. These results indicate that genetic variability within these genes besides conferring risk for SCD. Mendelian rhythm disorders are also associated with ECG traits in the general population and may thus play a role in susceptibility to the more common arrhythmias affecting a larger portion of the population, as already indicated in some studies. The identification of common genetic variants in these genes modulating the ECG-intervals in the general population is consistent with the concept that genes harbor a spectrum of variants ranging from rare highly deleterious variants leading to Mendelian disease to common small-effect variants that may in aggregate impact on susceptibility to complex disease in the general population. Besides NOS1AP and the ion channels subunits, transcription factors known to be involved in cardiac development (e.g. NKX2.5, PITX2 and TBX5 & Ca2+ homeostasis genes (CASQ2 and RYR2)) have also been identified as candidates for variability of the ECG parameters (NKX2.5 and TBX5), risk factors for SCD (CASQ2 and RYR2) and AF (PITX2) in the general population. The finding of these developmental transcription factors illustrates the challenge to link the vast information on genetic variation in developmental genes to function and the myocardial electrical properties or qualitative arrhythmias in the adult human population.

One might naively hope the full exonic sequencing approach to be of value in discerning the molecular basis of defined inherited arrhythmogenic disorders but we are currently confounded by our lack of knowledge of how to threshold variant frequency and the pathophysiological effects of proposed variants. This is very evident in the investigation of sudden arrhythmic death syndrome (SADS) where the phenotype is simply sudden death in the context of a structurally normal heart. In a recent international study conducted by my group investigating 65 index SADS cases, the diagnostic hit rate for ion channel and cardiomyopathy mutations was 10% taking a threshold of 0.02% variant frequency rising to 65% if the threshold was raised to the conventional 0.5% level including VUS. This highlights the critical importance of undertaking a critical bionformatic approach integrated with a careful phenotyping strategy and determination of the pathogenicity of the variant utilising clinical, functional and in silico prediction. This requires better informed rigorous data bases where the clinical pathogenicity of a variant is validated by co-segregation as opposed to simple isolated case reports which are clouding the field. The utilisation of induced pluripotent stem cell technologies may offer the opportunity to better define the electrophysiological effects of a specific variant in vitro in the context of a patient's own genetic background.

This lecture will outline what genomic approaches have taught us so far in the field of ion channelopathies & common arrhythmia disorders and how they should ideally be applied to investigate complex phenotypes such as AF, early repolarisation syndromes and SADS.

Dr Lorenzo Monserrat

Dr Monserrat was born in A Coruña, Spain, in 1966. He graduated in Medicine in Santiago de Compostela and obtained a Research Fellowship in Cardiomyopathies at St George's University Hospital in London. Dr Monserrat is a specialist in Cardiology and obtained a PhD in A Coruña University and a Diplomature in Design and Statistics in Health Sciences (Autonoma University, Barcelona). Dr Monserrat works as a Researcher with the Galician Health Service and is Chief of the Inherited Cardiovascular Diseases Reference Unit in A Coruña University Hospital.

Dr Monserrat has authored over 80 papers on inherited cardiovascular diseases and cardiovascular genetics. He has participated in and taken leadership of multiple research projects in the field of cardiovascular genetics. He is founder and CEO of Health in Code SL.

Abstract

Next generation molecular diagnosis for inherited cardiovascular diseases and arrhythmias

The inherited cardiovascular diseases (cardiomyopathies, channelopathies and inherited vascular diseases) are a heterogeneous conjunct of primary diseases usually of genetic origin and familial presentation, which are associated with sudden death risk. The identification of multiple genetic causes for these diseases has opened a new window for their early diagnosis, the understanding of their natural history, and for the improvement in their risk stratification and management. However, in the last years, the clinical application of genetics has been limited by the cost and low yield of the available genotyping technologies. The irruption of Next Generation Sequencing has completely changed this scenario. This group of disruptive technologies allow the evaluation in parallel of hundreds or even thousands of genes at an affordable cost. Now the challenge is not the genotyping, but the interpretation of the complex results. In this presentation we review the main aspects related to the application and impact of Next Generation Sequencing in the study of the inherited cardiovascular diseases, with a special focus in the clinical validation and the interpretation of the results

