The Bulletin

of

The British Society for Cardiovascular Research

Registered Charity Number: 1011141

Vol. 22 No. 3
July 2009

www.bscr.org

The Bulletin

The Publication of The British Society for Cardiovascular Research

Contents

Editorial

Welcome to the July 2009 issue of *The* Bulletin! We hope our readers are enjoying the summer, even if the British weather has rather let us down.

Our review article for this issue has been written by Professor Graeme Nixon from the University of Aberdeen. Profesor Nixon elegantly summarises the importance of sphingolipids and their recptors in the vascular system, both their physiological roles and potential pathophysiological involvement.

It appears conference season is well and truly upon us and, for those of us left behind to endure the British "summer", an opportunity to read about some of the highlights of this year's major cavdiovascular meetings in our many travel reports. Catherine Risebro recounts proceedings at the Keystone symposium on "Cardiac Disease: Development, Regeneration and Repair" in North Carolina while Samantha Passey and Abigal Rickard share with us their experiences at "Heart Failure 2009" in delightful Nice. As consolation for those who haven't travelled, it rained for half of Catherine's trip and Nice was wetter than the UK in June. But we suspect the story for July was somewhat different!

We hope your next meeting will be one of our own. "Myocardial Energetics and Redox in Health and Disease", the BSCR Autumn meeting in Oxford, promises to be outstanding. We look forward to seeing many of you there.

Helen Maddock and Nicola Smart

Sphingolipids and the vascular system

by Graeme F. Nixon

School of Medical Sciences, University of Aberdeen

In recent years it has become apparent that one group of lipids, the sphingolipids, have particular relevance to the vascular system (Peters & Alewijnse, 2007; Takuwa et al, 2008). Several studies have now demonstrated that sphingolipids are naturally occurring in plasma and are increased in serum (Okajima, 2002). In addition, a family of selective sphingolipid membrane receptors have been cloned and are expressed on both endothelial and vascular smooth muscle (VSM) cells, as well as on many blood-borne cell types (Pyne & Pyne, 2002). Recent research has uncovered many different roles for sphingolipids in the vascular system. These include fundamental roles in vascular development, regulation of normal physiological functions in both endothelial cells (such as nitric oxide (NO) production) and VSM cells (effects on contractility), and potential roles in pathophysiology (VSM cell proliferation, inflammation). Uncovering this wide array of effects on the vascular system has led to a complex picture of vascular regulation which is not yet fully understood. This review will focus predominantly on the sphingolipid most studied to date, sphingosine 1-phosphate (S1P). Space constraints do not permit in depth analyses of all aspects of sphingolipids in the vascular system and, therefore, only some of the potential sphingolipid effects are highlighted below.

The Sphingolipid Metabolism and Sphingolipid Receptors

Sphingolipids are predominantly derived from sphingomyelin, an abundant lipid with a sphingoid backbone present in the plasma membrane of eukaryotic cells. The "sphingolipid cycle" is a cascade which results in the formation of several different sphingolipid species (see figure 1). Typically this cascade is initiated by activation of the enzyme sphingomyelinase which results in the breakdown of sphingomyelin to ceramide (Machesini & Hannun, 2004). Sphingomyelinase can be activated by a variety of stimuli including growth factors and cytokines (Goni & Alonso, 2002). Once formed, ceramide can be further metabolised to sphingosine and ultimately to S1P via phosphorylation of sphingosine by sphingosine kinase (SK) (Alemany et al, 2007). S1P metabolism occurs through dephosphorylation (by sphingosine phosphatase) to sphingosine. Alternatively, S1P can be removed from the sphingolipid cycle following degradation by S1P lyase.

It is generally assumed that S1P effects occur by paracrine and/or autocrine action via transport of intracellular S1P (passive or otherwise) to the outside of the cell (Rosen & Goetzl, 2005). A compelling argument for an extracellular action of S1P was the identification of a family of 7-transmembrane, G-protein-coupled receptors with high affinity for S1P (Sanchez & Hla, 2004). Other sphingolipids have lower affinity at these receptors. Originally cloned from endothelial cells (and termed endothelial differentiation gene receptor, or EDG) (Sanchez & Hla, 2004), the S1P receptor family consists of five subtypes, $S1P_{1\text{-}5}$. Almost all mammalian cells express at least one subtype of $S1P_1$, $S1P_2$ or $S1P_3$. $S1P_4$ and $S1P_5$ have a more focussed cell-type specific expression pattern and are less well documented (Meyer zu Heringdorf & Jacobs, 2007). As in other receptor families with high structural homology, differences in functional responses to receptor activation occur through alternate intracellular signalling pathways. $S1P_1$ is coupled to activation of the heterotrimeric G-protein subunit,

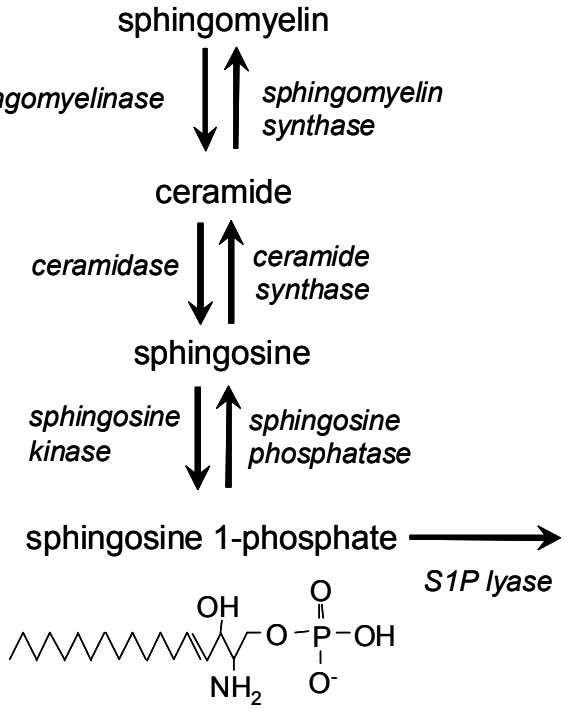

Figure 1: The intracellular synthesis and degradation of sphingosine 1-phosphate (S1P).

Gαi, whereas $S1P_2$ and $S1P_3$ are predominantly coupled to Gα12/13 and Gαq (Windh et al, 1999). $S1P_1$ can activate mitogen-activated protein kinase isoforms and also activates Rac, a monomeric G-protein associated with cell migration. $S1P_2$ and S1P3 activation leads to increases in intracellular Ca^{2+} and activation of the monomeric G-protein, RhoA (involved in regulation of the actin cytoskeleton and VSM contractility) (Sanchez & Hla, 2004). Several other signalling pathways have also been reported. The ultimate effects on cell behaviour are therefore regulated by the relative expression of each S1P receptor subtype expressed in a particular cell type. In the vascular system, VSM cells express $S1P_{1-3}$ although this varies with the vascular bed examined (Peters & Alewijnse, 2007, Coussin et al, 2002). Endothelial cells express predominantly $S1P_1$ and $S1P_3$ although this is also dependent on vascular bed (Panetti, 2002).

Source of Sphingolipids in the Vascular System

S1P occurs in plasma under normal conditions at an estimated concentration of 200nM (Yatomi et al, 1997). Approximately 60% of this is bound to lipoproteins (Okajima, 2002). Recent studies have shown that the S1P levels in plasma are probably regulated by erythrocytes (Hänel et al, 2007). Erythrocytes do not express S1P lyase or sphingosine phosphatase and therefore can accumulate higher concentrations of S1P than most other cell types. Erythrocytes are required for maintenance of plasma S1P levels although the mechanism of this regulation is not yet clear.

An important discovery that highlighted the intimate relationship between S1P and vascular function was that S1P concentrations were increased in serum, to around 900nM (Yatomi et al, 1995). This increased S1P in serum is released from platelets, which have a high basal sphingosine kinase activity and, as in erythrocytes, do not express S1P lyase (Tani et al, 2005). This results in a significant increase in the local S1P concentration and, if the site of platelet activation is adjacent to disruption of the endothelial cell layer, S1P could have direct access to VSM cells.

