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The Bulletin

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Contents

Editorial

Welcome to the April 2004 issue of *The* Bulletin!

In this issue, we bring you a fascinating review article describing remote ischaemic preconditioning (RIPC). Dr Raymond MacAllister and colleagues provide an insight into a recently developed model of RIPC in humans and the possible therapeutic benefits that this approach may offer.

As highlighted in the Secretary's Column, the time is upon us once again when we must look to appoint new members to the BSCR Committee. Any BSCR members who feel that they would like to play a more active role in the running of the society may like to consider nomination and should refer to the form on pages 13-14.

Following another successful meeting of the Society in Manchester, we can begin to look forward to this year's Autumn meeting, to be held at King's College, London. The organisers, Professor Ajay Shah and Dr Alison Cave have put together a fascinating scientific programme, details of which can be found on page 12.

Finally, we bring you the latest details of grants awarded to researchers in the Cardiovascular field, by the British Heart Foundation and the Wellcome Trust.

Helen Maddock and Nicola Smart

Therapeutic Potential of Remote Ischaemic Preconditioning

Stavros P. Loukogeorgakis, Anna T. Panagiotidou and Raymond J. MacAllister

Centre for Clinical Pharmacology and Therapeutics, British Heart Foundation Laboratories, University College London, UK

Introduction

Ischaemia of vital tissues due to thrombosis-induced arterial occlusion is the leading cause of morbidity and mortality in the Western World and is increasing in importance in the Third World. Amongst the successful therapeutic strategies in common usage is reperfusion, either through administration of a thrombolytic agent or mechanical removal of thrombus. Timely reperfusion facilitates tissue salvage, decreasing morbidity from stroke (1) and reducing mortality following myocardial infarction (2). Nonetheless, substantial morbidity and mortality remains, despite new techniques for reperfusion and intense efforts to reduce the time between arterial occlusion and reperfusion. Therefore, adjunctive treatments to reperfusion therapy are required to further reduce tissue injury following vascular occlusion.

Mechanisms of Ischaemia Reperfusion Injury

Hypoxic cell death following interruption of the blood supply to tissues accounts for many of the pathological consequences of arterial thrombosis. Reduced oxygen supply to tissues during ischaemia prevents mitochondrial respiration, depleting cells of ATP with subsequent build up of anaerobic metabolites, reactive oxygen species and intracellular calcium, leading to cell death via necrosis or apoptosis (3). Although successful reperfusion is mandatory for tissue salvage, re-establishing blood flow initiates a cascade of events similar to an inflammatory response. This involves adhesion of circulating neutrophils to the vascular wall with subsequent tissue invasion and release of proteases, elastases and reactive oxygen species. Whilst this may be an integral part of the healing process, animal data suggests that it may also contribute to tissue injury (4). Many investigators have reported reduction in infarct size by measures that reduce the inflammatory response and have stimulated clinical trials in this area. Unfortunately, the results of such studies to limit the inflammatory response in patients with myocardial infarction have been largely negative (5;6). An entirely different approach is to limit the degree of ischaemic injury in the first place.

Ischaemic Preconditioning

Endogenous protective mechanisms against a range of tissue insults have been identified in all mammalian species studied to date. The best characterised is ischaemic preconditioning, whereby sub-lethal ischaemia induces a state of protection against subsequent prolonged ischaemia. This phenomenon has been extensively investigated in the myocardium of many species, where it can reduce infarct size by up to 75% (7). An early phase of ischaemic preconditioning ("classic" preconditioning) occurs within minutes of the preconditioning stimulus and lasts for up to 4 hours (8). The early phase of preconditioning is triggered by a number of stimuli that are generated during hypoxia, including adenosine, bradykinin, endogenous opiates and reactive oxygen species (9). These mediators act on G_i coupled cell surface receptors to initiate a cascade of second messengers, including activation of phospholipases C and D, stimulation of the ε isoform of protein kinase C (PKCε) (10), and activation of tyrosine and mitogen activated protein kinases (ERK, JNK, p38 MAPK) (11). The end effectors of preconditioning remain uncertain and include opening of mitochondrial ATP sensitive potassium (K_{ATP}) channels (12), prevention of the opening of the mitochondrial transition pore (in association with K_{ATP}

channel opening) (13), and blockade of the sodium/hydrogen exchanger (14) (**Figure 1**). It is unlikely that early preconditioning involves gene up-regulation and expression of new proteins. The fact that the preconditioned state can be achieved within minutes makes a reversible post-translational modification (phosphorylation or translocation) of pre-existing protein more likely.

A late phase of preconditioning occurs 24 hours after the preconditioning stimulus, which is more prolonged than the early phase and lasts up to 72 hours (15-17). This delayed phase of resistance to ischaemic injury has been termed second window of protection, distinguishing it from early or "classic preconditioning". The prolonged (24-hour) interval between the preconditioning event and its renewed protection one day later is consistent with new protein synthesis. The triggers for second window ischaemic preconditioning resemble early preconditioning, and similar second messengers are recruited (9). The transcriptional regulator NF-κB may well be the common pathway through which the multiple signals generated by ischaemic preconditioning initiate cardiac and other tissue gene expression (18). Activation of NF-κB leads to increased production of proteins, such as heat shock proteins (HSP 27, 70 and 72i) (19), antioxidant enzymes (superoxide dismutase; SOD) (20), cyclooxygenase (COX-2) (21) and inducible nitric oxide synthase (iNOS) (22), which may contribute to tissue protection. Opening of mitochondrial K_{ATP} channels has also been implicated in late preconditioning (23) (**Figure 2**).