Professor Perry Elliott

Professor Elliott is a Reader in Inherited Cardiovascular Disease at The Heart Hospital, University College London, and The Institute of Child Health, Great Ormond Street Hospital, London. Dr Elliott studied Medicine at St. Thomas's Hospital Medical School, London, United Kingdom. After qualifying in 1987 he trained in General Medicine, gaining membership of the Royal College of Physicians in 1991. He completed his general cardiology training at St. George's Hospital Medical School, London, U.K. Over the past 17 years he has established an international reputation in the field of heart muscle disease, authoring more than 200 peer reviewed papers on the subject. Professor Elliott is Chairman of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases and Vice-President of the Cardiomyopathy Association. He is a member of the British Cardiac Society, and was elected as a Fellow of the AmericanCollege of Cardiology in 2001 and the European Society of Cardiology in 2005. Professor Elliott is chair and co-founder of the UK Cardiac Pathology Network. In 2009, he was appointed as Deputy Editor of *The Heart Journal*. He is currently a member of the NCEPOD Surgery in children study, The Cardiac Devices National Action Group (CDNAG) and the European Society of Cardiology Cardiac Pacing and Cardiac Resynchronization Therapy Task Force.

Professor Elliott, together with Professor Bill McKenna provides a national referral centre for inherited cardiovascular disease in the young. These specialist clinics supported by Clinical Nurse Specialists, Genetic Counsellors, and underpinned by a developing clinical genetics service, aim to implement DNA diagnosis into clinical practice.

Abstract

Diagnostic dilemmas and Controversies for inherited myopathies

Information not supplied

Dr Duncan Cole

Dr Cole is Clinical Senior Lecturer and Honorary Consultant in Medical Biochemistry and Metabolic Medicine at Cardiff University. He trained in Wales, and obtained the MRCP in 2002 and FRCPath in 2010. Appointed to his current position in 2011, Dr Cole leads the adult metabolic service in Cardiff, which includes the Wales Lysosomal Storage Disease Service. Dr Cole's academic interests are in instructional design and online learning. He can be followed on Twitter @DuncanMedBio.

Abstract

Current strategies in the management of metabolic cardiomyopathies

Cardiomyopathy may be a feature of a wide range of inherited metabolic diseases, and may present in both paediatric and adult settings. In this talk I will focus on current treatment strategies that aim to alter the underlying metabolic pathophysiology of these disorders. I will focus on enzyme replacement therapies for lysosomal storage disorders, including Fabry and Pompe disease; dietary modification in glycogen storage disease type III; and briefly discuss the treatment of other disorders of energy metabolism that affect cardiac muscle.

Dr Andrew Wood

Consultant Cardiac and Interventional Vascular Radiologist, University Hospital of Wales, Cardiff and Vale University Local Health Board Clinical Director Radiology, medical physics & clinical engineering
Dr Wood is a cardiac and vascular radiologist with particular interest in MR & CT imaging of the heart. He has practiced cardiac radiology for over 20 years including a fellowship in Chicago with Professor Lipton where he gained particular experience with EBCT. Dr Wood currently runs a busy cardiac imaging unit in Cardiff with a broad spectrum of cardiac MR imaging including ischaemic heart disease, complex congenital heart disease and heart muscle disease imaging.

Abstract

Recent trends in imaging for cardiomyopathy

Information not supplied

Professor Tom Treasure

Professor Tom Treasure was trained in Cambridge and London in the UK, and received a Hunterian professorship from the Royal College of Surgery in 1983. He was first at St Georges Hospital in London and then became Professor of Cardiothoracic Surgery at Guy's Hospital in 2001. Currently, he is a professor with the Clinical Operational Research Unit at UCL. In his honorary role, Tom contributes his considerable knowledge and clinical experience to ongoing projects concerning outcomes following surgery and hospital acquired infections, as well as conducting his own research regarding the evidence base for thoracic surgery.

