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Contents

Editorial

Welcome to the July 2008 issue of The Bulletin! Our review for this issue has been written by Mr Lakshman Goonetilleke and Dr John Quayle from the Division of Human Anatomy & Cell Biology, University of Liverpool. The authors present a comprehensive review of the two-pore domain K^+ channels in the cardiovascular system including their potential regulatory effects on both cardiovascular function and dysfunction.

Once again, there are vacancies to be filled on the Executive Committee of the BSCR and, as six candidates have been nominated, an election is required. To assist you with voting, biographical summaries and statements from the candidates are included within this issue. Members are urged to make their preferences known by completing the enclosed ballot form and returning it to the Secretary, Dr Chris Jackson, by the 31st of August.

Following the recent successful joint conference with the British Cardiovascular Society in Manchester, we are pleased to include a full meeting report which can be found in this issue of the Bulletin. Kelly Lammerts van Bueren returns from the Weinstein Cardiovascular Conference and shares the highlights and her experiences with us - as well as an entertaining photograph of Professor Eric Olson and his band, The Transactivators.

We then look ahead to an exciting Autumn meeting at the University of Bristol on September 15th and 16th, organised by Joanne Ferguson, Elinor Griffiths, Jason Johnson, Cressida Lyon and Oliver Stone. A full programme and registration details are included herein and on the BSCR website: www.bscr.org. As is customary, we finish by bringing you the latest details of grants awarded to Cardiovascular researchers, by the British Heart Foundation and the Wellcome Trust.

Helen Maddock and Nicola Smart

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Two-pore domain K^+ channels in the cardiovascular system

by Lakshman Goonetilleke and John Quayle

Human Anatomy & Cell Biology, University of Liverpool

Potassium (K^+) channels are integral membrane proteins that selectively conduct K^+ ions across biological membranes. They play a central role in the regulation of cardiovascular function (e.g. see 1;2). For example, in the heart, many distinct types of K^+ channels are involved in the genesis and duration of the cardiac action potential which sustains cardiac rhythm (reviewed in 1). In the vasculature, a similar diversity of K^+ channels contribute to the regulation of vessel tone which is an important determinant of peripheral vascular resistance and hence blood pressure (reviewed in 2). Many clinically important drugs act by modulation of the gating properties of K^+ channels (e.g. the class III anti-arrhythmics and the direct acting vasodilator drugs; (3)). Thus the therapeutic potential of K^+ channels as drug targets in cardiovascular medicine is well recognised (4). Further exploitation of K^+ channels as therapeutic drug targets will be greatly assisted by the molecular identification of native K^+ currents.

The human genome project, as well as an intense cloning effort, has unveiled a large number of genes (~ 80) encoding K^+ channel pore-forming (α) subunits (5). Based on membrane topology of the constituent subunits, three K^+ channel superfamilies have emerged. Channels composed of 6/7 transmembrane segments (TMS) and 1 pore (P) forming domain comprise the voltage-gated (K_V) and large-conductance calcium (Ca^{2+}) activated (BK_{Ca}) K^+ channels, respectively (1;6). Inward rectifier (K_{ir}) and ATP-sensitive (K_{ATP}) K^+ channels from a second, structurally distinct family composed of subunits having 2 TMS and 1 P domain (1;7). The third and most recently identified K^+ channel pore-forming subunit has 4 TMS and 2 P domains in tandem. Functionally, these subunits constitute the tandem or two-pore domain K^+ channel (K_{2P}) superfamily which will be the topic of this article. We provide an overview of the biophysical and pharmacological properties of recombinant K_{2P} channels, as well as review current literature on K_{2P} channels in the cardiovascular system.

The Two-Pore Domain K^+ (K_{2P}) channels

Two-Pore domain K^+ channels are encoded by 15 KCNKx genes; the x denoting a number corresponding to the order in which the gene was discovered. Common names have been assigned for individual channel types based on their functional attributes, which in turn distinguishes six subfamilies (**Fig. 1**): TWIK (Tandem of P domains in a Weak Inward Rectifier K^+ channel), TREK (TWIK-RElated K^+ channel) and TRAAK (TWIK-Related Arachidonic Acid activated K^+ channel), TASK (TWIK-related Acid Sensitive K^+ channel), TALK (TWIK-related ALkaline activated K^+ channel), THIK (Tandem-pore domain Halothane Inhibited K^+ channel) and TRESK (TWIK-RElated Spinal chord specific K^+ channel).

In contrast to the tetrameric structure of K_V and K_{ir} channels, K_{2P} channels are likely to function as dimers (8;9; **Fig. 1**). Such an arrangement would maintain the canonical contribution of 4P loops per channel necessary to make up the K^+ selectivity filter (10). As the 2 P motifs may not necessarily be conserved per subunit monomer (e.g. see TWIK-1 and -2), K_{2P} channels exhibit 2 fold symmetry. This is in contrast to the 4 fold symmetry of K_V and K_{ir} families and is thought to endow the channels with more diverse permeation and gating properties.

Recombinant K_{2P} channels expressed in model systems generally lack intrinsic voltage- and time-dependence. Under symmetrical K^+ conditions, the steady-state current-voltage (I-V) relationship may show (i) open rectification (i.e. currents pass equally well in both the inward and outward direction (ii) inward rectification or (iii) outward rectification. Active across the physiological voltage range, K_{2P} channels are ideal candidates to underlie background or 'leak' K^+ conductances (K_B). Such conductances are likely to make an important contribution to the resting membrane potential. Thus K_B conductances are principle determinants of cellular excitability.

Although generally voltage insensitive, K_{2P} channels (the molecular counterparts of K_B conductances) are regulated by a myriad of chemical and physical stimuli. As will be discussed, their diverse mechanisms of regulation suggest they will modulate the membrane potential of cells in response to a wide variety of environmental signals. The following description for the regulatory properties of the K_{2P} subfamilies has come from voltage- or patch-clamp studies of the recombinant channels expressed in *Xenopus* oocytes, mammalian cell lines or both.

TWIK channels

The TWIK subfamily consists of the members TWIK-1, -2 and the structurally related although non-functional subunit, KCNK-7 (11). TWIK channels are weakly inwardly rectifying under symmetrical K^+ conditions hence their name (12;13). Weak inward rectification has been attributed to internal Mg^{2+} for TWIK-1 but is likely to be distinct for TWIK-2 (e.g. see 12;13). TWIK channels are down-modulated by acidification of the intracellular medium and potentiated by activators of protein kinase C (PKC; 12;14). Whether the effects of PKC are a consequence of channel phosphorylation remains to be determined (e.g. see 12). Additional properties of TWIK-2 channels include: potentiation by arachidonic acid (10 µM, +70%) and donors of nitric oxide (NO; e.g. sodium nitroprusside; 100 µM, +20%; 13) and weak inhibition by the inhalational anaesthetics chloroform and halothane (13). TWIK-2 is also the only reported K_{2P} channel that exhibits inactivation with long (10 s) depolarising voltage pulses, the kinetics for which is temperature sensitive (13).

TREK channels

Cloned TREK (TREK-1 and -2) and TRAAK channels are activated by membrane stretch and so constitute a subfamily of mechano-gated K_{2P} channels (reviewed in 15). Stretch activation may be the consequence of a convex curvature of the membrane which is conveyed to the channel through the lipid bilayer (16-18). TREK and TRAAK channels are also extremely temperature sensitive with maximal activity recorded at physiological temperature (37°C; 19;20). Reported Q_{10} values are in the order of 7 for TREK-1 and ~14 for TREK-2 and TRAAK (19;20).

In addition to their sensitivity to physical stimuli, TREK and TRAAK channels are also gated by chemical stimuli. A universal feature of these channels is their high sensitivity to lipids. Polyunsaturated fatty acids such as arachidonic acid (10 µM) strongly potentiate TREK and TRAAK channels (>500%; 16;18;21). Activation appears to be direct and is independent of arachidonic acid metabolites (16;21). Saturated fatty acids on the other hand (e.g. palmitate) are without effect on TREK and TRAAK channel activity (16;18;21). Lysophospholipids are also potent activators of TREK and TRAAK channels (22). However, activation by these lipids may involve their different extra- and intracellular signalling pathways (e.g. see 22;23).

Indicative of different physiological roles, TREK channels are activated by internal acidification while TRAAK is activated by internal alkalanisation (18;24;25). TREK channels (but not TRAAK) are regulated by the G_s and G_q signalling pathways whereby receptor activation leads to channel inhibition (16;18). The inhibitory effects of the G_s signalling pathway are likely due to channel phosphorylation by protein kinase A (PKA; 16). Inhibition of TREK channels through the G_q signalling pathway is largely unresolved but may be mediated by PKC phosphorylation (26;27), diacylglycerol and phosphatidic acids (28) and/or phospholipase C (PLC) depletion of the membrane lipid phoshphatidylinositol 4,5-bisphosphate (PIP_2; 29). Additionally, NO donors have been shown to activate TREK-1 channels via PKG mediated phosphorylation (30). Collectively, these findings demonstrate that TREK channels are tightly regulated by signal transduction pathways.

Another salient feature of the TREK channels is their strong potentiation by the volatile general anaesthetics (18;31). Halothane, chloroform and isoflurane have all been shown to activate TREK channels, albeit with varying efficacy between the TREK isoforms (18;31). Thus TREK-1 is more sensitive to activation by chloroform while TREK-2 is more sensitive to halothane (18;31).

TASK channels

The TASK subfamily consists of the two functional members, TASK-1 and -3, and the non-functional subunit, TASK-5 (32). TASK channels are characterised by their strong sensitivity to fluctuations in external pH within the physiological range; acidification causes channel inhibition and alkalanisation leads to channel activation. Experimentally determined IC_{50}s for TASK-1 and TASK-3 are ~7.4 and 6.7, respectively (33-36). Like TREK channels, TASK channels are also activated by the volatile anaesthetics halothane and isoflurane (31;37). In addition, TASK-1 channels are insensitive to chloroform and partially inhibited by diethylether (31). TASK channels are also strongly inhibited after activation of G_q coupled receptors. Several theories attempting to explain the mechanism of inhibition have been proposed. These include channel inhibition by hydrolysis products of PIP_2 after PLC activation (38), PLC depletion of PIP_2 (28;29;39) and a direct effect of the G_q protein on the channel (40;41). Although volatile anaesthetics and G_q coupled receptor activation have opposite modulatory effects on TASK channels, they may share a common molecular site of action (37).

Another important regulatory property of TASK-1 is its sensitivity to oxygen (O_2) tension. In Human Embryonic Kidney (HEK) 293 cells stably transfected with TASK-1, lowering O_2 reduced TASK-1 currents evoked by external alkalanisation (42). No similar reports have been documented for cloned TASK-3 channels however, they may be O_2 sensitive in some cell types (e.g. see 43).

