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Contents

Editorial

Welcome to the July 2007 issue of *The* Bulletin!

Our review for this issue 'Are endocannabinoids Cardioprotective?: a current perspective', written by Simon Kennedy and colleagues at Strathclyde Institute of Pharmacy and Biomedical Science, evaluates the cardioprotective effect, mechanisms of action and therapeutic potential of cannabinoid-derived drugs.

Another "reshuffle" of the BSCR Executive Committee will soon occur as four current members reach the end of their term of office. With eight nominations to replace them, an election is once again required. We include profiles and personal statements of all nominees to assist you with your vote, using the official stamped ballot form included as an insert with this issue of *The* Bulletin.

Following the Autumn 2006 Joint BSCR/BAS Meeting, Peter Weinberg provides a report of the proceedings discussing 'Biomechanical Signalling in Atherosclerosis'.

Last year saw Dr Nicola King, BSCR Committee member, move from the Bristol Heart Institute to take up a position at the Institute of Medicine, Universiti Brunei Darussalam. Nicola shares this fascinating experience with us in her "Postcard from Brunei".

The Summer conference season has started. It was delightful to see many BSCR members at the recent ISHR World Congress and we willl include a report from Bologna in the next issue. In this issue, Anabelle Chase reports from Chicago on the AHA Arteriosclerosis, Thrombosis and Vascular Biology Meeting and Catherine Risebro shares tales from the Weinstein Cardiovascular Development Conference in Indianapolis. To all who are heading off on their travels soon, we wish you an enjoyable trip and please contact us if you wish to write a report for *The* Bulletin.

Helen Maddock and Nicola Smart

Are endocannabinoids cardioprotective?: a current perspective

by Emma Robinson, Kathleen A. Kane & Simon Kennedy*

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Although the psychotropic effects of cannabinoids have been appreciated for centuries, several comparatively recent discoveries have renewed interest in the therapeutic potential of cannabinoid-derived drugs. The identification of at least two cannabinoid receptors and the discovery of endogenous generation of several putative endocannabinoids by peripheral tissues has led to speculation that these compounds may have a role in cardiovascular heath and disease. Although there is some published evidence for a cardioprotective effect of endocannabinoids, the mechanism is still controversial. In the majority of arterial preparations, endocannabinoids mediate vasodilation, possibly via generation of secondary vasodilators such as sphingosine-1-phosphate and prostaglandins and this could be one factor which contributes to their cardioprotective effects. This review will examine the evidence for a cardioprotective effect of endocannabinoids and the mechanisms, in particular the vasodilator response, which could produce cardioprotection in the ischaemic-reperfused heart.

Introduction

Cannabis, derived from the hemp plant, has been in recreational and medicinal use for thousands of years and continues to be used as such today. Medicinal uses of cannabinoids are to some extent hampered by the insolubility of the compounds and the psychotropic effects which accompany their use. The main active constituent of the cannabis plant, Δ9-tetrahydrocannabinol was first isolated by Mechoulam in 1964 [1] and led to a search for cannabinoid receptors in the body and endogenous activators of these receptors. Over 40 years on, our understanding of cannabinoids, endocannabinoids and cannabinoid receptors is still incomplete. However, it is now apparent that cannabinoid receptors exist outwith the central nervous system and several different endocannabinoids are generated by cells within the cardiovascular system. Recent evidence, which will be examined in this review, has suggested that endocannabinoids exert important vascular effects in the coronary circulation and that these effects may be protective under certain circumstances.

Cannabinoid Receptors and Endocannabinoids

Interest in the pharmacological use of cannabinoids was relatively limited until the discovery of a specific endogenous stereoselective cannabinoid receptor in the brain [2,3]. Subsequently this was named the CB_1 receptor and was followed by the discovery of a second receptor, CB_2 cloned from spleen [4]. Current evidence suggests that CB_1 receptors are also found outwith the brain on peripheral nerves and the testis while CB_2 receptors are primarily found on immune cells [5]. Apart from a CB_1 splice variant, recent evidence suggests a novel and as yet uncharacterised receptor subtype in rat isolated hearts [6,7]. Interestingly, it is this uncharacterised receptor which appears to mediate the reduction in infarct size induced by the endocannabinoid anandamide in the rat heart and it may therefore represent an important therapeutic target. Importantly, cannabinoids may well exert effects via pathways which do not involve cannabinoid receptors and the absence of cannabinoid receptors from a particular tissue does not imply an insensitivity of that tissue to locally-derived or circulating cannabinoids.

CB_1 and CB_2 are both G-protein coupled receptors and activation inhibits activity of adenylate cyclase and generation of cAMP [8]. In addition, activation of the CB_1 receptor modulates ion channels

including several voltage sensitive calcium channels and inward rectifying potassium channels (for review see [9]). Since activating potassium channels produces a hyperpolarisation of the vascular smooth muscle cell, the cannabinoid anandamide has in fact been proposed as an endothelium-derived hyperpolarising factor (EDHF) in the rat coronary artery [10]. CB_2 receptors do not seem to signal through ion channels but may exert important effects on cell survival and proliferation [11]. However, the situation is more complicated and it is becoming clear that cannabinoid signalling mechanisms may depend on the species and tissue studied [12]. Recent published evidence as well as some of our own data which we will present later indicates that cannabinoids may signal through ceramide and generation of sphinogsine-1-phosphate [13,14].

Identification of cannabinoid receptors implied the presence of endogenous ligands and rapidly led to the discovery of endogenous cannabinoids or endocannabinoids. The first endocannabinoid to be identified was anandamide, an ethanolamide of arachidonic acid [2] and the second was 2-arachidonyl glycerol (2-AG) [15]. The latter is reportedly the endogenous ligand of CB_2 receptors expressed in the immune system [16]. Subsequently identified endogenous ligands for the cannabinoid receptors include N-arachidonoyldopamine (NADA) and arachidonyl glycerol ether (noladin ether). Anandamide is formed by the action of a phospholipase-D-like enzyme on the membrane phospholipid, N-arachidonoyl-phosphatidyl-ethanolamide [17] while 2-AG is thought to be synthesised via the hydrolysis of sn-1-acyl-2-arachidonoyl-glycerols by sn-1-selective-diacylglycerol lipases [18]. Anandamide is an unstable molecule and is readily metabolised [19] via the enzyme fatty acid amide hydrolase (FAAH) or via the arachidonic acid pathway [20]. Prior to inactivation by intracellular FAAH, anandamide is removed by a specific carrier, [21] although some cells capable of degrading anandamide such as rabbit platelets, lack this transporter [22].

In any study involving endocannabinoids, the results are often complicated by a number of factors namely: the labile nature of the substances- anandamide and 2-AG both have a half-life of minutes [19,23], the incomplete characterization of receptor subtypes and distribution, non-receptor mediated effects of cannabinoids and, especially in earlier studies, use of agonists and antagonists with some non-specific effects.

Cannabinoid agonists and antagonists

The most extensively studied synthetic antagonists are SR141716A [24], for the CB_1 receptor and SR144528 [25] for the CB_2 receptor. However, both have the potential to act as inverse agonists, which suggests that under normal conditions, there may be some degree of receptor activation [5]. Some newer antagonists are also available and are now commonly used in vascular studies. AM251 [26] and AM281 [27] are structurally related to SR141716A and are CB_1 antagonists while AM630 [28] is a CB_2 antagonist. Several agonists are also available: a synthetic version of anandamide, methanandamide, is an agonist at the CB_1 receptor [29] and HU-308 [30] and JWH-133 [29] act as synthetic agonists at the CB_2 receptor. Methanandamide is not broken down by FAAH and is widely used in assessing the influence of cannabinoid metabolic products on vascular tone [31]. The selectivity of some other agonists has been brought into question due to conflicting findings in studies employing these compounds. HU-210, CP55940 and WIN55,212-2 are commonly used synthetic cannabinoid compounds but their lack of selectivity for one receptor type can make interpretation of their effects difficult.

Another strategy used to study the cardiovascular effects of cannabinoids has been the use of transporter inhibitors such as AM404 or FAAH inhibitors such as URB-597 [32] to boost endogenous cannabinoids. Such an approach has obvious advantages in that it obviates the need to administer chemically labile cannabinoids and in theory should augment endocannabinoid concentrations at the site of production rather than globally since cannabinoids are synthesised on demand.

Cardiovascular responses to cannabinoids

The presence of the gene product coding for the cannabinoid CB_1 receptor in renal endothelial cells, mesenteric resistance arterioles and cerebral microvessels, implies that CB_1 receptors are expressed on vasculature [10,33,34]. The mRNA for cannabinoid receptors and cannabinoid binding sites have also been identified in human endothelial cells [35], implying that these receptors may mediate the cardiovascular action of cannabinoids.

Ellis et al [36] found anandamide and 9-THC caused dilation of cerebral arterioles. The effect was inhibited by indomethacin, suggesting that the cannabinoid was acting via release of arachidonic acid and metabolism to vasoactive substances. However,

several studies have shown that anandamide does not relax large vessels such as the rat aorta [34] or rat carotid arteries [37] and we have replicated these findings in rat carotid artery (Robinson et al., unpublished data). In small resistance vessels studies by Randall and Kendall have shown that anandamide acts as a vasorelaxant and they have suggested that anandamide is acting directly as an endothelium derived hyperpolarizing factor (EDHF) [38]. Since EDHFs are secondary relaxing factors whose influence on vascular tone depends on the size of the vessel, [39] this response to anandamide may be more unlikely in the large coronary arteries used in studies to date. Indeed in rat hepatic smooth muscle cells, anandamide does not appear to act as a typical EDHF in that its effect was not blocked by apamin plus charybdotoxin [40]. It has been proposed that in some preparations anandamide relaxation is via inhibition of intracellular calcium stores [41] or smooth muscle calcium channels [42].

In conduit arteries such as the guinea pig carotid artery only very high doses of anandamide caused hyperpolarisation and in the porcine coronary artery, no hyperpolarisation or relaxation to anandamide was observed [43]. Fleming et al [44] also found that anandamide caused no relaxation in rabbit carotid or porcine coronary artery but induced a cycloxygenase-dependent relaxation in rabbit mesenteric artery associated with a reduction in EDHF. Other reports have implicated arachidonic acid metabolites in anandamide-induced relaxation in the sheep [45] and bovine coronary artery [46]. In some specialised vascular beds such as the kidney, anandamide may relax by endothelial release of nitric oxide [33].

