The Bulletin
The Publication of The British Society for Cardiovascular Research

Editors
Dr Nicola Smart
UCL Institute of Child Health
30 Guilford Street
London WC1N 1EH
Tel.: 020 7905 2242 Fax: 020 7404 6191
E-mail: N.Smart@ich.ucl.ac.uk

Dr Helen Maddock
Pre Hospital, Emergency & Cardiovascular Care Applied Research
James Starley Building, Coventry University
Priory Street
Coventry CV1 5FB
Tel: 024 76 888559 Fax: 024 76 888702
E-mail: h.maddock@coventry.ac.uk

Dr Melanie Madhani
School of Clinical and Experimental Medicine
The Medical School, Vincent Drive
The University of Birmingham
Birmingham
B15 2TT
Tel: 0121 414 4042 Fax: 0121 414 3713
E-mail: m.madhani@bham.ac.uk

Chairman and BAS Representative
Dr Chris Newman
Clinical Sciences Centre
University of Sheffield, Northern General Hospital
Herries Road
Sheffield S5 7AU
Tel: 0114 271 4456 Fax: 0114 261 9587
E-mail: c.newman@sheffield.ac.uk

Secretary
Dr Chris Jackson
Bristol Heart Institute, University of Bristol
Level 7, Bristol Royal Infirmary
Bristol BS2 8HW.
Tel/Fax: 0117 928 2534
E-mail: chris.jackson@bristol.ac.uk

Treasurer
Dr Michael J. Curtis
Cardiovascular Research
Rayne Institute, St. Thomas’ Hospital
London SE1 7EH
Tel.: 020 7188 1095 Fax: 020 7188 3902
E-mail: michael.curtis@kcl.ac.uk

Committee
Dr. M. Yvonne Alexander. PhD
Lecturer In Molecular Medicine
School of Clinical & Lab. Sciences, University of Manchester,
46 Grafton St
Manchester. M13 9NT
Tel: +44 (0) 161 2751224 Fax: +44 (0) 161 2751183
E-mail: yvonne.alexander@manchester.ac.uk

Dr Katrina Bicknell
School of Pharmacy, The University of Reading
PO Box 228, Whiteknights
Reading, Berkshire RG6 6AJ
United Kingdom
Tel: 0118 378 7032 Fax: 0118 931 0180
E-mail: k.bicknell@rdg.ac.uk

Professor Barbara Casadei
University Department of Cardiovascular Medicine
John Radcliffe Hospital,
Oxford OX3 9DU
Tel: 01865 220132 Fax: 01865 768844
E-mail: barbara.casadei@cardiov.ox.ac.uk

Dr Alison Cave,
Medicines and Healthcare Products Regulatory Agency
Market Towers, 1 Nine Elms Lane
London SW8 5NQ
Tel: 020 7084 2000 Fax: 020 7084 2353
E-mail: alison.cave@mhra.gsi.gov.uk

Dr Andrew Grace
Section of Cardiovascular Biology
Department of Biochemistry, University of Cambridge
Tennis Court Road, Cambridge CB2 1QW
Tel: 01223 333631 Fax: 01223 333345
E-mail: ag@mole.bio.cam.ac.uk

Dr David Grieve
Department of Physiology, Queen's University Belfast
Medical Biology Centre, 97 Lisburn Road
Belfast BT9 7BL
Tel: 028 9097 2097 Fax: 028 9097 5775
E-mail: d.grieve@qub.ac.uk

Dr Derek Hausenloy
The Hatter Cardiovascular Institute, University College London
67 Chenes Mews, London WC1E 6HX
Tel: 0207 380 9894 Fax: 0207 380 9505
E-mail: d.hausenloy@ucl.ac.uk

Dr Richard Heads
Dept of Cardiology
The Rayne Institute, St Thomas’ Hospital
Lambeth Palace Rd, London SE1 7EH
Tel: 020 7188 0966 Fax: 020 7188 0970
E-mail: richard.heads@kcl.ac.uk

Dr Cathy Holt
Division of Cardiovascular and Endocrine Sciences
University of Manchester
3.31b Core Technology Facility
46 Grafton Street, Manchester M13 9NT
Tel: 0161 275 5671 Fax: 0161 275 1183
E-mail: cathy.holt@manchester.ac.uk
Contents

Editorial 3
Meet our new Editor .... 4
Review: Unravelling Mechanisms of Cardioprotection in Ischaemia/Reperfusion Injury: Spotlight on Sphingosine-1-Phosphate Signalling by Emmanuel Eroume A Egom, Yunbo Ke, R John Solaro and Ming Lei 5
Secretary's Column 11
Breaking News: BSCR Receives Major Endowment 12
Travel Report: Weinstein Cardiovascular Development Conference by Catherine Roberts 17
Travel Report: European Society of Cardiology Congress by Kelly Farrell 23
Forthcoming Cardiovascular Meetings 26
British Heart Foundation Grants 27
Cardiovascular Related Wellcome Trust Grants 27
BSCR/BAS Joint Spring Meeting "New Frontiers in Cardiovascular Research" 28

Editorial

Welcome to the October 2009 issue of The Bulletin! Apologies for the late publishing of this issue. A number of recent developments have required the inclusion of late-breaking news items in this issue. The most significant being the announcement of a major endowment to the BSCR, full details of which can be found herein.

Another change that we're pleased to announce is the expansion of The Bulletin's editorial team since Dr Melanie Madhani agreed to join us. We welcome Melanie on board and look forward to working together over the coming years.

This issue's review article has been written by Dr Ming Lei and colleagues from the University of Manchester. Dr Lei eloquently highlights the involvement of sphingosine-1-phosphate in cardioprotection against ischaemia-reperfusion injury.

In our travel reports for this issue, Catherine Roberts recounts proceedings from the Weinstein Cardiovascular Development Conference in San Francisco while Kelly Farrell shares her experiences at the European Society of Cardiology in Barcelona.

We will have to wait until June 2010 for the next meeting of the Society as, once again, our meeting is to be held within the British Cardiovascular Society meeting in Manchester, in collaboration with the British Atherosclerosis Society. Preliminary announcements for this and the Autumn 2010 meeting can be found within. Further details will be announced on the BSCR website and in the next issue of The Bulletin.

Nicola Smart, Helen Maddock and Melanie Madhani
Introducing our New Editor....

We are delighted to announce that Dr Melanie Madhani has agreed to join us to co-edit the BSCR Bulletin. Dr Melanie Madhani graduated from the University Of Wales College Of Medicine in 1998 with a BSc (Hons) in Pharmacology. She obtained a PhD in Cardiovascular from the Ivy League School, Dartmouth College, New Hampshire, USA and University Of Wales in 2002. She then joined University College London (UCL) as a post-doctoral research fellow, to work under Dr. Adrian Hobbs. Here, she investigated the role of cGMP in cardiovascular diseases. During her time at UCL, she was awarded a UCL Bogue Fellowship to work with Nobel Laureate, Dr Louis Ignarro, University of California, Los Angeles, USA. In 2005, she joined Dr. Philip Eaton's research group at The Rayne Institute, King's College London, where she broadened her experience in cardiac physiology in order to complement her vascular knowledge and skills into cGMP regulation during myocardial ischaemia reperfusion injury. In 2009, Dr. Madhani was appointed as a Lecturer in Cardiovascular Medicine at University of Birmingham. Melanie is currently an associate editor for Pharmacology and Therapeutics.

Visit the BSCR Website: www.bscr.org

- Information on forthcoming meetings, workshops and symposia
- All the latest BSCR News
- Job and Study Opportunities
- Download The Bulletin in pdf format
- Contact details and profiles of BSCR Committee members

Submission Deadlines for The Bulletin:

<table>
<thead>
<tr>
<th>Volume</th>
<th>Date</th>
<th>Deadline</th>
</tr>
</thead>
<tbody>
<tr>
<td>23 (1)</td>
<td>January 2010</td>
<td>1st December</td>
</tr>
<tr>
<td>23 (2)</td>
<td>April 2010</td>
<td>1st March</td>
</tr>
<tr>
<td>23 (3)</td>
<td>July 2010</td>
<td>1st June</td>
</tr>
<tr>
<td>23 (4)</td>
<td>October 2010</td>
<td>1st September</td>
</tr>
</tbody>
</table>
Unravelling Mechanisms of Cardioprotection in Ischaemia/Reperfusion Injury:
Spotlight on Sphingosine-1-Phosphate Signalling

by Emmanuel Eroume A Egom¹,², Yunbo Ke³, R John Solaro³ and Ming Lei²

¹Victoria Hospital, Cardiology, Hayfield Road, Kirkcaldy, Fife KY2 5AH.  ²Cardiovascular Group, School of Clinical and Laboratory Sciences, The University of Manchester, Manchester, M13, 9NT UK.  ³University of Illinois at Chicago, Department of Physiology and Biophysics, Center for Cardiovascular Research, College of Medicine, University of Illinois at Chicago, Chicago, Illinois 60612, USA

It is known that complex signal transduction cascades are involved in regulating cardiomyocyte death and survival during the acute cardiac ischaemia-reperfusion process, but detailed survival signalling pathways are not clear. This review presents and discusses the recent findings on the cardioprotective effect of sphingosine-1-phosphate (S1P) in acute cardiac ischaemia-reperfusion, particularly, through activation of p21-activated kinase.