Diversity within the TASK subfamily is enhanced by the ability of TASK-1 and TASK-3 channels to form heteromeric complexes (44). Coexpression of TASK-1 and TASK-3 in *Xenopus* oocytes produced channels with

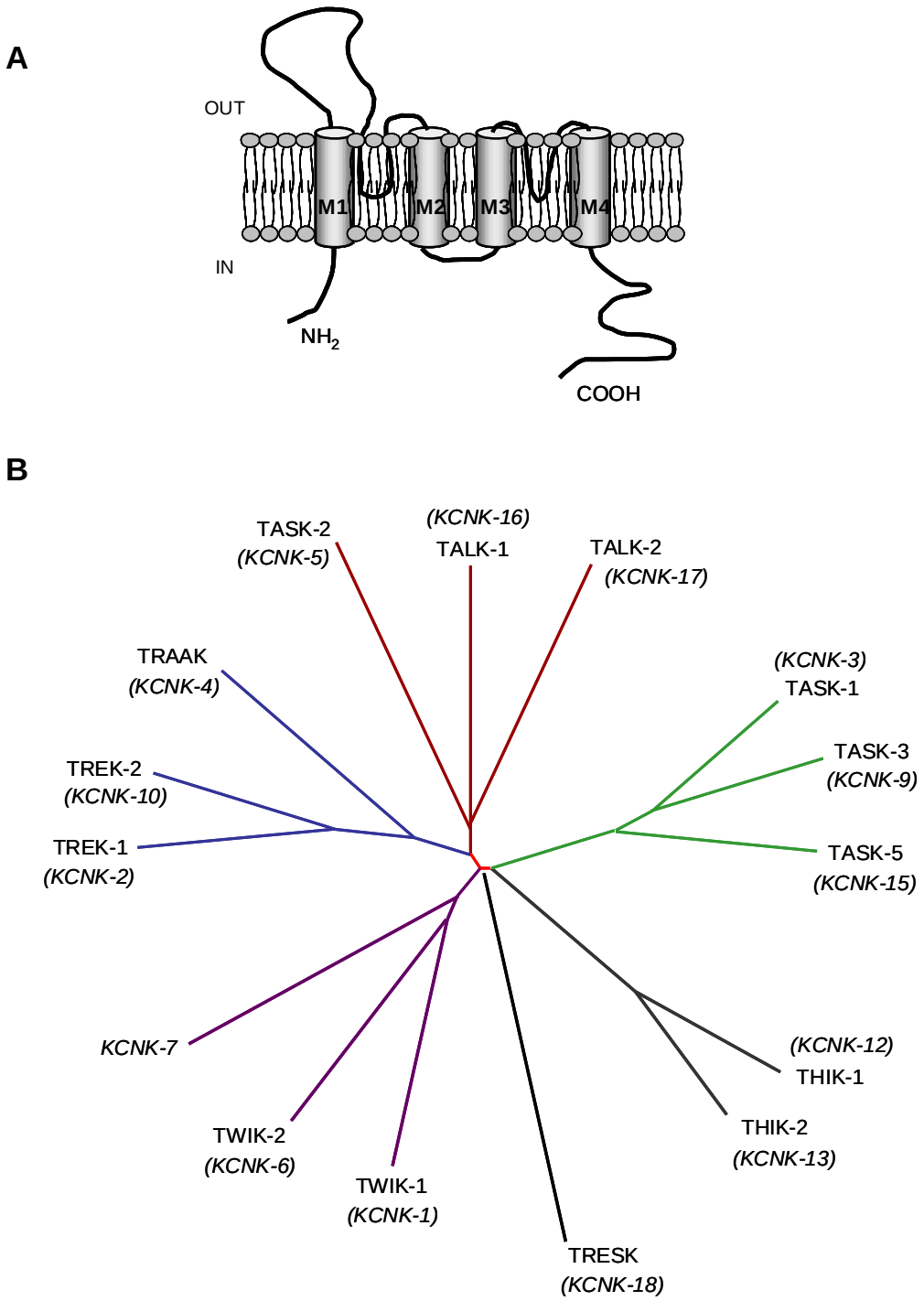

Figure1. A. Each mammalian K_{2P} subunit has 4 putative transmembrane segments and 2 P domains in tandem. They also possess a large extracellular loop between the M1/P1 region as well as an intracellular oriented N- and C-termini. B. Phylogenetic tree illustrating the 6 K_{2P} subfamilies with KCNK gene names illustrated in italics.

pH sensitivity intermediate to that of homomeric TASK-1 and TASK-3 channels (44). While the heterodimeric TASK-3/TASK-1 channel was also inhibited by activators of G_q coupled receptors, sensitivity to inhibition was weaker than that of homomeric TASK-1, but greater than that of homomeric TASK-3 channels (44).

THIK channels

The THIK subfamily consists of THIK-1 and the non-functional subunit, THIK-2 (45). The defining characteristic of THIK-1 is its sensitivity to inhibition by halothane (45). THIK-1 channels are weakly inhibited by extracellular acidification, although this inhibition is not as pronounced as with TASK channels. The channel is also potentiated by arachidonic acid (5μM +85%) and

weakly activated by lysophosphatidylcholine (45). Recombinant THIK-1 channels may also be reversibly inhibited by hypoxia suggesting this channel may also function as an O_2 sensor (46).

TALK channels

Composed of the members TALK-1, TALK-2 and the more distantly related TASK-2, TALK channels like TASK are modulated by extracellular pH (47;48). While acidification of the extracellular medium to pH 6 inhibits TALK-1 and TASK-2 channels, basal TALK-2 currents are not further affected (49). Conversely, external alkalanisation strongly potentiates all three channel members (49). Reported IC_{50}s are in the order of pH 7.8-8.3 for TASK-2 (48;50), pH 7.8 for TALK-1 and pH 8.8 for TALK-2 (51). TALK and TASK-2 channels are regulated by donors of reactive oxygen species (ROS) and nitrogen oxide species independent of the PKG pathway (49).

In addition, TALK-2 and TASK-2 (but not TALK-1) are also strongly potentiated by superoxide anions suggesting channel modulation through by-products of oxidative metabolism (49). Additional characteristics for TASK-2 which is not observed for TALK channels include; activation by the volatile anaesthetics (chloroform, halothane, isoflurane and desflurane; 52), modulation by cell volume (50) and sensitivity to fluctuations in intracellular pH (52). Furthermore, the TASK-2 promoter may be down-regulated by hypoxia (53). Thus although TASK-2 is not directly modulated by O_2 tension, gene expression is likely to be down-regulated under hypoxic conditions.

TRESK channels

Originally cloned from human spinal chord, TRESK is the most recently identified K_{2P} subunit (54). TRESK channels are reversibly inhibited by polyunsaturated fatty acids (e.g. arachidonic acid) but are insensitive to saturated fatty acids (54;55). Currents through TRESK channels are also weakly inhibited and potentiated by extreme external acidification and alkalanisation, respectively (54;55), and more strongly modulated by variations in intracellular pH (54;55). Strong potentiation of TRESK channels by halothane and isoflurane make them the most sensitive of the volatile anaesthetic-activated K_{2P} channels (reviewed in 56). As discussed, the phosphorylation state of K_{2P} channels is a primary mechanism of regulation. TRESK channels are potentiated by agonist evoked stimulation of G_q coupled receptors (57). This is in contrast to the inhibitory effects observed for TREK and TASK channels and may involve channel dephosphorylation by the Ca^{2+}-calmodulin dependent phosphatase, calcineurin (57).

K_{2P} channels in the heart

Identification of K_{2P} channels responsible for native K_B conductances has often come from a comparison of the biophysical and pharmacological properties of the native channel, with that of recombinant channels heterologously expressed in model systems. This experimental approach is frequently supported by studies of K_{2P} subunit transcript and protein expression in either isolated myocytes (e.g. see 58;59) or whole tissues (60;61). Using quantitative polymerase chain reaction, Liu et al (60) screened rat heart for most members of the K_{2P} gene family (TWIK-1, -2 & KCNK-7, TASK-1, -2 & -3, TREK-1, -2 & TRAAK). Transcripts encoding each of these subunits were identified in at least one chamber of the heart with a prevalence of TWIK-2, TASK-1 and TREK-1 expression (60). These genes may be regulated developmentally with an altered expression between the adult and embryonic heart (60;62). Although little is known about the contribution of TWIK-2 channels to cardiac electrical activity, more detailed information has emerged regarding the roles of TASK-1 and TREK-1.

Native K_B conductances have been electrophysiologically recorded from cardiomyocytes (63;64). One such Ba^{2+}-sensitive K_B current ($I_{K,p}$) is active across a range of membrane potentials including those corresponding to the plateau phase of the cardiac action potential (64). Inhibition of the current by Ba^{2+} (1 mM) prolongs duration of the cardiac action potential by ~20% and also elevates height of the plateau phase (64). Kim et al (65) subsequently cloned an alternatively spliced variant of TASK-1 (named TBAK-1) from a mouse heart cDNA library. This variant had an additional 9 amino acid residues at the NH_2 terminus, but was biophysically and pharmacologically indistinguishable from TASK-1 (58). Whether TBAK-1/TASK-1 is the functional correlate of $I_{K,p}$ requires further investigation (e.g. see 58;63). Native TBAK-1/TASK-1 like currents have been recorded from both atrial and ventricular myocytes making these channels potential candidates to underlie $I_{K,p}$ (58;66).

Support for TASK-1 in the regulation of ventricular repolarisation has more recently been documented by Putzke et al (59). These authors dissected native TASK-1 currents in rat ventricular myocytes using extracellular acidification and a putative TASK-1 inhibitor (A293; 59). Their results demonstrate a significant contribution of outward current through TASK-1 channels in the plateau range of membrane potentials (59). Inhibition of I_{TASK} with A293 was associated with ~30% and 20% increases in action potential duration frequencies at 50% and 90% (APD_{50} & APD_{90}) repolarisations, respectively (59). The authors further show that I_{TASK} can be completely inhibited by stimulation of α_1-adrenergic receptors (which operate via the PLC pathway). Thus TASK-1 channels may contribute to prolongation of the cardiac action potential through α_1-adrenergic receptor activation (59). Inhibition of TASK-1 channels has also

been implicated in the arrhythmogenic effects of platelet activating factor (PAF) which also operates via the PLC pathway (67). Channel inhibition in murine ventricular myocytes was shown to occur through PKCε phosphorylation of the channel (38). Whether this same signal transduction pathway is involved in TASK-1 down modulation following α_1-adrenergic receptor activation is a topic for future studies.

Native K_B conductances that are activated by free fatty acids have also been recorded from mammalian cardiomyocytes (e.g. 68; reviewed in 69). Kim et al isolated a K_B current ($I_{K(AA)}$) from rat atrial cells that was activated by arachidonic acid, membrane stretch and internal acidification (68). It was further shown that $I_{K(AA)}$ was reversibly activated by clinical concentrations of volatile anaesthetics (chloroform, halothane and isoflurane) and inhibited by membrane permeable analogues of cAMP (70). These properties are consistent with that of recombinant TREK-1 channels making $I_{K(AA)}$ the likely native correlate. Expression in atrial myocytes and stretch sensitivity may implicate TREK-1 channels in the regulation of atrial natriuretic peptide (ANP) secretion which is essentially a stretch-induced process (71).