Effects on vascular function - angiogenesis

The essential role for S1P in vascular development was revealed using S1P receptor knockout mice. In $S1P_1$ -/- mice, the resultant phenotype is embryonic lethal (Liu et al, 2000) whereas $S1P_2$ and $S1P_3$ knockout mice are viable with moderate phenotypes not obviously related to cardiovascular development (Brinkmann, 2007). Embryonic lethality in the $S1P_1$ -/- mice is due to a failure of the vasculature to develop properly. Specifically, VSM cells were not recruited to developing endothelial tubules. This suggests that S1P is required for migration of VSM cells during development. Further studies using conditional knockout of $S1P_1$ in endothelial cells only, revealed that such signals to recruit VSM cells to the developing blood vessel are initiated by $S1P_1$ receptor activation in endothelial cells (Allende et al, 2003). Studies have now shown that S1P can induce angiogenesis via $S1P_1$-dependent Rac signalling and also may involve $S1P_3$ (Sugimoto et al, 2003; Lee et al, 1999). This is complicated by other studies where S1P incubation with endothelial cells inhibits angiogenesis and this is probably due to signalling via the $S1P_2$ receptor which leads to Rho activation (Inoki et al, 2006). The ultimate response is therefore likely to depend on the relative expression of S1P receptor subtypes which may

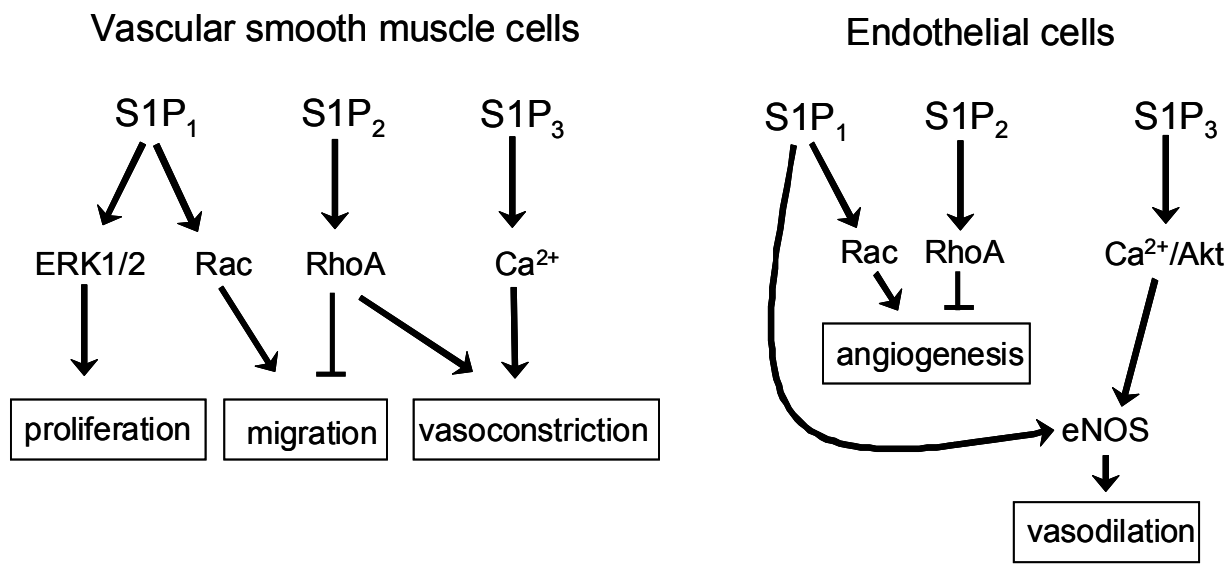

Figure 2: Diagram summarizing some of the effects of S1P receptor activation in vascular smooth muscle cells and endothelial cells. This is not a complete list of S1P effects in the vascular system but serves to highlight the main points raised in this review. Abbreviations: S1P, sphingosine 1-phosphate; ERK1/2, extracellular signal-regulated kinase 1/2; eNOS, endothelial nitric oxide synthase; Akt, protein kinase Akt.

be dynamically regulated depending on environment and vascular bed.

Local angiogenesis is a pathophysiological response to hypoxia following either myocardial infarction or stroke and this could be exploited therapeutically to help perfuse hypoxic tissues (Ferrara & Kerbal, 2005). A recent study has also demonstrated that S1P can induce angiogenesis following hindlimb ischaemia and this consequently improves blood flow recovery *in vivo* (Oyama et al, 2008).

Effects on vascular function -vascular tone

Vascular contractility is regulated by several signalling pathways (Somlyo & Somlyo, 2003). Typically this is initiated by an increase in intracellular Ca^{2+}. Another pathway which also has an important regulatory role in vascular tone is the activation of RhoA and its downstream kinase, Rho-kinase. Rho-kinase inhibits the smooth muscle myosin phosphatase. The consequence of this is an increase in myosin light chain phosphorylation and increased contractility (Somlyo & Somlyo, 2003).

S1P perfused *in vivo* in rats produces a decrease in blood flow in mesenteric and renal vascular beds (presumably due to a vasocontrictor effect) although the mean blood pressure was unchanged (Bischoff et al, 2000). This indicates a selective effect on some vascular beds. S1P can also induce contractility in rat cerebral arteries, probably via the $S1P_2$ and/or $S1P_3$ receptors resulting in an increase in intracellular Ca2+ and RhoA activation (Coussin et al, 2002). However, vascoconstriction is not observed in aorta, probably due to relatively lower expression of $S1P_2$ and $S1P_3$ receptors. In cerebral arteries from $S1P_3$-/- mice, S1P-induced vasoconstriction was greatly reduced (Salomone et al, 2008). In conclusion, S1P does have vasoconstrictor properties, although this is dependent on the blood vessel type. The apparent greater sensitivity of constrictor effect in cerebral arteries may have some physiological relevance. As these arteries are more prone to haemorrhage (subarachnoid haemorrhage), S1P release from platelets may provide a protective mechanism against excessive bleeding via its prolonged vasoconstrictor response.

Paradoxically, there is also evidence that S1P can produce a relaxant effect on blood vessels. This is not a direct effect on VSM cells but is via the

well-described vasodilatory pathways associated with NO (Igarashi & Michel, 2008). S1P can activate the endothelial form of nitric oxide synthase (eNOS) in endothelial cells *in vitro* from different vascular beds. In freshly isolated mouse mesenteric arteries under pressurized conditions, S1P administration produced a relaxation which was not apparent in mesenteric arteries from eNOS -/- mice (Dantas et al, 2003). The activation of eNOS appears to be via the $S1P_1$ receptor (Igarashi et al, 2007). Expression of $S1P_1$ can be upregulated in endothelial cells by vascular endothelial growth factor (Igarashi et al, 2003) and this may represent a mechanism for regulating sphingolipid-dependent relaxation under certain conditions. In addition, it has been suggested that part of the vasodilatory effect of S1P *in vivo* may be from the sphingolipid component of lipoproteins. This includes S1P and the related sphingolipid, sphingosylphosphorylcholine (SPC) (Nixon et al, 2008). The activation of eNOS by sphingolipids bound to lipoproteins was predominantly via $S1P_3$ which produced an increase in intracellular Ca^{2+} and activation of protein kinase Akt (Nofer et al, 2004).

Effects on vascular function - vascular disease

The ability of S1P to induce proliferation in VSM cells provided an indication this could be a mechanism involved in the pathogenesis of vascular disease. This mitogenic effect in cultured VSM cells occurs through $S1P_1$ and subsequent activation of the mitogen-activated protein kinase isoforms, extracellular signal-regulated kinase 1/2 (ERK1/2) (Kluk & Hla, 2001). S1P can also activate ERK1/2 in cerebral arteries (Mathieson et al, 2006). ERK1/2 is closely associated with a mitogenic effect in many cell types. Therefore one possible scenario is that, following acute endothelial cell damage, platelets are recruited to the site and release their contents, which includes S1P. This results in a direct exposure of VSM cells to S1P which can initiate mitogenesis and ultimately result in inappropriate cell proliferation leading to neointimal formation. In addition, the $S1P_1$ receptor has been shown to be up-regulated in human neointimal lesions (Zohlnhöfer et al, 2001) and would further drive the proliferative effect of S1P. However, the differential expression of S1P receptor subtypes, as in other S1P-mediated effects, can influence this mitogenic response. One study has reported in $S1P_2$ -/- mice that neointimal formation following carotid artery ligation is significantly enhanced compared to wild type (Shimizu et al, 2007). This was possibly through an effect on VSM cell migration as $S1P_2$ would normally inhibit migration by activating the RhoA pathway. From the above studies, it is possible to envisage the therapeutic benefits of blocking $S1P_1$ or upregulating (or stimulating) $S1P_2$ on VSM cells following acute vascular injury.