Introduction

Despite tremendous advances in the knowledge of the causes that lead to ischaemic heart disease (IHD), it still remains the leading cause of human mortality with some 7.6 million deaths worldwide attributed to the disease in 2005(1). Ischaemia/reperfusion (I/R) injury is a major contributory factor to cardiac dysfunction and infarct size, which determines patient prognosis after acute myocardial infarction. However, such injury can be minimized by a cardiac self-protective mechanism called ischaemic preconditioning, in which a brief period of myocardium ischaemia/reperfusion significantly reduces injury resulting from subsequent long-term I/R. Since the appearance of the first publication on ischemic preconditioning in 1986(2), our knowledge of this phenomenon has increased immensely. It has been demonstrated that cardioprotective pathways can be induced effectively by ischaemic pre- and post-conditioning or pharmaceutical post-conditioning treatment during the reperfusion period. The application of increasingly refined experimental strategies has provided insights into the complex signal transduction cascades involved in regulating cardiomyocyte death and survival in ischaemia-reperfusion. Although precise mechanisms are far from clear, it is now known that multiple signalling pathways regulate the critical balance between cell death and cell survival in ischaemia-reperfusion.

New evidence indicates a definitive role for sphingolipid metabolites, particularly sphingosine-1-phosphate (S1P), as an important component of the intracellular signalling processes induced in ischaemic pre-conditioning(3). Experimental studies have also demonstrated protection against cardiac I/R injury achieved by pre-treatment with exogenous S1P.(3) More recently, Vessey and colleagues also demonstrated that S1P is an important endogenous cardioprotectant released by ischemic pre- and post-conditioning in experimental animal models.(4) We and others have further identified the signaling pathways downstream of S1P cardioprotection.(5,6) This review highlights the recent progress in understanding the cardiac protective effect of S1P signaling in I/R injury and raises the question of whether modulating the sphingolipid pathway may lead to potential therapeutic benefit both before and during an I/R injury in ischaemic heart disease (IHD).

S1P and S1P Receptors in Cardiac Tissues

The lysophospholipid, sphingosine-1-phosphate (S1P), is a circulating bioactive lipid metabolite that has been known for many years to induce cellular responses, including proliferation, migration, contraction, and intracellular calcium mobilization.(7-10) S1P is present in human plasma and serum in high nanomolar concentrations, associated with some lipoproteins,
especially the high-density lipoprotein (HDL). One of the main sources for S1P in plasma and serum are platelets. High concentrations of S1P are stored in platelets as these do not have the enzyme S1P lyase, an enzyme that catalyses the degradation of S1P to hexadecanal and ethanolamine-phosphate. The stored S1P is released upon activation of the platelets. S1P has unique properties as it can act both as an intracellular messenger and also as an intercellular/extracellular messenger.

The extracellular effects of S1P are mediated via its interaction with G protein-coupled receptors (GPCR). To date, a family of five structurally related receptors with high affinity for S1P has been identified. The first member of the Endothelial Differentiation Gene (EDG) family of GPCR to be cloned, S1P1/EDG-1, was originally identified as an inducible transcript of endothelial cell differentiation in vitro and therefore, it was named EDG-1. At the time, the ligand for the receptor was unknown, but subsequent investigation revealed S1P to be a high affinity ligand for EDG-1. The other GPCRs in this subfamily bind either S1P or a structurally related lysophospholipid (lysosphosphatidic acid, LPA) as high affinity ligands. Thus, this family of receptors fall into two subfamilies; one whose receptors bind S1P as their high affinity ligand (S1P1/EDG-1, S1P2/EDG-5, S1P3/EDG-3, S1P4/EDG-6 and S1P5/EDG-8) and a second whose members bind LPA as their high affinity ligand (LPA1/EDG-2, LPA2/EDG-4 and LPA3/EDG-7).

Tissue expression of the S1P1/EDG1, S1P3/EDG3, and S1P2/EDG5 receptors in mice indicates that heart and lung have the highest overall expression of these genes, whereas S1P4/EDG6 and S1P5/EDG8 receptors are mainly expressed in lymphoid and brain tissues, respectively.

We employed real-time (RT)-PCR to determine the expression of S1P1, S1P2 and S1P3 transcript pools in rat cardiac tissues. The transcripts were detected and analysed in tissues dissected from sinoatrial node (SAN), right atrium (RA) and left ventricle (LV). The S1P1 receptor isoform expression level was higher than S1P2 and S1P3 in these tissue types (Figure 1), which indicates that the S1P1 receptor is the dominant isoform in rat heart tissues. Our Western blot and immunocytochemistry analysis further confirmed the expression profile of S1P1-3 receptors in rat heart tissues and myocytes.

The differential G protein-coupling of the individual S1P receptor subtypes and associated signaling pathways have been extensively studied and the major pathways have been proposed (for review, see Brinkmann, 2007). Whereas the S1P1 receptor couples exclusively to Gi proteins, the S1P2 and S1P3 receptors are more promiscuous, coupling to the Gq, G12/13 families of heterotrimeric G-proteins. Coupling of S1P2 and S1P3 receptors to these G-proteins has been confirmed by GTPγS binding assays. Analysis of the signaling pathways downstream of these receptors, which includes activation of phospholipase C and Rho also implicates Gi, Gq, and G12/13 in
Cardioprotection by S1P and its analogue, FTY720, in myocardial I/R injury

Several recent studies\(^{(7;9;25;26)}\) have provided evidence for a role of S1P signalling in protection against I/R injury, in particular its role in pre-conditioning and post-conditioning mechanisms to rescue hearts from I/R injury.\(^{(25;27)}\) The addition of S1P to neonatal rat ventricular myocytes was shown to confer cardioprotection against hypoxia,\(^{(27)}\) and S1P also protects against global I/R damage in isolated mouse hearts.\(^{(28)}\) Hofmann and co-workers have recently shown that S1P and its agonists, FTY720 and SEW2871, can limit cell death even when applied during reperfusion and can induce a cardioprotective effect.\(^{(29)}\) Moreover, Vessey and co-workers also reported that both sphingosine and S1P were able to protect the ex vivo rat heart from ischaemia reperfusion injury when added to the reperfusion medium after a 40 min ischaemia (postconditioning).\(^{(29)}\) Activation of sphingosine kinase (SK), the upstream kinase responsible for producing S1P, has more recently been suggested to protect the isolated perfused heart from I/R damage.\(^{(30)}\) Moreover, an S1P agonist, FTY720, has been shown to attenuate small-for-size liver graft injury by activation of cell-survival Akt signalling and down-regulation of the MAPK pathway.\(^{(31)}\) We also have evidence that S1P analogue FTY720 effectively antagonized both brady- and tachy-arrhythmias induced by I/R and protected against hypoxic and ischaemic insults\(^{(5)}\).

Pak1/Akt signaling as a potential intracellular pathway underlying FTY720 cardiac protection effect

The key underlying mechanism(s) and signaling pathway(s) for S1P cardio-protection were largely unknown until recently.\(^{(32)}\) Hofmann and colleagues first showed the activation of Akt underlies the protective effects of S1P receptor agonist treatment after myocardial ischaemia-reperfusion. These findings open the door for understanding key mechanism(s) and signaling pathway(s) for S1P cardio-protection.\(^{(29)}\) Another significant insight into the mechanism came from experiments in a mammalian cell line, which demonstrated that p21 activated kinase (Pak1), a Ser/Thr kinase downstream of small G-proteins, is activated by sphingosine and several related long chain sphingoid bases in a time- and dose-dependent manner.\(^{(33)}\) There is a large body of evidence that Pak1 activity is a key regulator of a number of cellular functions, including cytoskeletal dynamics, cell motility, growth and proliferation, cardiac ion channel activity, and contractility.\(^{(34;35)}\) Pak1 also facilitates Akt stimulation and aids recruitment of Akt to the membrane. This reveals an important scaffolding function of Pak1 in the Akt pathway.\(^{(36)}\) However, the signal-transduction pathways mediating these effects have not been established. Niether has an in vivo metabolism for endogenously released S1P been demonstrated during acute cardiac ischaemic conditions. On the basis of these data, we speculated that Pak1 participates in the cardiac effect of S1P signaling.