The TREK-1 current has also been recorded from rat ventricular myocytes (72;73). In the rat ventricular wall, TREK-1 transcript expression is heterogeneously distributed with highest levels reported in endocardial rather than epicardial cells (74). Consistent with this observation, TREK-1 current density induced by chloroform was significantly larger in endo- as opposed to epicardial cells (74). The differential TREK-1 gene expression has been suggested to correlate with varying levels of mechanoelectric feedback (MEF) experienced in the different regions of the ventricular wall (reviewed in 73). Such a distribution of mechano-sensitive K^+ channels could act to synchronise action potential repolarisation across the myocardium of the heart, which may otherwise be arrhythmogenic (73).

The involvement of TREK-1 channels in MEF has recently received independent support from other groups (72). Li et al cloned two isoforms of rat TREK-1 (TREK-1a & b) which were biophysically and pharmacologically indistinguishable in the HEK 293 expression system (72). Interestingly, from single channel recordings both variants exhibited a dual mode of unitary conductance; a 'large' (~132 pS) conductance channel and a 'small' (~42 pS) conductance channel (72). Both TREK-1 variants were identified at the transcript level in isolated cardiomyocytes using RT-PCR. Compatible with a channel poised to respond to stretch, longitudinal stripes of TREK-1 protein were localised to the cell surface of isolated cardiomyocytes (72). Single channel recordings from ventricular myocytes demonstrated a native channel that also had two modes of conductance (72). The high-and low-conductance channel are likely to contribute to whole cell K^+ currents activated by stretch in ventricular myocytes (72). Despite these studies, direct evidence for the involvement of TREK-1 in MEF is currently lacking. Nevertheless, the development of selective K_{2P} channel blockers and activators should help to elucidate the contribution of TREK-1 to MEF in the future.

TREK-1 channels may additionally have a role in various pathophysiological conditions. During ischemia, purinergic agonists (e.g. ATP) cause the release of arachidonic acid which lowers intracellular pH. Aimond et al (75) identified an extracellular ATP activated I_{TREK}-like current in rat ventricular myocytes. The ATP-induced I_{TREK} current required translocation of cytosolic phospholipase A_2 ($cPLA_2$) and subsequent arachidonic acid (AA) release (75). The ATP-dependent activation of $cPLA_2$ required the simultaneous involvement of p38 and p42/44 mitogen activated protein kinases (75). Thus TREK-1 channels may contribute to membrane potential stabilisation of cardiac myocytes during cardiac ischemia.

K_{2P} channels in the vasculature

In addition to their putative roles in the mammalian heart there is accumulating evidence to support expression and function for some K2P channels in the vasculature. The membrane potential of arterial smooth muscle cells (SMCs) is an important determinant of vessel tone, and consequently peripheral vascular resistance and blood pressure (2). Rabbit pulmonary arterial smooth muscle cells (rtPASMCs) express a non-inactivating, hypoxia-inhibited KB conductance (IKN) that contributes to genesis of the resting membrane potential in these cells (76). Characterisation of this native current demonstrated sensitivity to inhibition by hypoxia, external acidification, anandamide and Zn^{2+} ions (77). Conversely, current potentiation was observed upon alkalanisation of the external medium and by the volatile anaesthetic, halothane (77). Acidification was associated with an ~20 mV depolarisation of rtPASMC membranes whilst alkalosis caused membrane potential hyperpolarisation (77). Although a contribution to IKN from voltage-gated K+ channels cannot be totally eliminated (e.g. see 78), the properties of the conductance were consistent with the involvement of TASK-1 channels (77). The authors further postulated that TASK 1 channels may contribute to the physiological mechanism of hypoxic pulmonary vasoconstriction (HPV). Thus TASK-1 may behave as an O_2 sensor promoting depolarisation, Ca^{2+} entry and vasoconstriction in response to hypoxia. The associated vasoconstriction diverts blood flow from hypoxic to well ventilated alveoli in the lungs ensuring efficient gaseous exchange. Involvement of TASK-1 channels in HPV has received independent support by other groups. Us-

ing siRNA knockdown of TASK-1, Olschewski et al demonstrated an ablation of the O_2 sensitive conductance in human PASMCs (79). Furthermore, cells lacking TASK-1 protein exhibited more depolarised resting membrane potentials.

Single-cell patch clamp electrophysiology has been supported by studies using intact vessels devoid of endothelium (80;81). These studies have suggested that TASK channels may also function as molecular sensors of pH in certain vascular beds. Gardener et al observed reversible changes in the membrane potential of rat pulmonary and mesenteric arteries in response to varying external pH (80). Acidification to pH 6.4 caused membrane potential depolarisation, while alkalanisation to pH 8.4 caused hyperpolarisation; observations consistent with the presence of a pH-sensitive K+ conductance in these vessels (80). At pH 8.4 and 7.4 the TASK-1 inhibitors anandamide (10μM), bupivacaine (100μM) and Zn^{2+} (200μM) depolarised the membrane potential to a value close to that seen at pH 6.4. These data are consistent with extracellular alkalanisation causing membrane potential hyperpolarisation via activation of a TASK-1 conductance (80). The putative TASK-2 inhibitor, clofilium (100μM), was less effective at repolarising the membrane potentials of alkaline-treated vessels (80). Nevertheless, a functional role for TASK-2 was further investigated in intact rat pulmonary arteries that had been treated with anti-TASK-2 siRNA (81). Membrane potentials of these vessels were more depolarised compared to control (scrambled siRNA treated) vessels (81). Moreover, hyperpolarisation of VSMCs induced by external alkalanisation was significantly smaller in TASK-2 siRNA-treated vessels (81).

As well as TASK-1 and -2, TWIK-2 has been reported at the transcript and protein level in rat pulmonary (80), mesenteric (80;82), middle cerebral (83) and femoral arteries (82) among other vascular tissues (e.g. see 13). Despite strong evidence for TWIK-2 channel expression in the vasculature, native TWIK-2 conductances have not been recorded to date. Bryan et al recorded an arachidonic acid (AA) activated K^+ conductance in rat middle cerebral arterial smooth muscle cells which could not be attributed to K_V, K_{Ca} K_{ir} or K_{ATP} channels (83). The conductance mediated membrane potential hyperpolarisation and arterial vasodilation. These authors screened for the AA-activated K_{2P} channels at the transcript and protein level (i.e. TREK-1 and -2, TRAAK, TWIK-2 and THIK-1) of which only TWIK-2 could be detected in cerebral arterial smooth muscle myocytes (83). Due to a lack of selective TWIK-2 activators or inhibitors, the involvement of this channel in mediating the AA-activated K^+ conductance remains ambiguous.

Given the absence of selective pharmacology for individual K_{2P} channels, targeted gene knockdown is an important tool for elucidating channel function. Studies with transgenic models have provided useful insights into the function of vascular TREK-1 channels (e.g. see 84;85). Until recently, dilator functions have been attributed to members of the 6/7TMS/1P or 2TMS/1P K^+ channel superfamilies. Blondeau et al however, have shown that the polyunsaturated fatty acid (PUFA), α-linolenic acid (an activator of TREK-1 channels), induced vasodilation of rat and mouse basilar arteries (84). The induced dilation was independent of the nitric oxide (NO) and prostanoid pathways and was not observed in basilar arteries of TREK-1 knock-out mice (84). This evidence implies that TREK-1 channels were the likely mediator of the PUFA-induced dilation. Whether TREK-1 activation by PUFA was of an endothelial or smooth muscle origin was not addressed by the authors. Patch-clamp recordings of PUFA-induced TREK-1 currents from isolated basilar smooth muscle and/or endothelial cells will help to resolve this issue.

Support for vascular endothelial TREK-1 channels has recently been provided by Garry et al (85). These authors have shown that endothelium-dependent dilations in response to acetylcholine and bradykinin are significantly weakened in mesenteric arteries of TREK-1 knockout mice (85). In contrast, endothelium-independent dilations in response to sodium nitroprusside were reportedly identical in TREK-1 wild-type and knockout mice (85). This evidence strongly suggests TREK-1 is likely to influence the NO signalling cascade (between receptor activation and NO production) in endothelial cells, as acetylcholine and bradykinin largely induce vasodilation through this pathway.

Versatility of TREK-1 and TASK-1 channels in the regulation of vascular function is perhaps demonstrated by their possible involvement in hypertensive states (86;87). Pokojski et al recorded a TREK-like conductance from murine carotid endothelial cells (mCECs) which was potentiated by TREK channel stimuli (e.g. membrane stretch, PUFAs, intracellular acidification, isoflurane and riluzole; 86). Although consistent with the properties of TREK-1 & -2 channels, only TREK-1 transcripts could be detected in isolated mCECs (86). Activation of the TREK-1-like conductance was associated with hyperpolarisation of the endothelium and vasodilation of murine carotid artery (86). Using two different models of elevated blood pressure (i.e. spontaneous hypertensive rats (SHR) and a $K_{Ca}3.1^{-/-}$ knockout mouse), the authors further show an up-regulation of TREK-1 currents and mRNA in mCECs of hypertensive compared to normotensive mice. Accordingly, the vasodilator effects of TREK-1 activators were also increased in the hypertensive models (86).

A separate study investigating TASK-1 expression

also reported altered gene and current expression between aortic smooth muscle cells (ASMCs) of SHR and those of Wistar-Kyoto rats (WKR; 87). The TASK-1-like currents were smaller in ASMCs of SHR rats, as was TASK-1 transcript and protein expression. Furthermore, the resting membrane potentials of aortic smooth muscle cells from SHR rats were more depolarised than WKR rats, suggesting TASK-1 down-regulation during hypertension (87). Thus it is likely TASK-1 and TREK-1 channels represent important therapeutic targets for the future development of anti-hypertensive medicines.

Concluding remarks

Our understanding of the physiology and function of K_{2P} channels in the cardiovascular system is very much in its nascent stage. Exciting discoveries have been made suggestive that K_{2P} channels are likely to regulate both cardiovascular function and dysfunction. The TASK and TREK channels could modulate cardiac and vascular responses in accordance with changes in membrane stretch, pH and PUFAs. Exactly what roles the TWIK, TALK and THIK channels have is unclear at this time, partly due to the lack of selective channel pharmacology. Transgenic mouse models and RNA interference techniques should play an important role in elucidating the function of these channels. Continued research into K_{2P} channels in the cardiovascular system should ultimately see some members used as drug targets for the treatment of cardiovascular disorders.

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Secretary's Column

It is a pleasure to report on a successful joint conference with the British Cardiovascular Society in Manchester recently: a full meeting report can be found in this issue of the Bulletin. Our Spring Meeting next year is already planned, but it is certainly worth considering making the joint effort with the BCS a regular feature of our meetings calendar thereafter

Speaking of meetings, I would like to draw your attention to an excellent programme for our Autumn Meeting this year. Themed around "Cell Signalling in Cardiovascular Disease: Life or Death", it will be held at the University of Bristol on September 15th and 16th. The organisers (Joanne Ferguson, Elinor Griffiths, Jason Johnson, Cressida Lyon and Oliver Stone) have placed a special emphasis on younger investigators, so there are twelve slots open for oral presentations to be selected from submitted abstracts as well as a large number of posters. There will as usual be two prizes each of £250 on offer, for the best oral presentation and the best poster presentation. Abstracts can be submitted through the Society's website at www.bscr.org.