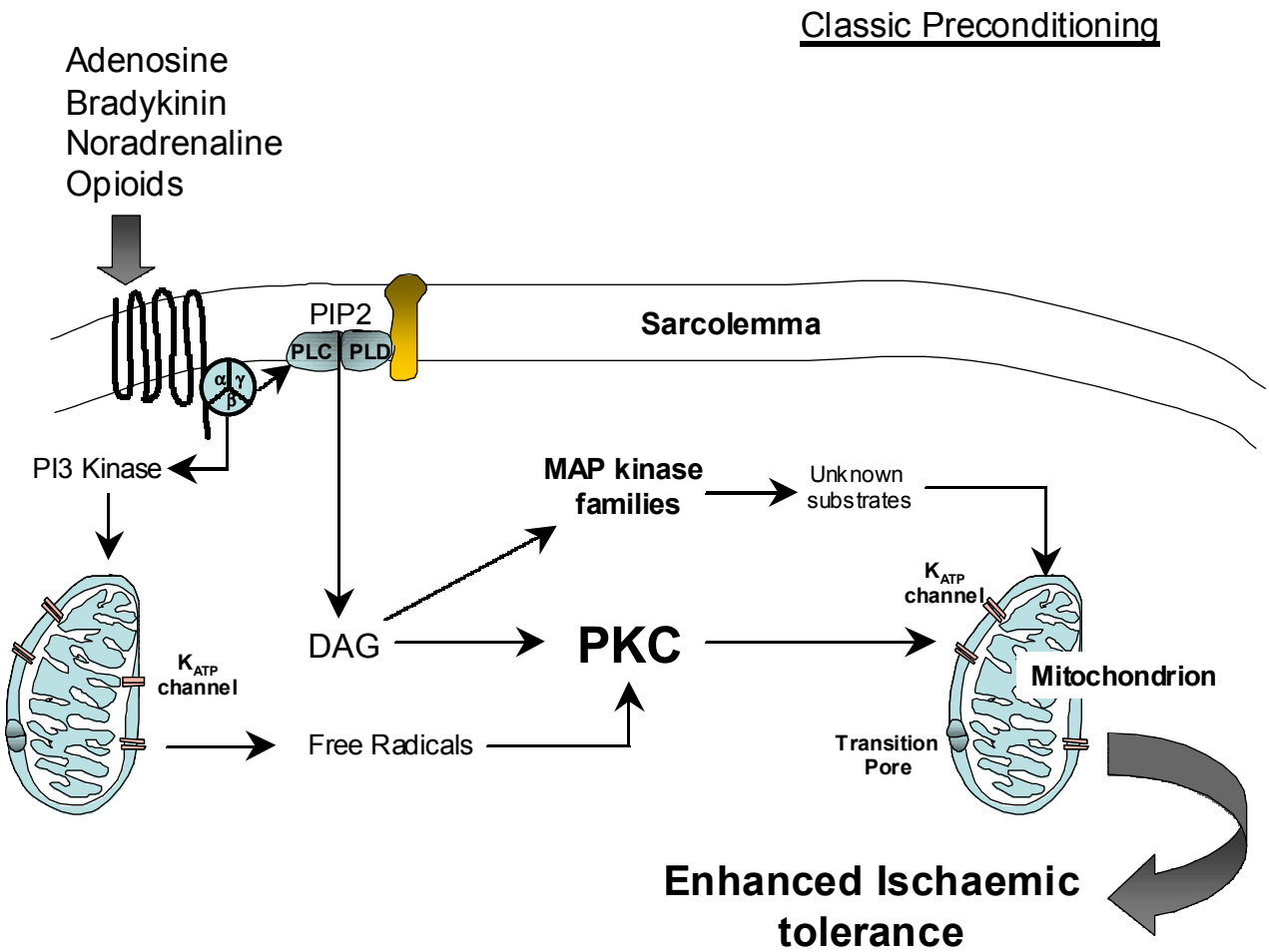

Figure 1. Mechanisms of "classic" ischaemic preconditioning. Release of triggers during ischaemia activates complex second messenger systems that converge on the mitochondria to activate K_{ATP} channels. Activation of these channels has also been implicated early in the pathway leading to release of free radicals.

