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Contents

Editorial

Welcome to the April 2005 issue of *The* Bulletin!

We are pleased to bring you an intriguing review of the antihypertensive and antiatherosclerotic properties of calcium channel blockers (CCBs), written by Dr Gerard Clunn of the National Heart and Lung Institute at Imperial College London. Dr Clunn discusses the mechanisms of action of CCBs and their therapeutic potential in the treatment of occlusive vascular disease.

This issue also includes a report on last year's spring meeting, held at the University of Manchester: *"Frontiers in Cardiovasculr Signalling"*. The report, written by the organisers David Eisner and Cathy Holt, summarises all talks, keynote lectures and oral presentations. Abstracts presented at the meeting have been published by *Heart* online at: http://heart.bmjjournals.com/cgi/content/full/90/4/DC1

Included in this issue is the first announcement of this year's Autumn meeting, organised by Professors Michael Marber and Metin Avkiran. A detailed programme is printed herein and further details for those interested in attending the meeting and in submiting an abstract may be found on the back page and, of course, via the Society's website www.bcs.com/affiliates/bscr.html.

Finally, details of the latest grants awarded to researchers in the Cardiovascular field by the British Heart Foundation are listed towards the end of this issue.

Helen Maddock and Nicola Smart

Calcium channel blockade and the transition from hypertension to occlusive vascular disease

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Introduction

Hypertension is firmly established as a major independent risk factor for the development of occlusive vascular disease. Accordingly a range of antihypertensive drugs have been developed for long term management of the condition. They include calcium channel blockers (CCBs), diuretics, angiotensin converting enzyme (ACE) inhibitors and beta blockers. It is recognised that lowering blood pressure (BP) by any means reduces the risk of developing occlusive vascular disease [1]. However it is increasingly appreciated that certain antihypertensive agents have direct antiatherosclerotic actions in addition to and independent from their BP lowering effects [2,3]. Since the various classes of antihypertensive drugs act via different mechanisms it follows that they have the capacity to influence different aspects and phases of the atherosclerotic process. This article assesses calcium channel antagonism as a potential direct antiatherosclerotic strategy. It proposes upper limits to the efficacy of current CCBs based on recent findings concerning plasticity in Ca^{2+} signalling pathways. Further, it reviews emerging data on recently identified classes of Ca^{2+} channels which may represent targets in the future. The main focus is on vascular smooth muscle cells (SMCs), the clinical target of CCBs.

CCBs in BP lowering and early occlusive vascular disease

CCBs inhibit the passage of extracellular Ca^{2+} through the L-type voltage operated Ca^{2+} channel (also denoted $Ca_V1.2$) of the SMC plasma membrane [4]. They act as direct vasodilators, lowering peripheral vascular resistance. They are generally well tolerated and exhibit a low side-effect profile. These points, and issues regarding contraindications, side-effects and matters of long term safety have been reviewed elsewhere [5,6]. CCBs are divided into three subclasses: dihydropyridines (including amlodipine, lacidipine, lercanidipine, nifedipine), phenylalkylamines (verapamil) and benzothiazepines (diltiazem). They constitute a heterogeneous group, even within the dihydropyridine subclass which comprises three generations of drugs with distinct chemistry, pharmacokinetics and pharmacodynamics [7].

Recent clinical trials (ELSA, VHAS and INSIGHT, see refs 8-10 for definitions) have compared CCBs to other antihypertensive classes in terms of BP reduction, development of early occlusive disease and outcome. Early stage occlusive disease was revealed using ultrasound to measure carotid artery intima:media thickness (IMT), increase of which indicates asymptomatic atherosclerosis progression. Outcome was defined as a combination of mortality, morbidity and serious cardiovascular and cerebrovascular events [8-10]. ELSA (lacidipine versus beta blocker), VHAS (verapamil versus diuretic) and INSIGHT (nifedipine versus diuretics) found that regression, or inhibition of progression of carotid IMT, was consistently greater in the CCB treated groups even though BP reduction was comparable. Overall outcome was similar in ELSA and INSIGHT, and favoured the CCB in VHAS. A study in patients with type 2 diabetes showed that amlodipine had greater beneficial effects on carotid IMT progression compared to ACE inhibition [11]. Earlier trials showed that CCBs inhibited the appearance of new lesions and the progression of minimal lesions but had little or no effect on more advanced plaques [12,13]. Together these data show that CCBs possess direct,

BP independent, antiatherosclerotic actions. Moreover their greatest effects are on the early stages of occlusive disease, but effectiveness decreases as plaques advance. An insight into why this occurs would help to design more effective antiatherosclerotic strategies based on Ca^{2+} channel antagonism. To understand the time dependent decrease in CCB efficacy we first give brief overviews of SMC Ca^{2+} influx pathways and the changes that occur in SMCs during plaque formation.

Ca^{2+} influx pathways in contractile SMCs

SMC plasma membrane Ca^{2+} channels can be divided into two types. (a) Voltage operated channels (VOCs). They comprise the L-type and in some cases, T-type channels. VOCs open in response to depolarisation of the plasma membrane potential [14]. The resulting influx raises intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) to initiate the classical Ca^{2+} dependent contractile response. (b) Receptor operated channels (ROCs). ROCs are defined here as all non-VOC Ca^{2+} influx pathways. The majority are non-specific cation channels, also permeable to Na^+ and K^+. Channel opening arises in response to extracellular ligands, mechanical forces and in reaction to depletion of intracellular Ca^{2+} stores (see [15,16] for comprehensive reviews and refined definitions). Ca^{2+} influx channels form only part of a more elaborate Ca^{2+} handling system [17].

Ca^{2+} entry into contractile SMCs is dominated by influx through the L-type VOC. This accounts for the efficacy of CCBs in vasorelaxation. The contribution of ROCs to $[Ca^{2+}]_i$ elevation varies according to vessel and vasoconstrictor. ROCs are directly activated by vasoconstrictors and neurotransmitters. Moreover some may enhance membrane depolarisation due to similar K^+ and Na^+ permeabilities, so augmenting Ca^{2+} entry through VOCs. Further, their role in replenishing Ca^{2+} stores makes a distinct contribution.