The Annual General Meeting of the Society will also take place during the Autumn Meeting, on September 15th at 3.30 pm.

Close scrutiny of the BSCR Constitution – a job more suited to a lawyer than a scientist – reveals that we need to find five new committee members before the end of 2008. We have four members coming to the end of their standard three-year terms, and Chris Newman will become Chair at the end of the year thus creating the fifth opening. Of the four non-officer members of the committee, three must be clinically qualified. I have received three nominations for clinically qualified people, so those three will be recommended at the AGM to be appointed to the committee without ballot: they are Barbara Casadei, Andrew Grace and Derek Hausenloy. The other two committee members will be elected by ballot, so please have a careful look at the personal statements of the candidates in this issue of the Bulletin and vote for the two you think would best serve the interests of the Society, using the official ballot paper. We are very lucky to have six strong candidates in Carolyn Carr, Richard Heads, Cathy Holt, Yalda Jamshidi, Nicola King and Melanie Madhani.

It remains only to say that I hope to see many of you in Bristol. Maintaining Britain's traditional strength in cardiovascular research will depend on good young investigators coming through, so please come along to the Autumn Meeting to hear about the latest work and to see the stars of the future in action.

Chris Jackson

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BSCR Committee Nominees

Carolyn Carr

I am a senior post-doc in the Cardiac Metabolism Research Group in the Department of Physiology, Anatomy and Genetics in Oxford. I am investigating stem cell therapy following myocardial infarction using both mesenchymal stem cells isolated from the bone marrow and the endogenous cardiac stem cell population. We use high field MRI to get accurate measurements of cardiac function in rodents so that we can measure changes to heart morphology and function over a number of weeks after infarction and cell administration.

I began my career in the late '70s as a chemist at Oxford University using NMR to study organic molecules. After a career break to have children, I returned initially to Oxford chemistry and then progressed through biological chemistry to physiology and cardiovascular research.

I would like to serve on the Committee of the BSCR as I feel that collaboration between research groups within the UK is essential to promote first class research. The conferences organised by the Society allow junior researchers a useful opportunity to develop presentational skills and provide a valuable forum for the exchange of ideas which may engender such vital collaborations. I am currently involved in organizing a basic science meeting for the UK cardiovascular stem cell community and a symposium on research ethics for medical science students within Oxford University and would enjoy being involved in arranging conferences for the BSCR.

Year of first joining the Society: 2005 **Proposed by**: Kieran Clarke **Seconded by**: Sian Harding

Richard Heads

I graduated with a BSc(Hons) in Pharmacology from Portsmouth School of Pharmacy in 1983 and then undertook a PhD in Protein Biochemistry and Cell Biology in the Biophysics Department at Portsmouth, graduating in 1987. My first post-doc was in the Biochemistry Department at the University of Liverpool and following this, I moved to University College London, where my career in Cardiovascular Research began, at The Hatter Institute for Cardiovascular Studies and the Medical Molecular Biology Unit with Derek Yellon and David Latchman studying the role of stress proteins in myocardial protection. In 1996 I moved to the Cardiology Department at St Thomas's Hospital (King's College London School of Medicine) as a lecturer with Mike Marber. Currently my interests lie in studying-the role of inflammatory signaling pathways and stress-transcription coupling in gene regulation in cardioprotection and myocardial remodeling.

I have been a member of the society for approximately 15 years and have always found the BSCR meetings to be stimulating and very useful and an opportunity to share work and be part of a thriving UK Cardiovascular research community. It will be an honour to serve the society and have the opportunity to contribute more to the Society by being a committee member.

Year of first joining the Society: 1992 **Proposed by**: Michael Curtis **Seconded by**: Michael Marber

Cathy Holt

I am currently serving on the BSCR committee and am seeking to extend my term of office as I feel that I have valuable contributions to make with the experience gained during my short term of office. I was awarded a PhD from the University of Sheffield in 1989, on the involvement of the vasculature in the pathogenesis of autoimmune diseases. This sparked my interest in all things vascular and I subsequently went on to a BHF funded post doctoral position followed by appointment as Lecturer in Cardiac Sciences in 1992. In 2001, I moved to the University of Manchester as Senior Lecturer in Cardiovascular Biology. My research interests include the biology of the vessel wall and what happens following injury such as occurs during the pathogenesis of atherosclerosis and following angioplasty and stenting. I am a strong advocate of the BSCR and have spoken at various meetings held by the Society. I see the BSCR as the main forum for Cardiovascular Researchers within the UK, encompassing both vascular and myocardial biology. I was co-organiser of the Spring BSCR meeting, entitled: "Frontiers in Cardiovascular Signaling" hosted in Manchester, 2004. I am currently co-organising the 2008 BSCR meeting being held jointly with The British Cardiovascular Society. BSCR meetings are an ideal forum for graduate students to present their data and meet scientific colleagues. If re-elected to the BSCR committee I will be committed to encouraging younger members of the cardiovascular scientific community to attend and present at BSCR meetings. In addition, having spent my entire career to date in Clinical Departments, I would like to enhance the link between cardiovascular clinicians and basic scientists.

Year of first joining the Society: 1992 **Proposed by**: David Eisner **Seconded by**: Christopher Jackson

Yalda Jamshidi

I obtained my BSc in Human Genetics (1997) and PhD in Cardiovascular Genetics (2001) from University College London and I am currently a Senior Lecturer in Human Genetics at St. Georges University of London. My PhD focused on investigating the role of PPAR polymorphisms in cardiovascular disease. I subsequently spent 3 years as a post-doctoral research fellow at the Institute of Child Health investigating the molecular signalling pathways involved in cardiac hypertrophy and later a Wellcome Trust funded post-doctoral position at Kings College London examining the genetics of obesity and leptin insensitivity. I am a member of the SGUL Cardiovascular Research Committee and have recently been involved in organizing our annual symposium (Microcirculation: Abnormalities in Vascular Disease, September 2008). I have a long-standing interest in the genetics of cardiovascular related disorders such as cardiac hypertrophy, cardiomyopathy and arrhythmias. My current research focuses on analysis of SNP/genome wide association data, gene expression and protein expression arrays in a number of disease and disease-free population cohorts.

The BSCR provides cardiovascular researchers within the UK with a great opportunity to meet scientific colleagues and promote future collaborations. If elected I would like to further encourage through the BSCR a network for communication between both clinical and basic scientists involved in cardiovascular research. I will also endeavour to increase the opportunities for junior researchers to participate in BSCR activities and events; and promote interaction with other societies with overlapping interests.

Year of first joining the Society: 2006 **Proposed by**: Nicholas Carter **Seconded by**: Stephen Jeffery

Nicola King

My involvement in cardiovascular research started during my first post-doctoral position in Professor R.A. Chapman's labs in Physiology at the University of Bristol. At this time, and throughout later Research Fellowships in Professor M.-S. Suleiman's laboratories in the Bristol Heart Institute, I focused on the role of amino acids in the normal and hypertrophic heart with an emphasis on transporter expression and activity, oxidative stress and protection. In July 2006, a new adventure began when I moved overseas to join the Universiti Brunei Darussalam as Senior Lecturer in Human Biochemistry. Here, my current roles and responsibilities include leadership of the team which has founded, developed and implemented the new degree, Bachelor of Health Sciences (Biomedical Sciences). We will enroll our first cohort of students for this new Honours degree, of which I am Programme Coordinator, in August 2008.

My continuing aim as a committee member is to promote cooperation at all levels between clinical and basic scientific cardiovascular research. Such relationships are borne out of good communication for which I have the experience of facilitating team work between people of different ethnic and philosophical backgrounds in a foreign country. I also offer the unique perspective of a non-UK cardiovascular researcher which may be important in the current climate of globalization in order to meet the national and international challenge of heart disease.

Year of first joining the Society: 2003 **Proposed by**: Saadeh Suleiman **Seconded by**: Christopher Jackson

Melanie Madhani

I graduated from the University Of Wales College Of Medicine in 1998 with a BSc (Hons) in Pharmacology and obtained a PhD in Cardiology from Dartmouth College, USA and University Of Wales in 2002. I then joined University College London (UCL) as a post-doctoral research fellow, to work under Dr. Adrian Hobbs. Here, I investigated the role of cGMP in cardiovascular diseases. During my time at UCL, I was awarded a UCL Bogue Fellowship to work under Dr Louis Ignarro, University of California, Los Angeles, USA. In 2005, I joined Dr. Philip Eaton's research group at The Rayne Institute, KCL, to broaden my experience in cardiac physiology in order to complement my vascular knowledge and skills. Here, I'm currently conducting research into cGMP regulation during myocardial ischaemia reperfusion injury.

BSCR is a well respected society and I would very much like to be part of the committee.

Year of first joining the Society: 2005 **Proposed by**: Michael Curtis **Seconded by**: Michael Marber

Joint BSCR Late Spring Meeting with the British Cardiovascular Society

"Causes and Consequences of Myocardial Infarction: New Concepts"

2nd-3rd June, 2008, Manchester Central Convention Centre

A meeting report by Drs Nicola King and Nicola Smart with contributions from symposium organisers

Manchester Central Convention Centre

This year the BSCR embarked on an ambitious alternative to the usual spring meeting. This involved joining forces with the British Cardiovascular Society (BCS) to hold an inaugural joint meeting in Manchester. While the concept of a joint meeting had always appeared an attractive proposal, a number of logistical differences in the way the two Societies traditionally ran their meetings (preferred dates, local organisation, registration fees, student accommodation) had previously deterred the respective Committees. Once these tricky problems had been resolved the result was a refreshing change in routine without signs of compromise which left the participant with the satisfying sense that the joint venture had been a resounding success of mutual benefit to both Societies.

One notable difference was in the organisation of the meeting. Although BSCR meetings are traditionally organised locally by one or two individuals, the arrangements for this meeting were made through the team work of the Committee, past and present. Responsibilities for the scientific programme, abstract submission, poster and oral presentations, the conference dinner and liaison with the BCS, were allocated to various members to lighten the workload. Particular thanks are due, however, to Professors David Eisner (Chairman) and Barbara McDermott (former Secretary) for coordinating the arrangements and ensuring that all ran smoothly.