Anandamide has been assumed in many of these studies to be a selective cannabinoid receptor agonist

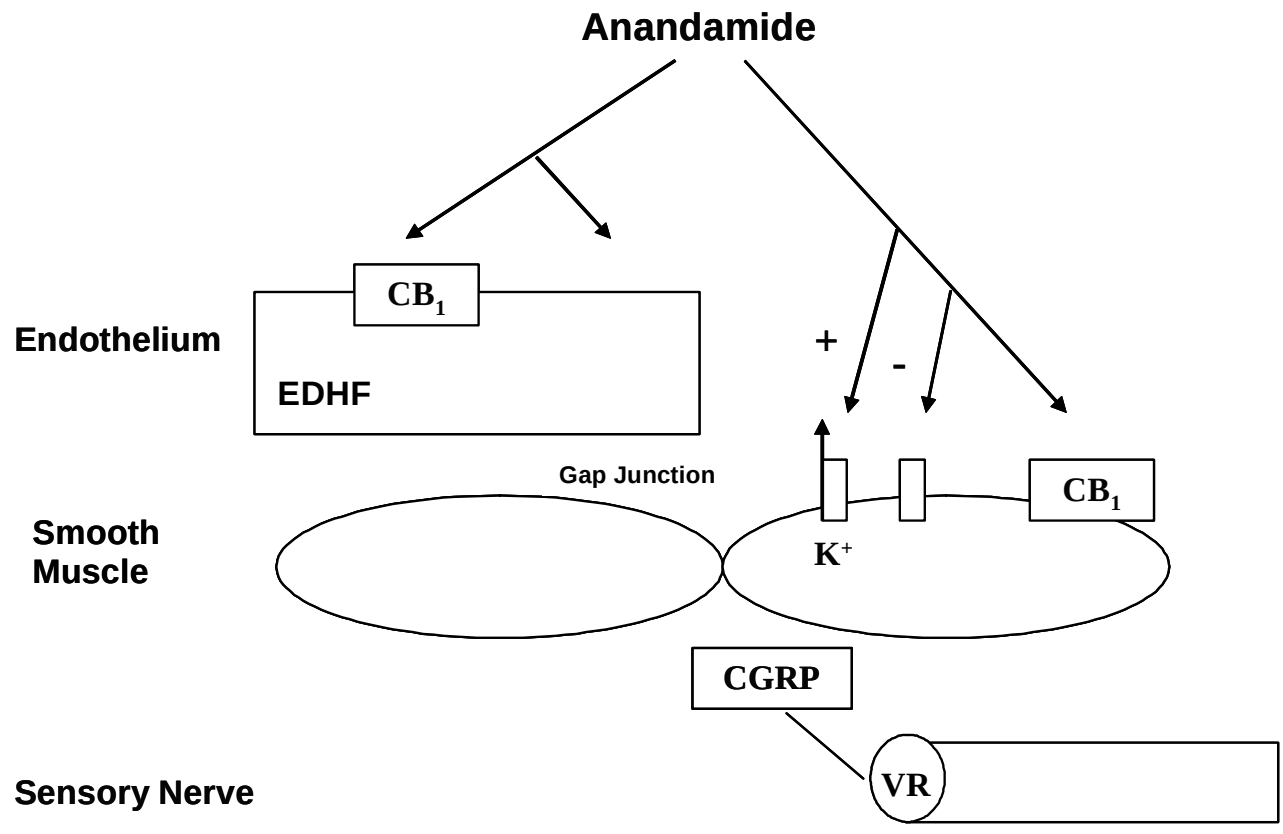

Figure 1 Schematic diagram showing possible mechanisms of vasorelaxation to anandamide. Mechanisms include (a) endothelium-dependent relaxation coupled to classical and novel endothelial cannabinoid receptors (CBx) which could potentially be coupled to EDHF (endothelium-derived hyperpolarizing factor) (b) activation (+) of potassium channels on vascular smooth muscle, anandamide acting as an EDHF; (c) inhibition (-) of calcium channels on vascular smooth muscle; (d) the participation of cannabinoid (CB) receptors on vascular smooth muscle; (e) the release of CGRP from sensory nerves coupled to vanilloid receptors (VR); (adapted from Randall et al., 2004)

but its selectivity has recently been brought into question by the discovery that it can act at vanilloid receptors [47-49]. Zygmunt et al [49] showed that anandamide induces vasodilation that is consistent with activation of the vanilloid receptor (VR1) but not consistent with the activation of CB_1 receptors. Hence in some preparations, vasodilation may involve stimulation of vanilloid receptors on sensory neurones causing the release of the potent vasodilator calcitonin gene-related peptide. As cannabinoids can act via cannabinoid receptors to cause inhibition of neurotransmitter release and anandamide can act via vanilloid receptors to promote neurotransmitter release, anandamide can be said to have a dual action [48]. Thus, the difference in responses to anandamide in different vascular beds may be due to differing levels of expression of the vanilloid receptor and the anandamide uptake transporter which appears to be required for activation of the vanilloid receptor [47].

Recent studies have highlighted the possibility of a novel cannabinoid receptor. Wagner et al, [50] demonstrated that in rat mesenteric arterial vessels the vasorelaxation was via an SR141716A sensitive receptor that was independent of CB_1 and, more convincingly, abnormal cannabidiol, which does not bind to CB_1 receptors, caused mesenteric vasodilation in mice [51]. In the isolated rat heart, Ford et al, [6] demonstrated that the vasodilator response to anandamide is inconsistent with an action at a CB_1 or CB_2 receptor and proposed that vasodilation and negative chronotropic effects were mediated through a novel cannabinoid binding site.

In summary, the complex responses to anandamide, as depicted in **Figure 1**, may explain the differences in its vasodilator effect in different vascular beds. In support of this, O'Sullivan et al [52] studied resistance and conduit mesenteric arteries and found that vasorelaxation was mediated via different mechanisms in different vessels. Thus identification of one pathway of vascular relaxation to anandamide which is present in all vessels is unlikely. Cannabinoid receptors, arachidonic acid metabolites and sensory nerves are the main mediators of the cannabinoid response and the particular pathway employed will depend on receptor population, innervation and pathology within individual tissue beds.

Could the anandamide response involve sphingoplipids?

Some studies have suggested a potential link between cannabinoid receptor activation and sphingosine hydrolysis [13,14] although at present it is unclear if sphingosine metabolites may contribute to the vasorelaxation induced by anandamide. The primary sphingosine metabolite sphingosine-1-phosphate (S1P) (for review see [53]) is formed from sphingosine by the action of the enzyme sphingosine kinase (SK), and binds to a family of G-protein coupled receptors termed $S1P_{1-5}$ [55-60]. These receptors are integral membrane proteins predicted to have seven transmembrane domains and exhibit approximately 50% amino-acid sequence identity. Once formed, S1P may be released from cells where it can bind to $S1P_{1-5}$ receptors to stimulate cell responses in an autocrine manner.

The literature on the vascular effects of S1P is contradictory, with some studies demonstrating vasodilation [61] and others vasoconstriction [62,63] in a variety of arterial preparations. The effects of S1P on coronary artery tone have not been fully examined. Compelling evidence of the link between cannabinoids and S1P was provided by a study which demonstrated that sphingosine analogues are capable of acting at cannbinoid receptors [64]. In the rat coronary artery, we have data which indicates that the vasodilator response to anandamide involves S1P or vasodilator substances, eg. prostanoids regulated by S1P acting at receptors on the coronary artery.

Both anandamide and S1P induce a relaxation of a similar magnitude (**Figure 2a, b**) which is partially sensitive to the cycloxygenase (COX) inhibitor indomethacin, suggesting a common pathway involving a vasodilator prostanoid. Since L-NAME was without effect on S1P or anandamide relaxation, a role for nitric oxide or the $S1P_1$ receptor (which dilates via NO release) can be ruled out. Inhibiting S1P formation with the SK inhibitor N, N, dimethylsphingosine also reduces relaxation to the cannabinoid agonist HU210, indicating that cannabinoids may initiate relaxation through S1P formation. The final piece of evidence was obtained using the compound JTE013, an $S1P_2$ receptor antagonist. Addition of JTE013 reversed the relaxation to anandamide, resulting in a strong contraction (**Figure 2c**).

Under normal circumstances, activation of $S1P_2$ stimulates cAMP formation which leads to phosphorylation and activation of cytosolic PLA_2 by ERK1/2 in smooth muscle cells. The resulting arachidonic acid is converted via the indomethacin-sensitive COX pathway to prostanoids [65]. In the presence of JTE013, we believe that this pathway is blocked and S1P acts via the $S1P_3$ receptor to induce contraction in the rat coronary artery. $S1P_3$ is the most

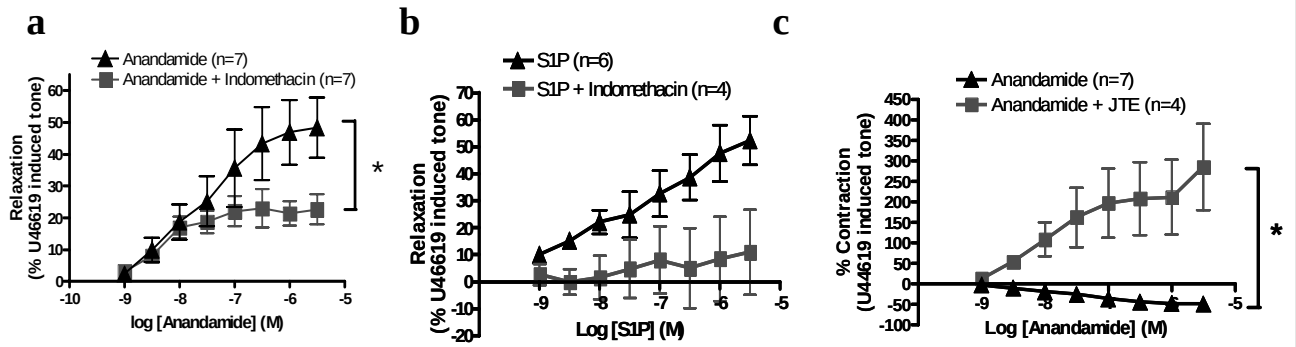

Figure 2: (a) Vasodilation induced by anandamide in the rat coronary artery is significantly inhibited by the COX inhibitor indomethacin. (b) S1P caused a relaxation of a similar magnitude to anandamide and this was also attenuated by indomethacin. (c) The $S1P_2$ receptor antagonist JTE013 converted the relaxation induced by anandamide into a constriction, possible mediated via $S1P_3$ receptors (E Robinson 2006, unpublished data).

likely receptor involved in the constrictor response as it is coupled to Gq and, when bound with S1P, activates phospholipase C to form inositol (1, 4, 5)P_3 (which mobilizes intracellular calcium, and which is required for initiating contraction) and diacylglycerol (which activates PKC and is involved in the calcium-independent phase of excitation-contraction coupling). Anandamide binding to cannabinoid receptors on the coronary artery may stimulate the synthesis of S1P which then regulates vasodilator prostanoid (PGE_2/PGI_2) production by binding to $S1P_2$. In addition, the principal prostanoid produced from COX-2 metabolism of anandamide is prostaglandin E_2 ethanolamide (PGE_2 ethanolamide) [20] and this prostanoid may mediate part of the anandamide/S1P-induced relaxation of the rat coronary artery. This would account for the data showing an inhibition of relaxation to anandamide and S1P by indomethacin. What remains to be determined is the cannabinoid receptor(s) involved and the precise details of the pathway involved in mediating relaxation.

What is the physiological relevance of endcannabinoid-induced vasorelaxation?

Systemic administration of anandamide to anaesthetised rats elicits bradycardia and a triphasic blood pressure response [66]. Upon injection of anandamide a large drop in heart rate is observed and this drop is associated with a transient decrease in blood pressure (Phase I). A short pressor response is then observed (Phase II) before the blood pressure drops again to a maintained depressor level (Phase III) [66-68]. Phase three appears to involve pre-junctional inhibition of peripheral sympathetic outflow via CB_1 receptors [66,67] although this view has been challenged by Vidrio et al [69] who found no effect on the depressor response to a synthetic cannabinoid following sympathectomy. However, based on the *in vitro* data already discussed, cannabinoids have the potential to induce vasodilatation by acting on vascular cannabinoid receptors and this is likely to be part of the depressor response seen following *in vivo* administration [70].