Early plaque development: critical role of SMC dedifferentiation

Early plaque development is viewed as an inflammatory process initiated by endothelial dysfunction, injury and/or permeation of low density lipoproteins into the vessel intimal layer. In the hypertensive state vasoactive peptides such as angiotensin II may also play prominent roles [18]. Following these disturbances there is an infiltration of monocytes/macrophages, release of growth factors and cytokines, disruption of the local extracellular matrix and reduction of local nitric oxide production [18,19]. Crucially, the resulting alteration in the microenvironment induces dedifferentiation of the adjacent medial contractile SMCs. They lose contractile capability but gain the capacity to respond chemotactically and mitogenically. The non-contractile, mitogenically responsive cells are termed synthetic SMCs [20]. Under control of growth factors, cytokines and extracellular matrix components synthetic SMCs migrate into the intimal layer. There they proliferate, undergo apoptosis and secrete matrix proteins, ultimately forming the largest cellular component of the developing plaque. A number of similar processes occur in restenosis after bypass grafting or percutaneous transluminal angioplasty [21]. A synthetic SMC phenotype is also implicated in hypertensive pathophysiological remodelling [22].

Ca^{2+} dependent antiatherosclerotic effects of CCBs

Ca^{2+} plays multiple roles in differentiation, migration and proliferation including regulation of gene expression, cell attachment, actin organisation, and modulation of signalling molecules [23-26]. Therefore inhibition of SMC Ca^{2+} influx provides the simplest mechanism whereby CCBs could exert direct effects on vessel occlusion. Most studies *in vitro* have shown inhibition of SMC chemotaxis and proliferation by CCBs, though with some exceptions [27-29]. Many animal studies have demonstrated inhibition, or delay, of atherosclerosis by CCBs (reviewed in [30]). Interpretation in some cases may be confounded by effects independent of inhibition of Ca^{2+} influx (see later section). It has been observed in several cases that efficacy of CCBs relied on pretreatment, ie the drug needed to be administered prior to the atherogenic stimulus. In this regard Donetti *et al* [31] noted that lacidipine "preferentially interferes with early atherogenic processes," in accord with the human data. Thus CCBs can directly impair plaque development by inhibition of Ca^{2+} influx. To address the time dependent decrease in efficacy we turn to results from a number of groups working independently in different contexts. The unifying theme is that the primary target of CCBs, the L-type VOC is not a static one.

Ca^{2+} influx pathways in dedifferentiating and synthetic SMCs

Gollasch *et al* [32] found using a7r5 rat aortic cells that L-type Ca^{2+} currents were significantly reduced

when SMCs were induced to dedifferentiate. They recovered when cells were induced to redifferentiate. Quignard *et al* [33] used a rat aortic injury model to study restenosis. They found that in the first few days after injury, L-type current from local (dedifferentiating) SMCs decreased markedly. During neointimal formation (when SMCs were proliferating and migrating) no L-type current was detectable from the neointimal SMCs. However as SMC proliferation and migration subsided, L-type current largely recovered. In aortic neointimal plaque isolated from fowl, membrane depolarisation produced only a slight $[Ca^{2+}]_i$ rise in SMCs from within the plaque itself but produced a large response from SMCs around the plaque [34]. In another context, L-type current was found to be undetectable in neonatal rat aortic SMCs but clearly detectable in those of adult tissue [35].

We have used saphenous vein SMCs derived from patients undergoing bypass surgery [36]. These cells undergo dedifferentiation, migration and proliferation within the context of human restenosis so represent a clinically relevant system. We found that quiescent cells (withdrawn from the cell cycle) exhibited VOC dependent and ROC dependent components of $[Ca^{2+}]_i$ elevation. When stimulated to enter the cell cycle the VOC component was lost.

Crucially, functional evidence of VOC downregulation in our study and those described above was confirmed by loss of the inhibitory effect of L-type CCBs on stimulated Ca^{2+} influx. We took the next step by examining the consequences of VOC loss on CCBs to influence a SMC function associated with occlusive disease. We had previously characterised the chemotactic responses of these cells to platelet-derived growth factor (PDGF, ref 37). It is the archetypal SMC chemoattractant, induces SMC dedifferentiation and is essential for neointimal formation in saphenous vein organ culture [38,39]. When quiescent cells were pretreated with amlodipine and subsequently exposed to PDGF, the induced migration was significantly inhibited. Conversely the CCB had no effect on PDGF induced migration on cells that had previously been stimulated to enter the cell cycle. These findings show that the functional (and therefore therapeutic) effect of the CCB critically depends on the phenotypic status of the SMCs prior to drug administration.

Taken together the findings from different contexts may be summarised and unified into a more general model as follows. In normal adult blood vessels SMC Ca^{2+} influx is dominated by the L-type VOC pathway, the primary function being regulation of tone. Under conditions of flux (development, wound healing, plaque progression) where synthetic SMCs dominate, the L-type VOC pathway is progressively functionally downregulated. Ihara *et al* [40] provided evidence that activation of mitogen activated protein kinases (MAPKs), ubiquitous regulators of phenotypic state and proliferation, induced downregulation of L-type VOC expression.

When the VOC pathway is downregulated the ROC pathway becomes dominant. At the basic level this helps to address wider points concerning how Ca^{2+} is utilised in diverse SMC functions. The distinct structures, subcellular locations and biophysical properties of ROCs compared with VOCs allow interaction with different combinations of signalling molecules, thereby adapting the Ca^{2+} signals for use in altered cellular functions (migration and proliferation compared to contraction). Critically, the relationship between membrane potential and Ca^{2+} influx is also transformed. We propose that VOC downregulation is a mechanism by which SMCs in a local area of a vessel become electrically uncoupled from the surrounding region. Consider a wound healing situation. Synthetic SMCs in the local affected area would no longer elevate $[Ca^{2+}]_i$ in response to membrane depolarisation. This allows them to migrate, proliferate, etc to effect wound repair whilst contractile SMCs in the surrounding region of the vessel still respond to neuronal depolarising stimuli.

From the pharmacological standpoint, the model presented here predicts that Ca^{2+} dependent actions of CCBs diminish as SMCs dedifferentiate. It is therefore consistent with data showing the greatest effects of CCBs on early occlusive disease and animal studies demonstrating reduced effect when the drug is administered after the atherogenic stimulus. It could also account for apparent inconsistencies between studies *in vitro*. This is clearly demonstrated by our study on migration in which phenotypic state of the SMCs alters efficacy.

Ca^{2+} independent actions of CCBs

CCBs may also affect vessel structure in ways unrelated to inhibition of Ca^{2+} influx. Most attention is now focussed on the third generation dihydropyridines, particularly amlodipine, lacidipine and lercanidipine. They are extremely lipophilic which permits a high degree of membrane partitioning. Biophysical studies have shown that their interaction with phospholipids yields

beneficial effects such as increased resistance to lipid oxidation (in cells and in lipoproteins), reduction in accumulation of lipoproteins in the intma and reversal of adverse effects of cholesterol on membrane structure. Moreover membrane partitioning allows for interactions with other cell types. CCBs have been shown to increase nitric oxide production in endothelial cells, which are devoid of L-type Ca^{2+} channels. See Mason *et al* [3,41] for in depth discussions of these and other potentially important Ca^{2+} independent effects.