We investigated the effect of the S1P analogue, FTY720, on I/R injury-induced cardiac arrhythmias in an ex vivo rat heart model. Our results demonstrate cardio-protection by FTY720 signaling through the S1P cascade to Pak1. To determine Pak1 activation we employed Western blotting with an anti-phospho Thr 423 Ab and Akt activation with an anti-phospho-Thr 308 Ab\(^{(36)}\) to probe the hearts used in the arrhythmia studies (in the presence or absence of FTY720) for phosphorylation of Pak1/Akt. Compared to baseline control levels, there was a significant depression in the levels of phospho-Pak1 and phospho-Akt decreased by 62% and 64% in ischaemic conditions and by 73% and 63.5% in reperfusion conditions. However, in the presence of FTY720, phospho-Pak1 and Akt levels decreased by only 22% and 24%, in ischemic conditions and by 30% and 29%, respectively in reperfusion conditions. In the presence of S1P, phospho-Pak1 and Akt levels increased by 10% and decreased only by 26%, respectively in ischemic and decreased by only 13% and 28.8%, respectively in reperfusion conditions, compared to baseline level under the control condition\(^{(5)}\).

We then addressed the important question of whether FTY720-mediated Pak1 and Akt activation was through Gi by treating neonatal rat cardiac myocytes with 100 ng/ml PTX overnight and then stimulating with 25 nM FTY720 for 5 min. FTY720 induced a 1.6-fold increase in Pak1 phosphorylation, and a 1.45-fold increase in Akt phosphorylation relative to vehicle. After PTX treatment, FTY720-mediated activation of Pak1 was reduced by 87%, and activation of Akt was reduced by 53%. These data demonstrate that a significant component of FTY720-mediated Akt and Pak1 activation in cardiomyocytes occurs through a Gi-coupled S1P receptor.\(^{(5)}\).
Thus, our data are the first to demonstrate a down regulation of phospho-Pak1 during I/R. Moreover, we found a strong correlation of the activity of Pak1 and Akt with the incidence of I/R induced arrhythmias with and without FTY 720. Pak1 is not only involved in regulation of myofilament activity, but also regulates activities of ion channels which are directly related to ischemia/reperfusion induced arrhythmia. It remains unclear if Pak1 and Akt are related to other cardioprotective signals, such as PI3 kinase, eNOS etc. The inhibitory G protein is a key upstream signal for Pak1 in cardiomyocytes. Abbreviations: LCC-L-type Ca channel; PLB-phospholamban; cTnI-cardiac troponin I; MyBP-C-myosin binding protein C; SK-1-sphingosine-1 kinase, S1P-sphingosine-1 phosphate

Figure 2. Previous studies of ours have indicated that Pak1 executes its anti-adrenergic function in the heart through activation of phosphatase PP2A. Both Pak1 and Akt may play a significant role in S1P1 and S1P3 mediated cardioprotective effects during cardiac ischemia and reperfusion. Pak1 is not only involved in regulation of myofilament activity, but also regulates activities of ion channels which are directly related to ischemia/reperfusion induced arrhythmia. It remains unclear if Pak1 and Akt are related to other cardioprotective signals, such as PI3 kinase, eNOS etc. The inhibitory G protein is a key upstream signal for Pak1 in cardiomyocytes. Abbreviations: LCC-L-type Ca channel; PLB-phospholamban; cTnI-cardiac troponin I; MyBP-C-myosin binding protein C; SK-1-sphingosine-1 kinase, S1P-sphingosine-1 phosphate

Thus, our data are the first to demonstrate a down regulation of phospho-Pak1 during I/R. Moreover, we found a strong correlation of the activity of Pak1 and Akt with the incidence of I/R induced arrhythmias with and without FTY 720. The precise mechanisms underlying the cardioprotective effect of Pak1/Akt activation on I/R induced arrhythmias is likely to be complex, and may involve primary effects on ion channels/transporters and secondary effects to protect cardiac myocytes from hypoxia-induced stress and cell death. Earlier studies also indicated that sphingosine and several related long chain sphingoid bases can directly activate Pak1 in vitro at a higher concentration than the FTY720 we used in this study.(33-37) Whether FTY720, which is structurally similar to S1P, can directly activate Pak1 in cardiac cells without prior conversion to FTY 720 phosphate remains unclear. Recent studies also indicate that FTY720 activates PP2A and induces dephosphorylation of Erk-1/2 in immuno-cells, which also provides a mechanistic insight into understanding the cardiac effects of FTY720 demonstrated in this study.(38) Figure 2 illustrates our proposed possible mechanisms underlying the cardioprotective effects of S1P.

Conclusion and future directions

Although the precise mechanisms underlying the activation of Pak1/Akt signaling by S1P in preventing
cardiac I/R injury require further investigation, recent results reported by ourselves and others suggest that activation of Pak1 and Akt signaling pathways play a role in FTY720/S1P-mediated cardioprotection. Our evidence that FTY720 prevents arrhythmias induced by I/R injury and that it is potentially an important novel agent protecting against I/R injury and its associated arrhythmias. The detailed mechanisms for the production of sphingolipids as a consequence of cardiac ischaemia or hypoxia require further study. Such investigations should raise the question of whether modulating the sphingolipid pathway may lead to potential therapeutic benefit both before and during an ischaemic coronary event.

**ACKNOWLEDGEMENT**

The work was supported by The Wellcome Trust (ML), The British Heart Foundation (ML) and National Institute of Health grants RO1 HL 64035 and PO1 HL 62426 (Project 1) (RJS).

**References:**


Correspondence to:
Dr Ming Lei,
Cardiovascular Research Group,
School of Clinical and Laboratory Sciences,
The University of Manchester,
Manchester M13 9NT,
Tel: 44-161-2751194
Fax: 44-161-2751183
E-mail: ming.lei@manchester.ac.uk.

Articles for The Bulletin

Would you like to write a Review or Laboratory Profile for the BSCR Bulletin? These articles provide an excellent opportunity to let BSCR members know about your research activities and also provide an insight into your research field.

We are keen to hear from anyone in cardiovascular research who would be willing to write for The Bulletin.

If you are interested, please contact the Bulletin editors with your ideas:
Helen (h.maddock@coventry.ac.uk), Nicola (N.Smart@ich.ucl.ac.uk) or Melanie (m.madhani@bham.ac.uk)
Secretary's Column

I write this just a couple of days after the Society's Autumn Meeting in Oxford. "Myocardial Energetics and Redox in Health and Disease" attracted an excellent attendance and superb speakers, and the organisers - Barbara Casadei, Kieran Clarke and Saadeh Suleiman - even managed to arrange for us to enjoy some pleasantly non-autumnal weather. Lively discussions during the breaks and an enthusiastic poster session are reflected in the photos on the website (www.bscr.org/autumn-2009-photos.html).

An innovation at the meeting was the webcasting of some talks, an idea put forward by committee member Derek Hausenloy. His colleague Andy Flett did a great job of capturing the Powerpoint slides and synchronising them with the recorded audio. The results are available on our website (www.bscr.org/autumn_2009_meeting.html). The war between builders and sound engineers continues to be waged, so Andy had to do quite a bit of post-processing of the audio tracks to reduce the input from Messrs Bodgit and Novat, but I hope you find the webcasts useful and recommend them to your colleagues.

Our next Spring Meeting will, like last year's, be held jointly with the British Atherosclerosis Society and will form part of the British Cardiovascular Society's annual conference. Organised by Derek Hausenloy and Manuel Mayr, the topic is "New Frontiers in Cardiovascular Research" and it will be held on June 7th and 8th next year in Manchester.

Finally, I'd like to leave you with a photo competition. The caterers at Trinity College for the Autumn Meeting dinner constructed a dessert that I reckon was meant to represent the three officers of the BSCR; myself, Chris Newman and Mike Curtis. Your task is to work out which bit is which officer. Answers on a £20 note please to The Bulletin Editors, Hotel Plush, Cayman Islands. The winner will receive a signed version of the photo.

Chris Jackson
The BSCR has just heard that it is to benefit from a major bequest, likely to be in excess of £200,000, from the estate of the late Bernard and Joan Marshall. The bequest is specifically intended to: encourage, recognize and support the work of young investigators, and to facilitate a keynote lecture at the annual meeting of our Society.

Bernard and Joan Marshall were the uncle and aunt of Professor David Hearse from the Rayne Institute, St Thomas' Hospital in London. In 1970, David returned from a post-doctoral fellowship at New York University Medical Centre and embarked upon his career in cardiovascular research. Working alone and feeling rather isolated David regularly met up with Keith Gibson from the Cardiothoracic Institute to discuss their research. At that time, the British Cardiac Society did not admit basic scientists and believing that there were other researchers in need of a discussion forum David and Keith set up the 'Cardiac Muscle Research Group'. Expecting no more that 20 attendees they were amazed to have almost 100 at the Group's first meeting. The Cardiac Muscle Research Group went on to become the BSCR.