He is a past president of the European Association of Cardio-thoracic Surgery, he was chairman of the European Society of Thoracic Surgeons metastasectomy guideline project, he was on the NICE guidelines committee for lung cancer management in the UK, and more recently he has worked as the principal investigator of the MARS trial and currently the PULMIC trial, which is a randomized multicenter controlled trial on resection versus conservative therapy for colonic lung metastases.

Abstract

Aortic root surgery to prevent aortic dissection in Marfan: The proposed Big Aortic Root Study (BARS)

With technical refinements and improving skill in practiced hands root replacement to pre-empt dissection in people with Marfan Syndrome has become a routine intervention. As perioperative mortality reduced there was growing confidence to intervene earlier to save those who dissect at smaller root size.

For patient cohorts whose average age is about 30 at the time of root replacement the cumulative long-term burden of complications is considerable.

Valve related event rates for mechanical and valve sparing root replacement are 1.3% and 1.9% per year respectively. Reoperation rates are 1.3% per year for valve sparing surgery. The cumulative rates during a reasonable expectation of life are therefore considerable. In 2000 Golesworthy proposed the use of the patient's digital images in computer assisted design to manufacture a personalised external aortic root support (PEARS). The first operation was in 2004 and since then 40 PEARS procedures have been performed to the same engineered standard. The pliant macroporous mesh is inert and becomes incorporated in the aortic adventitia. Myocardial and cerebral hazards are obviated because there is no need to open the aorta. Cardiopulmonary bypass is infrequently needed. The aortic root and the valve architecture are stable over years. The first 30 patients (median age 28 years; IQR 20-44) have been followed up for two to nine years. During a total of 150 patient years, among these patients with root and valve conserving surgery, there have been no cerebrovascular, aortic, or valve related events.

No prospective comparative evaluation of the different operations has yet been done. Advice given to patients tends to lead to the surgery preferred by the surgical team. We now propose the Big Aortic Root Study of the three operations available. BARS will ensure evidence based advice, uniform data acquisition, and random allocation when equipoise exists.

Laura Zahvich

Laura Zahavich has been a genetic counsellor at the Hospital for Sick Children in Toronto, Canada since 2009. She currently works in the Division of Cardiology with a focus on cardiomyopathies, inherited arrhythmias and connective tissue disorders in the pediatric population. Laura received her Master's of Science in Genetic Counselling degree from the University of Toronto in 2009, and was certified by the American Board of Genetic Counseling in 2010.

Abstract

Genetic Causes of Cardiomyopathy in Paediatric Transplant Recipients

Cardiomyopathies are a heterogeneous group of disorders with many different aetiologies. In children, cardiomyopathy is associated with a high degree of mortality and morbidity. Death within 2 years or requirement for heart transplant is seen in about 40% of children. Certain pre-transplant risk factors have a major impact on post-transplant survival however, little is known about the impact of a specific genetic aetiology of cardiomyopathy on the outcome of transplantation. This session will review the results of a retrospective analysis of clinical phenotypes and gene panel testing in paediatric cardiac transplant recipients with cardiomyopathy over a ten year period at the Hospital for Sick Children. This session will also explore some of the benefits and challenges associated with genetic testing and genetic counselling for cardiomyopathies in the context of paediatric cardiac transplantation.

Dr Annemieke Aartsma-Rus

Dr Annemieke Aartsma-Rus is an associate professor at the Department of Human Genetics of the LUMC. She studied Biomedical Science at the Leiden University from 1995 to 2000. As a PhD student at the Human Genetics Department (LUMC) from 2000-2005, she focused on the development of antisense-mediated exon skipping therapy for Duchenne muscular dystrophy, under supervision of Dr Judith van Deutekom and Professor Dr. Gert-Jan B van Ommen. After obtaining her PhD she continued her work on the optimization of antisense-mediated exon skipping towards clinical application as a postdoc. Since February 2007, Dr Aartsma-Rus has been project leader of the DMD Genetic Therapy group.