In the setting of ischaemia-reperfusion cannabinoids should decrease cardiac work and increase blood supply to tissues. Therefore theoretically cannabinoids should have a positive effect on ischaemia-reperfusion injury and some studies have supported this concept. Krylatov et al have demonstrated cardioprotection (via an antiarrythmic effect) of anandamide and the non-selective cannabinoid receptor agonist HU210 in rat hearts subjected to ischaemia-reperfusion [71,72]. Generation of endocannabinoids by platelets and monocytes is increased during ischaemia-reperfusion [73] and administration of the antagonist SR141617A increased mortality after 2 hours of reperfusion. This suggests that endocannabinoids may be important in maintaining perfusion pressure when cardiac output is decreased. In addition, cannabinoids may prevent endothelial dysfunction during reperfusion and promote remodelling of the damaged area [74,75] and may decrease the area of necrosis [76].

The mechanism of cannabinoid-induced cardioprotection is still under investigation, but an involvement of CB_2 receptors has been proposed [77].

Lepicier et al. [78] found that administration of 2-AG and palmitoylethanolamide improved myocardial recovery via a CB_2 mediated mechanism and a study by Di Filippo et al [79] showed that a CB_2 antagonist reduced the beneficial effect of an administered cannabinoid agonist on inflammatory cytokine levels in the mouse. Interestingly, in isolated rat hearts, anandamide reduced infarct size following ischaemia/reperfusion and although this effect was sensitive to both CB_1 and CB_2 antagonists, the effect was not mimicked by selective CB_1 or CB_2 agonists [7]. This suggests that cannabinoids may be mediating their effects via a novel cannabinoid site or via a novel pathway.

Could the cardioprotective effect of cannabinoids involve sphingolipids?

The first question to be addressed is whether or nor sphingolipids themselves are cardioprotective. In the murine heart, S1P and ganglioside GM-1, which enhances endogenous S1P production protect the heart against ischaemic damage [80]. The same group also demonstrated that ischaemic preconditioning caused a PKC induced activation of sphingosine kinase (SK), which may then generate S1P which protects the heart against a subsequent ischaemic insult [81]. In the isolated perfused rat heart, cell permeable ceramide conferred preconditioning-like cardioprotection against post-ischaemic contractile dysfunction and this cardioprotective effect was attenuated by NOE [82], an established inhibitor of ceramidase activity [83]. The fact that NOE blocks the cardioprotective effect of ceramide against infarction suggests that it is the intracellular conversion in the heart of both short and long chain ceramide via sphingosine to S1P that is the important step in the cardioprotective process. Indeed, these same authors showed that application of S1P itself (either acting on cell surface receptors or taken up into cells via specific transporters) was also cardioprotective [82]. For S1P to be cardioprotective in our model there has to be a means of forming S1P within the heart and we have data indicating that the enzyme sphingosine kinase is expressed in the rat heart (**figure 3**; unpublished data Pyne & Pyne).

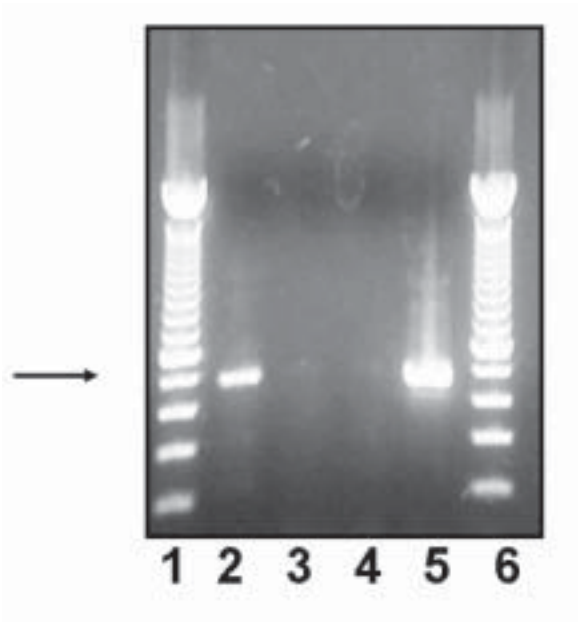

Figure 3: Identification of SK1 transcript in rat heart. RNA was extracted from rat heart and used in a polymerase chain reaction in the presence (lane 2) or absence (lane 3) of reverse transcriptase and gene specific primers designed to amplify a 420 base pair fragment of SK1. Lane 4, without RNA; lane 5, positive control (SK1 plasmid construct); lanes 1 and 6, 100 base pair ladders.

The link between anandamide, S1P and cardioprotection remains speculative. However, our data suggest a strong link between anandamide and S1P in mediating coronary vasodilatation. Clearly, a vasodilator response in an area of ischaemia would improve re-oxygenation that might therefore function to reduce apoptosis of cardiomyocytes. Alternatively, or in addition, anandamide might act directly on cardiomyocytes to prevent their apoptosis by increasing intracellular S1P (involving activation of cardiomyocyte SK). Another possibility would be formation of prostanoids induced by S1P which might act directly on the heart. Thus there are several pathways which could account for the cardioprotective effects of cannabinoid substances in the rat heart. The involvement of S1P or an S1P related substance in anandamide-induced vasodilatation is supported by our data but what remains to be established is whether this is important in protecting the heart during ischaemia and if so, by what means.

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Secretary's Column

I have not written for some time and so there is much to catch up on. I report here on the schedule of BSCR main meetings, BSCR input to the British Cardiovascular Society annual meeting, the planned joint meeting with the BCS and some routine matters of committee business.

Main meetings for this year are in Reading and London. The Spring meeting held at the end of March at the University of Reading was led single-handedly by Katrina Bicknell. Unfortunately, her co-organiser Gavin Brooks was in hospital around that time. Katrina did a marvellous job in bringing it all together on the day and keeping everything on track. Michael Curtis will host the Autumn meeting at St Thomas' Hospital on 24-25 September. Details are advertised in this issue of the Bulletin, and forms for abstract submission and registration etc. are available on the website.

The BSCR, along with other BCS affiliate groups, made a significant contribution to the BCS annual scientific meeting held at the SECC in Glasgow in early June. I had the opportunity to attend three of the four sessions and noted the considerable interest and enthusiasm for the basic science elements. This augurs well for next year, when the BSCR 'Spring' meeting will become a 'Summer' meeting to run jointly with the BCS. This will take place on 2-3 June 2008 at G-MEX in Manchester. As usual, the meeting will take place over one and a half days, the first symposium starting just after lunch on Monday. There will be a keynote lecture followed by the BSCR dinner on the Monday evening and a poster session and further symposia held on Tuesday. All of the BSCR sessions will map onto the BCS format, so that there can be easy movement between parallel sessions. A preliminary programme has been put together focusing on the topic 'Cause and Consequence of Myocardial Infarction: new concepts'. It is hoped that this will have appeal both for basic and clinical scientists, encourage further interaction and promote ideas for translational research.

The end of this year will see a number of significant changes on the BSCR Committee. After a very enjoyable six years as Secretary, I will stand down and am delighted to announce that Chris Jackson has been elected by the present Committee to succeed me. Subject to approval by the membership at the next AGM to be held in London on 25 September, he will take up the position in January 2008. Chris has been a member of the Committee since 2005 and has been particularly active in maintaining and developing the website. He is ultra efficient and will have no problem keeping all in order. In addition to the vacancy left by Chris, there will be three further vacancies for ordinary membership at the end of 2007, when Andy Baker, Katrina Bicknell and Gillian Gray come to the end of term of office. Eight nominations have been received for the four vacancies and biographies of the individuals are given in this issue of the Bulletin. Now we need to hold a postal ballot and a voting paper for the purpose has also been included. I would encourage you all to make your choice known, using only the official stamped form. The result will be announced and approval sought from the membership present at the AGM. I hope to see many of you there.

Barbara McDermott

Nominations for Membership of the BSCR Executive Committee

Yvonne Alexander

Originally from Ireland, Yvonne Alexander graduated in Biology from Strathclyde University in 1987 and gained her PhD from The University of Glasgow. She is currently a Lecturer in the Faculty of Clinical and Laboratory Sciences, Cardiovascular Research Group, University of Manchester. Yvonne has had a long-standing interest in endothelial and vessel wall dysfunction, and her work has involved the use of rodent models and adenoviral-mediated gene transfer as a study tool to understand gene regulation and protein function in relation to cardiovascular disease mechanisms. Yvonne collaborates in a wide network of International Researchers, has published original papers and invited reviews, acts both on review panels and as reviewer of manuscripts for International Journals and also holds a number of research grants. Dr Alexander has given a number of invited lectures, communicating enthusiasm for cardiovascular biology and strives to translate scientific discoveries into improved clinical practice.

My research now focuses on the understanding of how endothelial dysfunction leads to the development of atherosclerosis. In particular we are focusing on endothelial shedding, modulation of smooth muscle cell phenotype and development of calcification in the advanced plaque lesion, and how these three phenomena interlink to predispose to coronary heart disease. The research uses human studies and cellular and in vivo models. As a basic scientist with many clinical collaborators, the goal of my research is to provide a better molecular understanding of atherosclerotic disease so that improved therapy can be designed. Should I be elected to Council, I shall devote my energies and experience to strengthen the membership and endeavour to foster a network with collaborative opportunities. I will strive to build on the credibility of BSCR through continuing interaction, where the young enthusiastic scientist can learn from and interact with the more established and experienced cardiovascular biologist.

Joined Society: 1997 **Proposed by:** Cathy Holt **Seconded by:** Katrina Bicknell

Katrina Bicknell

After graduating from The University of Melbourne in 1994 with a Science degree in Microbiology, I undertook doctoral training in the Department of Medicine (St Vincents' Hospital, Melbourne), where I studied the role of prohormone processing in breast and bone cancers. I completed my PhD in 1998 and was awarded a Juvenile Diabetes International Junior Fellowship to continue my work on prohormone convertases at the Barbara Davis Center for Childhood Diabetes in the University of Colorado Health Sciences Center (USA). After two years in the USA, I moved to the UK and joined the laboratory of Professor Gavin Brooks at the University of Reading where my interests in cardiovascular research were fostered. As a post-doc., I investigated the role that cell cycle regulators play in controlling cardiac myocyte proliferation and cardiac hypertrophy. In 2003, I was awarded a BHF Intermediate Fellowship that allowed me to develop my own research programme at the University of Reading, which focuses on the elucidation of the transcriptional and translational control mechanisms that limit cardiac myocyte proliferation and promote cardiac myocyte hypertrophy.

I wish to stand for re-election to the BSCR executive committee. For the last three years, I have thoroughly enjoyed serving on the BSCR committee with the highlight being organising and hosting the last Spring BSCR meeting (March 2007) in Reading. If re-elected, I will continue to raise the awareness of our Society within the cardiovascular research community and will endeavour to increase the opportunities for early-career cardiovascular researchers to participate in the activities of the BSCR.

Joined Society: 2000 **Proposed by:** Gavin Brooks **Seconded by:** Jonathan Gibbons

Carolyn Carr

I am a senior post-doc in the Cardiac Metabolism Research Group in the Department of Physiology, Anatomy and Genetics in Oxford. We use high field cine MRI and isolated heart perfusion to study cardiac function and metabolism in rodent models of heart failure. In particular I am investigating adult stem cell therapy following myocardial infarction. Hitherto we have used mesenchymal stem cells isolated from the bone marrow, but we are now progressing to study the endogenous cardiac stem cell population.

I began my career as a chemist at Oxford University using NMR to study organic molecules. After a career break for family reasons, I returned initially to Oxford chemistry and then progressed through biological chemistry to physiology and in vivo MRI.

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.