Bernard and Joan Marshall were always fascinated by David's research and his commitment to training young investigators and creating multi-disciplinary research groups. After serving in the Royal Navy during the Second World War, Bernard Marshall married Joan and joined the Ministry of Agriculture, Fisheries and Food, working in various parts of the UK and progressing to a very senior level. Among his activities was membership of the team responsible for building the Thames Barrier. In the latter part of his career Bernard and Joan lived in Reading and in 1981, after his retirement, Bernard embarked upon several new careers, firstly setting up the Tenant Farmer's Association and becoming its first Director General. In 1987 he took an appointment at the University of Reading as an Honorary Research Fellow at the centre for Agricultural Strategy where for 10 years he
organized various projects and national conferences. During that period, he and David often exchanged tips and suggestions on meeting venues, the organization of academic meetings and the challenges of research. It was on such an occasion that Bernard and Joan discussed with David the possibility that part of their estate might be bequeathed to an organization such as the BSCR.

After his period at Reading University, Bernard, although in his 80's, embarked on yet another career handling public relations and marketing for a local herb farm and garden centre. He frequently traveled to London to meet with David and was extremely active right up until two days before his unexpected death from a myocardial infarction in March 2009. His wife Joan died in January 2005.

The BSCR is indeed fortunate to receive this generous gift. In this issue there are details of the 2010 Bernard and Joan Marshall Young Investigator Prize, the Bernard and Joan Marshall Research Excellence Prize and the Bernard and Joan Marshall Distinguished Investigator Lecture. The Society and its members, in expressing their appreciation, also wish to relay their condolences to surviving family members.
Bernard and Joan Marshall Research Prizes

Nominations sought

The Bernard and Joan Marshall Research Prizes are awarded annually for outstanding research by young scientists. This year (2010) will hold the inaugural competition.

The prizes

The prizes are intended to reward excellence in research in any area of cardiovascular biology or medicine. There are two prizes: the Bernard and Joan Marshall Young Investigator Prize (3,000 Euros) and the Bernard and Joan Marshall Research Excellence Prize (5,000 Euros). Prizes, together with commemorative plaques, will be presented during the BSCR Autumn Meeting dinner.

Eligibility

There are no citizenship restrictions and applications are welcome from academia and the pharmaceutical industry. The Young Investigator Prize is for persons who have not yet attained a higher degree (PhD, DPhil, or MD) and the Research Excellence Prize is for persons below the age of 38 who already have a higher degree. Payment of the prizes is contingent on the winners presenting a 20 minute talk at the BSCR autumn meeting (in 2010 this will be held in London at St Thomas' Hospital, details to be announced on BSCR website) and submitting a short article describing their research interests and their award-winning work (of between 1,500 and 3,000 words) for publication in the BSCR Bulletin.

How to apply

Please submit by email attachment to the Chair of the BSCR (c.newman@sheffield.ac.uk) the following three items:

- your Curriculum Vitae
- a full manuscript that is in preparation, or submitted, or is a pdf of a paper published after June 1 2009, of the research to be considered
- a supporting letter from your research supervisor or Head of Department that briefly summarises your role in the work.

It is expected that the applicant will have been responsible for the bulk of the work and would be first author of the paper. The deadline for submission is July 1 2010. Please note that any unpublished material presented will be treated with the strictest confidence and that the material, whether unpublished or not, will not be published by the British Society for Cardiovascular Research, meaning that no copyright issues should arise as a consequence of entering the competition.

The judging and announcement of the winners

A panel of six experts appointed by the Committee of the Society will choose the winners during the first two weeks of July 2010, and the winners will be contacted at the beginning of August, in good time for them to make arrangements to attend the Autumn BSCR meeting.

Annual 'Bernard & Joan Marshall Distinguished Investigator Lecture'

The BSCR is pleased to announce that from 2010, there will be a named lecture at each Autumn Meeting. The inaugural lecture will be given by Dan Roden (Vanderbilt, USA) at the London meeting (details of which can be found on the BSCR website).
Birth, Life and Death of the Cardiac Myocyte Conference
June 2-4, 2010 | Napa Valley, US

4 for 3 promotion:
Register 3 people from the same institution and get a fourth place for free!*

Invited speakers:
Gerald Dorn, Jonathan Epstein, Thomas Eschenhagen, Norbert Frey, Joshua Hare, Richard Lee, Jeffery Molkentin, Kenneth Poss, Deepak Srivastava, Yibin Wang

Organizers:
Joseph Hill, Eric Olson, Jay Schneider & Abcam

Register at:
www.abcam.com/napacardio

*promotion only applies to participants staying in twin rooms.

The Leukocyte in Cardiovascular Disease Conference
January 27-28, 2011 | Geneva, Switzerland

Topics:
Cytokines, Chemokines, M1/M2 monocytes/macrophages, Lymphocytes, Dendritic cells, Atherosclerosis, Immunity, Transcription factors, Signalling

Organizers:
Beat Imhof, François Mach & Abcam

More information at:
www.abcam.com/geneva
The British Society for Cardiovascular Research announces its Autumn 2010 meeting

The Future of Arrhythmia Research: 
Lambeth Conventions Update

Dates: 6th-7th September, 2010
Venue: Lambeth Palace, London UK
Organiser: Michael J Curtis PhD, KCL, London

The Lambeth Conventions is a guidance paper for basic and clinical antiarrhythmic research. It was generated from a meeting held in London in 1987, and published in Cardiovascular Research. The paper is the journal's most highly cited of all time (701 cites as of Nov 2009). Our meeting will update the Lambeth Conventions in the light of advances during the past 20 years.

Venue: Lambeth Palace was the venue for the original Lambeth Conventions meeting in 1987, so it is fitting that we reconvene here (http://www.archbishopofcanterbury.org/108).

Invitation to Participate (and submit an abstract) How will new antiarrhythmic drugs be found? What are the best models and approaches? What about proarrhythmia (torsades de pointes) and channelopathy? International experts have agreed to present talks that address current problems and identify possible solutions in arrhythmia research. You are invited to submit an abstract so that you may influence the content of the Lambeth Conventions update. Most abstracts will be selected for poster presentation but, if you so indicate, your abstract may be considered for the free oral communication session. This will be competitive. Additionally the meeting attendance is limited to 130 registrants. We encourage early online abstract submission (http://www.bscr.org/autumn_2010_meeting.html). Check the BSCR website for the date of commencement of registration (provisionally May 1 2010).

Confirmed participants (speakers, session chairs, etc.) GE Billman (Columbus, OH, USA), AJ Camm (London, UK), H Clements-Jewery (Lewisburg, WV, USA), MJ Curtis (London, UK), S Demolombe (Nantes, France), A Farkas (Szeged, Hungary), JC Hancox Bristol UK), MJ Janse (Amsterdam, Netherlands), MK Pugsley (Raritan, NJ, USA), D Roden (Nashville, USA), MJ Shattock (London UK), CL Stables (Ann Arbor, MI, USA), MJA Walker (Vancouver BC, Canada), AAM Wilde (Amsterdam, Netherlands),

Sponsorship: We are actively seeking meeting sponsorship. Sponsors will be acknowledged at the meeting and in the resultant publication (which will be submitted to a leading cardiovascular research journal). Please contact the organiser (michael.curtis@kcl.ac.uk).
The Future of Arrhythmia Research: Lambeth Conventions Update

Programme

DAY 1

12:30 - 13:50  Registration and Buffet Lunch
13:50 - 14:00  Welcome and Introduction

Session 1: Antiarrhythmic drug discovery - why has the pipeline dried up?
14:00-14.25  Clinical trial failures from CAST to 2009 - what went wrong? George E Billman (Columbus Ohio, USA)
15.00-16.00  The inaugural Annual Bernard & Joan Marshall Distinguished Investigator Lecture: Is there an impersonal future for antiarrhythmic drug discovery? Dan M Roden (Nashville TN, USA)
16.00-16:30  TEA

Session 2: Antiarrhythmic drug discovery - are our methods and models adequate?
16:30-16.55  The importance of pathological setting - is one model sufficient? Hugh Clements-Jewery (Lewisburg WV, USA)
17.00-17.25  The role of transcriptomics in target identification - a new approach to antiarrhythmic drug discovery? Sophie Demolombe (Nantes, France)

Session 3: Posters
17:30-18:30  With Wine Reception, followed by Dinner at 19:30

DAY 2

Session 4: Challenges to the Lambeth Conventions
09:00-09.25  The Lambeth conventions - can we agree on what to retain? Michael JA Walker (Vancouver BC, Canada)
09.30-09.55  New challenges arising from mouse arrhythmia models Catherine L Stables (Ann Arbor, MI, USA)
10.00-10.25  New challenges arising from proarrhythmia models Andras Farkas (Szeged, Hungary)
10.30-10.55  New challenges arising from our better understanding of arrhythmia mechanisms Arthur AM Wilde (Amsterdam)
11:00-11:30  TEA

Session 5: Free Communications from selected abstracts (authors are instructed to present work that identifies or addresses problems with the Lambeth Conventions)
We especially encourage abstract submissions for 10 min talks that offer new guidelines for the following:
  Choice and impact of animal species
  Choice and impact of "setting" (e.g., ischaemia vs infarction)
  Use of nonphysiologic arrhythmia trigger methods (PES, drug intoxication)
  Use of surrogate biomarkers for lethal arrhythmias
  Study of supraventricular arrhythmias
  Study of proarrhythmia
12:45-13:30  LUNCH

Session 6: Bernard & Joan Marshall Research Prize Lectures
13:30-14.30  Chaired by David J Hearse
14.30-14:45  TEA

Session 7: Drafting of an update to the Lambeth Conventions
Roundtable discussion-led questions and audience participation followed by audience vote. Majority decision prevails. Session to be lead by expert panel Chaired by A. John Camm
14:45-15:30  Summary of items to be transformed into conventions (starting with a list prepared over lunch, informed by foregoing presentations, and including items suggested by the audience)
15:30-17.00  Discussion and voting on each new or modified convention.
17.00  Meeting close
In the field of cardiovascular development, the Weinstein meeting has long been regarded as one the top conferences to attend, providing unrivalled opportunities to hear about leading edge work and to meet and exchange ideas with those engaged in similar research. The tradition of the Weinstein meeting is to select all the platform presentations from submitted abstracts and the emphasis is upon selecting talks from more junior scientists, thus allowing graduate students, postdocs and new PI’s to present their work at this prestigious forum.