We can now construct an overall working model of CCB antiatherosclerotic actions. Ca^{2+} dependent actions are greatest in differentiated SMCs but decline with the emergence of the synthetic SMC phenotype. Ca^{2+} independent actions derive from individual CCBs and act over different sites and phases of the occlusive process. A recent experimental study can be used to illustrate these two facets. Using a rabbit model Kahn *et al* [42] found that amlodipine retarded induced lesion development. But isolated arterial segments also revealed the development of a SMC Ca^{2+} influx pathway that was "uninhibitable" by CCBs. The framework developed here accounts for these observations. Early lesion formation could be impaired by Ca^{2+} dependent and independent mechanisms, the former diminishing with time. We identify the uninhibitable Ca^{2+} influx as the functional signature of ROC pathways upregulated to compensate for reduction of the VOC pathway and to facilitate change of SMC roles. Importantly it is not known what effect maintenance of initial levels of Ca^{2+} influx inhibition would have had. Herein lies the means to extend the potential of Ca^{2+} channel antagonism. We need to understand the ROC pathways.

Multiple SMC ROC pathways

Many studies have revealed non-VOC Ca^{2+} influx in SMCs through multiple types of channel (see [15,16] for reviews). Most studies have concentrated on contraction but ROCs have also been implicated in synthetic SMC function. Kawanabe *et al* [43] found that ROC activity was essential in endothelin-1 (ET1) induced mitogenic responses in carotid artery SMCs, whereas L-type VOCs played only minor roles. These channels were shown to comprise the Ca^{2+} influx routes in transactivation of the epidermal growth factor receptor (EGFR, ref 44). Transactivation is a Ca^{2+} mediated process in which G protein coupled SMC mitogens such as catecholamines, angiotensin II and ET-1 activate EGFRs (and downstream signalling pathways) independently of the EGF ligand [45]. Transactivation also plays a role in the development of cardiac hypertrophy [46]. It therefore represents a point of convergence for multiple ligand/receptor systems and could form a clinical target.

Whilst much progress has been made in ROC research a major limitation has been that they have existed as functional entities largely without associated molecular identities. Therefore it has been difficult to compare findings from different sources and contexts. Beech *et al* [15] have pointed out that a single channel could exhibit diverse patterns of activity depending on experimental circumstances and so appear to arise from separate molecular entities. So studies from different fields have remained largely isolated. But recent developments are now beginning to alter this situation. They stem from the molecular identification of a ubiquitous superfamily of ROCs known as transient receptor potential (TRP) channels.

The term TRP derives from the mutant *trp* gene, whose product was originally characterised in photoreceptors of *Drosophila melanogaster* and found to be an ion channel (see [47]). Mammalian homologues of this prototype now number nearly thirty. The most widely characterised families are TRPC, TRPM and TRPV (canonical, vanilloid and melastatin respectively). TRPs are distributed across virtually all tissue and cell types and function as monovalent and divalent cation channels. They are activated by extracellular ligands and environmental stimuli (such as mechanical force and temperature change) and are modulated by intracellular signalling molecules [47,48].

Specific TRP channel mRNA and protein has been detected in SMCs from artery and vein [15]. Functional studies on SMC TRP channels are now beginning to reveal some patterns. Dreja *et al* [49] noted an increase in store operated, CCB insensitive Ca^{2+} influx in organ cultured rat tail and basilar arteries. Recently Bergdahl *et al* [50] made a similar observation in rat cerebral artery. Further they found increased TRPC1 and TRPC6 expression and provided evidence that store dependent Ca^{2+} influx was mediated by TRPC1. Moreover, it has been shown in human pulmonary artery SMCs that store operated Ca^{2+} influx increases with mitogenic activity and that PDGF stimulated proliferation of SMCs depends on upregulation of TRPC1 and TRPC6 expression [51]. Shukla *et al* [26] have shown that Ca^{2+} store release causes translocation of MAPKs to the nucleus to drive cell cycle progression. These are the MAPKs previously reported to downregulate L-type VOCs [40]. A