Joined Society: 2005 **Proposed by:** Kieran Clarke **Seconded by:** George Radda

Alison Cave

I graduated from King's College London in 1987 and then moved slightly up the river to study for a PhD in the field of cardioplegic protection under the supervision of David Hearse at St. Thomas' Hospital. During this time I became interested in the phenomenon of ischaemic preconditioning which led to a very enjoyable 2 year American Heart Fellowship in the lovely town of Boston, USA with the late Carl Apstein. I returned from the USA in 1994 to work with Dr Pamela Garlick investigating the metabolic basis of preconditioning using NMR spectroscopy before eventually taking up a lectureship position with Ajay Shah in 1998, this time south of the river, at the Denmark Hill Campus of King's College. My research interests are now split between the role of reactive oxygen species, specifically those derived from the NADPH oxidase in the development of cardiac hypertrophy/diabetic cardiomyopathy and the mechanisms underlying contractile dysfunction in septic shock.

I first joined the BSCR during my PhD studies. An important role of the BSCR is to provide a forum whereby scientists can meet to interact on a more informal basis. The best scientific discussions often take place in the bar after the meeting!!! Such a forum also allows younger scientists, particularly PhD students, to present their work in a less intimidating atmosphere. Hence I would wish to encourage the organisation of more focussed workshops in addition to the regular Spring and Winter meetings.

Joined Society: 1990 **Proposed by:** Michael Curtis **Seconded by:** Ajay Shah

David Grieve

After being awarded an honours degree in Anatomy and Physiology by the University of Dundee in 1995, I moved to The Royal Veterinary College in London where I undertook my PhD on the role of dietary lipoproteins in the initiation of atherosclerosis. In 1999, I joined the newly-established laboratory of Professor Ajay Shah at King's College London, where I worked as a post-doctoral scientist for almost 7 years on two BHF program grants. Here my research was mainly focused on investigating the role of NADPH oxidase-derived reactive oxygen species in left ventricular hypertrophy and heart failure. In December 2005, I was appointed as a lecturer in the Department of Physiology at Queen's University Belfast, where I am currently aiming to establish myself as an independent researcher. I have recently managed to secure grant funding, including an MRC New Investigator Award, which will enable me to continue my research interests in the role of oxidative stress in cardiovascular pathophysiology.

I would welcome the opportunity to join the BSCR committee and contribute to its established role in supporting UK cardiovascular research. As a young researcher, I always found the BSCR to be an excellent forum at which to present my data and exchange ideas with other like-minded scientists in a friendly environment. I believe that it is especially important to encourage the further involvement of PhD students and junior scientists in the society, as this will undoubtedly benefit their career development. I would also like to promote interaction with other UK societies with parallel interests (such as certain special interest groups of The Physiological Society), with the aim of widening participation in the BSCR.

Joined Society: 2000 **Proposed by:** Barbara McDermott **Seconded by:** Ajay Shah

Derek Hausenloy

I graduated from the University of Manchester Medical School in 1996 having obtained a first class Honours BSc in Biomedical Sciences from my intercalated year in 1993. It was during this period that my interest in Cardiovascular Research and my decision to pursue a career in Cardiology, were initiated. After completing my early clinical training in Addenbrooke's Hospital, I re-entered the field of Cardiovascular Research between 2001 and 2004, undertaking a British Heart Foundation funded PhD under the supervision of Professor Derek Yellon, at the Hatter Cardiovascular Institute, UCL. Following this, I resumed my clinical training in Cardiology in the North West London Deanery, whilst maintaining active research at the Hatter Cardiovascular Institute. In 2006, I obtained a 4-year British Heart Foundation Clinical Science Fellowship, which has allowed me continue as a Lecturer at the Hatter Cardiovascular Institute, whilst completing the clinical component of my Cardiology training (CCST expected Jan 2008). As a future Honorary Academic Cardiology Consultant and Senior Lecturer, my intention will be to integrate my clinical speciality of non-invasive cardiovascular imaging with my research interests of myocardial protection. This encompasses identifying novel targets for cardioprotection in the laboratory setting and translating the findings into the clinical arena for the benefit of patients presenting with an acute myocardial infarction and undergoing cardiac bypass surgery.

For me the BSCR meetings and workshops provide a national forum for active discussion amongst cardiovascular researchers, both clinicians and scientists alike, from the different sub-specialties of Cardiovascular Research. As a BSCR committee member and a clinician- scientist, I would aspire to further involve investigators from both Clinical Cardiology and Science in the activities organised by the BSCR, by underscoring the importance and necessity of translational cardiovascular research. In this regard, I am keen to encourage aspiring clinicians who may wish to pursue and develop a career in cardiovascular research.

Joined Society: 2001 **Proposed by:** Derek Yellon **Seconded by:** Michael Marber

Yalda Jamshidi

I completed my BSc (Hons) in Human Genetics at UCL in 1997. I then joined the laboratory of Prof Steve Humphries at the Rayne Institute, UCL to undertake my post-graduate studies. During my PhD, I investigated the role of genetic polymorphisms in the PPARa gene in the response to fibrates, dyslipidemia and heart disease. I carried out some of my PhD work at the Pasteur Institute (Lille, France) in the lab of Prof Bart Staels. In 2001 I took up a BHF post doctoral position with Prof David Latchman investigating the molecular signalling pathways involved in cardiac hypertrophy. In 2004 I accepted a Wellcome Trust post to investigate the genetics of obesity and leptin insensitivity at KCL. In January 2006 I was appointed Lecturer in Biomedical Sciences at St. George's University of London. My main research interests are investigating cardiac hypertrophy and arrhythmias using basic molecular biology techniques as well as genome wide association studies, expression arrays and genetic twin studies.

I see the BSCR as the main forum for cardiovascular researchers within the UK and find the BSCR meetings to be a great opportunity to meet scientific colleagues and promote future collaborations. As a relatively young researcher who is just beginning to establish herself, I would like to increase the participation of the younger members of the cardiovascular scientific community in order to support and encourage their professional and academic development.

Joined Society: 2006 **Proposed by:** Dongling Zheng **Seconded by:** Steve Jeffery

Jian-Mei Li

I obtained my MBBS in China, undertook my MD at the Centre of Cardiology in Geneva University, Switzerland, and completed a PhD in Kings College London. Even while practicing as a cardiologist, I was very active in research and finally decided to pursue a career in science. From 1993 to 2005, I worked as post-doctoral research fellow in London at Imperial College, Institute of Child Health, UCL and KCL. I won the Menarini Academy Cardiovascular Research Award for the year 2000, and the American Heart Association Merit Award for Young Investigators in 2002. I moved to University of Surrey in 2005 as a Reader in Integrative Physiology, and my research team is focused on redox-signalling, endothelial function and cell cycle regulation.

I have been a member of BSCR for ~12 years, and found it of great benefit to me and others through participating excellent conferences and reading reviews published in the Bulletins. I am keen now to be more involved in the running of this useful society. I would be honoured to have a chance to serve on the BSRC Committee. I can bring extra value to BSRC due to my background and experience in both clinical cardiology and cardiovascular research. I am keen to extend the influence of the BSRC in Surrey and surrounding institutions by organising conferences and attracting new members.

Joined Society: 1995 **Proposed by**: Michael Curtis **Seconded by**: David Chambers

Autumn 2006 Joint BSCR/BAS Meeting: Biomechanical Signalling in Atherosclerosis

Report by Dr Peter D. Weinberg, Imperial College London

The Autumn 2006 meeting, held at Queens' College, Cambridge on September 21st and 22nd was the first to be jointly run by the BSCR and the British Atherosclerosis Society (BAS). It was organised by Dorian Haskard (Imperial College London) and Qingbo Xu (King's College London) of the BAS Committee and Peter Weinberg (Imperial College London) of the BSCR Committee, who felt that the two societies significantly overlap in their interests and that a joint scientific gathering might bring them closer together. The societies have different traditions concerning registration fees, student bursaries, abstract submissions, and so on, and much hard work by the officers of both societies, particularly Chris Newman and Barbara McDermott, was required to resolve these issues. Their achievement should make the task of organising future joint meetings much easier.

The subject of the meeting was Biomechanical Signalling in Atherosclerosis, a research area motivated by the belief that the non-uniform distribution of atherosclerotic lesions within the vasculature is determined by local mechanical stresses. Peter Weinberg (Imperial) noted that this topic is rarely a programme item at atherosclerosis meetings and speculated that this might be due either to the opinion that the main facts in this field are now well-established, or to the opinion that the predilection of disease for certain sites is of little clinical interest. In his own talk, he disputed the first of these, showing that the intra-arterial distributions of mechanical stresses and lesions differ with age and between species, and cannot easily be explained by current orthodoxy. A joint presentation from Colin Caro (the originator of the low-shear stress theory of atherosclerosis) and surgeon Nick Cheshire (both at Imperial) contradicted the second of these opinions, showing that in arterial bypass surgery and in the construction of bypass grafts, proper attention to geometry (which determines blood flow characteristics and hence wall biology) can have substantial clinical impact. A talk by Rob Krams (now also at Imperial) further highlighted the potential clinical importance of biomechanics by describing how the development of lesions into stable or unstable plaques is determined by the pattern of haemodynamic shear stress experienced by the wall; some of the signalling pathways involved in this critical dichotomy have been identified by his group in Rotterdam.

After lunch, Martin Schwartz (Charlottesville) presented his studies of shear-dependent signalling in endothelial cells. These represent something of a revolution by showing that responses to shear - including changes in NF-kB, p38 and PAK - can be modulated by the composition of the extracellular matrix, which varies from site to site. Alain Tedgui (Paris) discussed transduction of pressure-induced stretch, a topic that unjustifiably receives much less attention than flow-induced shear; the talk focused on the activation of FAK by stretch, mediated through matrix-integrin interactions and Src. Stretch also seems to lead to NF-kB translocation, mediated by NADPH-oxidase generated reactive oxygen species. Justin Mason (Imperial) concluded the main afternoon session by describing how laminar but not disturbed flows induce C59 expression, which protects endothelial cells from the complement system.

Julian Gunn (Sheffield) was the first speaker in a mini-symposium entitled "Stents: mechanical influences on the cell." He introduced, in a self-effacing manner, a number of wide-ranging and stimulating ideas about stents. It was only after dinner, however, that the full extent of his modesty and breadth was revealed - more anon… Eva Qwarnstrom (Sheffield) described sophisticated techniques of confocal microscopy for investigating shear stress-mediated signal transduction and an even more complex mathematical analysis that shows great promise of leading to a quantitative understanding of the molecular networks involved. Finally, Andy Scott (Sheffield) gave an entertaining talk that highlighted similarities between bone and vascular cell responses to mechanical stress.

The Hugh Sinclair Lecture, a BAS tradition, was given by Shu Chien (La Jolla). In a characteristically relaxed style, he gave a masterful summary of his group's work over many years on Flk-1 and integrin-mediated mechanotransduction in endothelium, including

an astonishing video of Ca^{2+} waves emanating from a point where a cell was being "tweaked" by applying tension to a microbead adhering to its membrane. The lecture was followed by an excellent and wide ranging Poster Session (Andrew Bond of Imperial College winning the BSCR prize for work described in the January edition of the Bulletin), by a dinner with the sort of ambience only to be found in Oxbridge colleges and then, to the surprise and delight of the organisers, by an impromptu organ recital in the chapel, given in an unassuming fashion by one Julian Gunn, revealed as a musician of professional merit as well as an expert on stents.