The meeting originated over 20 years ago and in 1995 was renamed the Weinstein Cardiovascular Development Conference to honour Dr Constance Weinstein of the NHLBI, who was greatly involved in initiating NIH funding of this area of research and in organizing the first meetings. Although Dr Weinstein has since retired, she and her husband Howard, still continue to attend the meeting every year. This year, the conference was held in the palatial Hyatt Regency on Embarcadero in the heart of San Francisco, close to the waterfront. The venue provided excellent facilities, including several spacious meeting rooms, a large room for the poster sessions and great catering. Equally convenient were the hotel bar and near-by hostellries for those all important evening networking sessions, plus sight-seeing opportunities in the amazing city of San Francisco.

After brief welcoming remarks from the two main local organisers, Brian Black and Benoit Bruneau, events kicked off on Thursday afternoon with the first platform session on "Progenitors and Lineages" chaired by Takashi Mikawa. The first talk, by Stephane Zaffran, concerned the possible role of retinoic acid (RA)-regulated genes in anterior-posterior patterning of the cardiac field. He provided evidence that both Hoxa1 and Hoxb1 are expressed within early Raldh2 expression domains, adjacent to and overlapping with cardiac progenitor cells respectively. Lineage tracing of Hoxa1 and Hoxb1-positive cells revealed that they both contribute to the outflow tract (OFT) and right atrium with Hoxb1-positive cells also being found in a number of other cardiac lineages. Brett Harris then spoke about work demonstrating distinct contributions of the primary heart field (PHF) and secondary heart field (SHF) to the conduction system, which suggest SHF contributes to the AV node and His-Purkinje system. Next, Ralston Barnes replaced the original speaker Rieko Asai, who was not allowed to travel thanks to the swine flu threat. Ralston presented a Hand1 fate map and a knockout of Hand2 within the Hand1 lineage, which results in embryonic death at E14.5, with widespread oedema, acute vascular haemorrhage, ventricular hypertrophy and in 20% of cases, ventricular septal defects (VSDs). Katerina Ragkousi described elegant work investigating the role of Gata 4/5/6 factors using the chordate model of Ciona intestalis. This model has only one Gata 4/5/6 orthologue allowing complications of redundancy seen in vertebrate systems to be avoided. Targeted disruption of Gata in heart precursor cells prevents both migration and proliferation. Targeting the
construct specifically to endoderm cells also prevents heart migration and fusion. However, proliferation is unaffected, leading to two separate pools of cardiac precursors on either side of the embryo, a situation reminiscent of cardia bifida. Ian Scott closed the session with the first presentation using a zebrafish model system to investigate the function of the G-protein-coupled receptor agtrl1b in the migration of myocardial progenitors to the anterior lateral plate mesoderm, where cardiomyocyte differentiation is first observed. In parallel experiments, he showed over-expression of "myocardial" factors tbx5, baf60 and gata5 are sufficient to increase heart size and confer the ability to migrate to the heart.

After a brief coffee break, the second session of the afternoon, "Stem Cells and Regeneration", chaired by Maurice van den Hoff, began with two very enjoyable talks. In the first, Mary Hutson shared her experimental technique for deriving multipotent progenitor cells from the chick secondary heart field and showed that BMP and FGF signalling cascades have differing effects on these cells, such that myocardial differentiation requires BMP signalling in combination with a down-regulation of the FGF/Ras/Erk pathway. In the second talk, Elaine Shelton sought to understand the mechanisms underlying the use of the omentum (OM), an abdominal serosal mesothelium, as "clinical duct tape" in gut injury. Her grafting experiments showed that the OM upregulates smooth muscle markers in response to gut injury, suggesting the wound is signalling to the OM graft. Chulan Kwon then described her work on the regulation of expansion and differentiation of cardiac progenitor cells into cardiomyocytes, smooth muscle or endothelial cells, via the interaction of the Notch and Wnt/β-catenin pathways.

In the next presentation we learned from Martin Bakkers that inducing Tbx3 expression in cardiomyocytes of adult mice will repress the gene transcription programme associated with working myocardium. However, Tbx3 is not sufficient alone to induce automaticity in non-presumptive pacemaker cardiomyocytes. Finally, Wenging Cai discussed her data suggesting that TGFβ and Cerberus-like are paracrine signals that mediate Nodal/Cripto/ALK4 induction of cardiac fates in mouse ES cells.

Delegates then headed to the top of the amazing 15-storey atrium of the Hyatt Regency to enjoy an excellent buffet with several different styles of cooking on offer. A lively atmosphere was certainly generated by 350 scientists all taking the opportunity to both make new friends and catch-up with old ones.

After an hour and a half of eating, drinking and talking, it was back to the lecture hall to hear the keynote speaker, Professor Stuart Orkin, whose research focuses on the molecular genetics of haematological diseases, the fundamental mechanisms of blood cell development and stem cell biology. His theme was "Transcriptional Control in Stem Cells" in the haemopoietic system. He gave a wide-ranging talk which encompassed a number of topics including: the protein network surrounding Nanog and how these factors have a dual role in the maintenance of pluripotency; the role of chromatin repressive Polycomb family members Ezh1 and 2 in the exit from the pluripotent state and the action of transcriptional repressor Jarid2/Jumonji as a modulator of the balance between self-renewal and commitment. Finally, he discussed the possible antagonism between Swi/Snf and PcG proteins in gene regulation and whether low expression of Swi/Snf factors promotes cancer as does the over-expression of PcG's.

On Friday, the first full day of the conference began bright and early with breakfast before the platform presentations began with Tony Firulli chairing the "Transcriptional Regulation" series of talks. Calvin Hang described work showing that the essential Brg1 subunit of BAF complexes, controls cardiac growth, differen-
tiation and stress-dependent cardiac hypertrophy via two parallel pathways involving respectively, Bmp10/p57kip2 and HDAC-mediated α-MHC repression. Paul Grossfeld then shifted the emphasis to human genetic disease by talking about cloning Ets1 as a candidate gene for Jacobsen syndrome, a lethal human hypoplastic left heart syndrome (HLHS). The Ets1 transcription factor is expressed in the early endocardium and neural crest and a targeted null deletion on a C57Bl6 background causes a fully penetrant membranous VSD, a characteristic of Jacobsen syndrome, and small left ventricular apex. The following talk by Youngsook Lee, returned to the function of the histone demethylase Jarid2, with an endothelial knock-out of Jarid2 partially recapitulating the full null phenotype, including VSDs and hypertrabeculation. He proposed that this was the consequence of failure to regulate Notch1 expression leading to up-regulation of Nrg1. ChIP analysis suggests Notch1 is a direct target of Jarid2, with Jarid2 functioning as a transcriptional repressor. Moving back to the conduction system, Shang-Shang Zhan presented work suggesting Irx3 is required for His-Purkinje functional maturation and that this function maybe mediated a conserved Irx3 binding site overlapping with and adjacent to Nkx2.5 and Tbx5 sites in the Cx43 promoter. The last presentation before the coffee break was given by Jun Takeuchi on the subject of the zinc finger transcription factor SPALT-like 4(Sall4). He presented data supporting the idea that Sall4 modulates chromatin/histone remodelers such as the NurD Swi/Snf and Baf complexes, to regulate cardiomyocyte proliferation and inhibit progressive cardiac hypertrophy.