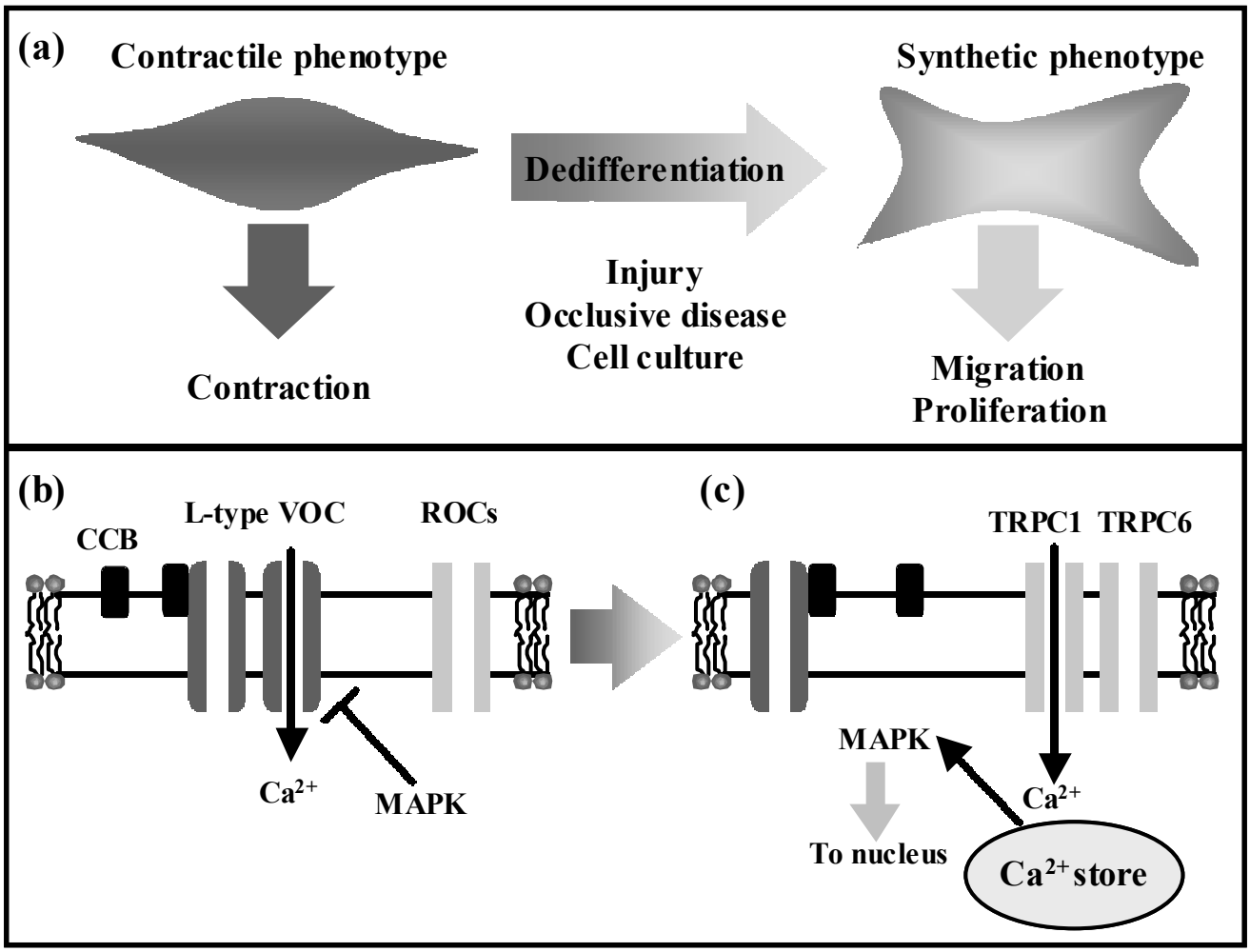

Figure 1: (a) SMC dedifferentiation. The sketch depicts contractile and synthetic SMC phenotypes with different functions. They form the extremes of a spectrum of such phenotypes. (b) Ca^{2+} influx pathways in contractile SMCs. VOC pathway dominates in contractile SMCs. Activation of mitogen activated protein kinases (MAPKs) downregulates expression of VOCs. (c) Ca^{2+} influx pathways in synthetic SMCs. ROC pathway dominates in contractile SMCs. The store operated channels TRPC1 and TRPC6 are upregulated. Ca^{2+} release causes translocation of MAPKs to to the nucleus to enable cell cycle progression. CCBs are efficacious in contractile cells but less so in synthetic cells.

tentative composite model can be constructed linking these findings (see figure 1). It is likely that many previously functionally characterised ROCs will be identified as members of the TRP family.

Pharmacology of ROCs

Basic research into ROCs has been hindered by a lack of specific agents to discrimination between them [16]. However some progress has been made in different areas. Kawanabe *et al* [43] distinguished two types of ROCs in SMCs using the imidazole derivatives SK&F 96365 and LOE 908. A synthetic drug TAS 301, which reduced neointimal thickening after balloon injury, was found to inhibit a CCB insensitive ROC pathway and PDGF stimulated DNA synthesis over the same concentration range in rat aortic SMCs [52]. We found that Ca^{2+} influx through ROCs in response to PDGF was inhibited by lovastatin, which may partly account for our earlier finding of inhibition of human SMC proliferation by this agent [53,54]. The mechanism is most likely inhibition of a regulatory G protein rather than direct channel blockade. Bosentan, a dual endothelin receptor antagonist used in pulmonary arterial hypertension has been shown to inhibit ET-1 and PDGF induced SMC proliferation and TRPC6 expression [55]. Thus strategies aimed at direct blockade, and modulation of intracellular regulators and

channel expression are all possibilities.

Anti-inflammatory approaches are increasingly viewed as attractive and potentially powerful antiatherosclerotic strategies because they target early stages of disease [56]. Since CCBs also target this phase Ca^{2+} channel inhibition could form part of an anti-inflammatory approach. Tranilast, an antiallergic agent was found to inhibit monocyte/macrophage infiltration in a rat myocardial fibrosis model, and in another study to inhibit SMC growth and PDGF induced Ca^{2+} influx [57,58] although the mechanism is under debate. Here we glimpse the wider potential of ROC antagonism. ROCs have been described in all classes of leukocytes and in endothelial cells. Some have been identified as TRP channels and are recognised as potential therapeutic targets [59,60]. Thus there is scope for ROC antagonists to act as anti-inflammatory agents on early stage disease and as "antiocclusive" agents (by limiting chemotaxis and proliferation) on later plaque development, thereby maintaining levels of Ca^{2+} channel antagonism in a changing environment.

Perspectives

Current antihypertensive CCBs are effective at lowering BP and show beneficial effects on early occlusive disease. But the full potential of Ca^{2+} channel antagonism in atherosclerosis is not, and cannot, be realised with these agents. However, future drugs may be able to take advantage of the plasticity of Ca^{2+} signalling pathways. If specific subsets of Ca^{2+} channels are differentially expressed according to varying functional requirements then the functions themselves may be targeted. More generally, knowledge will accumulate at an increasing rate now that ROC (in the form of TRP channel) studies from other fields may more readily be interpreted and applied. Specific TRP channels have already been implicated in a number of pathologies [61], and more will surely follow. So therapeutic opportunities and financial incentives may spur the search for agents that can selectively modulate Ca^{2+} based signalling pathways in ways more subtle and sophisticated than has so far been possible.

Acknowledgements

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Joint BAS/BSCR Symposium

at the British Cardiac Society annual scientific meeting

(23 – 26 May 2005, MICC / GMEX Centre, Manchester)

Tuesday 24 May – Porters Room – 14.30h to 16.00h

Oxidative Stress and Cardiovascular Disease

Chairpersons: Keith Channon and Michael Marber

Cardiovascular genomics and oxidative stress	Anna Dominiczak (Glasgow)
Oxidant signalling and cardiac hypertrophy	Ajay Shah (London)
Oxidative stress and inflammation in cardiovascular disease	Garret Fitzgerald (Philadelphia)
Oxidative stress and vascular homeostasis – basic science and clinical implications	Keith Channon (Oxford)

For up to date information on forthcoming meetings, workshops and symposia, please remember to check the BSCR Website:

http://www.bcs.com/affiliates/bscr.html

Secretary's Column

We are now looking forward to the first meeting of 2005 to be held at the University of Leicester on 21-22 April. The committee will meet on the morning of 21st and welcome three new members, Dr Andrew Baker (Glasgow), Dr Katrina Bicknell (Reading) and Dr Chris Jackson (Bristol). Dr Gillian Gray (Edinburgh) was elected for a further term, but I imagine will send apologies having her hands full with new baby, Jennifer, who was born just before Xmas. Congratulations also to Dr Helen Maddock, one of the Bulletin editors, who also had a baby recently. Creche facilities could be on the agenda. But seriously, the meeting will address a number of issues, mostly surrounding the enhancement of the main scientific meetings, especially for the student membership, including citable abstract publication, reduced fees for joint BSCR / ISHR membership and a new 'Clinical Science' prize. But more of this at a future date.

