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Contents

Editorial

Happy New Year and Welcome to the January 2005 issue of *The* Bulletin!

Our review article for this issue is written by Drs Farisa Syeda and Caroline Wheeler-Jones from the Royal Veterinary College, London and provides a fascinating overview of the role of Proease-activated receptors in the Cardiovascular system both in terms of normal physiology and disease.

We are pleased to include a report on the recent BSCR meeting held at Kings College London on the subject of entitled *"Integrative Cardiovascular Physiology in Gene-Modified Models"*. The report, written by the organisers Ajay Shah and Alison Cave, summarises all talks, keynote lectures and oral presentations. We will no longer be presenting meeting abstracts within *The* Bulletin, as these are now published by *Heart* online at: http://heart.bmjjournals.com/cgi/reprint/90/12/e68.

Following the success of the Autumn meeting, plans are now coming together for next year's Spring meeting,which will be organised by Professors Nilesh Samani and Alison Goodall. A detailed programme of the meeting is printed inside this issue 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.**

As is customary, 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

Protease-activated receptors in the vasculature – Mechanisms of activation, Signaling pathways and physio-pathological roles

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Protease-activated receptors (PARs) represent a unique subclass of G-protein coupled receptors (GPCRs) that respond to extracellular proteases and initiate appropriate biological responses. Their unique mechanism of activation involves the proteolytic unmasking of a cryptic N-terminal receptor sequence that binds to and triggers receptor function while remaining tethered. There are currently four members of the PAR family: PAR1, PAR2, PAR3 and PAR4. Proteases and PARs constitute a complex system that influences many fundamental mechanisms involved in physiology and disease including tissue injury, repair and remodeling, inflammation, embryogenesis and cancer (1-2).

Mechanisms of activation and modulation

The general mechanism of activation of a PAR is: (i) proteases cleave the receptor at specific sites within the extracellular amino terminus; (ii) this cleaved amino terminus that serves as a tethered ligand is then exposed to the cleaved receptor and binds to a conserved region in the second extracellular loop, thereby resulting in the initiation of signal transduction (**Figure1**). This unique mechanism of activation of PARs occurs through an irreversible proteolytic event.

PAR1 is cleaved and activated mainly by thrombin, a serine protease of the coagulation cascade, and plays a central role in coagulation and wound healing. PAR2 is activated by trypsin-like serine proteases including trypsin, tryptase, and coagulation proteases upstream of thrombin, factors VIIa and Xa, but not by thrombin. In contrast, PAR3 and PAR4 have been identified as thrombin receptors. Although thrombin cleaves PAR1, PAR3 and PAR4, the kinetics of activation and desensitization, and the magnitude of response varies for each of these receptors. For example, PAR4 is a low affinity receptor for thrombin and displays a slow desensitization compared to PAR1 (3). PARs can also be activated by synthetic peptides that mimic the tethered ligand domain by directly binding to the uncleaved receptor without the requirement of hydrolysis by proteases. These agonist peptides (APs) are currently used to study the physiological functions of PARs *in vitro* and *in vivo*. Synthetic peptides corresponding to the tethered ligand domain TFLLRN selectively activate PAR1 without the need for receptor cleavage. Similarly, SLIGKV and GYPGKF are PAR2- and PAR4-selective APs respectively. However in contrast to PAR1, PAR2 and PAR4, PAR3 is not activated by peptides corresponding to its tethered ligand domain. In fact, recent studies provide evidence that peptides based on either the human or murine PAR3-derived tethered ligand sequences (TFRGAP-NH2 or SFNGGP-NH2) do not activate PAR3, but rather activate PARs 1 and 2 (4). Interestingly, proteolytic fragments derived from *in vivo* protein hydrolysis may play a role in PAR-induced signaling. For example, B-50/GAP-43, a protein associated with neuronal