Over 120 BSCR members registered for the two day event in which the four BSCR scientific sessions ran in parallel with the BCS sessions, enabling all delegates to attend either BCS or BSCR sessions according to their interests. It was heartening to see the considerable interest shown in the BSCR sessions by BCS members and, at times, the 160-capacity lecture theatre had standing room only

The first session on 'Unstable Plaque: To Inflammation and Beyond' was chaired by Drs Cathy Holt and Chris Jackson. The audience were treated to four talks of the highest quality. Professor Erik Biessen (University of Maastricht) made light of a very early start and a throat infection to give an excellent update on his group's work on the involvement of mast cells in mouse unstable atherosclerosis. He also generously shared unpublished data on CXCL4. Next up was Professor Juan Carlos Kaski from St George's in London, giving a critical and entertaining overview of the interpretation of biomarker data for acute coronary syndromes. He highlighted the characteristics of useful biomarkers, and suggested that combinations of biomarkers may be the best route forward. Dr David Grainger (University of Cambridge) described remarkable progress towards a chemokine inhibitor-based therapy for unstable atherosclerosis. His work was a good illustration of the principle that although there are always plenty of reasons why something should not work, quite often the real world is much more accommodating of a risk-taking approach. The session was wrapped up with a tour-de-force from Professor Mark Pepys (University College London), a forthright

analysis of the status of C-reactive protein as a biomarker and as a bioactive agent.

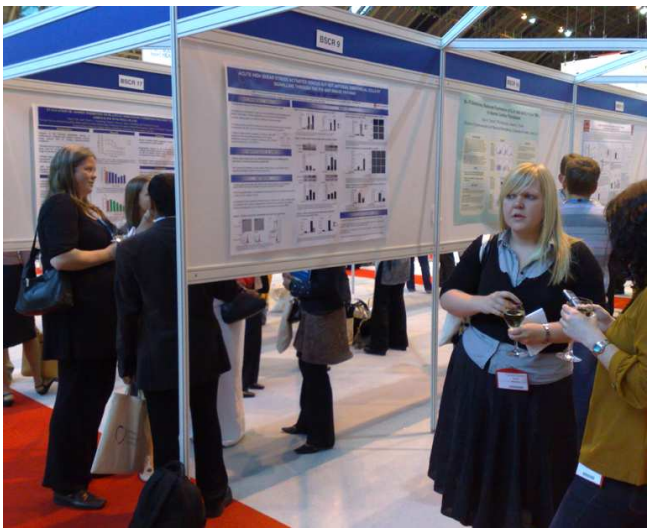
The second session, 'Targeting acute and chronic remodelling post-myocardial infarction (MI)', was chaired by Drs Gillian Gray and Nicola King. This was kicked off by Professor Allan Struthers (University of Dundee) who gave an overview from a clinical perspective, introducing the concepts of acute remodelling during infarct healing in the hours to days after MI, to the chronic remodelling in non-infarcted myocardium from months to years post-MI. His presentation then focused on the success of -adrenoreceptor antagonists and the mineralocorticoid receptor (MR) antagonist spironalactone in reducing long term remodelling in patients. The theme of MR antagonism was continued by Professor Johann Bauersachs (University Clinic, Wurzburg), showing that early intervention with eplerenone in experimental MI enhances monocyte infiltration and angiogenesis during infarct healing, resulting in improved cardiac function. Dr Nicola Smart (UCL Institute of Child Health) continued the theme of early intervention in acute remodelling. After presenting evidence for mobilisation of multipotent progenitor cells from the adult epicardium by thymosin β4, she went on to show that administration of thymosin β4 after experimental MI increased vascularisation of the infarct from the epicardium and improved cardiac function. The session was completed by Dr Emma Birks (National Heart & Lung Institute, London) who provided an elegant demonstration of reversal of ventricular remodelling following implantation of mechanical assist devices in patients with chronically failing hearts.

Professor Allan Struthers' presentation on acute remodelling post-MI

After a short break for tea, BSCR delegates joined BCS delegates to hear the BCS Keynote Lecture delivered this year by Professor Nilesh Samani (University of Leicester). Professor Samani began his talk by highlighting key milestones in the understanding of the genetic basis of disease and the dramatic progress seen, particularly in the last year, which have allowed new approaches for disease prediction and prevention, as well as opportunities for developing novel treatments and individualised therapies. Professor Samani then explored approaches to studying the genetic basis of coronary artery disease, from linkage analysis through to association analysis and described the emergence of some robust genetic variants that affect cardiovascular risk, from the BHF Family Heart Study, a genome wide linkage study. He then demonstrated how evidence from genetic findings facilitate clinical progress, with his work on the 5-lipoxygenase-activating protein (FLAP) gene and its association with the risk of MI, and how this led to investigators studying leukotriene inhibition in biomarkers associated with MI risk. Professor Samani described a strong association between locus 9p21.3 and coronary artery disease. He went on to consider the use of genetic information to identify individuals at increased risk of coronary artery disease and concluded that although this goal is achievable, there is still much work to do.

Professor Nilesh Samani

Posters were displayed in the large exhibition hall conveniently located near the main entrance. The BSCR poster session was held alongside the BCS Basic Science poster session on the Monday evening just prior to the BSCR conference dinner. The free flowing supply of canapés and wine helped to create a friendly and relaxed atmosphere for discussion and to set the mood for the dinner to come. A total of 29 posters were presented covering a wide range of topics including calcium handling, endothelial function, diabetes, signalling and the effects of ischaemia reperfusion in various settings. During this session a Young Research Worker's Prize kindly donated by 'Clinical Science' was on offer. This posed the judges a pleasant but difficult task, as they were forced to choose between posters of a consistently high standard. Eventually, the decision was made to award the prize to Paul Armstrong from



BSCR Poster Session

Barts and The London School of Medicine and Dentistry who used an adaptation of a light-transmission method in 96 well plates to show that there is a linear relationship between platelet aggregation and thromboxane A_2 production.

Paul Armstrong was awarded the *Clinical Science* Poster Prize

The BSCR dinner was held on Monday evening at the Manchester Museum of Science and Industry, preceded by a private viewing of the Body Worlds 4 exhibition. On display were more than 200 human specimens that have been preserved using the process of plastination, invented by the German anatomist, Dr Gunther von Hagens. This fascinating exhibition gave a unique insight into the human body in health and disease. This was followed by the dinner, which was served in the "Power House" alongside the world's largest collection of working steam mill engines and historic locomotives that were demonstrated to us prior to dinner.

The second day started with a glimpse of the researchers of the future, with five oral presentations by young investigators, selected from submitted abstracts. The session, chaired by Professor Barbara McDermott and Dr Michael Curtis, got underway with a presentation from Cressida Lyon (nee Beeching, Bristol Heart Institute) who described the therapeutic potential of using soluble N-cadherin to reduce atherosclerotic plaque rupture via its anti-apoptotic effects on vascular smooth muscle cells. Agnieszka Kozak (University of Edinburgh) presented the dimethylarginine dimethylaminohydrolases, endogenous NOS inhibitors, as putative modulators of ischaemic cell death post-MI. From the same laboratory, Sara McSweeney

The BSCR Dinner at the Manchester Museum of Science and Industry

described studies to address the role of the corticosteroid regenerating enzyme, 11ß-hydroxysteroid dehydrogenase type 1 in modulation of the inflammatory response during myocardial infarct healing. Kirsten Riches (University of Leeds) demonstrated how reduction in MMP-2 activation, induced by hypoxia, inhibits the capacity of human cardiac myofibroblasts to invade, and the influence this may have on myocardial remodelling post-MI. The final speaker, Youyou Zhao (Queen's University Belfast), presented her data which implicate NADPH oxidase-derived reactive oxygen species in the cardiac remodelling that occurs following doxorubicin therapy. The impressively high standard of talks presented the

Kirsten Riches was awarded the BSCR Young Investigator Prize for her oral presentation

judges with an extremely difficult task but ultimately a unanimous decision was reached to award the BSCR Prize to Kirsten Riches. Many congratulations, Kirsten!

The electrophysiological consequences of myocardial ischaemia can be the most unexpected and devastating clinically. The purpose of the third session, chaired by Professor Barbara Casadei and Dr Andrew Grace, was to consider how impaired coronary flow impacted on the myocardium to predispose to ventricular arrhythmias. Each of the speakers have an international reputation and could provide state-of-the-art presentations incorporating unpublished data and giving the audience a sneak preview of what to expect in this rapidly moving field over the next few months. Gerd Hasenfuss, Chief of Cardiology from Göttingen was first up describing his group's latest observations on the way that calcium fluxes within and across cell membranes are modified in disease considering also the specific effects of ischaemia - calcium's widespread influences were highlighted with rigorous clarity. The BSCR Chairman, David Eisner (University of Manchester), gave a masterful overview of ventricular alternans and calcium sparks making the complexities of cellular electrophysiology accessible to the audience with his wonderfully enthusiastic delivery. Professor Nicholas Peters (Imperial College) is both a scientist and a clinician and was able to give a talk that travelled across the tricky boundaries between the bench and the clinic. He considered how ischaemia influences the vulnerability of the myocardium and the influences of cellular remodelling on the substrate that provides the basis for ventricular arrhythmias and sudden cardiac death downstream of index ischaemic events. Arthur Wilde, Head of the Cardiology Department in Amsterdam has been one of the leaders in the group of outstanding individuals that have unravelled the clues to the genetic basis of sudden cardiac death. His most recent work has concerned the genetic basis of arrhythmogenesis in the context of ischaemic triggers and his presentation beautifully wrapped the session up.

In keeping with the theme of the meeting, the first three sessions focused on the causes and consequences of myocardial infarction. The final session 'Novel therapeutic developments in gene and cell therapy', chaired by Professor Andrew Baker and Dr Chris Newman, addressed the question of how the consequences may be treated. In previous years, gene and cell therapy was presented almost as a futuristic vision but, as clearly demonstrated in this session, the first clinical trials are not only underway but already yielding valuable insight. Professor Sian Harding (National Heart and Lung Institute, Imperial College) opened the session by outlining the trials soon to commence in the UK and the US in which the gene for SERCA2a, responsible for re-uptake of calcium into the SR and which has been shown to reverse some of the clinical symptoms of heart failure, will be delivered using a replication-deficient adeno-associated viral vector (AAV6) by placement of a catheter into the coronary arteries of heart failure patients. While the first UK trial aims to determine the safety and feasibility of AAV6-CMV-SERCA2a, the ultimate goal is to apply SERCA2a gene therapy to all suitable patients with heart failure. Continuing the theme of clinical trials, Professor Keith Channon (Oxford) provided an exciting update on the ongoing multicentre study of HIF1 gene transfer for the treatment of peripheral and myocardial vascular disease. Combining both gene and cell therapy approaches for the treatment of angiogenesis, Professor Paolo Madeddu (Bristol Heart Institute) described the identification of novel angiogenic factors and their therapeutic application before going on to discuss stem cell transplantation for therapeutic angiogenesis. The tremendous potential for using stem cells to repair the damaged heart was elaborated by Dr Anthony Mathur (Barts and the London). Dr Mathur summarised current understanding of the use of autologous stem cells in the treatment of heart disease based on results of published and ongoing clinical trials and ended by considering whether autologous adult stem cells will ever have the potential to achieve cardiac regeneration.