The scientific meeting in Leicester on the subject of 'Emerging concepts in atherothrombosis' organized by Professors Nilesh Samani and Alison Goodall has been sponsored substantially by AstraZeneca. With a number of eminent European speakers signed up, covering topics of plaque rupture, platelet biology, therapeutic perspectives and epidemiology, this promises to be a top rate event. The Autumn meeting to be held at St Thomas' Hospital on 15-16 September is advertised on the back page. Professors Marber and Avkiran have put together an exciting programme with a focus on 'Stress signals in the cardiovascular system', the details of which are also included in this issue. Please note that the AGM will be held during this meeting.

In response to the British Cardiac Society's move towards jointly run symposia at its annual scientific meeting, the BSCR has teamed up with the British Atherosclerosis Society to organize a plenary session 'Oxidative stress and cardiovascular disease'. The full meeting runs from 23 to 26 May and the BAS / BSCR symposium is scheduled for Tuesday 24th at 14.30h. Details are given here and remember that the session is free to BSCR members.

Again this year we must think ahead to filling the gaps on the committee which will arise when four of the current members retire from their term of office at the end of December. Nominations are required for these posts, to be taken up from January 2006, and a form is included here for the purpose. All applications are welcomed, and those from medically qualified individuals particularly so, in order to fulfill constitutional requirements for the clinical scientist - basic scientist balance of the committee.

Barbara McDermott

BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Vacancies on Executive Committee

At the end of 2005 the following members will retire from the Committee, having completed 3 years of service: Professor Keith Channon, Professor David Eisner, Professor Nilesh Samani, Dr Peter Weinberg.

As such, there will be vacancies for 4 new members of the Committee. Nominations are therefore required for these posts, to be taken up from January 2006.

Nominations of both *clinically-qualified investigators* and *basic scientists* are encouraged. When retirements are taken into consideration, the composition of the Committee is biased towards basic scientists. Since at least three members of the Committee must be medically qualified, these nominations are particularly welcomed.

If the number of nominees exceeds the number of vacancies, elections will take place by postal ballot before the AGM. Clause 7b of the Constitution stipulates that "nominations for members of the committee must be made by full members of the Association in writing and must be in the hands of the Secretary at least 60 days before the Annual General Meeting". This year the AGM will be held at the BSCR Meeting to take place in London on 16 September 2005. To allow time for a postal ballot (if required) to be completed prior to the AGM, nominations must be received by **31 May 2005.**

Please cut out or photocopy the form on the reverse of this page for nominations.

BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Nomination Form for Committee Membership

Name of proposed Committee Member:

Year of first joining the Society:

Please provide brief biographical details and a statement of reasons for wanting to serve on the Committee (please do not exceed the space provided below). In the event that a postal ballot is required, these details will be printed in the Quarterly Bulletin along with a passport-sized photograph (which should be provided with the nomination).

I agree to stand for election to the BSCR Committee

Signature: Date:

Proposed by: Signature:
(BLOCK CAPITALS)

Seconded by: Signature:
(BLOCK CAPITALS)

Please return the completed form by **31 May 2005** to the Secretary:

Professor Barbara McDermott
Department of Therapeutics and Pharmacology, Queen's University Belfast,
Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL

BSCR Spring 2004 Meeting:

"Frontiers in Cardiovascular Signalling"

The University of Manchester
1-2nd April

The programme was designed to bring together people working in both vascular and cardiac muscle and to highlight areas of common interest. The meeting had 130 attendees and 56 poster abstracts. The talks comprised 4 keynote lectures, 12 other invited lectures and 4 oral communications selected by the judges (Tomoko Kamishima and Clive Orchard) from the submitted abstracts.

Proceedings began with Arthur Weston's (Manchester) typically "in your face" contribution concerning the role of EDHF in vascular function. While there may be controversies remaining in this field, the audience was treated to a tour de force of wit and powerpoint.

The rest of the afternoon comprised talks on the role of calcium. Clive Orchard (Leeds) began by talking about his studies designed to investigate the subcellular localization of various membrane channels and transporters. Much use was made of his recently developed method of detubulating cells. Ted Burdyga (Liverpool) showed Ca measurements in blood vessels in segments of ureter. The confocal imaging allowed simultaneous measurements of changes of $[Ca^{2+}]_i$ in both vascular smooth muscle cells and adjoining endothelial cells. The session ended with two complementary talks on mitochondria and calcium in cardiac (Michael Duchen, London) and smooth muscle (Tomoko, Kamashima, Liverpool).

The British Cardiac Society Lecture was given by Jon Lederer (Baltimore). Jon reviewed his work first identifying the calcium "spark" as the basic unit of calcium release from the sarcoplasmic reticulum and then moving on to his more recent work looking at changes of calcium handling in various diseases. The session finished with poster viewing accompanied by liberal amounts of wine (and politically correct alternatives). The standard of all the posters was of a very high level and the judges (Karen Porter and Clive Orchard) had difficulty in selecting the winner. The prize was awarded to A. Chase and colleagues from Bristol for their work entitled: "Cardioprotective techniques prevent reperfusion-induced rise in cardiac interleukin-6".

The dinner was held in the Whitworth Art Gallery. An after dinner talk given by Austin Elliott (Manchester) concerned cell signalling or, perhaps more correctly, giving talks on cell signalling. Perhaps forgetting that April Fools day ends at 12 noon, he presented a description of how KIT-KAT activates the novel SNAK kinase pathway via WMD (Weight-gain Mutant of Drosophila) and FCUK (Fat Control Upstream Kinase). He then described how the KIT-KAT-SNAK pathway activates transcription of the novel secreted protein EATS which feeds back into the KIT-KAT pathway!

The second day resumed the more serious aspects of signalling and commenced with a

session on phosphorylation signalling pathways. Angela Clerk (London) presented work on G proteins in cardiac myocytes and this was followed by Chris Proud (Dundee) who presented data on ERK pathways and MToR signalling. Robin Plevin (Glasgow) described his work on the NFkB pathway and in particular studies using adenoviruses to express dominant negative versions of inhibitory kappa B Kinases in vascular cells and their subsequent effects on adhesion molecule expression. Jaqui Ohanian (Manchester) then presented her work looking at SAPKs in small arteries.