After some much-needed caffeine, platform session IV on "Post-transcriptional Regulation" got underway under the auspices of Michiko Watanabe. This section of the meeting focused mainly upon the role of micro-RNAs (miRs) in development. Ye Tao described miR-451, which seems to promote the differentiation of vascular endothelial and blood cells block the production of beating cardiomyocyte and may regulate multiple processes in vasculogenesis/angiogenesis, haematopoiesis and cardiogenesis. Melissa Rodgers then spoke about an ultra-conserved region in the Bmp2 3' UTR which acts in vivo to repress unwanted expression in the heart, particularly the proepicardium, epicardium and their derivatives. Following on, Viravuth Yin talked about work on the role of micro-RNAs in zebrafish cardiac regeneration, in particular miR133, loss of which appears to promote cardiomyocyte proliferation close to sites of cardiac injury. Ronald Neppe

then reminded us that DEAD-box RNA helicases play an important role in micro-RNA processing and heart development. Cardiac specific knock-down of CHAMP/Csm prevents heart looping in zebrafish and cardiac overexpression in the mouse produces a hypoplastic heart, with increased mortality. Finally, Gene Kim's topic was ventricular hypoplasia and VSDs in the hearts of transgenic mice over-expressing mir130a, a phenotype which seems to result from miR130a repression of Fog2.

At lunchtime a mass picnic had been arranged outside in nearby Justin Hermann Plaza. SF is known for fog/mist and rain so the organizers were eager to take credit for the uncharacteristically hot weather. The bright sunshine made the outdoor lunch a fantastic opportunity to refuel, chat with fellow delegates, grab a famous SF coffee from the near-by Ferry Building and of course to top-up the tan. As an added bonus, the clear skies meant we finally got to see the whole of the Golden Gate Bridge, which was of course the inspiration for the 2009 conference logo.

After lunch came the chance hear more established PI's speak in two concurrent workshops. Del-
egates could choose between Paul Riley, Jay Schnei-
der and Ellen Lien in workshop 1 speaking about "Car-
diace Regeneration" or Deepak Srivastava, Da-Zhi Wang
and Eric Olson continuing the "Micro-RNAs" theme in
workshop 2. I chose to visit the latter as it afforded an
opportunity to learn more about a very rapidly expanding
field. All the seminars provided a nice overview of miR
crinciples. Deepak described work done in ES and iPS
ells to identify miRNAs required to produce cardiac
lineages, a collaborative project to generate mouse miR
kock-outs using a BAC vector approach and finished
by describing work on miR143/145 which are required
for smooth muscle differentiation. Da-Zhi Wang ranged
over several subjects beginning with the regulatory net-
work involving miR1 and 133 in cardiac and skeletal
proliferation and differentiation. He then spent some
time on the cardiomyopathic lethality seen in heart spe-
cific conditional Dicer knockout mice. Next, he dis-
cussed the intronic miR's encoded by cardiac myosin
heavy chains, in particular mir208a and talked about
the role of miR1 and 206 to promote satellite cell dif-
erentiation via repression of Pax7 in skeletal muscle.
In the last part of the workshop Eric Olson addressed
us on the subject of miR control of muscle disease. He
covered three different areas; miRs as mediators of
cardiac injury/repair, amyotrophic lateral sclerosis
(ALS), a motor neuron disease and the vascular re-
sponse to injury. The ALS section of his talk was espe-
cially interesting, describing a potential interaction be-
tween the superoxide dismutase (SOD1) model of ALS
and the mi206 null mouse. The ALS mouse is a late
onset model but when this is crossed to the miR206
null, disease onset appears 7 months earlier. Therefore
it appears miR206 mediates neuromuscular cross-talk
and future work will involve attempting to rescue ALS
with a mi206 gain-of-function transgenic mouse.

After tea we returned to the main meeting room
for the final set of platform presentations of the day.
Under the aegis of Anne Moon, contributors to this
session talked about a number of different approaches
under the umbrella of "Cardiac Signaling". Peng Li be-
gan the session with another talk on retinoic acid and
its regulation of SHF differentiation and TGFβ medi-
ated OFT septation. His work suggests that retinoic
acid receptors (RARs) function in Isl1+/Nkx2.5+ SHF
precursors to regulate their differentiation and commit-
tment to a Mef2+ fate, possibly using Gata4 as an in-
termediary. In RAR mutants, failed SHF differentiation
produces a short misaligned OFT in which Tgfβ2 is
overexpressed distally, causing septation defects. Mov-
ving to the subject of control of organ size via the Hippo
pathway, Todd Heallen described a null allele for the
mammalian Hippo orthologue, Salvador, which have
severe heart defects including an enlarged OFT. Robert
Garrioch then talked about results which imply that in
the chick, fusion of the dorsal aortae in the midline is
dependent upon down-regulation of Chordin in the
notochord. Yian Ting showed data revealing a novel
canonical Wnt2a-Gata6 feed-forward regulatory loop
involved in controlling the development of the poste-
rrior pole of the heart. In the last talk of the day Bram
van Wijk provided evidence that Tbx18+ mesoderm
covering the right vitelline vein contributes to pro-eпи-
cardium and inflow myocardium. To separate these
lineages, Mek1/2 mediated FGF signalling is dominant
to BMP signalling and separates the epicardium from the
Tbx18+ precursor pool whereas BMP signalling is re-
quired for myocardial differentiation.

The first poster session began immediately after
the platform presentations. Cheese and wine were avail-
able, providing a certain amount of social and scientific
lubrication, especially for those of us presenting our
posters in this first session. According to organizer Brian
Black "the poster sessions have always been at the heart
of the Weinstein" and this meeting was no exception.
General levels of interest in all the work presented were
high and it was a tricky juggling act to visit the many
posters I wanted to see without deserting my own for
too long. I enjoyed several discussions about my own
and others work until finally the crowd began to dis-
perse to a well earned dinner. We took the opportuni-
ty to enjoy the SF Friday night vibe with cocktails and
dinner at a lively bar/restaurant along the Embarcadero.

Despite this, we were ready and waiting early
on Saturday morning for platform session VI on "Vess-
sels and Valves" chaired by Adriana Gittenberger de
Groot. The first speaker, Sarah de Val gave an excel-
ent presentation of her data, recently published in De-
velopmental Cell, describing an endothelial-specific
enhancer within the Mef2c locus, which contains a com-
posite FOX:ETS motif conferring strong synergistic
activation. Her work provided ample evidence that this
motif is necessary and sufficient for vascular develop-
ment and the prediction of endothelial enhancers with
in the genome. Saulius Sumanas then showed us ex-
periments characterizing NF-ATc as an endocardial
specific marker in zebrafish and demonstrated that
hedgehog and Etsrp signalling is required for endocar-
dial formation. Shane Herbert proposed a novel mode
of blood vessel formation, whereby Efnb2-mediated
directional control of angioblast sprouting behaviour and sprout termination drives arterial/venous segregation and generation of separate parallel vessels from a common precursor vessel. Katharine Yutzey explained microarray, expression and in vitro experiments which suggest Wnt signalling is a critical regulatory pathway in heart valve remodeling and the pathogenic induction of gene programmes leading to the calcification of valve interstitial cells. In the last talk dedicated to valve development, Jose-Luis de la Pompa presented evidence that endocardial Notch1 works in combination with myocardial signals to promote and regulate EMT in presumptive valve forming regions.

The ultimate platform presentations of the meeting covered the topics of "Migration and Mechanics" with Joseph Yost chairing the session. Ryan Udan considered the cellular mechanisms which may be regulated by the haemodynamic force generated by blood flow during vascular remodelling. Using mouse yolk sac as a model he presented preliminary data that suggests that endothelial cell migration and not cell survival or proliferation is the primary mechanism involved. Rusty Lansford told us about some of the computational biology approaches, such as individual cell tracking and 4D reconstruction, that he is undertaking in wild type and transgenic quail embryos to understand spatiotemporal patterning of endothelial cells. Karen Occor described her optical method for analyzing and quantitating heart contraction in Drosophila and the zebrafish, both small genetically tractable models which should allow a rigorous analysis of genes involved in heart beat function and contractility. Continuing this theme, Neil Chi explained the in vivo optical mapping/calculator imaging techniques he has used in zebrafish mutants to determine if cardiac conduction can influence cardiac morphogenesis. His results suggest that cardiac electrical forces can indeed act as an epigenetic factor in cardiac morphogenesis and remodeling. Lastly, Sonia Nowotschin spoke about her progress in developing a new photoconvertible fluorescent protein Kikume Green-Red for use in transgenic ES cell and transgenic mouse lines for non-invasive selective cell labelling and fate mapping in vivo and live imaging of cell migration and behaviour.