A fitting end to a highly stimulating meeting was the BCS lecture by Professor Michael Schneider (Imperial College), entitled "Death and Regeneration: Cardiac Muscle Cell Number as a Therapeutic Target". Professor Schneider very eloquently presented the

Professor Michael Schneider

problem of cardiac muscle cell number and, in particular, the inadequate capacity of the mammalian heart to undergo self-repair, virtually thwarting functional recovery from heart disease. One approach explored by Professor Schneider was to dissect genetic circuits that impose the irreversible block on cell cycling in post-mitotic cardiomyocytes, work that led to the identification of Rb and p130 which together are critically required for cardiomyocyte growth arrest. Phenomenally, a 500 fold increase in myocardial cell cycling is observed upon deletion of both p130 and Rb, offering a promising strategy for cardiac regeneration. Professor Schneider then went on to describe how studying pathways implicated in embryonic cardiogenesis, such as the Wnt/ -catenin pathway may offer clues for stimulating regeneration of the adult heart. He described how the use of genome-wide expression profiling and RNA interference uncovered an essential role for Sox17 in cardiogenesis downstream of this pathway. Sox17 acts by controlling Hex, a transcription factor required for endodermal cells to make the heart-inducing factors that pattern primitive mesoderm. Professor Schneider ended his extraordinary lecture by describing another approach adopted by his laboratory, namely to rescue cardiac cell number by alleviating apoptotic cell death; as an example of this, he showed that forced expression of Bcl-2 or telomerase reverse transcriptase in mouse myocardium reduces infarct size. The overall message was that there are very many promising avenues to both minimise cardiomyocyte loss and promote myocardial regeneration which may eventually tip the balance and enable myocardial survival following infarction. We left the meeting encouraged and with the anticipation that the various gene and cell therapies discussed are perhaps a few steps closer to becoming a reality for repairing the injured human heart.

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
21 (4)	***October 2008***	*1st September*
22 (1)	***January 2009***	*1st December*
22 (2)	***April 2009***	*1st March*
22 (3)	***July 2009***	*1st June*

Articles for *The* Buletin

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)

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Young Investigators Meeting – Autumn 2008

Cell Signalling in Cardiovascular Disease: Life or Death

Provisional Programme

Monday 15th September

11.00 BSCR Committee meeting

12.00 Registration

12.50 Buffet Lunch

13.50 Welcome and Introduction

Session 1: Smooth Muscle Cells

14.00 ***Smooth muscle cell death in atherosclerosis - causes and consequences***
Professor Martin Bennett (Cambridge)

14.30 Free Communication from selected abstracts

14.45 Free Communication from selected abstracts

15.00 ***Cadherins and the Wnt pathway in regulation of smooth muscle cell behaviour***
Dr Sarah George (Bristol)

15.30 BSCR AGM and Break

Session 2: Young Investigator Award (PhD Students)

16.30 Communication 1

16.45 Communication 2

17.00 Communication 3

17.15 Communication 4

Session 3: Posters

17.30 Posters #1 and Wine Reception

19.45 Conference Dinner (Goldney Hall, University of Bristol)

Tuesday 16th September

Session 4: Myocardium

09.00 ***Gene therapy for the failing heart***
Professor Andrew Baker (Glasgow)

09.30 Free Communication from selected abstracts

09.45 Free Communication from selected abstracts

10.00 ***Reactive oxygen species and heart failure***
Professor Barbara Casadei (Oxford)

10.30 Break

Session 5: Inflammatory Cells

11.00 ***New anti-inflammatory approaches to reduce monocyte recruitment and macrophage activation in atherosclerosis***
Dr David Greaves (Oxford)

11.30 Free Communication from selected abstracts

11.45 Free Communication from selected abstracts

12.00 ***Homeostatic and inflammatory responses in arteries***
Professor Dorian Haskard (London)

12.30 Buffet Lunch and Posters #2

Session 6: Endothelial Cells

14.00 ***Controlling sprouting angiogenesis - a tale of leaders and followers***
Dr Holger Gerhardt (London)

14.30 Free Communication from selected abstracts

14.45 Free Communication from selected abstracts

15.00 ***Vascular endothelial growth factor and cardiovascular disease***
Professor David Bates (Bristol)

15.30 Prize giving and meeting close

Travel Report: Weinstein Cardiovascular Conference 2008 Meeting Report

by Kelly Lammerts van Bueren, UCL Institute of Child Health

The 2008 Weinstein meeting brought together scientists from across America, Europe and Asia to Houston, Texas, the 4th largest city in the USA and home to the 4th largest shopping mall, conveniently located just across the road from the hotel! Coming from a cold and wet London, I was looking forward to experiencing the hot, humid climate of Texas. However, I realised too late that Houston is known as "the most air-conditioned place on Earth" and I had failed to dress appropriately. Nevertheless, Houston proved the perfect host to one of the premier conferences in cardiovascular development.

J.W. Marriott Hotel, Houston, Texas

The annual Weinstein conference, founded by Dr Constance Weinstein in 1994, focuses on normal and abnormal development of the heart and vasculature and its relationship to human disease. This conference is unique in that it is not affiliated with any scientific society and all talks are chosen from submitted abstracts. This provides an opportunity for students and young scientists to speak at an international forum with the emphasis on sharing new and unpublished work.

This year the 3 day meeting was hosted by the Texas A&M System Health Science Centre at the JW Marriott Hotel, Houston, Texas. Nearly 200 abstracts were submitted from which 47 were chosen for platform presentations. These talks covered nearly all aspects of cardiovascular development which made for an

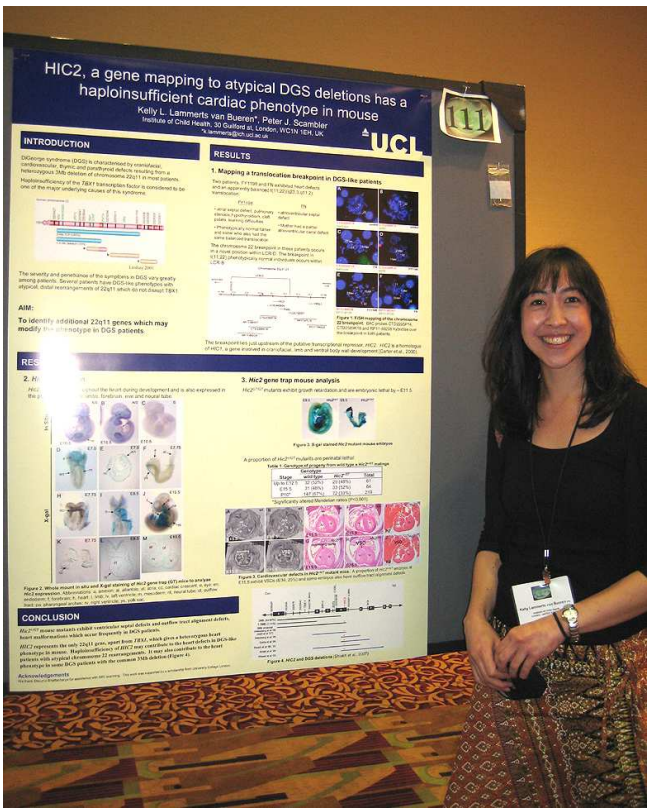
Houston Galleria Mall

intense but interesting 3 days! The conference began with a session on cardiovascular biology, in which Chinmay Trivedi, University of Pennsylvania School of Medicine, described a genetic interaction between Hopx and Hdac2. She showed that double knockout mice exhibit cardiovascular defects which suggest that these genes are important for regulating cardiac structural and proliferation pathways.

The second session on vascular development included a presentation by one of the members of our lab, Amelie Calmont, on the role of Gbx2 in pharyngeal arch artery development. She demonstrated that Gbx2 genetically interacts with Tbx1 in the pharyngeal ectoderm to control 4th arch artery formation. This interaction involves regulation of the Slit/Robo pathway which potentially mediates correct neural crest migration.

The last session of the day was on the second heart field (SHF) in which both Eon Joo Park, University of Utah and Jue Zhang, Texas A&M Health Science Centre demonstrated how Fgf signalling regulates outflow tract development. Both investigators showed that Fgf signals originating from SHF mesoderm primarily act in an autocrine manner to regulate proliferation of OFT precursors and induction of signals for epithelial to mesenchymal transformation.

The keynote presentation at this year's meeting



My Poster Presentation

was given by Dr. Eric Olson, Professor and Chair, Department of Molecular Biology, University of Texas Southwestern Medical Centre, who has dedicated his career to understanding the mechanisms controlling muscle development. Dr. Olson has trained over 50 PhD students in his lab, of which several have gone on to become successful principal investigators themselves in the field of heart development. During his talk, Dr, Olson described the history of his research into the regulatory pathways important for muscle development and showed how it has led to his most recent work on the role of microRNAs in cardiovascular disease. In addition to conducting groundbreaking basic research, he has also co-founded several companies which focus on translating his research into therapeutics for heart disease.

The first session of the next day continued on the topic of the second heart field. This time, several talks focused on the role of Bmp signalling in development of the SHF-derived outflow tract and right ventricle. Jun Wang, Texas A&M System Health Science Centre, demonstrated that Bmp2 and Bmp4 in the SHF are required for normal cushion morphogenesis and expansion of cardiac neural crest cells. In a complementary study, John Klingensmith, Duke University Medical Centre, showed that the Bmp receptor, Bmpr1a is also required within the SHF to regulate outflow tract and right ventricle development. Thus, similar to Fgf signalling, Bmp signalling may also act in an autocrine manner within the SHF to control development.

Another talk in this session given by Kimberley Cordes, Gladstone Institute of Cardiovascular Disease, showed that abrogating microRNA biogenesis within the SHF leads to a loss of SHF derivatives, demonstrating an important role for microRNAs in this tissue. Specifically, she showed that Srf, Myocd and Nkx2.5 synergistically activate miR-143 and -145 in cardiac progenitors and miR-145 is necessary for Myocardin-dependent smooth muscle conversion.

In the next session on the cardiac conduction system (CCS), Allison Haaning, Cincinnati Children's Hospital, described the relationship between the CCS and left-right patterning. Using the Zic3 heterotaxy mutant crossed to transgenic CCS-lacZ mice, she showed that the CCS was disorganised and failed to properly mature throughout development. This model should provide a useful tool to dissect the mechanisms underlying CCS development and pattern formation.

Concurrent workshops were held on two afternoons to discuss topical issues in the field of cardiovascular development. The first 2 workshops were on cardiac progenitors and microRNAs. In the cardiac progenitor session, Ken Chien, Massachusetts General Hospital described his work on defining a human heart cell lineage map and led a discussion on the inherent variability among different stem cells lines in their cardiogenic potential and the problems with using induced pluripotent stem cells vs embryonic stem cells. Also in this workshop, Robert Kelly, Developmental Biology Institute of Marseilles discussed the existence of distinct subdomains within the SHF and Eldad Tzahor, Weizmann Institute of Science, showed that there is significant developmental heterogeneity in head muscle development similar to the heart.

The role of Shh signalling in different aspects of cardiovascular development was a major topic in the next session on signalling pathways in cardiogenesis. In the first of 3 talks on Shh, Mary Hutson, Duke University Medical Centre demonstrated that blocking Shh signalling in neural crest-ablated chick embryos surprisingly rescues OFT septation defects by causing a dorsalisation of the neural tube and respecifying neural crest-like cells. Deborah Yelon, Skirball Institute of Biomolecular Medicine showed that in zebrafish, Shh is required to define the optimal number of

cardiomyocytes early in development and Andrew Hoffmann, University of Chicago revealed that disrupting Shh signalling in the posterior splanchnic mesoderm results in atrial and atrioventricular septal defects in the mouse.