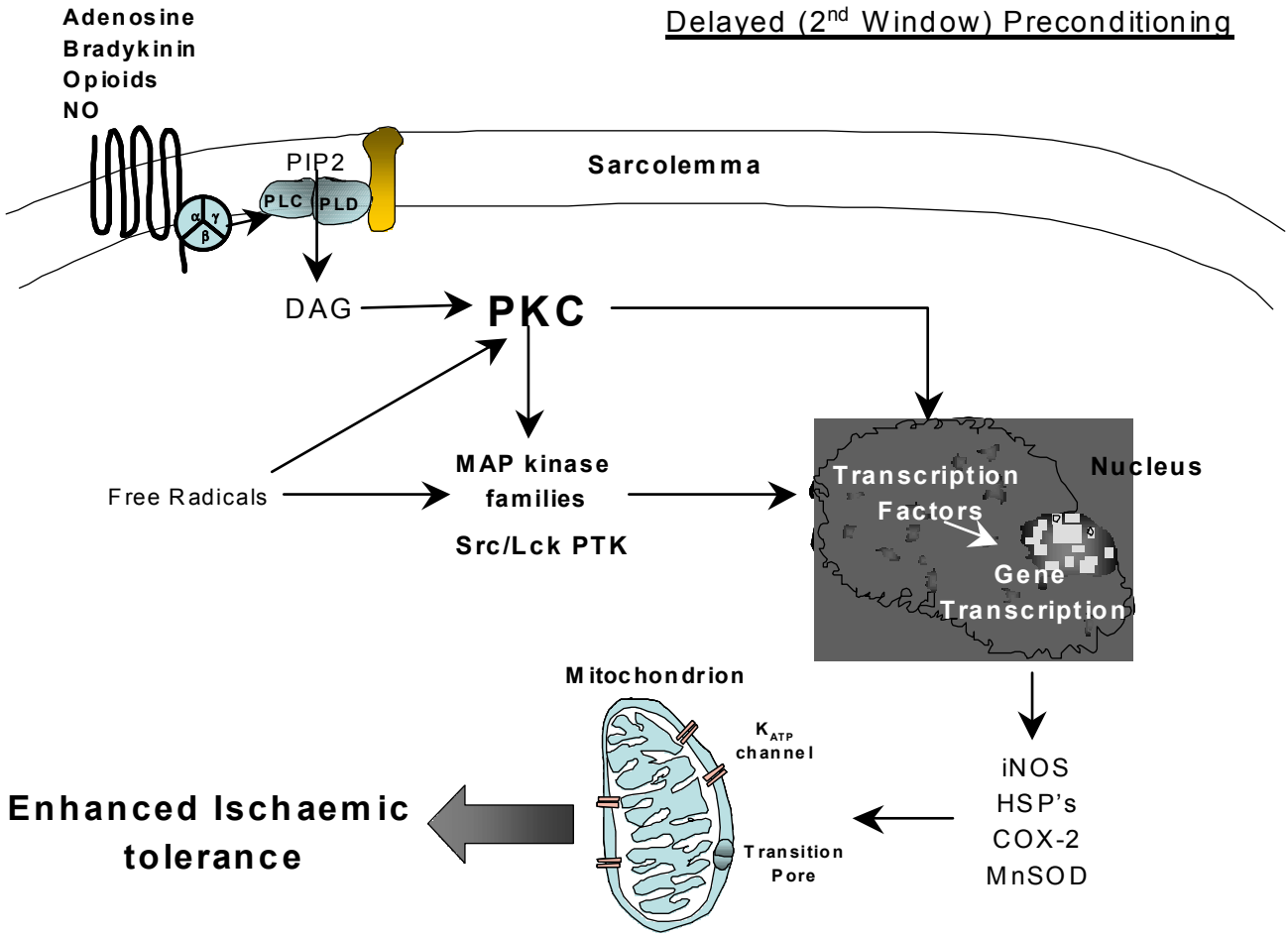

Figure 2. Mechanisms of late (2nd window) ischaemic preconditioning.

The full therapeutic potential of ischaemic preconditioning remains largely untested in the clinical setting. This reflects mechanistic uncertainties, which to date have precluded the development of selective preconditioning agents for use in humans. The scope for ischaemia *per se* as the preconditioning stimulus is limited. In part this is due to the fact that the protective effects of preconditioning have been largely attributed to local mechanisms, necessitating the preconditioning stimulus to be applied directly to the organ at risk. This poses obvious logistical difficulties, when that organ is the human heart or brain.

Remote Ischaemic Preconditioning

In 1993, Przyklenk et al demonstrated that ischaemic preconditioning could protect tissues that are remote from those undergoing preconditioning (24). This form of preconditioning (termed remote ischaemic preconditioning; RIPC) has subsequently been demonstrated in many species, and protects the myocardium and other tissues against ischaemia-reperfusion injury (25). The magnitude of this protection approaches that of local ischaemic preconditioning, certainly in the context of myocardial infarction. Moreover, RIPC may be induced by short periods of ischaemia and reperfusion of non-vital tissues, so providing a unique opportunity to harness and apply the protective effects of ischaemic preconditioning in humans.

In the original description in a canine model, 4 cycles of circumflex artery occlusion (5 minutes each, followed by 5 minutes of reperfusion) protected remote "virgin" myocardium against injury caused by a 1-hour occlusion of the left anterior descending coronary artery. The protective effect demonstrated was comparable to the protection by "classic" ischaemic preconditioning in a similar canine model. Since then RIPC has been described in rat (26), mouse (27), rabbit (28), dog (29), and sheep (30) models of cardiac ischaemia-reperfusion injury. RIPC reduces infarct size, improves ventricular

function, and reduces metabolic and electrophysiological abnormalities. In addition, RIPC has been shown to be protective against ischaemia-reperfusion injury of the kidney (31), muscle (32), small intestine (33), and brain (34).

Mechanism of RIPC

RIPC is elicited by brief ischaemia and reperfusion of the heart, intestine, liver and kidney. RIPC can also be induced by limb ischaemia, which is easier to achieve than preconditioning of internal organs. Birnbaum et al (35) were the first to demonstrate that limb ischaemia could reduce myocardial injury caused by prolonged coronary artery occlusion. More recently, our group demonstrated that in the pig, 4 cycles of 5-minute hind limb ischaemia and reperfusion could reduce infarct size by 53% (36). The triggers, mediators and effectors of RIPC appear similar to those of classical preconditioning. Adenosine (37), bradykinin (38), and endogenous opioids (39) have all been shown to trigger RIPC; protection has either been demonstrated to occur after remote infusion of each agonist, or be inhibited by administration of an antagonist. Protein kinase C has been implicated as a mediator (38), and K-ATP channels in the effector limb (40). A second window of protection induced by RIPC has been described (27;29;41;42), but mechanistic details are scanty at present.