Several studies have now shown that, despite evidence indicating S1P may increase neointimal formation, it may conversely also have beneficial effects in atherosclerosis. S1P improves endothelial cell survival *in vitro* (Kimura et al, 2003). In addition, treatment of macrophages with S1P results in a decreased release of inflammatory cytokines via an inhibition of the pro-inflammatory transcription factor, nuclear factor-κB (Hughes et al, 2008). As discussed above, S1P bound to lipoproteins can induce release of NO from endothelial cells via $S1P_3$. Specifically, this effect is observed with high density lipoprotein (HDL) and its associated sphingolipid component, suggesting that some of the anti-atherogenic properties of HDL may be due to bound S1P. The S1P component of HDL can also decrease vascular smooth muscle cell migration (Tamama et al 2005).

The apparent contradictory findings of S1P inducing both pro- and anti-atherogenic effects have still to be resolved. However S1P receptor-mediated effects may still provide a positive therapeutic target in vascular disease. Some studies have assessed the suitability of a novel S1P receptor agonist, FTY720 (Lynch & MacDonald, 2008), in animal models of atherosclerosis. FTY720 is a prodrug, phosphorylated *in vivo* by sphingosine kinase, which has immunosuppressive properties and is a high-affinity agonist at $S1P_1$, $S1P_3$, $S1P_4$ and $S1P_5$ but not $S1P_2$. In two different *in vivo* mouse models of atherosclerosis (LDL receptor-deficient mice and Apolipoprotein E (ApoE)-deficient mice, both fed high-cholesterol diets) treatment with FTY720 significantly reduced atherosclerotic lesion formation (Nofer et al, 2007, Keul et al, 2007). Various markers of inflammation were also significantly reduced, including blood lymphocyte count, plasma concentration of pro-inflammatory cytokines such as tumour necrosis factor-α and interleukin-6 and

decreased macrophage content in lesions. The latter effect on macrophage content is possibly via a $S1P_3$-induced decrease in monocyte chemoattractant protein-1 release. In contrast to these studies showing a beneficial effect of FTY720, another recent study in ApoE-deficient mice on a normal diet (not high cholesterol) administered with FTY720 displayed a more pro-atherogenic lipid profile (particularly an increase in very low density lipoprotein) with no change in atherosclerotic lesion development (Klingenberg et al, 2007). Further studies will be required to explain these differences and ultimately determine the therapeutic benefit of FTY720 in atherosclerosis. Partly this may be due to differential effects on the subtypes of S1P receptors and associated signalling. Studies also suggest that, as phosphorylated FTY720 is a high affinity ligand at S1P receptors, it may act to down-regulate those receptors thereby having an overall inhibitory effect (Matloubian et al, 2004).

Conclusions

There is now no doubt that sphingolipids and S1P receptors have important regulatory roles in the vasculature. These roles include vascular development, regulation of vascular tone at the level of endothelial cells and vascular smooth muscle cells, in addition to possible roles in the pathogenesis of vascular disease. The growth in information regarding these lipids and associated receptors serves to further underscore their relevance to the vascular system and will lead to novel therapeutic targets in atherosclerosis. Ultimately, as is likely to be the case with FTY720, these may be based on preventing S1P-induced vascular inflammation.

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Secretary's Column

This year's Autumn Meeting will be in Oxford on the 7th and 8th of September. Organised by Barbara Casadei, Kieran Clarke and Saadeh Suleiman, the topic is "Myocardial Energetics and Redox in Health and Disease". They have invited an absolutely top-notch array of speakers; full details of the programme can be found on the Society's website and elsewhere in this issue of the Bulletin. The Society's Annual General Meeting will also be held during the Autumn Meeting, on 8th September at 12:30 pm.

Once again, we have received a large number of abstract submissions and Barbara, Kieran and Saadeh are busy assigning them to oral or poster presentation as appropriate. Authors should hear from them very soon, but meanwhile I would like to take this opportunity to thank all those who submit work for our meetings. Our Society depends for its growth and vitality on cardiovascular researchers, especially younger ones, using our meetings as an opportunity to share their work with their peers and to give us all a glimpse of the new directions the field will be taking.

I look forward to seeing you in Oxford.

Chris Jackson

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Volume	*Date*	*Deadline*
22 (4)	***October 2009***	*1st September*
23 (1)	***January 2010***	*1st December*
23 (2)	***April 2010***	*1st March*
23 (3)	***July 2010***	*1st June*

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Autumn Meeting 2009

Myocardial Energetics and Redox in Health and Disease

Medical Sciences Teaching Centre, South Parks Road, Oxford, UK

Monday 7th September

11:00 - 13:00 BSCR committee meeting

12:30 - 13:45 Lunch and registration

13:45 - 14:00 Welcome: Prof Barbara Casadei

14:00 - 15:30 **Substrate Metabolism I**

Chair: Prof Kieran Clarke and Dr F Karpe

14:00 A molecular view of diabetes

Prof Fran Ashcroft (University of Oxford)

14:30 Free communication

14:45 Free communication

15:00 AMPK: Regulating energy metabolism?

Prof Dave Carling (Imperial College, London)

15:30 - 16:00 Break

16:00 - 17:00 **Substrate Metabolism II**

16:00 Free communication

16:15 Free communication

16:30 PPAR in cardiac physiology and disease

Dr Antonio Vidal-Puig (University of Cambridge)

17:00 - 19:00 Posters and wine reception

19:30 Conference dinner at Trinity College

Tuesday 8th September

09:00 - 10:30 **Myocardial Energetics and Redox in Health and Disease I**

Chair: Prof Barbara Casadei and Prof Stefan Neubauer

09:00 Redox-regulation of phosphorylation in the CV system

Dr Phil Eaton (King's College, London)

09:30 Free communication

09:45 Free communication

10:00 HIF1α and metabolism

Prof Peter Ratcliffe (University of Oxford)

10:30 - 11:00 Break

11:00 - 12:00 **Myocardial Energetics and Redox in Health and Disease II**

11:00 Free communication

11:15 Free communication

11:30 Mitochondrial control of myocardial calcium handling and redox signalling

Prof Andrew Halestrap (University of Bristol)

12:00 - 12:45 BSCR annual general meeting

12:45 - 14:00 Lunch

14:00 - 15:30 **Translational Aspects I**

Chairs: Prof Ajay Shah and Prof Saadeh Suleiman

14:00 Redox signalling, ROS damage and clinical trials of coenzyme Q-like molecules in the treatment of disease

Dr Michael Murphy (University of Cambridge)

14:30 Free communication

14:45 Free communication

15:00 Myocardial energetics as a therapeutic target

Prof Michael Frennaux (University of Birmingham)

15:30 - 16:00 Break

16:00 - 17:00 **Translational Aspects II**

16:00 Free communication

16:15 Free communication

16:30 Reductive stress: a new player in human cardiomyopathies

Prof Ivor Benjamin (Salt Lake City, US)

17:00 Announcement of prize winners and close of meeting

Keystone Symposium "Cardiac Disease: Development, Regeneration and Repair"

15th-20th March 2009, Grove Park Inn, Asheville, North Carolina, USA

A travel report by Catherine A. Risebro

Grove Park Inn, Asheville

This year's Keystone Symposium for cardiovascular development and disease was located in the Blue Ridge Mountains in western North Carolina. It was somewhat bizarre to attend a Keystone meeting with no skiing and no hint of snow, although there was beautiful scenery in abundance to inspire us all. Once the rain had stopped at least. The meeting was held at the Grove Park Inn, an imposing structure built in 1913 from granite boulders and modelled after the great railway hotels of the West. Being transatlantic visitors we arrived a day early and were able to take advantage of some of the hotel's fine facilities including indoor tennis courts and 'The Spa' (proudly ranked 13th hotel spa worldwide) with its underwater music and plunge pools.

The meeting proper began on Sunday evening with a single talk, the keynote address from George Daley entitled Reprogramming and Stem Cells: Prospects for Clinical Applications. He began by discussing the dangers of stem cell therapy and unscrupulous entrepreneurs who would take advantage of desperately ill patients. The need to put into place strict quality controls and standards across the field to ensure responsible translational stem cell research and clinical application was emphasised with particular reference to the study of 'faithfully' reprogrammed, rigorously tested induced pluripotent stem (iPS) cells. He went on to describe some of his group's work generating patient-specific iPS cell lines that can be used as models to study hereditary diseases and cancer, with a future directive of patient directed stem cell therapy.