The next session on valvulogenesis contained an interesting talk by Joy Lincoln, University of Miami on a novel role for the transcription factor, Scleraxis in heart valve formation. She showed that Scleraxis is required during remodelling for cell lineage differentiation and matrix deposition and is also required for connective tissue homeostasis in mature valves.

Following the talks, the second evening's poster session gave me the chance to discuss my work and gain feedback from the many experts in attendance. We also took the opportunity that night to go out for dinner and enjoy some of Houston's huge but delicious steaks!

Houston's enormous steaks!

The final day started with talks on stem cells and reprogramming. This session revealed the work of numerous groups into a novel myocardial lineage derived from the epicardium. Bin Zhou, Harvard Medical School and Chen-Leng Cai, Mount Sinai School of Medicine demonstrated that Wt1 and Tbx18-expressing epicardial cells in the embryo contribute to myocytes of the heart, in addition to smooth muscle cells, cardiac fibroblasts and endothelial cells during development. However, it still remains to be determined whether these epicardial cells retain their pluripotency in the adult heart and whether they can be used for cardiac repair and regeneration. In this respect, Jay Schneider, University of Texas Southwestern Medical Centre, has been investigating how synthetic small-molecules may promote cardiac differentiation in epicardial stem cells in order to identify new drugs to induce endogenous stem cell repair after injury.

The next session on transcriptional regulation included an interesting talk by Marcelo Nobrega, University of Chicago, on defining the genomic regulatory regions which regulate heart development. Using an unbiased screen to identify enhancers within the 500Kb Tbx20 locus, he showed that multiple, conserved enhancers direct expression to the heart in both a complementary and redundant fashion. However, instead of acting in an independent, additive manner to regulate gene expression, the enhancers are organised according to a hierarchy where some are required for the activity of others.

One of the workshops following this session also concerned transcriptional regulation and chromatin. Brian Black, University of California San Francisco, revealed some of his research into a transcriptional code for endothelial development which includes a highly conserved enhancer containing a non-canonical Fox:Ets motif. Benoit Bruneau, Gladstone Institute of Cardiovascular Research, demonstrated the importance of the Baf60 chromatin remodelling complex in potentiating transactivation. He showed through transient transfection of E6.5 mouse embryos that cardiac differentiation can be induced in vivo just by adding the cardiac transcription factors, Tbx5 and Gata4 in the presence of Baf60.

The final session of the conference was based around emerging issues in cardiovascular development. Benoit Bruneau gave an interesting talk on the evolution of the interventricular septum by analysing Tbx5 expression in reptilian hearts. In addition, Bernard Thienpont, University of Leuven, demonstrated the power of Array Comparative Genomic Hybridisation in detecting submicroscopic chromosomal imbalances which may be the underlying cause of congenital heart defects.

The conference was concluded with a banquet at which we were entertained by none other than Eric Olson and his band, The Transactivators who got us all on the dance floor with covers of old rock and roll tunes!

Eric Olson and the Transactivators

On our last day in Houston, we visited NASA's Johnson Space Centre, where the first manned space flight to the moon was launched. A tram tour around the complex visiting mission control, seeing where astronauts train and viewing one of the huge space rockets up close were just some of the highlights of the trip.

Overall, the variety and quality of the talks and posters ensured a very successful meeting. I really enjoyed this opportunity to learn about and discuss the latest heart research in a friendly and informal atmosphere. Many thanks to the local Weinstein committee, BradAmendt, Antonio Baldini, Yasuhide Furuta, Elizabeth Illingworth, Randy Johnson, Aarif Khakoo, Jim Martin, Pierre McCrea and Robert Schwartz for organising such an interesting conference. Next year's meeting which will be held in San Francisco, May 7-9 promises to be just as good if not better! I hope to see you all there!

NASA's Johnson Space Centre

Space Rocket

Cardiovascular Meetings

ESC Annual Congress 2008, 30th August 2008 - 3rd September 2008 Münich, Germany. Further information can be found at: http://www.escardio.org/

Keystone Symposium: Metabolism and Cardiovascular Risk will take place in Breckenridge, Colorado on 23-28 September, 2008. For details of this and other Keystone Symposia, visit: http://www.keystonesymposia.org

Mitochondrial Biology in Cardiovascular Health and Disease Conference to be held at the National Institutes of Health, Bethesda, Maryland on 6th-7th October, 2008. Further information regarding the programme, registration and abstract submission can be obtained from http://www.mitochondrial2008.com/

2008 Scientific Sessions of the American Heart Association will be held at the Ernest N. Morial Convention Center, New Orelans, Louisiana on 8th-12th November. All details including key dates can be found at: http://scientificsessions.americanheart.org/portal/scientificsessions/ss

British Pharmacological Society 2008 Winter Meeting, 18 December 2008, Brighton, UK. Mending a broken heart: Advances and challenges of stem cell therapy. Further information regarding the programme can be obtained by contacting Prof. Anwar Baydoun (University of Hertfordshire, UK) or online at http://www.bps.ac.uk

Keystone Symposium on Cardiac Disease: Development, Regeneration and Repair, organised by Michael D. Schneider and Nadia A. Rosenthal, will be held at Grove Park Inn, Asheville, NC on March 15 - 20, 2009. Further details can be found at http://www.keystonesymposia.org/

7-9 May 2009, Focused Meeting: New Drugs in Cardiovascular Research. Joint Meeting with the German Societies for Pharmacology & Clinical Pharmacology.Dresden, Germany. Early bird registration deadline: 31 January 2009. Further information regarding the programme, registration and abstract submission can be obtained http://www.bps.ac.uk

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!

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

WINTER BSCR WORKSHOP 2008

A joint workshop with the British Heart Foundation

"NEW FRONTIERS IN CARDIOPROTECTION"

DATE: Monday 1st December, 2008

VENUE: The Elias Library,
3rd Floor, The Hatter Cardiovascular Institute,
University College London,
London, WC1E 6HX.

ORGANISORS: Dr Derek Hausenloy & Prof Derek Yellon

STRUCTURE: This BSCR Winter Workshop will be a one day symposium comprising presentations from National and International speakers interspersed with plenty of time for discussion.

PROGRAMME (with confirmed speakers)**:**

1. Cardioprotection: Lost in translation	Prof Lionel Opie	Cape Town, South Africa
2. Ischaemic Postconditioning	Prof Michel Ovize	Lyon, France
	Prof Michael Marber	London, UK
3. Remote Ischaemic Pre/Postconditioning	Prof Hans Bøtker	Copenhagen, Denmark
	Dr Rajesh Kharbanda	Oxford, UK
	Mr Michael Gaunt	Cambridge, UK
4. Adenosine and its agonists	Prof James Downey	Alabama, US
5. Metabolic Modulation in AMI	Prof Lionel Opie	Cape Town, S Africa
6. The RISK Pathway-Erythropoietin	Dr Derek Hausenloy	London, UK
7. The RISK Pathway-Natriuretic Peptides	Prof Gary Baxter	Cardiff, Wales
8.The Mitochondrial Permeability Transition Pore	Prof Andrew Halestrap	Bristol, UK
	Prof Michel Ovize	Lyon, France
9. Imaging Cardioprotection using Cardiac MRI	Dr Stuart Cook	London, UK
10. Comorbidites and Cardioprotection	Prof Derek Yellon	London, UK
11. Adipocytokines and Cardioprotection	Dr Chris Smith	London, UK

Attendance is limited to BSCR members only (www.bscr.org) and places are strictly limited to the first 50 interested participants. *Please contact:* Dr Derek Hausenloy E-mail – d.hausenloy@ucl.ac.uk

British Heart Foundation Grants

January to May 2008

Research Excellence Awards

Professor J Mullins, University of Edinburgh £7,600,000

Professor M D Schneider, Imperial College London £8,900,000

Professor A M Shah, King's College London £9,000,000

Professor H W Watkins, University of Oxford £8,400,000

Strategic Initiative Grant

Professor H W Watkins, University of Oxford. "Cardiovascular medicine laboratory – conversion works" £1,955,350

Infrastructure Grant

Professor R I Lechler, King's College London. "Cardiovascular clinical research facility – building works" £500,000

Special Project Grants

ESRC"UKCRC Public Health Research Centres of Excellence (Newcastle, Cardiff, Belfast, Cambridge and Nottingham)" £2,500,000

Professor M J Brown, University of Cambridge. "A program for prevention and treatment of resistant hypertension with algorithm based therapy (PATHWAY)" 5 years £1,740,984

Mr P J Kirkpatrick et al, University of Cambridge. "Simvastatin for aneurysmal subarachnoid haemorrhage (STASH) - a multi-centre randomised controlled clinical phase III study" 3 years £1,251,331

Professor P J Scambler, University College London. "A four year, interdisciplinary, PhD studentship programme: Complexity in cardiovascular biomedicine" 7 years £1,500,000

Professor A F Dominiczak, University of Glasgow. "Collaborative strategy for a definitive genome scan in essential hypertension: high fidelity phenotyping and 'hypercontrols" 3 years £861,456

Professor A Ahluwalia et al, University College London. "Investigation of the benefits of dietary and non-dietary sources of nitrate/nitrite on cardiovascular disease: mechanisms and cellular target" 3 years £494,518

Programme Grants

Professor A P Halestrap et al, University of Bristol. "The role of mitochondria in the life and death of the heart" 5 years (renewal; years 6-10), £834,066

Professor N W Morrell, University of Cambridge". Cellular and molecular mechanisms of pulmonary arterial hypertension due to mutations in BMPR-II" 5 years (renewal; years 6-10), £1,286,688

Dr P R Riley, University College London. "Lineage characterisation of adult EPDCs: stemness, multipotency and contributions to cardiovascular homoeostasis and endogenous repair" 5 years, £1,090,811

Professor P J Grant et al, University of Leeds. "Inhibition of factor XIII/fibrin interactions: Impact on in vitro and in vivo thrombus formation" 3 years (renewal: years 6-8), £316,151

Dr G Lombardi & Professor R Lechler, King's College London. "Manipulating regulatory T cells to promote clinical transplant tolerance" 5 years (renewal: years 6-10), £1,245,538

Professor R C Tremabth, King's College London. "The molecular genetics basis of pulmonary arterial hypertension" 5 years (renewal: years 7.5-11.5), £978,895

Project Grants

Prof P G Camici et al, MRC Clinical Sciences Centre. "Coronary microvascular dysfunction is the link between cardiovascular risk and rheumatic diseases" (1 year) £78,902

Dr H Philippou et al, University of Leeds. "Homocysteinylation of end-stage coagulation proteins: effects on fibrin structure/function in relation to cardiovascular risk" (3 years) £148,715

Dr A J Vidal-Puig et al University of Cambridge. "Plasmalogen lipids: role in obesity, insulin resistance and atherosclerosis" (2 years) £145,520