It remains unclear how protection is transferred form one tissue to another. There is evidence for a role of the autonomic nervous system in several studies where ganglionic blockade prevented remote ischaemic preconditioning (37;43) without affecting local preconditioning. However, unidentified humoral mediators have been suggested in other studies, protection being transferred from one animal to another by the administration of a plasma fraction (44) or transfusion of whole blood (45).

RIPC in Humans

To study the mechanism of RIPC in humans, it is essential to be able to induce transient quantifiable ischaemia-reperfusion injury *in vivo* without risk of harm. We recently developed a model that satisfies these criteria in humans. In these studies of healthy volunteers, the arm is made ischaemic for 20 minutes after which reperfusion occurs. This initiates transient dysfunction of the vascular endothelium of the brachial vasculature. Endothelial function can be measured by the degree of vasodilatation that occurs in response to an endothelium-dependent stimulus. In our studies, the dilatation that occurs in response to increased blood

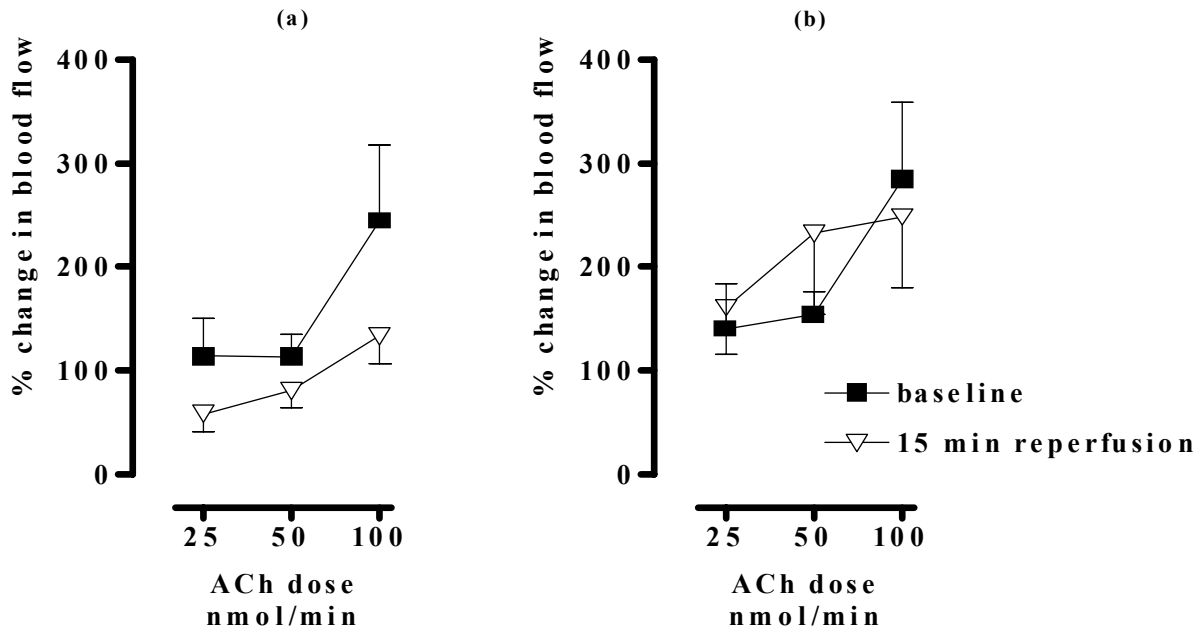

Figure 3. (a) Ischaemia reperfusion (open triangles) reduces the response of the forearm vasculature to acetylcholine consistent with endothelial dysfunction. **(b)** Remote preconditioning of the contra-lateral arm prior to ischaemia reperfusion protects the endothelium from subsequent injury.

flow, or in response to infusion of acetylcholine are both measures of endothelial function in the brachial vasculature. Ischaemia-reperfusion reduces endothelium-dependent dilatation by about 50%, and the endothelial dysfunction persists for about 60 minutes (46). RIPC is initiated by three five-minute cycles of ischaemia to the contra-lateral arm, and largely prevents endothelial dysfunction in response to ischaemia-reperfusion (36) (**Figure 3**). Using skeletal muscle magnetic resonance spectroscopy we have also shown that RIPC reduces metabolic dysfunction in muscle caused by ischaemia-reperfusion (unpublished results). These data indicate that protection caused by RIPC in humans is not limited to the vasculature. The time course of protection mirrors that described in animal models, with an early phase of protection and a second window 24 hours later, lasting for up to 48 hours (47).

Clinical Possibilities of RIPC

Although much remains to be done to understand more fully the mechanism of RIPC in humans, our current level of understanding already indicates that it may have therapeutic potential in the clinical setting. The animal data implies that it offers a similar degree of protection to classical preconditioning. RIPC also occurs in humans and is similar in time-course to that identified in animals. The stimulus is a simple risk-free procedure that can be applied in advance of planned procedures associated with ischaemia-reperfusion injury (such as cardio-pulmonary bypass grafting or organ transplantation). It may provide a window of protection 24 hours later that lasts long enough to cover the procedure and its immediate aftermath. It is even possible that for patients at risk of unpredictable ischaemia-reperfusion syndromes (such as myocardial infarction or stroke), RIPC may induce a state of ischaemic preconditioning lasting several days that could minimise tissue injury in the event of vascular occlusion. The next stage is to optimise the stimulus to elicit maximal protection and then test the therapeutic utility of RIPC in clinical trial.