The first plenary session, Stemness and Cell Fate in Pluripotent Cells, commenced with Gordon Keller speaking about his work on Flk1+ cardiovascular progenitors and their intention to identify other specific markers of the cardiac mesoderm population using both human embryonic stem (ES) cells and iPS cells. He discussed in detail one such marker, Pdgfra (platelet-derived growth receptor alpha), that differentiates cardiac from blood mesoderm. Sean Wu followed with a comparison between ES and iPS cells from the same source, comparing the pluirpotency of each population. Although he observed no difference in the overall capacity to differentiate, maturation and maintenance of cardiac cells generated from iPS cells was impaired and suggests this may be due to inherent, residual epigenetic differences. Cedric Blanpain introduced research into the transcription factor Mesp1 indicating that appropriate transient expression Mesp1 accelerates differentiation of various cardiac lineages, and provided evidence that Mesp1 directly regulates key cardiac transcription factors including Hand2.

The second plenary session was 'Making Myocardium: Lessons from Organogenesis'. Margaret Buckingham began with an elegant study dissecting the FGF signalling pathways in the secondary heart field (SHF) showing that the cardiac

mesoderm is the target of SHF FGF signalling. In addition, she presented a retrospective clonal analysis in the outflow tract (OFT) that demonstrated a common progenitor for the 2nd branchial arch muscles and OFT myocardium, and an intriguing association between the right branchial arch muscles and the aorta, the left with the pulmonary trunk. Jon Epstein discussed the importance of Notch signalling in various aspects of cardiac development including the OFT, valves and the conduction system. In particular, Notch is required in the neural crest and secondary heart field cells for epithelial-mesenchymal transition and smooth muscle differentiation, and the Notch ligand, Jagged1, is required in endothelial cells to set up a Notch-Jagged1 positive feedback loop that induces neural crest differentiation. We then shifted to microRNAs with Deepak Srivastava and a short talk from Caroline Burns. Deepak presented a variety of topics including how miR-1 and miR-133 have opposite effects regulating alternate gene expression pathways during ES cell differentiation and proliferation. Caroline described her work in the zebrafish identifying the cytoskeletal protein adducin3 as a target of miR-143, attributing the miR-143 morpholino phenotype of failed elongation in cardiomyocytes to the inability to appropriately regulate the assembly/disassembly of the actin cytoskeleton.

The topic for Tuesday morning was 'Cardiopoiesis: Cardiac Muscle Cell Creation by Adult and Embryonic Cells', another busy session filled with great talks. Michael Schneider began detailing his work on understanding the mechanisms by which ES cells differentiate down the cardiac lineage and the Sox17-Hhex-Cer1 pathway that appears to act at the point of cardiac commitment from Mesp1/2 positive mesoderm to Nkx2.5 expressing cells. Richard Harvey then discussed his latest work on Nkx2.5 using a hypomorphic mouse model (Nkx2.5-IRES-Cre), particularly highlighting a putative negative role in compartmentalisation of early cardiac mesoderm into myocardium and the pro-epicardial organ, and also their attempts to rescue the hypomorph phenotype to identify variant(s) that confer 'resistance' to mild mutations in this vital gene.

After a short coffee break we heard from Ibrahim Domain about transcriptional profiling of cardiac progenitors, comparing various different populations with an interest in enhancing ventricular muscle formation from ES derived cardiac progenitors. Next, Mark Mercola gave an update on his small molecule screen to identify cardiac inducing factors in human ES cells and whether any of the identified compounds are able to synergise with molecules like nodal and activin, and at what time point during differentiation these molecules act. The session finished with two short talks from Michael Kühl on work on the cell adhesion molecule DM-GRASP/ALCAM/CD166 and non-canonical Wnt signalling in Xenopus and from Frank Conlon who introduced his work on the transcription factor CASTOR and its role in cardiac differentiation at the ventral midline.

The afternoon plenary session entitled 'Injury and Inflammation in Muscle Regeneration' started with Nadia Rosenthal and a plug for the European Mouse Mutagenesis and Phenotyping Program (EUCOMM; www.eucomm.org) where 'you may find the gene of your dreams and not have to knock it out yourself.' Nadia went on to describe the analysis of mouse models that showed how either increased or decreased Notch signalling perturbs cardiac development. She also discussed their work in adult heart observing that Notch signalling is transiently increased after myocardial infarction (MI), and showed that injection of a Notch-activating antibody can improve repair, reduce scar formation and suppress heart failure markers. Ken Poss then presented his work in zebrafish that indicates the endocardium as well as the epicardium has the capacity to support heart regeneration, potentially through the induction of Raldh2 and subsequent sustained retinoic acid production allowing cardiomyocyte proliferation after injury. Elisabeth McNally followed with the role of

Grove Park Inn Spa at Twilight

Myoferlin and its requirement for endocytic recycling to enable skeletal muscle repair and regeneration. Finally, there was a short talk from Santhosh Kumar Ghadge detailing a knockout of the chemokine SDF-1/CXCL12 suggesting it is required for normal cardiac function.

We had the evening free and there was an organised tour and dinner at America's largest home, George Vanderbilt's 250-room Biltmore House. We, however, opted for a delicious dinner on the sunset terrace (it was no longer raining) with a marvellous view over Asheville and the Blue Ridge Mountains.

On the morning of the third day we moved away from muscle with a session on 'Vasculogenesis and Angiogenesis: Developmental Insights and Therapeutic targets' starting with Bob Schwartz speaking about cardiac defects associated with overexpression of Senp2 and rescue by overexpression of Sumo1. Furthermore, he showed that Senp2 suppresses Nkx2.5 activity via desumoylation and provided evidence that defective Nkx2.5 sumoylation may underlie congenital heart disease. Mary Dickinson came next discussing the relationship between and the mutual requirement for blood flow, vessel formation/vascular remodelling and cardiac function. Paul Riley then described his group's latest work on Thymosin β4 in the injured and intact adult heart where it stimulates not only new vessel growth but also cardiomyocyte regeneration, and identified the epicardium as the most likely source of these new cardiomyocytes. The next speaker for this session was Brian Black who described the identification of a highly conserved 44 base pair endothelial-specific enhancer for Mef2c with a Fox:Ets motif bound by FoxC2 and Etv2, both necessary and sufficient for endothelial development. He also showed that there were many conserved Fox:Ets motifs throughout the genome and that they were over-represented in the non-coding regions of vascular genes. The morning ended with two more short talks. Kimberly Cordes spoke about miR-143/145 regulation of quiescent v. proliferative smooth muscle cell state and Mark Tjwa discussed the role of haematopoietic cytokines and placental growth factor in bone marrow progenitor mobilisation.

The next plenary session was 'Myocyte Death and Dysfunction in Heart Failure' begun by Richard Kitsis describing his work on mechanisms of cell death in human disease, in particular the multifunctional roles of ARC, provided evidence that necrosis is in fact subject to regulation. Jon Seidman then spoke about various mechanisms and modifiers of inherited cardiomyopathy. Next, we heard more about micro-RNAs in cardiovascular tissues from Eric Olson. He described a myomiR network involving α/β myosin heavy chain switching and miR-208a/b, miR-499 and Mef2c in heart disease, and a phenotype switching of proliferative and contractile smooth muscle cells in vascular disease involving miR-21, miR-126, miR-143/5 and miR-486. Eric also described work on miR-206 and its role in amyotrophic lateral sclerosis motor neurone disease. We finished with a short talk from Ching-Pin Chang about insights into BAF complex regulation of cardiac growth and differentiation from a Brg1 myocardial knockout.

The penultimate session on Thursday saw a shift from basic science to human clinical trials. 'Cardiac Repair in Human Trials: The Half-Full Cup' began with Andreas Zeiher who detailed prospects of using bone marrow stem cells (BMC) for cardiac repair and has seen that enhanced contractile recovery after BMC injection is confined to patients with failed initial recovery of left ventricular (LV) function. However, he also introduced some longer term clinical trial data that encouragingly suggests enhanced survival in treated patients, even if not directly correlated with significantly enhanced cardiac function. Douglas Losordo spoke about attempts to target the microvasculature in ischaemic tissue repair since capillary density in the infarct border zone is related to infarct size and briefly talked about a phase 2b trial injecting CD34+ EPCs into the ischaemic zone where there is some improvement in function. Joshua Hare spoke about clinical trials with mesenchymal stem cells after MI and Robert Simari spoke similarly about clinical trials using bone marrow stem cells. Stefanie Dimmeler presented work on a microRNA that is upregulated in patients with heart failure, miR-92, and its role in regulation of angiogenesis and vessel patterning via repression of integrin α5, and also suggested that antagomirs may be useful therapeutic agents. Sara Rankin demonstrated that mobilisation of bone marrow progenitor cell subsets is differentially regulated by growth factors that affect their retention and cell-cycle status. She showed that in mice pretreated with G-CSF there is maximal mobilisation of haematopoietic stem cells (HPCs), whereas endothelial progenitor cell (EPC) mobilisation is

Dinner at the Sunset Terrace Restaurant

submaximal and stromal progenitor cells (SPCs) are not mobilised. In contrast, when mice are pretreated with VEGF, mobilisation of EPCs and SPCs is stimulated while HPC mobilisation is suppressed. Clearly, this has implications for development of therapeutic strategies designed to mobilise specific bone marrow cell subpopulations for regenerative medicine.