Abstract

Antisense oligonucleotide therapy

Duchenne muscular dystrophy (DMD) is a severe, progressive muscle-wasting disorder, while Becker muscular dystrophy (BMD) is milder muscle disease. Both are caused by mutations in dystrophin, a protein, which stabilizes skeletal muscle fibers and cardiomyocytes during contraction by linking muscle actin to the extracellular matrix. In DMD patients mutations disrupt the open reading frame, generating prematurely truncated, nonfunctional dystrophins. In BMD patients, mutations maintain the reading frame allowing production of internally deleted, partly functional dystrophins.

The exon skipping approach uses antisense oligonucleotides (AONs) to induce skipping of targeted exons during pre-mRNA splicing, with the aim of reading frame restoration, converting of the severe DMD into the milder BMD phenotype.

After obtaining proof-of-concept in cultured patient-derived cells, this approach was further optimized in animal models. In each case AON treatment resulted in targeted exon skipping and dystrophin restoration. Towards systemic application, studies in animal models revealed that dystrophic muscles facilitated uptake of 2OMePS AONs and that subcutaneous delivery was feasible. However, this improved uptake was not observed for heart.

The clinical development of AON-mediated exon skipping is currently coordinated by Prosensa Therapeutics and GlaxoSmithKline. Preclinical work focuses on optimizing dosing, dosing regimens and AON modifications to improve delivery to heart.

Dr Matthew Daniels

Matthew has a long interest in the scientific and clinical aspects of inherited disease having completed a part II project with Prof David Brook during his BSc (Biochemistry and Genetics) prior to completeing the Cambridge MB/PhD program where he worked with Prof Ashok Venkitaraman on the consequences of inherited BRCA2 mutation. He began cardiology training in 2008 and has developed clinical interests in inherited cardiac conditions and percutaneous device closure of structural cardiac defects. His Wellcome Intermediate award supports his work generating in vitro models of inherited heart disease using induced pluripotency. An essential part of this program is the development of better ways to produce, and characterise the biology of living heart cells made in the dish. The group continue to make efforts to harness basic research for clinical application.

Abstract

Stem Cell Therapy for Inherited Cardiovascular Conditions

Since the first spontaneously beating cardiomyocytes were produced from a human embryonic stem cell progenitor in the mid 1990's there has been much hope (and hype) that regenerative applications would soon reach the clinic; however things have not been so simple, and a number of obstacles remain.

In this talk Matthew will:

- Discuss the different approaches being developed to realise cell based therapy for the heart
- Summarise the outcomes of clinical trials which have tended to focus on acquired DCM following myocardial infarction
- Discuss inherited heart disease in the context of emerging cell based approaches; highlighting crossover points where taking an inherited cardiac conditions slant may reduce some of the technical challenges associated with cell based repair of the heart

Dr Zaheer Yousef

Dr Yousef is a Consultant Cardiologist at the University Hospital of Wales and Llandough Hospital, and honorary senior lecturer at Cardiff University. Lead clinician for heart failure, devices for heart failure, and clinical governance at the University Hospital of Wales.

Dr Yousef regularly deliver lectures and trains physicians at National and International meetings. His special clinical interests include: heart failure, cardiomyopathies, biventricular pacemaker implantation (resynchronisation pacemakers for heart failure), implantation of internal defibrillators, and general clinical cardiology.

Research Interests include cardiac resynchronisation therapy (biventricular and pacing), heart failure and management of patients after myocardial infarction.

Abstract

New interventional therapeutic approaches for Inherited Cardiovascular Condition

Inherited cardiac conditions may be associated with mechanical/structural abnormalities, and/or disorders of cardiac rhythm and function. This presentation will provide an overview of the latest interventions designed to address these abnormalities