We would like to acknowledge the British Heart Foundation for supporting our research. We would also like to thank Dr F. Arrigoni for her assistance with diagrams in this review.

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**** Notice to current student **** members

Membership of the BSCR is now free to all students registered for a higher degree.

If you pay your membership of the BSCR by direct debit, please cancel and make this known to antonio.cavalheiro@kcl.ac.uk

There will continue to be a fee for Joint membership of the BSCR/ ISHR

Secretary's Column

I have just returned from the Spring meeting held at the University of Manchester. Over 50 abstracts were presented, undoubtedly the largest number ever at a recent BSCR meeting. What's the secret of this success? Perhaps engendered by the free student membership initiative at the beginning of the year, which has doubled student membership, there was greater participation by postgraduates. Possibly the guarantee of a citable publication was also attractive. It will be the first time that abstracts of a BSCR meeting will be published in a mainstream journal, eHeart. What's more, the dynamic organization of Professor David Eisner and Dr Cathy Holt and cutting edge programme 'Frontiers in cardiovascular signalling', no doubt played a major part in what turned out to be a resounding triumph.

The next events on the BSCR calendar will take place during the British Cardiac Society annual scientific meeting at the end of May in Manchester. I say 'events', as not only is the Society organizing the usual symposium (on Tuesday 25th) as highlighted elsewhere in this issue, but also a 'teach-in' session on the 24th (13.30h–15.00h) focused on 'The measurement and manipulation of myocardial collaterals'.

The programme for the Autumn meeting 2004 scheduled for 9-10 September has been finalized. 'Integrative cardiovascular pathophysiology in gene-modified models' is being organized by Professor Ajay Shah and Dr Alison Cave on the Guy's Campus of King's College London. Then, Professors Nilesh Samani and Alison Goodall have put together an exciting proposal for the Spring 2005 meeting to be held in Leicester on 21-22 April on the subject of 'Atherothrombosis'.

At this time of the 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 this year. Nominations are required for these posts, to be taken up from January 2005, and a form is included here for the purpose.

Again, we are delighted to be the recipient of major sponsorship from Aventis, who have indicated that they will continue to fund BSCR activities in 2004, ensuring a healthy state of finances at least in the immediate future.

Barbara McDermott

BSCR AUTUMN 2004 MEETING

INTEGRATIVE CARDIOVASCULAR PATHOPHYSIOLOGY IN GENE-MODIFIED MODELS

9-10 September 2004, King's College London

DAY 1 P.M.

A. Cardiac Disease

Models of myocardial ischaemia and infarction	Michael Marber (London)
Cardiac hypertrophy models	Alison Cave (London)
Studying electrophysiology in mice	Andrew Grace Cambridge)
Gene modification and physiology in myocytes	Godfrey Smith (Glasgow)

British Cardiac Society Lecture:

State-of-the-art assessment of murine LV haemodynamics David Kass (Baltimore, USA)

POSTERS

DAY 2 A.M.

B. Vascular Disease

Studying atherosclerosis and restenosis in mice	Keith Channon (Oxford)
Thrombosis	Alberto Smith (London)
The interface between metabolic and vascular dysfunction	Mark Kearney (London)
Angiogenesis	Jean-Sebastian Silvestre (Paris)

Selected oral abstracts

L U N C H

DAY 2 P.M.

C. Imaging

Echocardiography in mice	Martin Denvir (Edinburgh)
Functional nuclear imaging	Andre Constantinesco (Strasbourg)
Murine MRI	Stefan Neubauer (Oxford)
In situ imaging in cardiac cells	Mathias Gautel (London)

National Heart Research Fund Lecture:

Identification of murine models of CV disease using mutagenesis

Karen Svenson, Jackson Labs (USA)

BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Vacancies on Executive Committee

At the end of 2004 the following members will retire from the Committee, having completed 3 years of service: Professor Gavin Brooks, Dr Gillian Gray, Professor Ajay Shah, Dr Saadeh Suleiman.

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 2005.

Nominations of both *clinically-qualified investigators* and *basic scientists* are encouraged. 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 in London, on 9/10 September 2004. To allow time for a postal ballot (if required) to be completed prior to the AGM, nominations must be received by **31 May 2004**.

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 2004** 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 Symposium

at the British Cardiac Society annual scientific meeting

24 - 27 May 2004, GMEX / MICC, Manchester

Tuesday 25 May 9.00 – 10.30h Palatine Room

Repairing the broken heart – the promise of stem cells

Chairs: Philip Poole-Wilson and Ajay Shah

1. Myocytes from ES cells	Christine Mummery (Netherlands)
2. Skeletal myoblasts	Philippe Menasche (Paris)
3. Cell transplantation	Andreas Zeiher (Germany)
4. Circulating endothelial progenitor cells	Stefanie Dimmeler (Germany)
5. Patience before enthusiasm	Philip Poole-Wilson (London)

**** Free attendance for BSCR members ****

Cardiovascular Related Meetings

XXVI Annual Meeting of ths ISHR - North American Section "Bench to Bedside and Back: Exploring new Paradigms - A Multifunctional Perspective of Cardiovascular Research in North America". May 2-5th, 2004. Westin Regina Resort, Cancun, Mexico. Enquiries: Dr Daniel Villarreal, SUNY Upstate Medical University Syracuse NY13210; Tel: (315) 464-9578; Fax: (315) 464-9571; E-mail: Villard@upstate.edu