The final session of this Keystone meeting was 'Get with the System: How Systems Biology is Transforming Biomedicine' starting with Shoumo Bhattacharya whose talk had many parts, the first describing the development of a 3D-MRI high throughput screening facility combining MRI with HREM (high resolution epifluorescence microscopy). He then described various mouse mutants generated by ENU mutagenesis and identification of the mutated genes, including a mouse aptly named 'George' that has a mutations in Tbx1 and recapitulates the pharyngeal arch phenotypes associated with Tbx1 deficiency and Di-George syndrome. He finished by emphasising the importance of maternal diet and the advantages of hybrid vigour! David Hill came next with some fur balls and massive data sets from their considerable efforts to map both the potential and dynamic interactome (via high throughput, large scale yeast-two-hybrid screening) since changes in interactions are important for understanding disease states and genetic basis of disease, and also with a view to using protein interactions to drive future therapies. Frustratingly however, David reported the prediction that despite the volume of data acquired the number of missed interactions was 'somewhere north of 50%'. This was followed by Stuart Cook speaking about genomic approaches to heart disease and his work in rat doing expression QTL mapping and linkage analysis then applying it to a study for LV mass. The secreted extracellular matrix protein Osteoglycin (Ogn) was identified as a candidate regulator of LV mass and may have other roles in the heart, for example, scar formation after MI. The final speaker was Tao Zhong who gave a short talk about identifying small molecules that modulate cardiomyocyte development.

Overall, the meeting was exceptional with a vast list of internationally recognised speakers who presented work of very high calibre with plenty of unpublished, hot off the press results to intrigue and inspire. Much of the work was based around breaching the intersection between stem cells and developmental biology, and further understanding how basic science research is essential to translational research and developing useful therapeutic strategies for heart diseases.

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!

Travel Reports on "Heart Failure 2009"

Joint meeting of the Heart Failure Association of the ESC and the European Section of the ISHR

30th May - 2nd June Nice, France

A report by Samantha Passey, University of Bristol

From 30th May to 2nd June 2009 the Nice Acropolis conference centre in beautiful Nice, France, played host to Heart Failure 2009 - a hugely successful meeting jointly organised by the Heart Failure Association of the European Society for Cardiology and the European Section of the ISHR. The meeting attracted over 4000 delegates from the worlds of clinical and basic science, and provided a stimulating and varied scientific programme with session topics ranging from the signalling pathways and molecular basis of heart failure through to the clinical management of heart failure patients and discussions about heart failure case studies.

The meeting began in earnest on the afternoon of the 30th May, culminating in the Opening Ceremony that evening followed by a drinks reception to kick off the meeting in style. Professor Donald Bers (California, USA) deservedly gave the Janice Pfeffer Distinguished lecture presenting his vast body of work on calcium handling and excitation-contraction coupling in the heart. Following this excellent prize lecture Professors Roberto Ferrari and Inder Anand presented a touching and emotional tribute to the late Philip Poole-Wilson, highlighting his enormous contributions to the field of heart research. This was followed by the HFA Honorary Lecture, presented by Professor Marc Pfeffer (Boston, USA) whose talk about 'The Gap between the Clinician and the Triallist' emphasised the importance of translating the discoveries made in clinical trials into clinical practice, viewing them not only as another publication but as an opportunity to improve the clinical management of heart failure in all patients including those that were outside the original trial.

As a basic scientist, my primary interest is in the molecular signalling mechanisms and cellular processes underlying heart failure and coronary disease. The excellent range of sessions offered at the meeting spanned the full spectrum from basic science sessions at the microscopic and molecular level, through to whole organism studies and clinical topics. In many instances I was spoilt for choice when deciding which sessions to attend!

The first session we attended was a basic science session entitled 'Quality control: autophagy and the proteasome', that focused on the importance of regulated protein degradation in maintaining cardiac function. Amongst the excellent presentations in this session was an interesting talk by Jens Feilitz (Berlin, Germany) on the role of muscle RING-finger (muRF) proteins in heart failure. MuRFs are RING finger E3 ubiquitin ligases and are important for regulating the appropriate degradation of proteins, particularly myosin heavy chains (MHCs). Knockout of MuRF proteins resulted in abnormal accumulation of MHCs in cardiomyocytes, leading to mitochondrial displacement and disruption of EC-coupling in the myocardium.

Following a welcome coffee break complete with delicious French pastries, I chose to attend the late morning session on 'Heart Failure, obesity and diabetes', a joint session organised by the HFA of Europe and the Heart Failure Society of America (HFSA). This popular session presented both European and American perspectives, highlighting the importance of the relationship between obesity, diabetes and heart failure and the growing problem of obesity and diabetes in western culture.

The poster sessions were arranged for each morning and afternoon and were divided into clinical and basic science sessions. Each poster session was lively and popular, and provided a great opportunity for discussion and to meet other researchers from around the world. My poster session resulted in some good feedback and encouragement which I very much appreciated,

The pebbled beach of the Cote d'Azur - on a sunny day!

along with some helpful suggestions on future experiments, and so overall was a useful and stimulating experience.

The final afternoon session on Sunday was 'Hypertrophic signalling: localisation and crosstalk', focussing at the molecular level on the signalling pathways underlying cardiac hypertrophy. In this session, Frank Lezoualc'h (Châtenay-Malabry, France) spoke about the involvement of the protein Epac (Exchange Protein Directly activated by cAMP) in regulating the activity of small GTPases of the Rap family in signalling to hypertrophy. Epac is activated in response to the increased cAMP levels arising from β-adrenergic stimulation, and leads to activation of Rap, signalling through the MAPK cascade and leading to increased myocyte size, altered sensitivity to calcium and cardiac hypertrophy.

Monday morning began with 'Response and adaptation to stress', an informative session with a great selection of talks. This session presented a range of stimulating talks, including some interesting technical aspects from Paul Schumacker (Chicago, USA) on measuring ROS production in different subcellular compartments using targeted expression of a redox sensitive Green Fluorescent Protein (roGFP) produced by Jim Remington in Oregon.

The highly attended session entitled 'EC-coupling: Sparks, waves and leaks' was chaired by Professors Donald Bers and David Eisner. Amongst the excellent lectures in this session, Godfrey Smith (Glasgow, UK) presented his exciting work on dysfunctional calcium release. He explained that there are two aspects to spontaneous release of calcium waves from the SR; they can be considered to be beneficial in terms of maintaining diastolic tone and reducing cellular calcium load, but can also be detrimental by causing delayed after depolarisations and arrhythmias. He went on to conclude that although it had previously been thought that there were different types of calcium waves, that in fact they are all equivalent but vary depending on the basal calcium levels. He also

explained that the activities of SERCA and the RyR differed at varying calcium concentrations which affected the release of calcium as waves, and that this was regulated by CaMK as a mechanism to allow the cell to resist calcium overload.

After lunch I decided to attend an unusual and interesting session entitled 'How-to on new model systems for cardiac disease', that explored alternative models of cardiac function and development. This proved to be a very educational session and attendees were treated to a series of fascinating talks on the use of zebrafish, drosophila and chicken hearts as in vivo models, comparing the hearts of these models with more conventional mammalian models such as rodents. The most memorable one for me was given by Thomas Brand (Würzburg, Germany), investigating the Popeye family of membrane proteins that are expressed in cardiac and skeletal muscle. Deletion of popdc2 resulted in a decrease in sinus node tissue and the development of sinus pauses, an effect that was beautifully demonstrated by some impressive live imaging of calcium fluxes and signal conductance in the zebrafish heart.