Dr M Bond & Prof A C Newby University of Bristol. "Regulation of Skp2 expression during vascular smooth muscle cell phenotypic modulation and neointima formation" (3 years) £185,807

Prof T Sethi & Prof D E Newby University of Edinburgh. "Role of Galectin-3 in atherogenesis" (1.5 years) £118,645

Dr M Lei et al University of Manchester, "Generation and initial characterisation of a conditional cardiac specific gene deletion of the P21 activated kinase-1" (3 years) £167,910

Dr K Hentges, University of Manchester. “Identification of an essential gene for cardiovascular development from studies on the *L11Jus8* mutant mouse” (3 years), £154,307

Dr S Kasparov et al University of Bristol. “Purinergic mechanisms in central sympathetic chemosensitivity. Role in pathophysiology of heart failure” (3 years) £329,279

Dr M D Randall & Dr S P H Alexander, University of Nottingham. “Cannabinoid-like novel fatty acid amides: vascular function and obesity” (2 years) £101,440

Dr D A Slatter & Dr R W Farndale University of Cambridge. “Vascular protein binding sites in heterotrimeric collagens” (3 years) £197,552

Prof R S Bonser et al University of Birmingham. “Enhancing patient protection in aortic arch surgery” (3 years) £213,893

Prof G F Baxter, Cardiff University “Serotonin-associated injury and survival signalling in myocardium: receptor-dependent and non-receptor targets for cytoprotection” (3 years) £141,823

Dr J V Patel et al University of Birmingham. “ Diabetes health, residence & metabolism in Asians: the DHRMA study” (2 years) £73,578

Dr R M A Sitsapesan University of Bristol. “Functional investigations of Mitsugumin23, a novel cation channel of cardiac sarcoplasmic reticulum” (1 year) £39,341

Dr R P Choudhury et al University of Oxford. “Optical coherence tomography: molecular and cellular imaging in atherosclerosis” (3 years) £169,730

Dr P C Evans et al Imperial College London. “Does the transcription factor NRF2 protect arteries from inflammation and atherosclerosis?” (2 years) £108,392

Dr S Egginton et al University of Birmingham. “The role of platelet surface receptors in angiogenesis” (3 years) £174,639

Prof D Noble CBE University of Oxford. “Determinants of repolarisation reserve and their dependence on pathology” (2.5 years) £172,515

Prof M T Kearney et al University of Leeds. “Predicting all cause mortality and mode of death in patients with chronic heart failure” (3 years) £166,228

Intermediate Research Fellowships

Dr N Smart, UCL Institute of Child Health. "Investigating the potential for Thymosin β4-induced neovascularisation in cardioprotection" (4 years) £505,130.

Dr S D Bamforth, University of Newcastle. “Cell autonomous mechanisms in aortic arch development” (4 years) £489,849

Dr G S Cottrell, University of Bath “Investigation of the mechanisms and functions of the post-endocytic sorting of the receptors for calcitonin gene-related peptide and adrenomedullin” (4 years) £362,482

PhD Studentships

Ms J Withall University of Bristol. “Can community-based social marketing increase recruitment and retention of low-income groups into local health programmes?” (3 years) £73,913

Miss C Kleinert Imperial College London. “Mechanisms of myocardial insulin resistance in patients with T2DM or LVD and characterisation of the effects of insulin resistance on cardiac gene expression”(3 years) £97,939

Mr K S Mascall University of Aberdeen “The importance of sphingolipids in the development of cerebral artery vasospasm” (3 years) £92,548

Unnamed and Dr H Zhang University of Manchester. “Defining the substrates for arrhythmia in the short QT syndrome” (3 years) £80,297

Miss A Brock, St George’s University of London. “Ethnic differences in dietary patterns in children and their contribution to emerging differences in cardiovascular disease and type 2 diabetes" (3 years) £98,736

Mr C Nash, University of Birmingham. “Investigation of the role of the adapter Dok-3 in platelets and Megakaryocytes”(3 years) £106,308

Unnamed and Dr C L Jackson University of Bristol. “Involvement of the vitamin D pathway in plaque development” (3 years) £92,225

Miss D Gruszka University of York. “Structural and functional studies of a Staphylococcus aureus protein involved in biofilm formation” (3 years) £87,172

Clinical Research Training Fellowships

Dr K E Robertson, University of Glasgow. “Optimisation and analysis of integrating and non-integrating lentiviruses for vascular gene transfer in vivo-application to in-stent restenosis with delivery of Nogo-B” (3 years) £148,557

Dr A L Kyriacou, Imperial College London. “Maximising clinical applicability of non-invasive methods for optimization of cardiac pacemakers and effect of optimisation on cardiac efficiency" (3 years) £207,083

Dr A Flett, University College London. “The development and clinical application of quantifying diffuse myocardial fibrosis using equilibrium contrast cardiovascular magnetic resonance” (2 years) £123,292

Dr E H Berger Imperial, College London. “A drop in the ocean; from calcium waves to arrhythmia” (2 years) £114,900

Cardiovascular Related Wellcome Trust Grants

January to May 2008

Project Grants

Dr Margaret Rayman, Sch of Biomedical & Life Sciences, University of Surrey, Guildford. Can Restoration of Adequate Selenium Status in Selenium-Deficient Pregnant Women Reduce Markers of Risk for Pre-eclampsia? 36 months £196,132

Dr Anne-Marie Minihane, School of Food Biosciences, University of Reading. Apolipoprotein E genotype as a determinant of the LDL-cholesterol response to dietary fat manipulation 30 months £283,686

Dr Simon M Hughes, MRC Muscle & Cell Motility Unit, The Randall Institute, King's College London. In vivo analysis of mechanisms underlying muscle sarcomere assembly 36 months £214,760

Dr Michael Emerson, National Heart & Lung Institute, Imperial College London. Characterisation of the Distinct Role of Isoform 4 of the Plasma Membrane Calcium ATPase in Platelets 18 months £75,552

Prof Nishi Chaturvedi, Dept of Clinical Pharmacology, National Heart & Lung Institute, Imperial College London at St Mary's. Ocular disease in older age in South Asians, African Caribbeans and Europeans in the UK - SABRE Eye 6 months £77,496

Research Training Fellowship

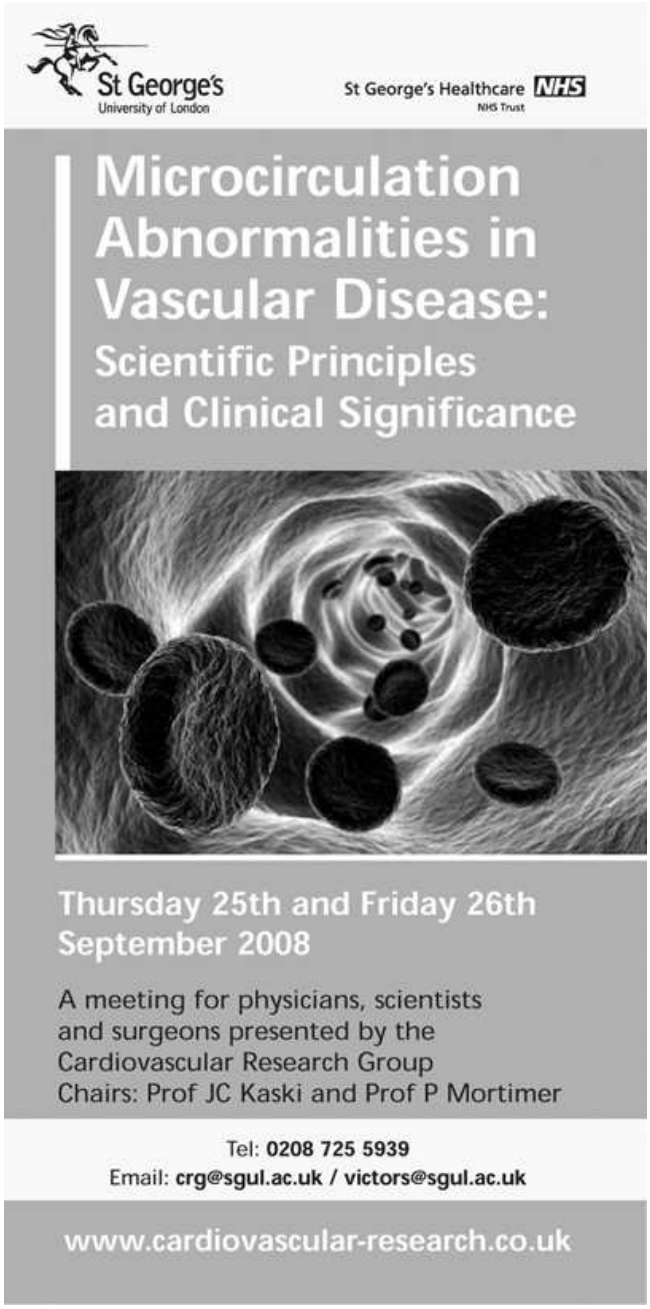
Mr Reza Motallebzadeth, Dept of Surgery, Addenbrooke's Hospital, University of Cambridge. Ectopic lymphoid tissue development in chronic allograft vasculopathy 36 months £283,666

Programme Grants

Prof Jane A Mitchell, Cardiothoracic Pharmacology, Imperial College London, National Heart & Lung Institute. Understanding the role of cyclo-oxygenase isoforms in cardiovascular health and disease 60 months £977,132

Prof Stephen Tollman, Dept of Community Health, Univ of the Witwatersrand, Parktown South Africa. Health, population and social transitions in rural Southern Africa: Elucidating pathways and testing interventions 60 months £2,774,321

Prof Tazeen H Jafar, Department of Medicine, Aga Khan University, Karachi Pakistan. Control of Blood Pressure and Risk Attenuation (COBRA)-Pakistan 6 months £50,315



Young Investigators Meeting Autumn 2008

Cell Signalling in Cardiovascular Disease: Life or Death

Dates: Monday 15th and Tuesday 16th September, 2008

Venue: University of Bristol

Organisers: Joanne Ferguson, Elinor Griffiths, Jason Johnson, Cressida Lyon and Oliver Stone

Objectives: To give a forum for early career scientists such as PhD and MD students and post-doctoral scientists (within 7 years of gaining a higher degree), the opportunity to highlight their research findings regarding the cellular mechanisms that underlie cardiovascular disease.

Programme: The programme will consist of state-of-the-art presentations by leaders in the field. Speakers will include: Martin Bennett (Cambridge), Sarah George (Bristol), Andrew Baker (Glasgow), Barbara Casadei (Oxford), David Greaves (Oxford), Dorian Haskard (London), Holger Gerhardt (London) and David Bates (Bristol).

Free Communications: Much of the meeting will be devoted to oral presentation of selected abstracts, and posters. There are two prizes of £250 each: the Clinical Science Young Investigator Award and the BSCR Young Investigator Award.

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

Deadlines:	Submission of abstracts	Friday 8th August
	Registration	Friday 29th August

Eligibility: Anyone can attend the meeting, but Free Communications will only be accepted from young investigators (up to 7 years post-higher degree).