ISHR XXIV European Section Meeting. Dresden, Germany, 2nd-6th June, 2004. Enquiries: Dr U. Ravens, Medical Faculty Carl Gustav Carus, Dresden University of Technology, Fetscherstrasse 74, 01307 Dresden, Germany. Tel +49 351 458 6251; Fax +49 351 458 6315; E-mail: ishr-dresden2004@mailbox.tu-dresden.de; Website: www.ishr-dresden2004.de

XVIII World Congress of the International Society for Heart Research, August 7-11, 2004, Brisbane, Australia. Enquiries: ISHR 2004 Congress, PO Box 164, Fortitude Valley QLD 4006, Australia. Tel +61 7 3854 1611; Fax +61 7 3854 1507; E-mail: heart2004@ozaccom.com.au; Website: www.baker.edu.au/ISHR

European Society of Cardiology Congress 28th August - 1st September, 2004, Munich, Germany. For further information: congress@escardio.org; Website: www.escardio.org.

Scientific Sessions of the American Heart Association. New Orleans, Louisiana, USA. Enquiries: American Heart Association, Meetings and Councils, 7272 Greenville Avenue, Dallas TX 75231. Tel +1 214 706 1543; Fax +1 214 373 3406; E-mail: scientificconferences@amhrt.org; Website: www.americanheart.org

3rd European Meeting on Vascular Biology and Medicine 2005, Hamburg, 28th-30th September, 2005. For further details: German Cardiac Society, Goethstr. 38a, 40237 Dusseldorf, Germany. E-mail: info@dgk.org; Website: www.dgk.org

BRITISH HEART FOUNDATION GRANTS

PROJECT GRANTS COMMITTEE SEPTEMBER 2003

DEFERRED APPLICATIONS AWARDED

Dr B D Keavney et al, University of Newcastle upon Tyne "Domiciliary echocardiography and BNP measurement in the North East 85+ study pilot project" (1 year) £39,325

Dr R N Poston & Prof J D Pearson, Guy's Hospital, London. "Properties and pathophysiological role of CD14 dependent monocyte adhesion to heat shock proteins in atherosclerosis" (1 year) £57,734

Professor L Poston et al, St Thomas' Hospital, London. "A role for mitochondria in fetal programming of adulthood disease" (2 years) £171,756

NEW APPLICATIONS AWARDED

Professor M L Rose, Harefield Hospital. "Role of autoimmunity in the pathogenesis of rejection after cardiac transplantation" (2 years) £121,032

Dr P R Kemp & Prof J C Metcalfe, University of Cambridge. "Functional analysis of alternatively spliced forms of serum response factor in genetically modified mice" (3 years) £153,845

Dr O B Spiller, University of Wales College of Med. "Soluble virus receptors as therapeutics in a mouse model of Coxsackie B virus-mediated myocarditis" (2 years) £88,643

Dr R S Elkeles et al, St Mary's Hospital, London. "Prospective evaluation of diabetic ischaemic heart disease by coronary tomography (PREDICT)" (3 years) £112,832

Dr J E Schneider et al, University of Oxford. "Development and application of advanced in vivo cardiac magnetic resonance imaging and spectroscopy methods for phenotype characterisation in rodent models of cardiovascular disease" (3 years) £267,224

Dr S J Cleland et al, Western Infirmary, Glasgow. "The effects of metformin on vascular function and adipocyte AMPK activation in Type 2 diabetes" (2 years) £95,492

Dr T H Thomas et al, University of Newcastle upon Tyne. "Tropomyosin isoform expression and cardiovascular disease in Type 2 diabetes" (2 years) £76,962

Dr V Ralevic & Dr W R Dunn, Queen's Medical Centre, Nottingham. "Endocannabinoid modulation of neurotransmission at the sympathetic neurovascular junction" (3 years) £164,228

Dr K M Naseem & Dr J M Gibbins, University of Bradford. "The molecular regulation of platelet nitric oxide synthase" (2 years) £80,369

Professor K M Channon et al, John Radcliffe Hospital, Oxford. "In vivo gene transfer of novel CC chemokine antagonists to inhibit macrophage recruitment in atherosclerosis" (2.5 years) £126,939

Dr S Loughna, Queen's Medical Centre, Nottingham. "Determination and analysis of novel endocardial-specific genes" (1.5 years) £65,708

Dr P E James et al, University of Wales College of Med. "Coronary utilisation of a stable nitric oxide reserve: importance during increased metabolic demand" (2 years) £129,463

Dr A F James & Dr J C Hancox, University of Bristol."Sex-related differences in drug-induced QT prolongation and risk of arrhythmia in the guinea pig" (3 years) £144,343

Dr B D Keavney & Dr M A Vickers, University of Newcastle upon Tyne. "Cytokine gene polymorphisms, plasma inflammatory markers and cardiovascular disease: family-based and case-control genetic association studies" (2 years) £127,557

Dr S Nourshargh & Prof M Perretti, Hammersmith Hospital, London. "Role of neutrophil elastase as a regulator of cytokine/chemokine generation in murine models of ischaemia/reperfusion injury" (3 years) £160,178

Dr R F Storey et al, Northern General Hospital, Sheffield. "The role of $P2Y_{12}$ receptor in murine models of inflammation" (3 years) £169,496

Professor G D Angelini et al, Bristol Royal Infirmary. "A pilot study of external stenting of autologous saphenous vein on early vein graft remodelling after coronary artery bypass surgery (EXTENT 1)" (1 year) £108,800

Dr T M Palmer, University of Glasgow. "Identification of the molecular mechanisms controlling atherogenic signalling from the lysophosphatidic acid receptors LPA_1 and LPA_3" (3 years) £164,978