Lunch once again was taken outside in the continuing glorious weather before a quick presentation for the Weinstein 2010 meeting which left us all looking forward to a trip to Amsterdam next year! We then reconvened for the final two workshops of the meeting. This time the choice was between "Stem Cells and Progenitors" and "Heart Fields and Lineages". The latter session was very relevant to my own interests and so I went to hear Deb Yelon, Vincent Christoffels and Robert Kelly speak about their work in this area of cardiac research. Deb Yelon gave a thought provoking presentation covering the work her lab is doing to answer 3 basic questions regarding regulation of heart size in zebrafish; 1.) Why does an individual cell committing to a specific cardiac lineage? 2.) What sets the number of cells in the cardiac progenitor cell pool? 3.) How do cardiac lineages diversify? In discussing these questions she alluded to the role of hedgehog signalling in cardiac competence, regulation of Hox5b by RA signalling from the forelimb field to limit heart field size and finally separate requirements for Fgf8 and Isl1 in the development of the arterial and venous poles of the zebrafish heart. Vincent Christoffels then spoke about the different roles of Tbx18, Tbx3 and Tbx2 in the development of the conduction system. Robert Kelly finished the session discussing his work on the identification of Notch pathway effector Hes1 as a regulator of SHF development. His data shows Hes1 null mice have SHF defects which may be attributed to derepression of Hes1 targets such as cell cycle regulatory genes and the consequent up-regulation/ectopic expression of p27kip1 which leads to cell cycle arrest and decreased SHF proliferation.

The second poster session followed the workshops and was as animated and popular as the first, with everyone taking the final opportunity to speak to authors of posters of interest. Then it was time for the main social event of the conference, the meeting banquet, which was held in the Carnelian Room, on the 52nd floor of 555 California St. This setting gave a panoramic view on all sides of the city of San

Sunset over San Francisco Bay viewed from the 52nd Floor of 555 California Street
Francisoco and a spectacular sunset. Organizers Benoit Bruneau and Brian Black and members of their labs were on hand to point out local landmarks, not least the Cardiovascular Research Institute and the Gladstone Institute at the University of California campus in SF. A fantastic meal was served, made all the better for us by the arrival of an old friend, starting a postdoc in SF. After dinner, many thanks were given to all those on the local organizing committee whose hard work had produced such an excellent meeting. Then the legendary Eric Olsen and his band "The Transactivators" belted out a selection of classic rock interspersed with the occasional Texan tune as cardiac researchers young and old, celebrated the conclusion of a very successful conference.

Having attended a Weinstein meeting, I now understand the rave reviews colleagues had given them in the past. The standard of all the talks had been incredibly high and the many fields of cardiac developmental research were covered in amazing depth for a meeting of just two and a half days. It was great to hear more junior scientists talking about their work, whilst the workshops allowed us also to hear from established PI's in the field. The friendliness and interest of everyone at the meeting could not be bettered, the poster sessions were truly a chance to interact with all the other attendees and the venue and logistics for the meeting were among the best I have experienced. I could easily have left my heart in San Francisco, but luckily there is the 2010 Weinstein meeting in Amsterdam to look forward to (http://weinstein.heartrepair.eu/). I will certainly be booking my place well in advance!

Sunset over the Golden Gate Bridge

*The Bulletin Book Reviews*

We would like to make book reviews a regular feature of The Bulletin. Anyone interested in reviewing the following title should contact the editors. In return, the review author may keep the book afterwards.

*Handbook of Venous Disorders 3rd Ed*

by Hodder Education

Officially the largest medical meeting in Europe, the European Society of Cardiology (ESC) Congress was this year held in Barcelona. The ESC was founded in 1950 and its first General Assembly was held during the World Congress in Paris in the same year. Initially, the ESC Congress was held every four years, organised each time by a different National Society, until 1988. Since then it has been an annual event. This year, there was an average of 30,000 attendants overall each day of the five day meeting held in the Fira Gran Via conference centre in the Hospitalet area of Barcelona. More than 2,000 scientific abstracts were presented across the duration of the Congress representing the latest research by investigators worldwide.

Prevention was the main focus of this year's meeting. A symposium entitled 'La Dolce Vita' presented research into the effects of diet and exercise on the heart. 'Olive oil, berries and chocolate' was the title of Michel de Lorgeril's (Grenoble, France) talk, which was based on cardioprotective diets. In fact, he informed us it is only the Mediterranean diet which is associated with low CHD risk, as shown by the Lyon Diet Heart Study. Foods such as olive oil, berries and chocolate are rich in polyphenols, yet little data had previously existed which showed any correlation between polyphenol intake and the incidence of coronary heart disease. The group investigated effects of a special anthocyanin-rich diet of corn seed powder on the infarcted heart, where infarction was created by performing coronary ligation. Subsequent observations included a lower body weight compared to controls, in addition to decreased infarct size. An increased myocardial resistance was observed overall, however the diet had no significant effect on endothelial function. Another study performed by the same group assessed effects of diet in relation to alcohol intake. As we are all aware, excessive alcohol consumption can lead to brain damage. The effects of alcohol on the brain were studied in the presence or absence of an anthocyanin-rich diet. It was shown that anthocyanins had a protective effect, by preventing an increase in deleted mitochondrial DNA in the brain, as measured by real-time PCR. One could hypothesise from this that changing our eating habits would help retain one's drinking habits. Another talk which focused on prevention was based on the impact of exercise on cardiac and vascular cell biology, presented by Volker Adams (University of Leipzig, Germany). He described the effects of different types of exercise on heart muscle and endothelium in several animal models. Beneficial effects on the heart that were noted included an increase in SERCA, improved calcium handling and up-regulation of heat shock proteins. In the endothelium, increased NO production was seen, thought to be a result of increased eNOS phosphorylation, in addition to a decrease in potentially harmful reactive oxygen species.

Ketil Lunde (Oslo, Norway) presented some interesting data on the pre-treatment of cells and tissues for optimal stem cell therapy. Stem cell therapy post-MI normally results in poor cell retention, high mortal-
ity and limited potential for cells to differentiate in vivo to cardiac cells. His message was that more successful cell therapy is required for improved homing, delivery and engraftment, by using pre-treatments such as genetic engineering or growth factors, or mechanical stimuli such as pre-conditioning and shock wave treatment. He gave an informative overview of some of these methods and the benefits seen so far. A study using mesenchymal stem cells (MSCs) engineered to over-express the protein kinase AKT1 was seen to prevent remodelling in a rat infarct model, improved LV function and led to a decrease in infarction size. However, a drawback of this is that permanent over-expression could be problematic due to the oncogenic properties of AKT and the possibility of neoplasia and tumourgenesis. Furthermore, MSCs incubated with SDF-1 (involved in homing) in a rat MI model led to increased cell retention, a reduction in apoptosis and increased AKT. Another method described was that of hypoxically pre-conditioning cells, by culturing under hypoxia - when used in an infarct model they increased homing to ischaemic myocardium and improved left ventricular function.

Stefanie Dimmel (Frankfurt, Germany), presented a wealth of data on progenitor cells and their role in the vessel wall. Stefanie described vessel-associated stem cells as reservoirs for repair, yet the fate of stem or progenitor cells once injected is relatively unknown, i.e. do they become integrated into vessels or just associated with vessels and just produce paracrine effects? Using a model of selective deletion of bone marrow cells or EPCs using the suicide gene gancyclovir, the cells of interest were deleted two weeks after injection and effects such as impaired heart function and vascularisation were noted. Therefore such progenitors can physically contribute to maintenance of cardiac function and neovascularisation, and this technique could be applied to detect the contribution of different progenitor lineages.

One of the State of the Art sessions in basic science was on the subject of the use of microRNAs as therapeutic targets in the cardiovascular system. MicroRNAs are short strands of non-coding nucleotides, which are important regulators of gene expression, having an ability to degrade mRNA and inhibit translation. Zhiguo Wang (University of Montreal, Canada) discussed the role of miRNAs in atrial fibrillation and demonstrated the importance of miR-328 and miR-101 and the possibility of their use in therapies. Thomas Thum (Julius Maximilians University, Wurzburg, Germany) discussed the benefits of miRNAs in cardiac hypertrophy and heart failure by controlling miRNA-21 expression in the failing heart, leading to prevention in fibrosis and hypertrophy, as well as functional improvement, reduced heart weight and cardiomyocyte size. Thomas also showed how miR-24 expression increased in endothelial cells post-MI, as well as under hypoxic conditions. MiR-24 was found to target an abundance of angiogenic genes which could be used therapeutically post-MI.

One of the most interesting sessions discussed recent developments in plaque imaging technologies which may help provide considerably more information on plaque stability and content. Takashi Akasaka (Wakayama Medical University, Japan) reviewed some intravascular imaging modalities which are currently available or in development. Imaging methods employed in combination with intravascular ultrasound include gray scale, integrated backscatter and virtual histology; others, namely elastography (detects the amount of strain the vessel is under) and palpography (assesses the lo-
cal mechanical properties of tissue using intraluminal pressure) are not yet commercially available. However, it is thought that optical coherence tomography (OCT) may prove more beneficial than IVUS in plaque imaging, due to its ability to detect ulceration of ruptures at a higher rate, in addition to thrombus identification, plaque macrophage accumulation and spotty calcification.