Four abstracts were selected for oral presentation. These were from Robert Bell (London) who talked about the role of $GP91^{PHOX}$ containing NADPH oxidase and protein kinase C on reactive oxygen species in ischaemic preconditioning. Chris Bell (Hull) spoke about the use of targeted aequorin to detect mitochondrial calcium transients in adult and neonatal rat cardiomyocytes. Katrina Bicknell (Reading) described her work showing alterations in foxo transcription factor binding during cardiomyocyte hypertrophy and this was followed by Fiona Wilkinson (Manchester) presenting data on a novel gene, C15, that is modulated by inflammatory agents in vascular cells. Fiona was awarded the prize for the best open communication.

The National Heart Research Fund Lecture was presented by Robert Wilensky, Director of Interventional Cardiology Research at the University of Pennsylvania, Philadelphia. Rob gave a review of restenosis and its inhibition via the targeting of various signalling pathways. He also presented data showing how basic research has been translated into the clinic, in particular the use of drug eluting stents for the prevention of in-stent restenosis.

The final session of the day was concerned with what happens when signalling gets out-of-control. Andy Trafford (Manchester) gave a presentation on what happens to Ca signalling in an animal model of heart failure. Adrian Saurin from London talked about MAPKs in ischaemia-reperfusion and Quingbo Xu from London presented data using mouse models of vascular injury. The meeting concluded with a presentation by Jean Luc Ballingand (Belgium) on the role of NO in heart failure.

We are grateful to the British Cardiac Society, British Heart Foundation, Physiological Society and National Heart Research Fund for their generous support of this meeting. The abstracts of the meeting are available at: http://heart.bmjjournals.com/cgi/content/full/90/4/DC1

David Eisner and Cathy Holt

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
18 (3)	***July 2005***	*June 1st*
18 (4)	***October 2005***	*September 1st*
19 (1)	***January 2006***	*December 1st*
19(2)	***April 2006***	*March 1st*

BSCR 2005 AUTUMN MEETING

Thursday 15th - Friday 16th September 2005
London, U.K.

Stress Signals in the Cardiovascular System

Organisers: Michael Marber and Metin Avkiran

Programme

Thursday, 15th September

12.30-14.00 Registration and Lunch

14.00-14.05 Welcome

Session 1: Stem cells and response to injury

Chair: Michael Marber (London) and Sian Harding (London)

14.05-14.45 Cell origins in atherosclerosis
Qingbo Xu (London)

14.45-15.25 Cardiac tissue replacement: native cells versus engineered tissue
Thomas Eschenhagen (Hamburg, Germany)

15.25-15.45 Coffee break

15.45-16.45 **The National Heart Research Fund Lecture**
Circulating progenitor cells in infarct repair
Stefanie Dimmeler (Frankfurt, Germany)

16.45-18.00 Cheese, wine and posters

19.30- Meeting Dinner

Friday, 16th September

Session 2: Stress-activated signalling

Chair: Angela Clerk (London) and Thomas Wieland (Mannheim, Germany)

09.00-09.40 Signal transduction of mechanical stress in vasculature

Stephanie Lehoux (Paris, France)

09.40-10.20 Signal transduction of mechanical stress in myocardium

Mathias Gautel (London)

10.20-10.40 Coffee

10.40-11.20 Oxidant signals in response to stress

Ajay Shah (London)

11.20-12.00 Anti-inflammatory strategies based on inhibition of p38-MAPK

Andrew Protter (Fremont, USA)

12.00-12.30 AGM

12.00-13.30 Lunch

Session 3: Free communications

Chair: Barbara McDermott (Belfast) and Michael Curtis (London)

13.30-14.30 Oral presentation of 4 selected abstracts (10 min presentation plus 5 min discussion)

Session 4: Novel mediators in stress signalling

Chair: Metin Avkiran (London) and Peter Sugden (London)

14.30-15.10 Mono/p63RhoGEF in myocyte signalling

Thomas Wieland (Mannheim, Germany)

15.10-15.30 Tea

15.30-16.30 **The British Cardiac Society Lecture**

Redox-mediated atheroprotective signals stimulated by laminar flow.

Bradford Berk (Rochester, USA)

16.30-16.45 Abstract prizes and meeting close

Cardiovascular Related Meetings

Heart Failure 2005. 11th-14th June. Lisbon, Portugal. For further information: EUROECHO Secretariat: ESC, 2035 route des Colles, Les Templiers - BP 179, 06903 Sophia Antipolis Cedex, France. Tel: +33 (0) 4 92 94 76 00; Fax: +33 (0) 4 92 94 76 01; E-mail: HFsecretariat@escardio.org; http://www.escardio.org/congresses/HF2005/general_information/

XXV European Section Meeting, Intenational Society for Heart Research. 22-26 June, 2005. Tromso, Norway. Enquiries: Dr T. Larsen, Department of Medical Physiology, Faculty of Medicine, University of Tromso, N-9037 Tromso, Norway. Tel: +47 77 644694; Fax: +47 77 645440; E-mail: ishr-tromso2005@fagmed.uit.no; Website: www.fm.uit.no/ishr2005.

International Academy of Cardiology - 12th World Congress on Heart Disease, New Trends in Research, Diagnosis and Treatment. 16 July 2005 - 19 July 2005. Vancouver, Canada. Contact: klimedco@ucla.edu; Website: www.CardiologyOnline.com

European Society of Cardiology Congress 2005. 3rd-7th September, 2005. Stockholm, Sweden. E-mail: congress@cardio.org.

3rd European Meeting on Vascular Biology and Medicine 2005. 28-30 September, 2005. Hamburg, Germany. For further information: Address: M:con, Rosengartenplatz 2, 68161 Mannheim, Germany; Tel: +49 621 4106-137; Fax: +49 621 4106 207; E-mail: daniela.ruckiegel@mcon-mannheim.de; http://www.embvm.org

World Congress of Cardiology 2006: Joint Congress of the European Society of Cardiology and the World Heart Federation. 2nd - 6th September 2006. Barcelona, Spain. Further information can be obtained from: EUROECHO Secretariat: ESC, 2035 route des Colles, Les Templiers - BP 179, 06903 Sophia Antipolis Cedex, France. Tel: +33 (0) 4 92 94 76 00; Fax: +33 (0) 4 92 94 76 01; E-mail:webmaster@escardio.org; Website: www.escardio.org

Travel Reports for *The* Bulletin

The Bulletin editors are happy to publishes 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 on travelling to a cardiovascular-related meeting and would like to write a report for the Bulletin, please contact the editors. A bursary of **£100** is available towards the cost of your visit, and this will be provided on receipt of the report. *Bon voyage!*