Friday morning started with a talk by Qingbo Xu (King's College London) who showed that endothelial cell turnover is flow dependent in apoE(-/-) mice, and that VEGF plays a role in recruiting endothelial progenitor cells to sites of vascular injury. Intriguingly, it seems that mechanical stress affects the fate of progenitors, smooth muscle cells being favoured by disturbed flow and endothelial cells by laminar flow. Qingbo was followed by Carlo Gaetano (Rome) who discussed the role of nitric oxide and histone deacetylases in epigenetic reprogramming during differentiation of mouse embryonic stem cells.

Six excellent free communications were then given, selected from submitted abstracts. The Young Research Worker's Prize, generously sponsored by Clinical Science, was won by Ziad Ali (Oxford) for his presentation showing that tetrahydrobiopterin-dependent eNOS coupling mediates endothelial regeneration and attenuates vein graft atherosclerosis.

The final session addressed the use of genomic, proteomic and siRNA techniques in the study of mechanotransduction in endothelial and vascular smooth muscle cells, these topics being addressed by Peter Davies (Philadelphia), Manuel Mayr (London) and Paul Cahill (Dublin), respectively. Although powerful, these approaches may not be for the faint hearted. For example, the results of Peter Davies concerning gene expression by small groups of endothelial cells exposed in vivo to specific shear stress patterns are well known but the meticulous procedures required to obtain linearity during the enormous amplification this requires are less so.

Understanding mechanotransduction in the vasculature is important because it could lead to new therapies for atherosclerosis, a "mechanosensitive disease". This, and the involvement of both societies, may explain the good turnout and enthusiastic feedback for the meeting, despite the unusually focused nature of the programme. We thank the speakers, chairs and above all, event organisers (particularly Natasha Dougall and Tony Cavalheiro), and gratefully acknowledge financial support from the BHF and the EPSRC-funded Network in Physiological Flow Modelling.

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
20 (4)	***October 2007***	*1st September*
21 (1)	***January 2008***	*1st December*
21 (2)	***April 2008***	*1st March*
21 (3)	***July 2008***	*1st June*

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)

A Postcard from Brunei

by Dr Nicola King

"The green heart of Borneo"

The plane is already on its descent into Bandar Seri Begawan (BSB) International Airport, when you swoop over the Brunei coastline. My impression in the remaining few minutes before landing is one of being surrounded by dense lush vegetation. I should not be surprised by this as Brunei, with over 70% jungle cover, is billed as "The green heart of Borneo". Yet scattered in and amongst the foliage are clusters of housing joined by wide well kept roads. My next sensation after the air-conditioned comfort of Royal Brunei Airlines is of heat and humidity, followed shortly after leaving the airport car park by a sense of a slowing in life's hectic pace, or, is this last simply my imagination?

The impressive sight of the Omar Ali Saiffuddin Mosque in the capital Bandar Seri Begawan.

For those who enjoy hustle and bustle, there is the Mall in Gadong. This is Brunei's newest shopping precinct and its surrounds are busy with cars endlessly searching for parking spaces, although strangely the inside of the Mall is never crowded. Personally, I prefer the places that suit the literal translation of Brunei Darussalam, "the abode of peace". Deserted beaches, where it is possible to walk for miles along soft sand or paddle in the deliciously warm and inviting South China Sea. Recreational parks, each of which has its own unique feature, e.g. Taman Sungai Basong contains reconstructions of the indigenous tribe people's wooden houses or Taman Tasek Lama, which is a few minutes walk from the centre of BSB. In Tasek Lama a long sweeping path meanders towards a manmade waterfall and for the more energetic there is a "jungle jogging track". The latter is a good aerobic workout as it plunges up and down offering extensive views over BSB and its surrounds, especially from the purpose built platform at the trail's beginning. Beautiful and tranquil this may be, but my main motivation for coming to Brunei is to take up a post at the Institute of Medicine (IM), Universiti Brunei Darussalam (UBD).

Undergraduate medical science in Brunei

UBD was formed in 1985. However local students would wait another 16 years before it would become possible to pursue health care related undergraduate courses in Brunei. This breakthrough was facilitated by the opening of IM in 2000 and subsequent enrolment in 2001 of the first cohort of students into the Bachelor of Biomedical Sciences. This was a twinning programme with the University of Queensland (UQ) where students were taught for 3 semesters at IM followed by 3 semesters at UQ. After graduating with a UQ degree, most students transferred into graduate entry MBBS programmes. This programme was replaced by the Bachelor of Health Sciences (BHSc) / medicine in 2005. The major difference between these 2 programmes is that the BHSc /medicine course is taught entirely by IM and adjunct staff and the students graduate with a UBD degree. Thereafter, the students will matriculate into partner medical schools in Australia, Canada or the UK for an additional 2-3 years before emerging as fully qualified medical doctors. In the longer term (5-10 years), it is anticipated that IM will be able to offer Bruneian students a complete medical training.

These are exciting and challenging times in IM because the development of the medicine programme was part of a broader vision to increase the availability of undergraduate training in several allied health care related

subjects. At the heart of these plans is a philosophy of interprofessional education where students from several professions share their working and learning. These ambitious aims are underpinned by an ongoing program of staff recruitment and the construction of large modern facilities that are due for completion later this year. The first fruits of this expansion will be seen in August 2007 when students will be enrolled into a second Honours degree, BHSc / Biomedical Sciences. Unlike the previous twinning programme, the new degree is specifically designed to train scientists to work for example in diagnostic labs or in research and development.

Personal teaching experiences

1st August 2006: am preparing, with some trepidation, for my first formal contact with our new second years. Previously, these students have had short cases but will switch this year to the progressive release style of problem based learning (PBL). There is a spark of tension in the air - how will the students adapt to the change in style? Will the learning objectives be achieved? I am concerned by this but at the same time am flattered to have been given the chance to be amongst the first to deliver second year teaching in the BHSc / medicine course.

A cross-section of 1st and 2nd year BHSc students. All of the women in this picture (myself included) are wearing the traditional Malay costume, Baju Kurong.

The students greet me with the shy politeness that is characteristic of Bruneians and we begin. This week's case features Puan Fatimah (fictitious) who has a high body mass index, hypertension and evidence of hypertrophy on her ECG (later in the week I will give a lecture on the pathophysiology of hypertension). We start with some ice-breaking strategies then work our way through the information with the students identifying their topics for self directed learning as we go along. Throughout the morning I refer to our patient as Puan, which no-one comments about, although I get some strange looks. Later that afternoon, I discover that Puan means Mrs and is not the patient's first name. We share a laugh about my mistake at the beginning of the next tutorial before the students report back on what they have discovered from their self-directed learning and the case continues. A few tutorials later and the students and I are more confident about the new format; they appreciate the more narrative style and greater clinical content compared to last year, whilst I am enjoying sampling the local foods that they bring to share.

Cardiovascular Research in Brunei

My initial strategy has been to seek answers to 2 questions: how big a problem is cardiovascular disease in Brunei and what is the current state of research? A quick glance at the 10 leading causes of death (see table below) in Brunei in 2005 shows that heart disease is second in this table, whilst related areas such as cerebrovascular disease and hypertension are 4th and 5th respectively. For indicators of Brunei's current cardiovascular research activities I refer to IM's 2nd annual academic sessions which were held in March 2007. A total of 73 abstracts from 5 subject areas comprising: medicine, surgery, biomedical sciences, ethics and education, and community health were presented. 10 abstracts focused on cardiovascular sciences encouragingly suggesting an interest in this area. Indeed, one of the invited international speakers was Professor Yacoub from Royal London and St Bartholomew's Hospital, who spoke about "Molecular mechanisms of cardiovascular diseases in uraemia". Of the remaining cardiovascular presentations, 7 were clinical and 2 featured classical laboratory bench-type research. These two (including my own) were from IM staff members who presented work carried out prior to the move to Brunei. In total 8 of the basic science abstracts in the Biomedical Sciences section were presented by IM staff members. This, in combination with the expected completion of our new building, speaks volumes about IM's capacity and potential for developing basic scientific, including cardiovascular, research.

Facts and figures

Location: North West coast of the island of Borneo

Area: 5,765km2

Coastline: spanning 161km of The South China Sea

Surrounded: on all other sides by the Malaysian state of Sarawak

4 districts: Brunei Muara (most densely populated and containing the capital and the airport); Tutong; Belait and Temburong (physically separated from the other three districts by Limbang)

Population: 375,000 (67% Malay, 6% Indigenous tribes, 15% Chinese, 12% others of which the highest proportion is Indians)

Climate: Equatorial with uniform high temperature (ave. 23ºC - 33ºC), high humidity and high rainfall (2,500 - 7,500mm annually)

Government:

Ruler: His Royal Highness, Haji Hassanal Bolkiah Muizziaddin Waddaulah (29th Sultan and Yang Di-Pertuan of Brunei Darussalam. Ascended throne 5th October 1967)

Sultan: is the supreme executive authority, assisted by an appointed cabinet

System: Independent sovereign sultanate governed on the basis of a written constitution in conjunction with the guiding principles of Melayu Islam Beraja (Malay Islamic Monarchy)

Ministries: Prime Minister's office, Foreign affairs, Home affairs, Finance, Defence, Education, Industry and primary resources, Development, Culture, youth and sports, Health, Religious affairs and Communications

Religion: Islam, although other religions are tolerated and practiced

Healthcare: provided free to native Bruneians and all government servants

Neonatal, infant, and <5s mortality rate: <10%

Ten leading causes of death for the year 2005 in Brunei Darussalam

Type of disease	♂	♀	*Total*	*%*	*Rate per 100,000 population*
Cancer (malignant neoplasms)	*118*	*97*	*215*	*20.1*	*58.1*
Heart Diseases	*113*	*63*	*176*	*16.4*	*47.6*
Diabetes Mellitus	*57*	*61*	*118*	*11.0*	*31.9*
Cerebrovascular Diseases	*35*	*36*	*71*	*6.6*	*19.2*
Hypertensive Diseases	*28*	*26*	*54*	*5.0*	*14.6*
Influenza and Pneumonia	*29*	*20*	*49*	*4.6*	*13.2*
Bronchitis, chronic & Unspecified	*25*	*21*	*46*	*4.3*	*12.4*
Transport Accidents	*28*	*17*	*45*	*4.2*	*12.2*
Conditions from Perinatal Period	*20*	*6*	*26*	*2.4*	*7.0*
Congenital Malformations, etc	*12*	*13*	*25*	*2.3*	*6.8*
Others	*156*	*91*	*247*	*23*	*66.7*
ALL DEATHS	*621*	*451*	*1,072*	*100*	*289.7*

The water village or Kampong Ayer is one of Bandar Seri Begawan's most iconic landmarks. This picture also shows a water taxi and the ever present closeness of the jungle.

Dr Nicola King joined IM, UBD in July 2006 as Senior Lecturer in Human Biochemistry. She is the programme coordinator for the BHSc / Biomedical Sciences Honours degree and is also a member of the BSCR Committee.

Travel Report: American Heart Association Arteriosclerosis, Thrombosis and Vascular Biology

Palmer House Hilton, Chicago, USA: 19th-21st April 2007

By Anabelle Chase, Bristol Heart Institute, University of Bristol, UK

The impressive foyer of the Palmer House Hilton

It had always seemed to me that one of the perks of a life in research was the "American conferences". Thousands of people, incredible venues, continual supply of refreshments and, of course, more 'free stuff' than is permitted in baggage allowance. So when I was offered the opportunity to attend an American Heart Association meeting in Chicago, I jumped at the chance. It was a focused meeting on arteriosclerosis, thrombosis and vascular biology, but nonetheless attracted over 1000 participants from 5 different continents. There were concurrent sessions running continuously on specialised fields of interest, as well as keynote speakers presenting more general approaches. With this vast amount of information (well over 100 oral presentations - not to mention the hundreds of posters presented over the 3 days) it struck me quite how overwhelming arteriosclerosis is. With all participants presenting data on new and unique proteins and products of metabolic pathways, it seems incredible that we have any understanding of it at all. In fact, in one talk, Chiara Buono (Maryland, USA), told us the incredible fact that two macrophages, derived from identical monocytes, but differentiated in the presence of two different growth factors differ by no less that 731 genes! One is either excited and inspired, or completely overwhelmed, and that, I leave up to you….