The final session on Monday was 'Cytokines - more than just inflammatory mediators', and included a lovely talk from the lab of Bente Pedersen (Copenhagen, Denmark) about the exercise-induced remodelling of cytokines and the production of beneficial cytokines by skeletal muscle in response to exercise training. These muscle cytokines or 'myokines' appear to be produced in response to reactive oxygen species and have a variety of beneficial effects on muscle metabolism, hypertrophy and exercise adaptation. Also in this session was a talk by Denise Hilfiker-Kleiner (Hannover, Germany) about novel cytokines/ chemokines as anti-inflammatory targets. Denise presented some excellent work using mutations in the cytoplasmic tail of the IL-6 receptor gp130 to dissect the different signalling pathways downstream of this receptor. A tyrosine 757 mutation in gp130 abolished ERK signalling downstream of gp130 whilst JAK-STAT signalling was prolonged, and mice with the Y757 mutation showed increased mortality and heart failure following myocardial infarction. Normalising the STAT signalling in these mice resulted in a reduction in cardiac inflammation and improved survival. She concluded that the signalling pathways activated downstream of gp130 must be balanced and that imbalances result in pathological signalling cascades leading to increased inflammation and reduced survival after cardiac insults. It was fantastic to see in one talk how the modification of signalling pathways at the molecule level related back directly to the pathology and disease phenotype.

For me this link between the events at the molecular level and the pathology of heart disease and heart failure in the organism embodied the meeting as a whole, and was reflected in the quality sessions offered at the meeting. I would like to congratulate the organisers on an excellent meeting at Heart Failure 2009. In particular I was impressed with the successful incorporation of a wide range of topics relevant to heart failure from basic science through clinical science, patient care and nursing. The availability of webcasts of selected talks from the meeting on the ESC website after the meeting was a useful additional feature, allowing people to watch presentations from speakers that they may have missed whilst at the meeting. The exhibition area was also very popular, with prominent presence from a number of clinical and pharmaceutical companies as well as companies offering products aimed more at the basic science researchers. Overall the meeting was very successful and I am very grateful for the opportunity to attend, learn more about heart failure and present my work in the form of a poster presentation - I have returned with lots of ideas and some great feedback!

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) or Nicola (N.Smart@ich.ucl.ac.uk)

Joint meeting of the Heart Failure Association of the ESC and the European Section of the ISHR

A report by Abigail Rickard, King's College London

The Nice Acropolis Conference Centre

As the whole of the UK bathed in glorious sunshine on the weekend of 30th May-2nd June, the French Riviera succumbed to overcast skies and on the Monday, was hit by an almighty thunderstorm and unforgiving downpour which left the streets of the beautiful ancient city of Nice glistening. The city was host to the Heart Failure 2009 congress which was co-organised by the Heart Failure Association of the European Society of Cardiology and the European section of the International Society for Heart Research.

What the city lacked in sunshine, the conference more than made up for with its array of scientific content focussed on everything from stem cell therapy and intracellular signalling to systems biology. The meeting warmly welcomed both basic scientists and clinicians alike with sessions tailored specifically towards them, with the gap between them bridged with translational sessions highlighting the very best of emerging, clinically relevant research. For the first time, the meeting also included sessions conducted entirely in French which were designed to educate the native speaking general practitioners and nurses in the diagnosis, treatment and care of patients susceptible to heart failure.

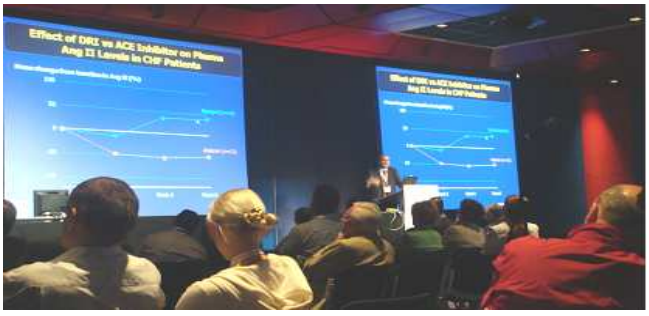
The opening ceremony presented attendees with 'The Janice Pfeffer Distinguished Lecture' in which Professor Don Bers gave an outstanding explanation of cardiac calcium handling. A worthy winner of the Pfeffer award, Professor Bers has contributed over 250 publications in the last 30 years and is particularly known for his diagrams which so elegantly describe excitation-contraction coupling.

The 'Heart Failure Association Honorary Lecture' was given by Professor Mark Pfeffer who spoke on the importance of translational research. The ceremony also paid homage to the world-renowned cardiologist, Professor Philip Poole-Wilson, who sadly died in March this year. In a highly moving tribute, Professors Roberto Ferrari and Inder Anand spoke both of the significant scientific contributions that Professor Poole-Wilson had made and also

Professor Philip Poole-Wilson

spoke of the love, admiration and respect that he commanded from both clinical and scientific communities alike. Needless to say, the untimely death of such an eminent man will leave a hole in the cardiology world, but his influential ideas and important contributions which underpin his legacy will live on.

As a basic scientist with a research interest in the Renin-Angiotensin-Aldosterone System (RAAS) and cardiac arrhythmias, the meeting had plenty to offer me, and on many occasions left me spoilt for choice in terms of the quality and content of sessions that were held. At a highly attended session entitled 'Optimising RAAS blockade in heart failure', delegates were treated to lectures on aspects of the RAAS ranging from currently used antagonists, to the future directions of RAAS inhibition. Professor Roberto Ferrari (Ferrara, Italy) opened this session and in the absence of Professor Masatsugu Hori (Osaka University, Japan) described briefly the idea that whilst in the short-term, activation of aspects of the endocrine system may be beneficial, a prolonged or inappropriate activation will frequently be of detriment to the region in which it is acting. He followed with an eloquent explanation of the idea that life and death are intertwined and as such, in the remodelled heart following myocardial infarction, both apoptosis and hypertrophy are essential, promoting death and life, respectively. In a talk entitled 'Extending the indications for aldosterone antagonists', Professor Faiez Zannad (Dommartin les Toul, France) gave a comprehensive overview of the clinical trial evidence supporting the use of inhibitors of aldosterone synthase and the aldosterone receptor as well as non-steroidal aldosterone inhibitors in patients with varying degrees of heart failure. In the final lecture of this session, Professor Henry Krum (Monash University, Australia) described and supported a role for direct renin inhibition in addition to the existing RAAS pharmacological antagonists which both complemented and completed the exploration of RAAS blockade which provided the theme for this session.



Professor Henry Krum presents a lecture on renin inhibition

Another popular session was that entitled 'New drugs on the horizon II' which examined the potential roles for novel vasodilators and adenosine A1 antagonists in talks given by Professor Mihai Gheorghiade (Chicago, US) and Professor Marco Metra (Brescia, Italy) respectively. Professor Faiez Zannad also spoke in this session and described further the role of direct renin inhibition and aldosterone synthase inhibitors. In his talk, he included slides with beautiful summaries of both the ways in which activation of the mineralocorticoid receptor can lead to a variety of conditions that ultimately lead to heart failure, and the pros and cons of various strategies that could be used to alleviate the effects of this activation.

Abstracts were presented throughout the congress in the form of poster presentations with contributions from groups across the world and showcased work on a whole host of themes from diagnostics and treatments in the clinic to molecular biology and stem-cell research conducted at the bench. Oral presentations showcased the very best of the abstracts that were submitted and were given in sessions throughout Sunday and Monday. Of these, Yassine Sassi (Paris, France) and Robin Weir (Glasgow, Scotland) won the young investigators award for basic science and clinical sections respectively for their presentations entitled 'Inhibition of the multidrug resistance associated protein 4, MRP4 promotes cardiac hypertrophy' and 'Serum soluble ST2: a potential novel mediator in left ventricular and infarct remodelling after acute myocardial infarction'.

Winner of the International Society for Heart Research (ISHR European section) outstanding in-

Professors Sian Harding and Metin Avkiran present Professor Mathias Gautel with his outstanding investigator award

vestigator award, Professor Mathias Gautel (King's College London, England) was described as being 'delighted' to have won the award for his speech on Titin-linked cardiomyopathies.

On the final day, in a session titled 'From ion movements to ventricular arrhythmias' chaired by Professors Ursula Ravens (Dresden, Germany) and Sian Harding (Imperial College London, England), Professor David Eisner (University of Manchester, England) gave a simple, yet elegant speech on the relationship between intracellular calcium handling and cardiac arrhythmias. This talk linked nicely with that given by Professor Ursula Ravens on Catecholaminergic Polymorphic Ventricular Tachycardia where she discussed the abnormal regulation of the ryanodine receptor and the opposing hypotheses of Marks and Chen in relation to calcium induced arrhythmogenesis.

The pebble beach of the Cote d'Azur

The organisers should be commended on the smooth running and exceptional organisation on every aspect of the conference and, in particular, the high standard and broad spectrum of scientific content presented within it.