University of Bristol, UK
17th - 20th July 2005

4th international symposium the mammalian myocardium

http://www.bristol.ac.uk/mm2005/

CHANNELS: Trafficking & Biophysics

W. Catterall (USA), I. Cohen (USA), D. Roden (USA), M. Sanguinetti (USA), D. Yue (USA)

CELL & TISSUE ELECTROPHYSIOLOGY

A. Kleber (Switzerland), D. Paterson (UK), R. Winslow (USA)

EXCITATION-CONTRACTION COUPLING

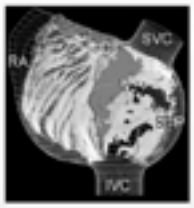
H. Cheng (USA), S. Gyorke (USA), G. Isenberg (Germany), A. Marks (USA), R. Sitsapesan (UK)

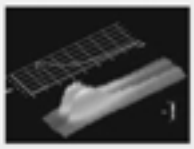
CELL SIGNALLING

R. Fischmeister (France), E. Kranias (USA), E. Moore (Canada), M. Rosen (USA)

HYPERTROPHY, FAILURE, ARRHYTHMIAS & REMODELLING

G. Hasenfuss (Germany), S. Houser (USA), J. Molkentian (USA), S. Nattel (Canada), U. Ravens (Germany), G. Smith (UK)





The Mammalian Myocardium
Bristol 2005

ORGANIZERS:
M.R. Boyett (Leeds, UK)
D.A. Eisner (Manchester, UK)
J.C. Hancox (Bristol, UK)
G. Hart (Liverpool, UK)
C.H.Orchard (Leeds/Bristol, UK)

BRITISH HEART FOUNDATION GRANTS

Chairs and Programme Grants Committee November 2004

Programme Grants

Prof WJ McKenna & Dr AL Shaw, University College London. "Arrhythmogenic right ventricular cardiomyopathy - a disease of the desmosome: gene identification studies to provide the basis for improved clinical diagnosis and the development of genetic diagnosis" 5 years (renewal) £1,261,038

Special Project Grants

Dr J Bradley, University of Cambridge. "Cambridge-Yale collaborative programme in cardiovascular research" 3 years £50,000

Prof DJ Field et al, Leicester Royal Infirmary. "Randomised trial to assess the neuro protective effect of mild cooling in neonates receiving extra corporeal membrane oxygenation (ECMO)" 5.5 years £383,321

National Prevention Research Initiative, "National Prevention Research Initiative" 5 years £1,250,000

Project Grants Committee November 2004

DEFERRED APPLICATIONS AWARDED

Professor D A Eisner et al, University of Manchester."Integrative analysis of Ca^{2+} cycling in cardiac myocytes in response to TNFα: the role of SERCA" (3 years) £82,473

NEW APPLICATIONS AWARDED

Dr K E Chapman et al, Western General Hospital, Edinburgh. "Adipocyte glucocorticoid receptors in the development of hypertension and the metabolic syndrome" (3 years) £176,789

Dr C M Shanahan, Addenbrooke's Hospital, Cambridge."A role for nesprin-1 in vascular smooth muscle cell function and atherosclerosis" (2 years) £81,948

Dr J A Huntington, University of Cambridge. "Molecular recognition determining the pro- and anti-thrombotic activities of thrombin" (3 years) £135,849

Dr J A Huntington, University of Cambridge."How antithrombin selectively inhibits thrombosis" (3 years) £145,305

Dr P Nihoyannopoulos et al, NHLI, London. "Molecular imaging of inflammation in myocarditis using targeted microbubble contrast enhanced echocardiography" (3 years) £250,379

Dr J C St John & Dr S Egginton, University of Birmingham. "The characterisation of mitochondrial DNA differentiation in cardiomyocytes derived from embryonic stem cells" (3 years) £159,179

Dr P Eaton & Dr J C Kentish, King's College London."An investigation of how small heat shock proteins protect the heart from ischaemia" (3 years) £151,362

Professor P J Chowienczyk et al, St Thomas' Hospital, London. "Modulation of vascular function through the beta-2-adrenoreceptor role of beta-2-adrenoreceptor responses in hypertension" (2 years) £97,658

Dr K O'Shaughnessy & Professor A Cuthbert, Addenbrooke's Hospital, Cambridge. "The use of Xenopus Oocyte expression to investigate the effects of WNK kinases on expression and trafficking of ion transporters and channels" (3 years) £139,548

Dr P Kohl, University of Oxford. "Stretch effects on the ATP dose-response curve of the ventricular ATP-dependent potassium channel (K_{ATP})" (1 year) £46,734

Dr R J Pease et al, Leeds General Infirmary. "The role of arylacetamide deacetylase in mobilizing hepatic lipids for secretion and its cellular distribution in the adrenal gland" (3 years) £152,007

Prof D Jordan & Dr A Ramage, Royal Free Campus - (UCL). "Investigation into the role of 5-HT_7 receptors in cardiovascular afferent integration" (3 years) £135,266

Dr D Thompson & Prof R Tyrrell, University of Bath. "A role for T lymphocyte and monocyte haem

oxygenase-1 (HO-1) in the atheroprotective effect of regular physical activity" (2 years) £117,736

Dr S A Deuchars & Dr J Deuchars, University of Leeds. "Properties and connections of a novel group of spinal interneurones influencing sympathetic neuronal activity" (3 years) £181,724

Professor N S Peters et al, St Mary's Hospital. "Pre-emptive ablation of myocardium prone to the development of functional conduction block in the infarcted heart to prevent defibrillator therapy" (3 years) £145,603

Dr E Davies et al, Western Infirmary, Glasgow. "Functional analysis of mutations/polymorphisms in steroidogenic genes and their implications for human cardiovascular disease" £88,508

Dr R Sitsapesan & Dr K Venkateswarlu, University of Bristol. "Investigation of the molecular mechanisms underlying adenine nucleotide interactions with the cardiac ryanodine receptor" (3 years) £158,412

Dr J Emsley, University of Nottingham. "Coagulation factor XI structure, activation and receptor binding" (3 years) £119,312

Dr J M Quayle et al, University of Liverpool. "Regulation of P_2Y receptor-mediated Ca^{2+} transients by membrane potential in arterial smooth muscle cells" (3 years) £96,384

Dr D E Newby et al, Royal Infirmary, Edinburgh. "Development of a clinical model of thrombosis and endogenous fibrinolysis" (3 years) £155,877

Mr W J Brawn et al, Birmingham Children's Hospital. "The impact of pulmonary artery banding on ventricular function in patients with a morphologic right ventricle in the systemic circulation" (3 years) £33,923

Fellowships Committee January 2005

Deferred Applications Awarded

Junior Research Fellowship

Dr A Gatt, Royal Hallamshire Hospital, Sheffield "The value of the endogenous thrombim potential in the management of anticoagulated patients" (2 years) £94,785