The major theme of this meeting was the molecular mechanisms of atherosclerosis. Emmanuel Gautier (Paris) grabbed our attention with a very interesting talk on the significance of apoptosis in the development of atherosclerosis. Apoptosis was induced by injection of diphtheria toxin (DT) in the lesions of apoE-/- mice with over expressed DT receptor. 2 days later, increased TUNEL staining in the aortic tissue was increased in DTR apoE-/- mice compared to apoE-/- controls, and this was associated with increased mRNA expression for chemokines MCP-1, MIP-1α, MIP-1β and MIP-2. Consequently, mRNA expression of monocyte markers was also significantly increased. But more significant was the presence of newly recruited macrophages in areas of apoptotic cell accumulation, indicative of monocyte recruitment. Indeed, monocyte

The crowded "State Ballroom" during presentations

tracing using fluorescent beads confirmed that these monocytes were recruited as a result of apoptotic cell deposition. It was therefore concluded that a deficiency in clearance of apoptotic cells results in newly recruited macrophages, which then contribute to the formation of lesions. Interception of apoptosis pathways or clearance of apoptotic cells might therefore be an attractive therapeutic target.

Jochen Schneider (Washington University) also presented an interesting talk on the possibility of regulating fatty acid synthase as a therapeutic target of vascular disease. It is well known that fatty acid (FA)

One of the many busy poster sessions

metabolism is disturbed in vascular disease, and that the FA composition of lesions changes during disease progression. But what is not known is whether this actually influences the progression or stability of atherosclerotic plaques. Much of the FA present is induced by the activity of FA synthase (FAS), and therefore a knockout mouse for macrophage specific FAS was developed and used to understand the effects of FAS on atherosclerosis. Knockouts had lower blood pressure and 40% less atherosclerosis in the abdominal aorta, however there were no differences in glucose, serum lipids or body weight. FAS is necessary for the activation of nuclear receptor PPARα and expression of its target genes. In the knockout mice there was no change in the expression of PPARα, but there was a decrease in target genes, consistent with a decrease of PPARα activation. In addition, in FAS KO mice, there was an induction of the anti-atherosclerotic oxystrol receptor LXRα compared to control macrophages. It was therefore concluded that FAS synthase in macrophages actually promotes atherosclerosis through decreasing LXRα through activation of PPARα. Again, FAS and its downstream targets/effects therefore provide another attractive point of intervention.

As with all recent cardiovascular related conferences, in which obesity, diabetes and metabolic syndrome take centre stage, this conference proved to be no different with sessions on diabetes and obesity taking place on each day. Ronald Kahn (Harvard University) gave a very interesting presentation on molecular insights into the currently very hazy connection between insulin signaling and cardiovascular disease. The insulin receptor, tyrosine kinase, activates a succession of millions and millions of signaling pathways that are so complex we cannot even begin to be aware of their functions. Therefore, understanding, what happens to the heart (and why) during insulin resistance is no easy task. Kahn and colleagues have, however, developed a tissue-specific insulin resistant KO mouse. Insulin resistance in many tissues and cells was found to lead to a 40% decrease in cardiac size, associated with increased triglycerides, increased free fatty acids and increased glucose uptake. These mice, however, had a normal life span and normal exercise tolerance. It was proposed that this was due to the insulin growth factor (IGF-1) receptor compensating for the lack of tyrosine kinase. When both IGF-1 AND tyrosine kinase double KO mice were used, both insulin signaling and IGF-1 pathways were impaired, and lifespan decreased to 2-3 weeks. However, this decrease in lifespan was not due to diabetes or any sort of metabolic syndrome. Fascinatingly, it was a cardiac death due to cardiomyopathy and hyperplasty (decreased wall thickness and loss of cardiac contractility), and not a metabolic death. It was therefore concluded that insulin receptors play a role in cardiac growth, however the precise mechanisms remain unclear.

Samuel Klein (Washington University) also gave

Are more people eating or looking at the posters?!!

a very entertaining and fascinating talk on the ever increasing metabolic syndrome, in which he surprised us all with the shocking statistic that over 50% of the middle aged American population suffer from this condition. Easily blamed on the increasing incidence of obesity, the question is why does an increased adiposity lead to metabolic syndrome? It is known that release of free fatty acids (FFA) from fat into the blood stream can have severe implications on glucose uptake and FA uptake by skeletal muscle. Additionally, FFA uptake in the liver can be very damaging and lead to increased VLDL content, inflammation, cirrhosis and fibrosis. Increased FA leads to increased PKC and NFkB signaling, as well as ROS production which all lead to endothelial dysfunction. The question is however; do obese people release more FA into the blood than non-obese people? On one hand, FFA release decreases with increased fat mass, however, if fat mass in increased significantly, the decreased FFA release is inadequate to compensate; cells are continuously bathed in FFA. However, this, as Klein so elegantly persuaded us, cannot be the only cause of metabolic syndrome. Firstly, women have very much-increased FFA release compared to men, but do not show increased metabolic disturbances, and secondly, studies on African-Americans have a very much-lowered FFA release compared to weight-matched Caucasians but yet an increased incidence of diabetes. It was therefore proposed that it might be the difference in rate of FFA release and the rate of FFA oxidation that is the key determinant of metabolic syndrome. Indeed, obese people have been shown to have an increased difference between rate of release and rate of oxidation. However this hypothesis is also challenged by the fact that endurance athletes have an even larger difference between release and oxidation. It was therefore suggested that perhaps metabolic syndrome might be linked, moreover, to the ability to dispose of glucose. It has been observed that efficiency of glucose disposal is linked with decreased hepatic fat. Indeed, obese people have an increased fat distribution to the liver (20% stored as hepatic fat as opposed to 5% in non-obese people).

Klein concluded his talk with a very positive notion that weight loss is the most powerful therapeutic tool we have for obesity related disorders. Diabetes has been almost eliminated after significant weight loss, and intra hepatic fat has been seen to decrease even after 48 hours of restricted calorie intake. Additionally, abnormal processes such as fibrosis and inflammation (as measured by IL-8 and MCP-1 levels) were drastically lowered 1-year after gastric bypass surgery. Although this was a very encouraging note to end on, it was slightly opposed by the enormous piles of cookies, muffins and doughnuts that were on offer roughly every 2 hours! Even on each day during poster sessions, there was a banquet available between individual poster viewings.

Gina Schatterman (University of Iowa) changed themes slightly to introduce the ever-popular concept of treatment using bone marrow cells. In a model of ischaemia using femoral artery ligation, injection of bone marrow cells did not lead to differentiation into endothelial cells or blood vessel growth. However, amazingly, in streptozotocin-induced diabetic rats with the same femoral artery ligation, flow was restored within 2 days of bone barrow cell injection. When looking at db/db diabetic mice, effects were similar, leading to the suggestion that perhaps there are differences in cytokine and growth factor levels (such as MCP-1, IL-1β and TNFα) in bone marrow cell-injected diabetic and non-diabetic tissues. A further question would then be how the bone marrow cells might be modulating these cytokines and growth factors. An interesting hypothesis is that the bone marrow cells are secreting the cytokines themselves and thereby initiating angiogenesis. Indeed, although the difference in IL-1 levels in diabetic and non-diabetic tissues with injected bone marrow cells were not different, huge differences were seen in TNFα levels between diabetic and non-diabetic tissues. However, this was complicated by the further observation that TNFα-/- bone marrow cells injected into diabetic tissues still induced healing. The final test, therefore, was MCP-1; when MCP-1-/- bone marrow cells were injected into ischaemic tissues of db/db mice, vessel growth was completely attenuated. It was therefore concluded that bone marrow cells might be secreting MCP-1, which in turn induces angiogenesis. Bone marrow cells could therefore be a very interesting therapeutic option for angiogenesis, however, the fact that they respond so differently in diabetic versus non-diabetic mice makes them, currently, unfeasible as a generic treatment for all patients requiring angiogenesis. Further understanding of the molecular mechanisms of their functioning, however is crucial and could lead to very exciting implications.

All in all the meeting was incredibly successful, with so much information packed into 2 days that it was almost impossible to take it all in. The variety of topics covered and the sheer number of participants was conducive to a meeting in which it was impossible not to take away exciting ideas and newfound

motivation. I strongly recommend any American Heart Association meeting to anyone, particularly the forthcoming one in Florida! I know I will be seeing you there…

The stunning and innovative Chicago skyline, peering over Lake Michigan

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 cardiovascular-related meeting and would like to write a report for the Bulletin, please contact the editors. A bursary of **£300** is available towards the cost of your visit, and this will be provided on receipt of the report.

Bon voyage!

Travel Report: Weinstein Cardiovascular Development Conference

10th - 12th May 2007, Indianapolis, USA

by Dr Catherine A. Risebro, Molecular Medicine Unit, UCL Instiute of Child Health

Travel reports from conferences abroad are often accompanied by a few words describing the breathtaking scenery. This year, the 14th Annual Weinstein Cardiovascular Development Conference was held in Indianapolis, Indiana, USA, home of the 'Indy 500'. Before heading off I decided to find out a bit more about the city. The most encouraging words I could find were that the city had 'shaken off such nicknames as India-no-place' and that developments in the 90's had 'brightened up its downtown to the point that it's not a bad stopover' (taken from http://www.roughguides.com/default.aspx). I wished I hadn't bothered. However, upon arrival we were greeted with glorious spring sunshine and friendly people who gave us plenty of inside information including the best place in town for a steak and shrimp cocktail. Added to this there was a buzz of excitement in the air as over 300 scientists from the USA, Europe and Japan descended upon Indianapolis.

Indianapolis Skyline

Crowne Plaza Hotel and Conference Center

The Grand Hall, Crowne Plaza

This year's meeting was hosted by the Cardiovascular Developmental Biology Research Group at Indiana University, Herman B Wells Center for Pediatric Research and was staged at the Crowne Plaza Hotel and Conference Center at Historic Union Station, conveniently located in the middle of downtown Indianapolis. The Circle Center shopping mall was just a short walk away for those of us who wished to utilise our lunch break to take advantage of the struggling US dollar, along with a host of bars and restaurants in which we continued forging fruitful relationships long after the evening sessions had ended!

The Weinstein Cardiovascular Development Conference, initiated in 1994 by Dr Constance Weinstein, is an annual meeting for scientists investigating normal and abnormal development of the heart and vasculature and how it impacts upon human disease and has become one of the most important meetings in the field of cardiovascular development. A unique feature of the meeting is that, except for the two keynote presentations, all speakers are selected from submitted abstracts. As such, there is an emphasis on generating an informal atmosphere and the inclusion of students and junior scientists as speakers, which focuses the meeting on new and emerging unpublished data rather than on presentations by principal investigators.