Professor J M Marshall, University of Birmingham. "Does chronic hypoxia *in utero* induce fetal programming and predispose towards hypertension at maturity?" (3 years) £126,481

Dr K E Porter & Dr N A Turner, University of Leeds. "Mechanisms of TNFα-induced human cardiac fibroblast invasion and MMP-9 secretion - Effects of HMG-CoA reductase inhibition" (2 years) £5,581

Professor N A Booth, University of Aberdeen. "Binding of the C-terminus of α_2-antiplasmin to human cells" (3 years) £127,511

Dr A D Hingorani et al, University College London. "Placental handling of asymmetric dimethylarginine (ADMA): role in pre-eclampsia and implication for later vascular disease in women" (3 years) £117,795

Dr H S Randeva & Dr G A Ng, University of Warwick. "Effects of orexins in the rat heart: potential roles in cardiovascular pathophysiology" (2 years) £90,180

Professor Q Xu & Prof J C Kaski, St George's Hospital Medical School, London. "Characterisation of soluble heat shock protein 60 from patients with atherosclerosis" (3 years) £136,337

Dr R Billeter & Prof C H Orchard, University of Leeds. "Regulation of expression of Ca^{2+} handling proteins in rat cardiac muscle" (3 years) £132,950

PROJECT GRANTS COMMITTEE NOVEMBER 2003

DEFERRED APPLICATIONS AWARDED

Professor C J Garratt et al, Manchester Royal Infirmary. "The role of atrial structural changes and the angiotensin I receptor in the self perpetuation of atrial fibrillation" (3 years) £221,032

Dr J D Erusalimsky, University College London. "Regulation of telomerase in endothelial cells" (3 years) £147,554

Dr N W Morrell et al, Addenbrooke's Hospital. "Do interactions between 5-HT and BMPR-II systems determine susceptibility to pulmonary hypertension?" (3 years)£202,098

Dr R J Schilling et al, St Bartholomew's Hospital. "A study to investigate the mechanisms of complex arrhythmias in congenital heart disease surgically repaired with the Fontan procedure" (2 years) £157,211

NEW APPLICATIONS AWARDED

Dr B D Keavney et al, University of Newcastle upon Tyne. "Candidate genes for blood pressure: family-based association studies and meta-analyses" (3 years) £133,090

Dr H Zhang & Professor C J Garratt, University of Manchester. "The role of atrial electrical remodelling in generation of atrial fibrillation: dissection of the proposed mechanisms using virtual human atrium" (3 years) £103,652

Dr X Y Xu et al, Imperial College, London. "Determination of flow patterns and stresses in patient-specific models of the abdominal aortic aneurysm" (2 years) £43,460

Dr M D Randall et al, Queen's Medical Centre, Nottingham. "Sensory nerve involvement in the cardiovascular effects of cannabinoids in pathological conditions" (3 years) £138,299

Dr R Chen & Prof H D Tunstall- Pedoe, Ninewells Hospital Med Sch, Dundee. "Association of passive smoking with other risk factors and subsequent 16-year cardiovascular disease in Scottish Heart Health cohort studies" (6 months) £25,376

Professor A D Hughes et al, St Mary's Hospital, London. "Endothelial progenitor cells as a mediator of ethnic differences in cardiovascular risk in South Asians and Europeans" (9 months) £33,389

Dr J M R Gill et al, University of Glasgow. "Physical activity, insulin resistance and adipose tissue gene expression in the offspring of patients with Type 2 diabetes" (3 years) £193,805

Dr F Karpe & Professor K N Frayn, Churchill Hospital, Oxford. "Mechanisms of dyslipidaemia in obesity/the insulin resistance syndrome: tissue-specific generation of remnant lipoproteins" (2 years) £150,210

Dr N Sattar et al, Glasgow Royal Infirmary. "Adipocyte lipolysis as a candidate pathway in the pathogenesis of pre-eclampsia" (3 years) £128,684

Dr M J White, University of Birmingham. "Muscle afferent inputs to human cardiovascular control in exercise: the interaction between metabolic and mechanical stimuli" (2 years) £54,623

Dr B A Levine & Prof S V Perry, University of Birmingham. "Molecular analysis of the role of troponin-I in the modulation of myocardial calcium sensitivity" (3 years) £135,774

Dr I Dransfield, University of Edinburgh. "Investigation of the functional consequences of monocyte platelet interactions" (3 years) £130,120

Professor S Akhtar et al, Cardiff University. "The role of EGFR signalling in diabetes-induced vascular dysfunction" (3 years) £113,091

Prof A D Struthers & Dr S D Pringle, Ninewells Hospital Med Sch, Dundee. "Left ventricular hypertrophy in coronary artery disease" (2.5 years) £121,995

Mr V Chandrasekaran et al, St George's Hospital Medical School, London "Effects of autotransfusion on systemic inflammatory response and lung injury in patients undergoing CABG with and without cardiopulmonary bypass" (1.5 years) £79,658

Dr A Sivaprasadarao, University of Leeds. "Molecular mechanism of voltage sensing in the HERG potassium channel" (3 years) £122,956

Dr I B Squire et al, Leicester Royal Infirmary. "Plasma matrix metalloproteinases as predictors of prognosis and left ventricular remodelling after acute myocardial infarction" (2 years) £122,941

Dr R A Barrett-Jolley, University of Liverpool. "Tachykinin regulation of *"pre-sympathetic"* neurones of the paraventricular nucleus" (3 years) £113,956