James Thomas (Cleveland Clinic Foundation, Ohio) presented work performed in collaboration with GE, Siemens and Philips, and discussed how difficult it is to diagnose a vulnerable plaque, or indeed to recognise an unstable plaque. He questioned the precursors of plaque stability and how reliable these are as markers, and when a plaque may be deemed as 'vulnerable' before becoming unstable. Ideal imaging methods would therefore provide info regarding its structure, content and activity. The more widely used imaging technologies have their limitations, and cannot assess plaque activity. Myocardial contrast echocardiography (MCE) is a technique where microbubbles act as surrogates for red blood cells and can be targeted to particular cells by conjugation to antibodies such as ICAM-1, VCAM-1 and p-selectin (post-ischaemia). The gas-filled microbubbles are inert and remain entirely within the vascular space, possessing an intravascular rheology similar to that of red blood cells. So far it appears very sensitive, in that it can detect markers in vivo at 10 weeks - considerably earlier than when plaque size may become significant.

Another informative presentation related to imaging of the vasa vasorum was given by Anton Van der Steen (University Medical Centre, Rotterdam). It is well known that neovascular vasa vasorum plays a role in inflammation and intra-plaque haemorrhaging, thereby implicating a role for vasa vasorum in atherosclerosis progression. Anton showed how more information can be gained about the vasa vasorum by assessing vibration patterns in microbubbles created by using ultrasound contrast agents at high frequencies. One can discriminate bubbles from tissue by pulse inversion, where linear reflection represents the tissue, and presence of the bubbles is shown by non-linear reflection of the pulse. From this, factors such as intensity, area, flow pattern and flow direction can be determined, yet technical issues still remain (interestingly, pulse inversion is also used by dolphins to recognise fish).

Overall, there were unfortunately too many interesting sessions to attend, and not enough time to do it in (it may have had something to do with the enormous size of the conference centre and the number of miles it was to get to each destination!). The exhibition area covered most of the ground floor, with many interactive activities, freebies and even the odd free back massage thrown in for good measure - which had to be taken advantage of, obviously. There were poster sessions twice each day, in addition to the moderated sessions (of which there were some twenty-five winners that I will not list here!). On Monday evening, a poster session organised by the Council on Basic Cardiovascular Science was held, as a chance for scientists to meet and share knowledge in a more informal environment, accompanied by a drinks reception. The Council was created in September 2004 to enhance the importance of basic science to clinical cardiology. A number of awards were presented on the evening, by Axel Pries, vice-chair of the Council. The winner of the Norman R. Alpert Visiting Scientist Award was Balazs Horvath from Debrecen, Hungary. This prestigious award allows a European scientist to join a US laboratory for one year as a visiting scientist. The Outstanding Achievement awardees Kai Wollert and Stefan Engelhardt accept their prizes at the Basic Science poster reception.
ing Achievement award was open to those involved in basic research who has recently established themselves as independent investigators. This prize was awarded to Kai Wollert and Stefan Engelhardt, both from Germany, who received a plaque and a monetary prize of 3,000 Euros. The winners of this year's Young Investigators and Moderated Poster received their certificates at a joint ceremony on the final day of the meeting. The awards were presented by Professor Fausto Pinto, Chairman of the Congress Programme Committee. The winner of the Young Investigator's award in basic science was Samuel Sossalla (Goettingen, Germany), who presented data showing that atrial fibrillation leads to electrical remodelling of sodium currents, and also concluded that the drug ranolazine had beneficial effects on atrial fibrillation and arrhythmias by improving diastolic function.

Next year's congress will take place from 28th August to 1st September in Stockholm, which I believe will be another fantastic meeting if the location is anything to go by.

Forthcoming Cardiovascular Meetings

American Heart Association Scientific Sessions 2009 will be held in Orlando, Florida, USA on 14th-18th November. For further information, please visit http://scientificsessions.americanheart.org/portal/scientificsessions/ss


XX World Congress of the International Society for Heart Research Kyoto 13-16 May 2010. For further details, please visit: http://www.ishrworld.org/. For details of the European Section symposium, see http://www.ishr-europe.org/

“Frontiers in Cardiovascular Biology” First Meeting of the Council on Basic Cardiovascular Science of the European Society of Cardiology will be held on 16th-19th July 2010, Berlin, Germany. Further details may be obtained from: www.escardio.org/congresses/cardiovascular-biology/

Next year's European Society of Cardiology Congress will be held in Stockholm from 28th August to 1st September 2010 including a spotlight on "Coronary Artery Disease: from Genes to Outcome". Details can be obtained from http://www.escardio.org/Pages/index.aspx

Travel Reports for The Bulletin

The Bulletin editors look forward to publishing travel reports written by BSCR members. These can be on any conference, course or laboratory visit of interest to other members and could perhaps contain photographs. If you are planning to travel to a relevant cardiovascular meeting and would like to write a report for The Bulletin, please contact the editors beforehand. A bursary of £300 is available towards the cost of your visit which will be provided on receipt of the report.

Bon voyage!


**British Heart Foundation Grants**

**Infrastructure Grants**
Professor S Plein, University of Leeds. "Funds towards the purchase and installation of a new 3T cardiac magnetic resonance scanner" £500,000

**Special Project Grants**
Professor J E Deanfield et al, ICH, University College London. "The impact of adiposity on risk profiles and the emerging arterial phenotype in the young" 6 months £115,604

Wellcome Trust "Biobank Consortium" 2 years £1,000,000

Medical Research Council "MRC/NPRI Phase 3: Translational Research" 5 years £1,000,000

**Programme Grants**
Professor A H Baker et al, University of Glasgow. "Integrating virology and vascular biology: development and evaluation of the next generation systems for genetic manipulation of the vessel wall" 5 years £1,036,054

Professor A C Newby, University of Bristol. "Vulnerable atherosclerotic plaques, foam cell phenotypes and extracellular proteinases" 5 years (renewal: years 16-20) £714,569

Professor S P Watson et al, University of Birmingham. "Mapping and functional investigation of genetic mutations in patients with mild, platelet bleeding disorders" 5 years £1,365,733

**Cardiovascular Related Wellcome Trust Grants**

**Programme Grants**
Prof Zhengming Chen Unit & Epidemiological Studies Unit, Radcliffe Infirmary, Oxford "The Kadoorie Biobank study". Clinical Trial Service 60 months £2,500,000

Dr Edward D Sturrock Dept of Medical Biochemistry, Medical School, University of Cape Town Observatory South Africa "Characterisation of a C-domain-selective ACE inhibitor's efficacy in the context of myocardial infarction". 12 months £103,499

**Project Grants**
Prof Joanna M Wardlaw Dept of Clinical Neurosciences, Western General Hospital, University of Edinburgh "Blood brain barrier dysfunction and cerebral small vessel disease". 36 months £374,777

Dr Anna David Department of Obstetrics & Gynaecology, Institute for Women's Health "Does uterine artery delivery of adenovirus VEGF increase uterine blood flow and birthweight in growth restricted fetal sheep?" 24 months £327,039

**Technology Development Grant**
Prof Charlie N Ironside Electronics & Electrical Engineering, University of Glasgow, Scotland "Non-cryogenic integrated optical magnetometers for magnetocardiography (MCG) and magnetoencephalography (MEG)". 36 months £354,019

**Masters Fellowships In Ph&tm**
Ms Kerryn van Veen Institute of Infectious Diseases & Molecular Medicine, University of Cape Town, South Africa "Immunological investigation of pericardial tuberculosis". 18 months £29,917
Joint BSCR/British Atherosclerosis Society
Late Spring Meeting 2010
with the British Cardiovascular Society
"New Frontiers in Cardiovascular Research"

DATES: Monday 7th and Tuesday 8th June, 2010

VENUE: Manchester Central Conference Centre, Manchester

ORGANISERS: Dr Derek Hausenloy and Dr Manuel Mayr

Programme: The programme will consist of state-of-the-art presentations by leaders in the field. Speakers will include: Jake Lusis (Los Angeles, USA), Manuel Mayr (London), Jenny van Eyk (Boston, USA), Andrew Pitt (Glasgow) Rob Gerszten (Boston, USA), Julian Griffin (Cambridge), Patrick Vallance (GlaxoSmithKline, UK), Lars Sundstrom (Bristol, UK), David Crossman (Sheffield, UK), Peter Weissberg (British Heart Foundation), Stefanie Dimmeler (Frankfurt, Germany) and GR De Meyer (Antwerp, Belgium).

Free Communications: There will be 11 oral presentations of selected abstracts, six of which will be selected for the Joint BSCR/BAS Early Career Investigator Award. A poster prize will also be awarded.

Student Bursaries: The BSCR will consider awarding travel grants of up to £200 to BSCR members who are bona fide students and application forms are available from the BSCR website (www.bscr.org).

Full programme details will be downloadable from the BSCR website shortly (www.bscr.org) and will be published in the January 2010 issue of The Bulletin. Enquiries may be addressed to the organisers, Derek Hausenloy (d.hausenloy@ucl.ac.uk) or Manuel Mayr (manuel.mayr@kcl.ac.uk).