Over the three day period the meeting covered virtually all key aspects of cardiovascular development, with over 40 platform presentations and more than 200 posters that were displayed throughout the entirety. Following the welcome address by Loren Field, Indiana University, the meeting began in earnest with the first platform session on cardiomyocyte cell cycle regulation. This session included an interesting talk by Airon Wills, Duke University, about cellular and molecular mechanisms of epicardial cell addition during cardiac homeostasis in the adult zebrafish. Airon described how inhibition of Fgf signaling, required for normal heart regeneration, blocked epicardial cell contribution during growth and also resulted in ventricular scaring in uninjured animals.

The second session on myofibrillogenesis saw my first outing onto the platform in an international forum where I presented work we are currently performing on the role of the homeobox transcription factor, Prox1, in the maintenance of appropriate sarcomere ultrastructure, which in the absence of Prox1 is completely disrupted. Despite the nerves, I was extremely grateful to have been given the fantastic opportunity to present my work to a large audience and for the feedback received afterwards.

However, the highlight of the afternoon was, without doubt, the fascinating and inspiring keynote presentation by Dr. Oliver Smithies, Excellence Professor of Pathology and Laboratory Medicine at The University of North Carolina at Chapel Hill, who regaled us all with tales of midnight and weekend experiments. Still working at the bench, Dr. Smithies has a long and distinguished career in molecular genetics, and is largely credited with the co-development of gene targeting techniques. Much of what he spoke to us about was during his early career when Dr. Smithies developed new methods for detecting genetic variation in proteins and, with the help of his mother's laundry habits, originated starch gel as a supporting medium for the electrophoretic analysis of proteins and enzymes. This later led to discoveries of protein polymorphisms and significant work on the heredity of important blood proteins - including haptoglobins, transferrins, and gamma globulins.

Dr Oliver Smithies

Having been stunned into reverential silence by the amazing life story of Dr. Smithies, the first poster session, buffet dinner and open bar got us all back on track, socialising and discussing the day's news. It also provided some lively discussion in the two workshops held concurrently that evening! The workshop on cardiomyogenic stem cells during development featured our lab's second contribution with a presentation from Nicola Smart about her work on Thymosin β4 and it's effect on epicardial derived vascular progenitors. The second workshop entitled single v. multiple development heart fields, discussed the presence of one, two or more heart fields, a topic that has been debated at length over the past few years. There was plenty of active group participation, yet the overriding opinion was that it didn't really matter how many there were or whether it was just one, but that it is crucial to understand the temporal regulation of each population's respective contributions to the developing heart.

On Friday morning we heard about transcription factors in cardiogenesis, including the identification of Msk1 and Msx2 as new binding partners for Tbx2 and Tbx3 by Kees Boogard, Heart Failure Research Centre in Amsterdam, and the generation of Nkx2.5 and Mef2c double null mutant embryos by Josh Vincentz, Indiana University, whose phenotype suggests a genetic interaction of these two key cardiac transcription factors. The second session of the day revolved around vascular development. Of particular interest was the presentation by Xiao-Qing Zhao, National Institute of Health, who described a Connexin 43 (Cx43) knockout model and used a 3-dimensional collagen gel assay to demonstrate increased epithelial-to-mesenchymal transformation (EMT) in Cx43 knockout epicardium, together with upregulation of genes involved in EMT including Tgf and Fgf family members, implicating Cx43 in epicardial EMT regulation.

After lunch we had the second round of concurrent workshops on cardiac neural crest and imaging cardiovascular development and physiology. The cardiac neural crest workshop mainly focused on the fate of the crest cells in the heart, but without providing any particular answer. Henry Sucov presented some intriguing findings from his work investigating retinoic acid receptors, RXR/RAR. Retinoic acid signaling has long been known to influence neural crest and yet Sucov showed that only loss of RXR/RAR in the early mesoderm (Mesp1-Cre) generated a cardiac neural crest phenotype. Loss of RXR/RAR in the second heart field (Mef2c-Cre), neural crest (Wnt1-Cre) and endothelial (Tie2-Cre) lineages all resulted in normal cardiac neural crest specification, differentiation and migration.

The final platform session of the day was centered around the development of the cardiac conduction system, and included a talk detailing further bounty from the retrospective clonal analysis technique employed here by Lucile Miquerol, University of Marseille. Her results indicate that conductive and contractile cardiac cells have a common progenitor and that the central and peripheral conduction systems develop independently.

Next was the second keynote presentation by Dr. Margaret Kirby, Professor of Pediatrics, Cell Biology and Biology Scientific Director, Neonatal-Perinatal Research Institute Department of Pediatrics (Neonatology) Duke University. Dr. Kirby, another highly distinguished scientist, is known world wide for her work on the role of neural crest cells in the genesis of congenital heart defects. Dr. Kirby described much of her current research, which focuses on outflow tract development, subdivision of the cardiogenic fields and early heart tube formation, and she of course continues to delve into the role of neural crest cells in controlling signaling in the pharynx that impacts early heart development.

The evening was rounded off with the second poster session, buffet and open bar until 10 pm, after which we sampled the local nightlife - including the 'world famous' shrimp cocktail we had heard so much about. Personally, I preferred their other cocktails…

Dr Margaret Kirby

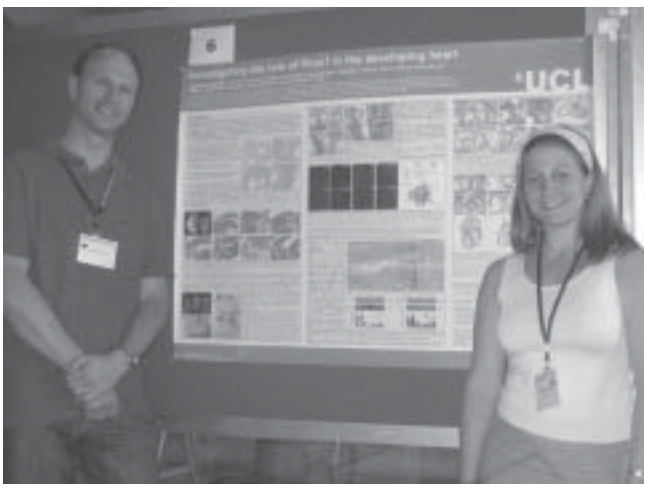
Saturday brought us another full day of hot off the press research news, beginning with a session on signaling pathways in cardiogenesis. The session began with the unusual, mostly ignored, topic of cardiac jelly and the importance of the extracellular matrix, particularly in trabeculation. Kryn Stankunas, Stanford University, described the requirement in the early endocardium of the core component of the BAF complex, Brg1, to repress expression of ADAMTS1, a secreted matrix metalloprotease. Endotheial loss of Brg1 (Tie2-Cre) resulted in derepression of ADAMTS1 and consequently caused premature breakdown of the cardiac jelly and termination of trabeculation. Another presentation in this session, delivered by Kai Jiao, University of Alabama, showed evidence that Smad4, a critical regulator of Tgfβ/Bmp signaling, plays an essential role in cardiac development contrary to previous studies suggesting that Smad4 was indispensable, and that N-myc is a likely downstream target of Smad4.

The seventh platform session was based upon the subject of valvulogenesis. Of particular interest, Tom Doetschman, University of Arizona, described an all encompassing role of Tgfβ2 in valve development, being necessary for both the initial stages of endocardial cushion formation by regulating and ensuring correct attenuation of EMT, and also acting as a differentiation factor during subsequent collagen fibrillogenesis and remodeling to mature valve leaflets.

The penultimate session was dedicated to animal models of congenital heart disease. One of the more striking studies was presented by Hongming Zhou, University of Indiana, who made use of compound null and hypomorphic alleles to titrate out the levels of the neural crest/neural tube transcription factor Pax3. It was found that, unlike other lineages in which Pax3 is expressed, the cardiac neural crest lineage can tolerate up to 90% loss of Pax3, presumably due to compensation by other neural tube factors. In the same session, Caroline Jenkins, University of Oxford, described the conditional targeting of the Polycomb Repressive Complex component Ring1b, a histone ubiquityl ligase, and demonstrated that it has a cell autonomous role in the mesoderm during heart development, and suggests that histone ubiquitylation plays a significant role in mesodermal cell specialisation.

In the closing session on translational models of congenital heart disease Eugene Yu, Roswell Park Cancer Institute, presented the generation of a more genuine mouse model with which to study Down syndrome, using Cre-loxP mediated long range chromosome engineering to establish a 22.9 Mb duplication spanning the entire human chromosome 21 syntenic region on mouse chromosome 16. The resultant cardiovascular defects were very similar to those of Down syndrome patients and they expect this new mouse model to be a powerful tool to dissect the molecular and cellular mechanisms of Down syndrome associated congenital heart disease.

The conference was rounded off with a successful banquet on Saturday evening that took place in the Grand Hall Ballroom, during which poster prizes were awarded. Entertainment for the evening was provided by The Uptown Jazz Quartet, who certainly managed to get a few feet tapping. A big thank you goes to the local organising committee, which includes Drs. Loren Field, Simon Conway, Anthony Firulli, R. Mark Payne, Michael Rubart, Weinian Shou, and Lei Wei. It was a fantastic meeting, particularly for the experience I gained on the platform, and I'm very much looking forward to attending another Weinstein. In 2008, the 15th Annual Weinstein Cardiovascular Development Conference will be hosted by the University of Texas, M.D. Anderson Cancer Center, Houston, USA.



Paul Riley and Catherine Risebro present their work at the poster session

British Heart Foundation Grants

Chairs and Programme Grants Committee February 2007

Infrastructure Grants

Professor G D Angelini, University of Bristol. "Equipment for the Bristol Heart Institute" £150,000

Programme Grants

Professor M J Shattock et al, King's College London. "Regulation of the cardiac Na/K ATPase in health and disease: role of phospholemman (FXYD1)" 5 years £1,249,302

Project Grants Committee March 2007

Dr C Dart & Dr J M Quayle, University of Liverpool. "The role of Exchange Protein directly Activated by cAMP (EPAC) in the regulation of arterial ATP-sensitive potassium (KATP) channels" (3 years) £156,065

Dr J Chamberlain et al, University of Sheffield. "Is endothelial progenitor cell therapy for in-stent restenosis good or bad?" (2 years) £136,315

Dr K M Naseem, University of Bradford. "The role of thrombospondin-1 in regulating platelet sensitivity to nitric oxide" (3 years) 135,021

Prof J C Hancox & Dr D O Bates, University of Bristol. "Investigation of the role of TRPC channel involvement in VEGF-mediated endothelial cell cation entry" (3 years) £161,096

Prof P J Scambler, University College London (ICH). "Role of the CHARGE syndrome gene Chd7 in cardiovascular morphogenesis and its interaction with the DiGeorge syndrome gene Tbx1" (3 years) £323,610

Prof J G F Cleland & Dr A L Clark, University of Hull. "A pilot study to examine risk associated with air travel in patients with chronic heart failure" (1 year) £48,411

Dr N P J Brindle, University of Leicester. "Receptors mediating angiopoietin-1 regulation of endothelial function" (2 years) £97,227

Dr R D Evans & Prof K Clarke, University of Oxford. "Metabolic, functional and molecular changes in heart with ventricular failure and unloading" (3 years) £177,211

Dr D P Ramji, Cardiff University. "Interferon-γ signalling and the control of cholesterol accumulation and efflux in macrophages" (3 years) £153,024

Dr S J Wort et al, Imperial College London. "The regulation of ET-1 production by the TGF-β1/BMP pathway in human pulmonary vascular cells" (3 years) £155,817

Prof P H Whincup et al, St Georges, University of London. "Early markers of vascular disease in British children of South Asian, African-Caribbean and white European origin" (1.5 years) £228,915