Forthcoming Cardiovascular Meetings

European Society of Cardiology Congress 2009 will be held in Barcelona, Spain 29th August - 2nd September 2009. Further details are available at: http://www.escardio.org/congresses/esc-2009/Pages/welcome.aspx; Tel: +33 (0)4 92 94 76 00

Cardiovascular Complications of Chronic Kidney Disease - A New Challenge. Thursday 17th September 2009 St George's Hospital Blackshaw Road London, SW17 0QT. Further details may be obtained by visiting: http://www.cardiovascular-research.co.uk/symposium-2009.

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

Keystone Symposium: Advances in Molecular Mechanisms of Atherosclerosis. Organizers: Russell A. DeBose-Boyd and Christopher K. Glass 12th - 17th February, 2010 Fairmont Banff Springs, Banff, Alberta. Further details are available from: info@keystonesymposia.org; Tel: 800-253-0685 http://www.keystonesymposia.org/

Keystone Joint Symposia: 'Cardiovascular Development and Repair' and 'Angiogenesis in Health and Disease'. Organizers: Doris A. Taylor and Brian Annex. 28th February - 5th March, 2010 Keystone Resort, Colorado. Further details are available from: info@keystonesymposia.org; Tel: 800-253-0685 http://www.keystonesymposia.org/

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

British Heart Foundation Grants

Chairs and Programme Grants Committee February 2009

Personal Chairs

Professor N W Morrell, University of Cambridge. "The BHF Chair of Cardiopulmonary Medicine" 10 years £1,047,535

Professor D E Newby, University of Edinburgh. "The BHF Chair of Cardiology" 10 years £1,195,320

Professor S Bhattacharya, University of Oxford. "The BHF Chair of Cardiovascular Medicine" 10 years £1,121,359

Infrastructure Grants

Professor D O Haskard, Imperial College London. "Funding towards the purchase of angiography equipment in a new preclinical imaging facility" £955,000

Professor H C Watkins, University of Oxford. "Funding towards building costs and equipment in a new clinical research facility" £420,000

Special Project Grants

Professor KGC Smith et al, University of Cambridge. "A whole genome association study of ANCA-associated vasculitis" 2 years £565,333

Professor J N Danesh, University of Cambridge. "Study of the interplay of genetic, biochemical and lifestyle factors in coronary heart disease in 10,000 incident cases and 10,000 controls (Joint funding with MRC)" 4 years £900,000

Programme Grants

Professor A S Ahmed & Dr P W Hewett, University of Birmingham. "Molecular mechanisms involved in the maintenance of maternal vascular homeostasis" 3 years £481,638

Dr F M Marelli-Berg et al, Imperial College London. "Programming regulatory T cell trafficking to optimise cell-based tolerance induction in heart transplantation" 5 years £977,299

Professor R W Farndale et al, University of Cambridge. "The role of blood vessel wall collagens in regulating vascular cell function in health and disease" 5 years (renewal: years 11-15) £663,169

Project Grants Committee March 2009

Dr I J Mackie et al, University College London. "Investigation of the influence of mutations and polymorphisms on the expression and functionality of ADAMTS13" (1 year) £51,826

Dr P N Monk, University of Sheffield. "Defining mechanisms of agonism and antagonism at the pro-inflammatory complement fragment C5a receptor" (3 years) £157,079

Dr I T Johnson et al, University of Manchester. "The role of K_{2P} channels in the acute and chronic response to PUFAs in an animal model of hypertension" (3 years) £218,111

Dr R Ajjan et al, University of Leeds. "Modulation of clot structure and platelet function by aspirin in individuals with diabetes: role of aspirin dose and glycaemic control" (2 years) £98,747

Dr W R Ford et al, Cardiff University. "Roles of trace amine-associated receptors in cardiovascular responses to dietary trace amines" (3 years) £182,805

Prof S Ebrahim et al, London School of Hyg. & Trop. Med. "British Women's Heart & Health Study: causes and consequences of cardiovascular disease" (3 years) £308,528

Dr E Hypponen et al, University College London. "Vitamin D and the risk of cardiovascular disease and related traits: a large scale genetic association study" (3 years) £217,599

Dr S G Wannamethee et al, University College London. "Pathways to prevention and prediction of cardiovascular disease and associated disability in older men: the British Regional Heart Study" (2 years, 11 months) £989,660

Dr J Emsley, University of Nottingham. "Coagulation factor XII activation and the role of platelet Glycoprotein Ibα:linking structure to function" (3 years) £144,939

Prof A Tinker, University College London. "Identification of proteins involved in trafficking checkpoints in a K^+ channel complex involved in the long QT syndrome" (2 years) £131,783

Dr C Denning et al, University of Nottingham. "New in vitro models of long QT syndrome by coupling induced pluripotency and cardiomyocyte differentiation" (3 years) £188,109

Dr A J Workman et al, University of Glasgow. "Atrial remodelling of calcium handling and electrophysiology in heart failure" (3 years) £204,134

Dr R Wade-Martins & Prof K Channon, University of Oxford. "Optimising delivery and expression of the low density lipoprotein receptor under physiological regulation for gene therapy of familial hypercholesterolaemia" (1 year) £78,315

Dr S McMullen, University of Nottingham. "Progression of renal injury in developmentally programmed hypertension - interactions between sex steroids and the renin-angiotensin system" (3 years) £269,338

Dr P Kohl, University of Oxford. "Load-dependency of apelin-induced positive inotropy in single cardiomyocytes" (3 years) £211,724

Dr K T MacLeod, Imperial College London. "Cellular factors underlying the progression towards heart failure and its prevention" (3 years) £244,545

Dr P S Hartley & Prof A J Harmar, University of Edinburgh. "The role of CLOCK in the control of megakaryocyte development" (2 years) £140,668

Prof J C Hancox & Dr C E Dempsey, University of Bristol. "Molecular basis of hERG potassium channel blockade by disopyramide and its enantiomers" (2 years) £109,151

Prof J N Danesh et al, University of Cambridge. "Relevance of apolipoprotein(a) isoforms to risk of myocardial infarction in South Asians" (1.5 years) £161,872

Prof N Sattar et al, University of Glasgow. "The intrauterine environment and differences in adiposity and insulin resistance between South Asian and European populations" (2 years) £144,001

Dr S E Ozanne et al, University of Cambridge. "A role for a programmed mitochondrial CoQ deficit in developmental programming of cardiovascular disease" (3 years) £241,777

Fellowships Committee April 2009

Non-Clinical Fellowships

PhD Studentships

Unnamed and Dr F Gavins, Imperial College London. "Evaluation of the role of the melanocortin receptor system in ischemia-reperfusion induced leukocyte endothelium interaction in the brain microcirculation" (3 years) £108,056 (plus £7,205 PPA and £1,000 travel).

Unnamed and Dr S Hoppler, University of Aberdeen. "The endogenous Wnt inhibitor FrzA/sFRP1 promotes myocardium differentiation during heart organogenesis" (3 years) £95,446 (plus £6,544 PPA and £1,000).

Unnamed and Prof S Nourshargh, Queen Mary, University of London. "Role and regulation of expression of TNF-alpha receptors in inflammation" (3 years) £112,570 (plus £7,199 PPA and £1,000 travel).

Unnamed and Dr J Potts, University of York. "Structure and function of N1 domain from staphylococcus aureus FnBOA - a domain implicated in MRSA biofilm formation" (3 years) £92,245 (plus £6,549 PPA and £1,000 travel).

Unnamed and Prof S Marston, Imperial College London. "Investigation of the disease mechanism in the ACTC E361G transgenic mouse model of familial dilated cardiomyopathy" (3 years) £106,336 (plus £7,139 PPA and £1,000 travel).

Clinical Fellowships

MBPhD

Mr M E Ibrahim, Imperial College London. "How does prolonged mechanical unloading affect calcium-induced calcium release in cardiomyocytes?" (3 years) £101,059 (plus £7,139 PPA and £1,000 travel).