PhD Studentship

Miss A Cook (previously Miss C Wagner), St Thomas' Hospital, London. "Role of the 90 kDa ribosomal S6 kinase RSK2 in the regulation of sarcolemmal Na+/H+ exchange" (3 years) £80,168

New applications awarded

Junior Research Fellowships

Dr A Bermudez-Fajardo,University of Surrey. "Immunomodulation of atherosclerosis using dendritic cells" (2 years) £87,045

Dr E J Shepherd, Freeman Hospital, Newcastle upon Tyne. "The anatomy and physiology of the pulmonary vein- left atrial junction in subjects with and without paroxysmal atrial fibrillation. The role of pressure and anatomical substrates in the development of atrial fibillation" (2 years) £101,862

Dr O S Dhillon, Leicester Royal Infirmary. "Urotensin-like peptides and prognosis after acute coronary syndromes" (2 years) £93,331

Ms P De Winter, King's College London. "Effects of selective estrogen receptor modulators(SERMs) on endothelial antioxidant gene expression in estrogen receptor knockout mice" (2 years) £89,883

Dr J E R Davies, St Mary's Hospital, London. "Coronary haemodynamics in hypertension and left ventricular hypertrophy" (2 years) £107,183

Mr N Cartwright. NHLI, London. "Gram negative bacterial sensing in human vessels: relevance to human sepsis" (3 years) £106,778

Clinical PhD Studentships

Dr M M Mahmoudi, Addenbrooke's Hospital, Cambridge. "Regulation of vascular smooth muscle cell senescence by DNA damage checkpoint kinases"(3 years) £156,933

Miss A Taylor, Addenbrooke's Hospital, Cambridge. "CD4 - CD8 T cell collaboration in alloimmunity" (2 years) £97,490

Dr A Muir, University of Glasgow. "Atrioventricular nodal function in a rabbit model of chronic heart failure" (3 years) £139,610

Ms N Summerfield, NHLI, London. "Cellular changes during the progression of myocardial hypertrophy to failure" (3 years) £140,621

PhD Studentships

Mr J Burgoyne, King's College London. "Oxidative stress in the ageing human heart: examining the roles of cardiac protein cysteine oxidation" (3 years) £79,500

Unnamed and Prof R J Plevin, University of Strathclyde. "The regulation and cellular effects of proteinase-activated receptor-4 in human endothelial cells" (3 years) £75,120

Unnamed and Prof N B Standen, University of Leicester. "Interrelationship between K_{ATP} channels, adenosine and protein kinases in protection of isolated cardiac myocytes" (3 years) £73,818

Unnamed and Dr N W Davies, University of Leicester. "Modulation of arterial Ca^{2+} - activated K^{+} (BK_{Ca}) channels by angiotensin II" (3 years) £71,308

Unnamed and Dr A W Poole, University of Bristol. "Cross-talk between $P2Y_{1}$ and $P2Y_{12}$ receptors for ADP in platelets" (3 years) £74,737

Ms A Power, University of Manchester. "Characterisation of the cardiac L-type voltage- gated calcium channel; the sum of its parts" (3 years) £74,061

Unnamed and Dr P K Luther, Imperial College, London. "Electron tomography of the I-band in mammalian cardiac muscle" (3 years) £79,991

Mr J D Mitchell, Addenbrooke's Hospital, Cambridge. "Neuromedin U: a novel transmitter in the human cardiovascular system with an emerging role in disease" (3 years) £81,778

Unnamed and Dr J Pease, Imperial College, London. "Molecular characterisation of the chemokine CXCL16/SR-PSOX and its receptor CXCR6: a potential axis for the therapeutic treatment of atherosclerosis" (3 years) £80,130

4 Year PhD Studentships (2 awards, 3 candidates each)

Prof J Mullins, University of Edinburgh. First intake 2004/2005 4 Year PhD Studentship Scheme (candidates: Mr Sanjay Thakar, Mr Mathieu Blanc, Miss Malgorzata Wamil) £299,832

Prof J D Pearson, King's College London. First intake 2004/2005 4 Year PhD Studentship Scheme (candidates: Miss Nadia Caro-Goldrine, Miss Catherine Stables, Mr Colin Murdoch) £310,116

Chairs and Programme Grants Committee February 2005

Programme Grants

Dr C M Shanahan,Addenbrooke's Hospital, Cambridge. "The role of vascular smooth muscle cells in the development and progression of vascular disease" 5 years (renewal). £986,195

Prof P J T Vallance et al, University College London. "ADMA and DDAH signaling in vascular disease" 5 years (renewal). £1,302,907

Dr D E Newby et al, Royal Infirmary, Edinburgh. "Atherothrombotic effects of air pollution" 5 years £1,178,407

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)

BSCR Autumn Meeting 2005

Stress Signals in the Cardiovascular System

Dates: 15th and 16th September 2005

Venue: Governors' Hall, St Thomas' Hospital

Organisers: Professor Michael Marber and Professor Metin Avkiran

Overall Aim: The aim is to provide a series of state-of-the-art overviews of how the vasculature and myocardium respond to stress by adaptive signalling pathways and recruitment of progenitor cells.

Invited Speakers include: Bradford Berk (*USA*), Thomas Eschenhagen (*Hamburg*), Stefanie Dimmeler (*Frankfurt*), Mathias Gautel (*London*), Stephanie Lehoux (*Paris*), Andrew Protter (*USA*), Ajay Shah (*London*), Thomas Wieland (*Mannheim*), Qingbo Xu (*London*),

Travel & Accommodation: The conference will be held at St Thomas' Hospital (nearest tube is Westminster and BR is Waterloo), with student accommodation potentially available nearby at Great Dover Street Apartments.

Communications: Part of the meeting will be devoted to oral presentation of selected abstracts and posters. Prizes will be awarded for the best oral and best poster presentations given by young investigators.

Registration: Free to BSCR members, £40 for non-members.

Bursaries: The Society will consider awarding travel grants of up to £150 to *bona fide* students.

Deadline for submission of abstracts and application for student bursaries: Tuesday, 30th June 2005.

A full programme, the abstract pro-forma, meeting registration form and forms for application for BSCR membership or student bursaries can be downloaded from: http://www.bcs.com/affiliates/bscr.html

Any further enquiries to: Professors Michael Marber and Metin Avkiran, Cardiovascular Division, King's College London, The Rayne Institute, St Thomas' Hospital, London SE1 7EH; Tel: 020 7188 1008; Fax: 020 7188 0970; tony.cavalheiro@kcl.ac.uk

Or: Professor 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