Dr Y Senis & Professor S P Watson, University of Birmingham. "Investigating the functional roles of CD148 and PTP-1B in platelets through the use of mouse models" (3 years) £167,990

Dr E O Balogun & Dr D J Chambers, King's College London. "Lung protection during deflation-induced injury associated with cardiopulmonary bypass: characterising the role of MAPK pathways" (3 years) £160,492

Dr T V Burdyga et al, University of Liverpool. "Calcium signalling mechanisms and contractility in pre-capillary sphincters: an in situ study" (3 years) £208,988

Prof J G F Cleland et al, University of Hull. "Effect of programmed heart rate on cardiac function in patients with a cardiac resynchronisation device" (2 years) £84,714

Prof E D Saggerson, University College London. "Adrenergic regulation of AMP-activated protein kinase in the heart" (2.5 years) £235,186

Dr A Graham, Glasgow Caledonian University. "Mitochondrial cholesterol transport: a key element in regulation of macrophage cholesterol homeostasis and foam cell formation" (3 years) £176,150

Dr H L Roderick & Dr M D Bootman, The Babraham Institute, Cambridge. "Investigation into the role of inositol 1,4,5-trisphosphate mediated calcium release in controlling cardiac hypertrophy" (3 years) £167,463

Prof S P Watson et al, University of Birmingham. "Regulation of migration of megakaryocytes by PECAM-1 and other surface glycoprotein receptors" (3 years) £172,155

Fellowships Committee April 2007

Intermediate Basic Science Research Fellowships

Dr B Rodriguez Lopez, University of Oxford. "Integrative computational and experimental investigation of the mechanisms of cardiac arrhythmias and defibrillation in acute myocardial ischaemia" (4 years) £294,529

Dr H A A Al-Khayat, Imperial College London. "Mammalian cardiac myosin filament ultrastructure in health and disease" (4 years) £222,754

PhD Studentships

Mr W J Kaiser, University of Reading. " A study of platelet tachykinins and the regulation of haemostasis: from mechanisms of action to physiological significance" (3 years) £90,969

Miss K Redding, University of Bristol."Oxidative stress in freshly isolated cardiomyocytes during different stages of postnatal development" (3 years) £84,237

Ms S Chapple, King's College London. "Regulation of eNOS/hsp90/Akt interactions and nitric oxide synthesis in human fetal endothelial cells in pre-eclampsia" (3 years) ££96,259

Unnamed and Ye, Queen Mary, University of London. "Analyses of matrix metalloproteinase-12 gene variations in relation to myocardial infarction susceptibility" (3 years) £97,207

Unnamed and Baker, University of Glasgow. "Assessing the potential of non-integrating lentiviruses for application to vascular gene therapy" (3 years) £92,655

Ms H E Ringham, Imperial College London. "Genetic studies on a confirmed chromosome 21q22.2-22.3 familial combined hyperlipidemia susceptibility locus and functional analysis on strong candidate genes" (3 years) £93,947

Unnamed and Turowski, University College London. "Spatio-temporal activation of endothelial PKC isotypes during

inflammatory leukocyte migration" (3 years) £96,895

Ms G Randall, University College London. "The role of the family in adjustment to cardiovascular disease" (3 years) £93,141

Miss M A Paul, King's College London. "The role of calcineurin and PKC signalling in COX-2 gene regulation and myocardial remodelling in response to angiotensin II" (3 years) £97,448

Mr A D Scott, Imperial College London. "Improved respiratory motion compensation for magnetic resonance imaging of the coronary arteries using a novel non-model based technique" (3 years) £83,648

Miss E L Evans, University of Nottingham. "Redox sensitivity of STAT3 and its role in the survival of cardiomyocytes during hypoxia/oxidative stress" (3 years) £82,511

Unnamed and Graham, University of Glasgow. "Mechanism of cardiovascular disease prevention by MitoQ, a novel mitochondria-targeted antioxidant" (3 years) £91,336

Clinical Research Training Fellowships

Dr I Webb, King's College London. "Postconditioning: the role of PKCepsilon and GSK3" (3 years) £190,636

Dr S Dass, University of Oxford. "The role of cardiac energy metabolism during stress in disease states - clinical studies with exercise 31P-MR spectroscopy at 3T" (2 years) £156,307

Dr J C Gomes, University College London. "Molecular manipulation of the electrophysiological substrate in the desmoplakin knockout mouse: a model of arrhythmogenic right ventricular cardiomyopathy" (3 years) £153,208

Cardiovascular Related Wellcome Trust Grants

February to April 2007

Programme Grants

Dr Martin Bobak, Department Of Epidemiology And Public Health, University College London. Determinants Of Cardiovascular Diseases In Eastern Europe: Longitudinal Follow Up Of A Multi-Centre Cohort Study (The Hapiee Project). 60 Months £1,234,672

Professor Andrew Tinker, Department Of Medicine, Rayne Institute, University College London. The Molecular Mechanisms Of Activation Of G-Protein Gated Inwardly Rectifying K+ Channels. 60 Months £1,039,333

Professor John Garthwaite, Wolfson Institute For Biomedical Research, University College London. Nitric Oxide Signalling In The CNS. 60 Months £1,220,044

Professor Keith N Frayn, Oxford Centre For Diabetes, Endocrinology And Metabolism, Churchill Hospital. Understanding Regional Fat Deposition In Relation To Metabolic Disease Risk In Humans: An Integrative Physiological Investigation. 48 Months £898,504

Senior Research Fellowships

Dr Patrick D'silva, Department Of Biochemistry, Indian Institute Of Science, Bangalore India. Regulation Of Mitochondrial Biogenesis: Role Of Molecular Chaperones In Protein Translocation Across The Inner Mitochondrial Membrane 60 Months £360,465

Dr Marko Vendelin, Institute Of Cybernetics, Tallinn Technical University, Tallinn Estonia. Analysis Of Structural And Functional Aspects Of Compartmentation Of Adenine Nucleotides In Heart Muscle Cells. 60 Months £722,259

Research Career Development Fellowship

Dr David Batty, MRC Social and Public Health Sciences, University of Glasgow. Life Course and Trans-Generational Influences on Cardiovascular Disease and Cancer 60 Months £574,957

Project Grants

Professor Derek Yellon, Department Of Cardiology, The Hatter Institute, UCL Hospitals. The Mitochondrial Permeability Transition Pore Plays A Central Role In Cardioprotection: An Investigation Using The Cyclophilin D Knockout Mice. 36 Months £144,844

Professor Hugh S Markus, Department Cardiac And Vascular Sciences, Centre For Clinical Neurosciences, St George's University Of London. Cognitive Impairment In Cerebral Small Vessel Disease: A Prospective Imaging Study. 60 Months £447,377

Dr Steven J Ennion, Department Of Cell Phys And Pharmacology, School Of Medicine, Medical Science Bldg, University Of Leicester. Purinergic Signalling In Dictyostelium Discoideum. 18 Months £120,525

Dr Ming Lei, Core Technologies Facility, School Of Medicine, University Of Manchester. Study Of Ion Channel Function In The Sinoatrial Node In Wild-Type And Genetically Modified Mice. 36 Months £378,578

Professor Mauro Perretti, Department Of Biochemical Pharmacology, William Harvey Research Institute, Queen Mary, University Of London. Biochemical And Functional Analyses Of The Glucocorticoid Receptor In Blood Platelets. 24 Months £134,091

Professor Cay M Kielty, Michael Smith Building, University Of Manchester. The Essential Contributions Of Fibulins -4 And -5 To Elastic Fibre Formation. 36 Months £298,135

Professor Robert J White, Division Of Biochemistry And Molecular Biology, Institute Of Biomedical And Life Sciences, University Of Glasgow. Regulation Of RNA Polymerase III Transcription By MAF1 In Mammals. 24 Months £115,258

Dr Graeme F Nixon, Department Of Biomedical Sciences, Institute Of Medical Sciences, University Of Aberdeen. Regulation Of Vascular Smooth Muscle Cell Phenotype By Changes In Phospholipase C Gamma Expression: Relationship To The Pathogenesis Of Vascular Disease. 24 Months £124,288

Dr Amrita Ahluwalia, William Harvey Research Institute, Queen Mary, University Of London. Vascular Autoregulation And Inflammation: Role Of Sensory C-Fibres And Trpv1. 36 Months £353,189

Professor P G Camici, Mrc Clinical Sciences Centre, Hammersmith Hospital, Imperial College School Of Medicine. Non Invasive Measurement Of Absolute Myocardial Perfusion In Humans: A Comparison Between Positron Emission Tomography And Cardiac Magnetic Resonance Imaging. 24 Months £267,657

BSCR Autumn Meeting 2007

THE QT INTERVAL AND DRUG-INDUCED TORSADES DE POINTES

Dates: Monday 24th and Tuesday 25th September, 2007

Venue: Governors' Hall, St Thomas' Hospital, London, UK

Organiser: Michael J Curtis PhD FBPharmacolS

Downloadable material: The full programme, abstract pro-forma, meeting registration form, and student bursaries application form are available for downloading from the BSCR website (www.bscr.org).

Objectives: The principal objective of the meeting is to highlight current issues surrounding drug-induced torsades de pointes and will focus on biomarkers, risk factors and preclinical investigational methods. Furthermore, the meeting aims to allow individuals active in Industrial Safety Pharmacology to engage with clinical and pre-clinical academic investigators.

Programme: This consists of three symposia. The first is a moderated debate, led by expert panel members, and is entitled "Is QT prolongation always intrinsically arrhythmogenic, or intrinsically antiarrhythmic?" The second and third symposia are entitled: "How validated are current models and biomarkers for testing drug-induced torsades de pointes liability?" and "Drug-induced torsades de pointes - now what?". The finalized list of speakers and panel members is: Luc Hondeghem, Dan Roden, Philip Sager, Russ Bialecki, Leif Carlsson, Marc Vos, Anthony Fossa, Bob Hamlin, Peter Hoffmann, Gan-Xin Yan, Jules Hancox, Craig January, Susan Coker, Keitaro Hashimoto, Gary Gintant, Rashmi Shah, Michael Pugsley.

Abstracts and free communications: Free communications are by poster. There are two poster prizes of £250 each: the Clinical Science Young Investigator Award and the BSCR Young Investigator Award (you must be a BSCR member to enter).

Registration: Free for BSCR members and £40 for academic non-members.

Student Bursaries: The Society will consider awarding travel grants of up to £200 per person to bona fide students who are members of the BSCR.

The deadline for the submission of abstracts, registration and application for student bursaries is 10th August 2007. Early registration is recommended owing to a limit of 150 persons for the meeting, and 100 for the conference dinner.

Travel & Accommodation: Attendees are requested to make their own arrangements for travel and accommodation. UK and mainland European attendees should require accommodation for the night of Sept 24th only. The meeting location is 5 minutes walk from Waterloo mainline station, Waterloo Underground, and Westminster Underground stations. Therefore hotels advertised on the web as located near any station on the, Bakerloo, Circle, District, Northern, or Jubilee underground lines will provide convenient access to the venue.

Enquires regarding BSCR membership or student bursaries should be directed to Prof. Barbara McDermott, BSCR Secretary, Therapeutics & Pharmacology, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL; Tel 02890-972242; Fax 02890-438346; b.mcdermott@qub.ac.uk

Other Correspondence: This should be directed to Mr Antonio Cavalheiro, Cardiovascular Division, Rayne Institute, St Thomas' Hospital, London SE1 7EH; Tel: +44 (0) 207 1881095; Fax: +44 (0) 207 1883902; E-mail: Antonio.cavalheiro@kcl.ac.uk.