Chairs and Programme Grants Committee May 2009

Professor Q Xu et al, King's College, University of London. "Stem cells and arteriosclerosis: from differentiation to experimental therapy" 5 years (renewal: years 6-10) £1,124,537

Project Grants Committee May 2009

Dr J T B Crawley et al, Imperial College London. "Function of the ADAMTS13 disintegrin-like and cysteine-rich domains" (3 years) £166,721

Dr G A Ng & Dr K Brack, University of Leicester. "An investigation into the mechanisms underlying non-excitatory electrical stimulation on cardiac mechanical performance" (2 years) £108,477

Dr M Emerson, Imperial College London. "Regulation of platelet function in vivo by endothelial products in health and during nitric oxide deficiency" (1 year) £69,131

Dr C L Shovlin & Dr M D Jones, Imperial College London. "Characterisation of the gene for hereditary haemorrhagic telangiectasia type 3 (HHT3) and splice variant regulation" (1 year) £67,762

Prof MT Kearney et al, University of Leeds. "The insulin like growth factor-1 receptor, insulin sensitivity and

nitric oxide bioavailability" (3 years) £208,209

Dr P R Riley, University College London (ICH). "Investigating an epistatic relationship between Prox1 and Nkx2.5 in the cardiac conduction system" (3 years) £253,875

Dr A Harper, University of Dundee. "Modulation of parasympathetic regulation of cardiac function in intracardiac ganglia by receptors: neurotransmitters and neuropeptides" (2 years) £87,352

Dr B J Wojciak-Stothard, University College London. "The role of ADMA in the regulation of pulmonary endothelial cell-to-cell communication and endothelial permeability" (3 years) £183,010

Dr A F James et al, University of Bristol. "The role of ATP-sensitive K^+ channels in atrial tachyarrhythmias associated with β-adrenergic stress: a 'proof of concept' study using isolated rat hearts" (1.5 years) £89,991

Dr I Dransfield & Prof K A A Fox, University of Edinburgh. "Investigation of the mechanisms underlying pro-inflammatory monocyte- platelet interactions" (2 years) £116,806

Dr M Delibegovic, University of Aberdeen. "Role of adipocyte- and macrophage-PTP1B in body mass regulation and insulin sensitivity" (1 year) £99,027

Prof N J Severs, Imperial College London. "Caveolins: their expression and interaction with connexins in the heart" (3 years) £185,765

Dr A P Davenport, University of Cambridge. "Function of vascular CCR5 receptors in vasoconstriction and intimal hyperplasia identified using novel selective antagonists in human and experimental atherosclerosis" (2 years) £152,380

Dr S C Calaghan & Dr K E Porter, University of Leeds . "Statins directly affect cardiac myocyte function through cholesterol-dependent and independent mechanisms" (3 years) £185,063

Dr X Wang et al, University of Manchester. "The signalling regulation of ventricular arrhythmias and cardiac gap junctions in mice with a cardiac-specific deletion of MKK4" (3 years) £184,714

Dr C M Stover & Dr S E Francis, University of Leicester. "Properdin: key in development and prevention of atherosclerotic plaque formation in mice?" (2 years) £99,843

Dr S Ponnambalam et al, University of Leeds. "Targeting LOX-1 scavenger receptor in vascular cells using viral gene therapy" (3 years) £183,676

Dr J F X Ainscough et al, University of Leeds . "Regulation of cardiac fibrosis through cardiomyocyte specific AT1 receptor dependent mechanisms: an inducible transgenic approach" (3 years) £199,141

Dr G C Churchill et al, University of Oxford. "A drug discovery based translational investigation of cADPR function in heart" (3 years) £192,992

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. The review author may in return keep the book afterwards.

'Handbook of Venous Disorders 3ED'

by Hodder Education

HODDER EDUCATION
www.hoddereducation.co.uk

Further details on this title available from http://www.hoddereducation.co.uk/Title/9780340938805/Handbook_of_Venous_Disorders_Guidelines_of_the_American_Venous_Forum_Third_Edition.htm

Cardiovascular Related Wellcome Trust Grants

Programme Grants

Prof Stuart G Cull-Candy, Dept of Pharmacology, University College London. TARP regulation of neuronal and glial calcium-permeable AMPARs in health and disease 60 months £1,127,351

Prof Stephen P Watson, Division of Medical Sciences, The Medical School, University of Birmingham. The early events in signalling by platelet ITAM and ITAM-like receptors 60 months £1,246,548

Senior Research Fellowships In Clinical Science

Dr Robin P Choudhury, Dept of Cardiovascular Medicine, John Radcliffe Hospital, University of Oxford. Molecular magnetic resonance imaging with microparticles of iron oxide 60 months £1,275,054

Technology Development Grant

Dr Richard Henderson, MRC Laboratory of Molecular Biology, Structural Studies Division, Cambridge. Methods for Stabilisation and Crystallisation of Unstable Eukaryotic Membrane Proteins 36 months £391,707

Project Grants

Dr Robert J Stewart, Section of Epidemiology & Gen Pract, David Goldberg Building, Institute of Psychiatry, London. Cardiovascular risk and cognitive function in three ethnic groups - the SABRE-COG Study 36 months £316,836

Prof Linda M Richter, Child Youth & Family Development, Human Sciences Research Council, Dabbridge South Africa. The COHORTS Consortium of Health Outcome Research in Transitional Societies - Brazil, Guatemala, India, Philippines, South Africa - Phase 3 36 months £350,865

Dr Melvyn Hillsdon, School of Sport & Health Sciences, University of Exeter. Is the built environment associated with physical activity? A feasibility study for the Four Hundred Area Study (FAST) 24 months £508,833

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

Dr David R Poyner, Pharmaceutical Sci Res Institute, Aston University. Cysteine mutagenesis of the CGRP receptor 12 months £56,054

Prof Sussan Nourshargh, Centre for Microvascular Research, William Harvey Research Institute, Queen Mary University of Lonon. Role of JAM-C in inflammatory and vascular events in vivo as studied using an experimental model of ovarian cancer 36 months £227,807

Professor Robin J Plevin, Dept of Physiology & Pharmacology, Institute of Biomedical Sciences, University of Strathclyde. PAR-2 mediated inhibition of TNFalpha JNK signalling - a novel paradigm for GPCRs 24 months £125,373

Research Training Fellowship

Dr Wing-Chiu C Sze, Dept of Endocrinology, School of Medicine & Dentistry, St Bartholomew's & Royal London. Analysis of BMP signalling in adrenal development, function and disease 24 months £135,337

Sir Henry Wellcome Postdoctoral Fellowships

Ms Jenna L Cash, Sir William Dunn School of Pathology, University of Oxford. Defining the role of chemerin peptides and ChemR23 in the endogenous anti-inflammatory network 48 months £250,000

Dr Marie A Schroeder, Dept of Physiology / Anatomy & Genetics, Sherringham Building, Universtiy of Oxford. Assessment of In Vivo Metabolism in Failing Hearts Using Hyperpolarised Carbon-13 Magnetic Resonance 48 months £250,000

Equipment Grant

Prof K Ravi Acharya, Dept of Biology & Biochemistry, University of Bath. An Upgrade of the Protein Crystallography Facility at University of Bath 60 months £336,486

Biomedical Resources

Prof Valerie B O'Donnell, Dept of Medical Biochemistry & Immunology, School of Medicine, Cardiff University. Generation of lipid standards for biological studies: oxidized phospholipids generated by activated immune cells 36 months £192,231

Genome Wide Association Studies

Dr James R Bentham,Dept of Cardiovascular Medicine, John Radcliffe Hospital, University of Oxford. A Genome-wide Association Study in Congenital Heart Disease 12 months £103,000

Prof Deborah A Lawlor, Department of Social Medicine, University of Bristol. Genome-wide association study of maternal pregnancy phenotypes and later-life maternal and offspring vascular and metabolic phenotypes 15 months £99,954

Dr Linda Morgan, Institute of Genetics, Queen's Medical Centre, University of Nottingham. Genome-wide association screen for susceptibility genes for pre-eclampsia in UK women 24 months £118,715

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Autumn Meeting 2009

" MYOCARDIAL ENERGETICS AND REDOX IN HEALTH AND DISEASE"

DATES: Monday 7th September and Tuesday 8th September, 2009

VENUE: Medical Sciences Teaching Centre/ Trinity College, Oxford

ORGANISERS: Barbara Casadei, Kieran Clarke and Saadeh Suleiman

Programme: The programme will consist of state-of-the-art presentations by leaders in the field. Speakers will include: Fran Ashcroft (Oxford), Dave Carling (London), Antonio Vidal-Puig (Cambridge), Phil Eaton (London), Peter Radcliffe (Oxford), Andrew Halestrap (Bristol), Michael Murphy (Cambridge), Michael Frennaux (Birmingham) and Ivor Benjamin (Salt Lake City).

Full programme details are downloadable from the BSCR website (www.bscr.org).

Free Communications: There will be 12 oral presentations of selected abstracts, one of which will win the BSCR Prize. There is also a Clinical Science Early Career Investigator Award of £250 for the best poster

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).

Deadlines

Submission of Abstracts: Friday 10th July, 2009

Registraion: Monday 24th August, 2009