Dr M Umpleby et al, St Thomas' Hospital, London. "Development and validation of a stable isotope method to measure triglyceride rich lipoproteins during postprandial lipaemia" (1 year) £54,617

Dr V Ralevic & Prof D A Kendall, Queen's Medical Centre, Nottingham. "Cannabinoid modulation of the efferent function of perivascular sensory nerves" (3 years) £152,224

Dr J C Fordham et al, Guy's Hospital, London. "Novel PDZ-interactions at the sarcomeric Z-disc of cardiac myocytes" (3 years) £160,394

Dr P Brindle et al, University of Bristol. "Improving coronary risk assessment in ethnic minorities by recalibrating the Framingham risk scoring method" (1 year) £35,248

Dr J A Ellis & Dr C M Shanahan, Guy's Hospital, London. "Elucidating the functional role of the interaction between emerin and nesprin in cardiomyocytes" (2 years) £99,082

Dr D A Middleton, University of Manchester. "Studies on the structure and function of sarcolipin, an atrium-specific regulator of calcium cycling in cardiac cells" (2 years) £83,432

Mr D Pagano et al, Queen Elizabeth Hosp, Birmingham. "Metabolic substrate support in left ventricular hypertrophy" (3 years) £175,762

Prof J M Ritter & Dr P J Chowienczyk, St Thomas' Hospital, London. "The effect of K^+-intake on K^+-mediated vasodilator tone" (2 years) £144,267

Dr D Lang et al, University of Wales College of Med,Cardiff. "The role of folic acid and its metabolites in reversing endothelial dysfunction" £102,941

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)

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
17 (3)	***July 2004***	*June 1st*
17 (4)	***October 2004***	*September 1st*
18 (1)	***January 2005***	*December 1st*
18(2)	***April 2005***	*March 1st*

Cardiovascular Related Wellcome Trust Grants

December 2003 to January 2004

Wellcome Programme Grant

Professor Stephen P Watson, Division Of Medical Sciences, The Medical School, University Of Birmingham Signalling By Itam And Integrin Receptors In Platelets. 60 Months £1,059,084

Project Grant

Professor C Roland Wolf, Biomedical Research Centre, Level 5 Ninewells Hospital Medical School, University Of Dundee. Role Of The Cytochrome P450 System In Embryonic Development. 36 Months. £316,776

Dr D S Steele, Department Of Biology, School Of Biology, University Of Leeds. Modulation Of Depolarisation-Induced Ca^{2+} Release By Endogenous Factors In Skeletal Muscle. 36 Months £197,217

Dr Ian M Clark, School Of Biological Sciences, University Of East Anglia, Norwich. Identification And Function Of A Novel Transcription Factor Binding To The Timp-1 Gene. 18 Months £88,566

Clinician Scientist Fellowship

Dr Jillian G Baker, Institute Of Cell Signalling, Queen's Medical Centre, University Of Nottingham. Molecular Mechanisms Underlying The Agonist And Antagonist Effects Of Beta-Adrenoceptor Ligands At The Human Beta1 And Beta2 Adrenoceptor. 60 Months £578,539

Training Fellowships for Medical and Dental Graduates

Dr Stephen Wright, Department Of Therapeutics And Pharmacology, The Whitla Medical Building, Queen's University Of Belfast. Omega-3-Polyunsaturated Fatty Acids And Atherosclerosis In Sle: Cellular Mechanisms And Functional Consequences. £107,615

Collaborative Research Initiative Grants

Professor A J Llanos, Department Of Physiology, University Of Cambridge. Effects Of Chronic Hypoxia On Fetal Cardiovascular And Endocrine Functions In The Sheep. 36 Months £17,000

Professor Vladimir S Markhasin, Laboratory Of Physiology, University Of Oxford. Sub-Cellular Mechanisms Underlying Physiological And Pathological Effects Of Myocardial Mechanical Inhomogeneity. 36 Months £88,386

International Collaborative Research Grant A/Nz

Dr R Scragg Department Of Epidemiology, University Of Auckland, New Zealand. The Pacific Opic Study - A Four Country Study Of Obesity Prevention In Communities. 60 Months £670,000

For up to date information on forthcoming meetings, workshops and symposia,

please remember to check the new BSCR Website:

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

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

BSCR Autumn Meeting 2004

Integrative Cardiovascular Pathophysiology in Gene-Modified Models

Dates: 9th and 10th September, 2004

Venue: Guy's Campus, King's College London

Organisers: Professor Ajay Shah & Dr Alison Cave

Overall Aims: The aim is to provide state-of-the-art presentations that utilise modern molecular physiological and imaging methods and techniques with a focus on gene-modified *in vivo* and *in vitro* models. Both cardiac and vascular pathologies will be covered.

Invited Speakers include: Keith Channon *(Oxford)*, Andre Constantinesco *(Strasbourg)*, Martin Denvir *(Edinburgh)*, Mathias Gautel *(London)*, Andrew Grace *(Cambridge)*, David Kass *(USA)*, Mark Kearney *(London),* Michael Marber *(London)*, Stefan Neubauer *(Oxford),* Jean-Sebastian Silvestre *(Paris)*, Alberto Smith *(London),* Godfrey Smith *(Glasgow)*, Karen Svenson (*USA)*.

Travel & Accommodation: The conference will be held at the Guy's Campus of King's (nearest tube and BR: London Bridge), with accommodation 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 PhD students.

Deadline for submission of abstracts, registration and application for student bursaries: 23 July 2004

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

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