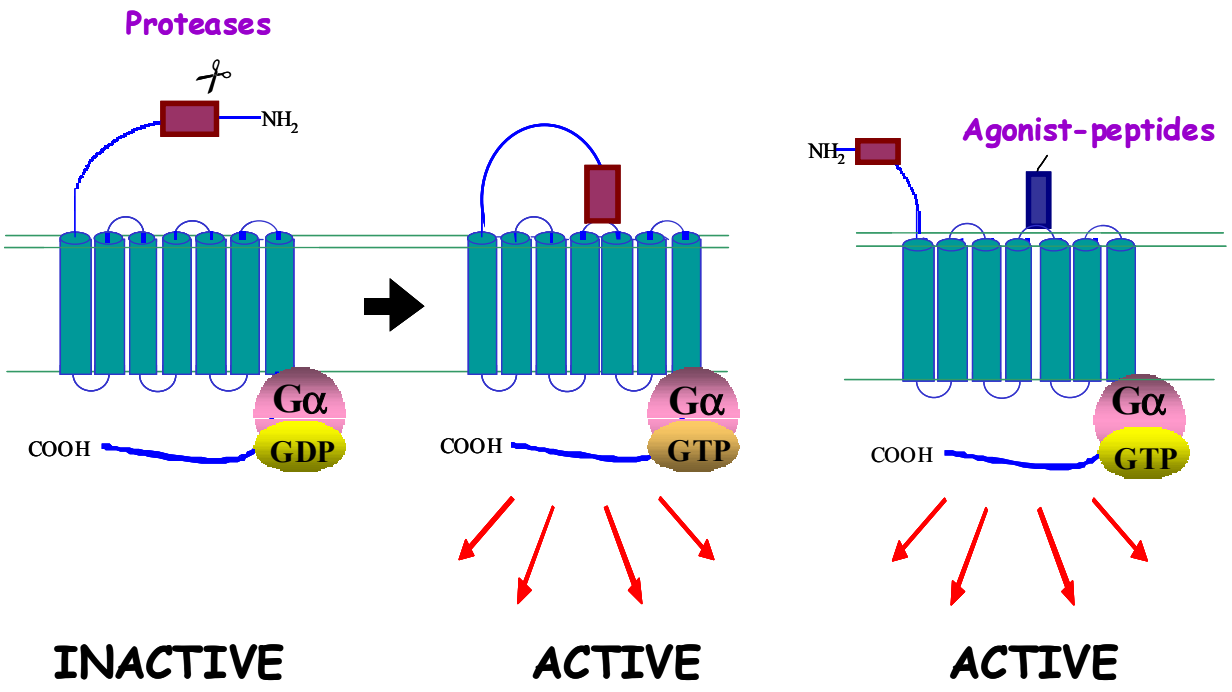

Figure 1. Schematic representation of Protease-activated receptor (PAR) activation by proteases or by agonist-peptides. PARs are activated by protease-mediated cleavage of the receptor within the extracellular amino terminus. The cleaved amino terminus then serves as a tethered ligand and binds to a conserved region in the second extracellular loop, thereby initiating signal transduction. PARs can also be activated by synthetic peptides that mimic the tethered ligand domain by directly binding to the uncleaved receptor without the requirement of hydrolysis by proteases.

growth, has an N-terminal sequence with similarity to those of the tethered ligands for PAR1 and PAR2. SFRGHITR, a proteolytically-derived fragment of B-50/GAP-43 can activate both PAR1 and PAR2 in human embryonic kidney cells resulting in increased intracellular calcium (5).

Although the principal mechanism of PAR activation is intramolecular, whereby the unmasked tethered ligand binds to its own cleaved receptor, PARs can also be activated by intermolecular activation. This mechanism is thought to occur between PAR1 and PAR2, where the tethered ligand domain of PAR1 can interact with uncleaved PAR2 to promote signaling (6-8). This novel mode of signaling between different PARs could be modulated by other cofactors or by anchoring proteins that may promote the cooperation between receptors in the membrane.

Activation of PARs by proteases is an irreversible mechanism since the cleavage causes the receptor to permanently expose its ligand-binding domain to interact with the ligand. However, this signaling is rapidly terminated by several mechanisms of desensitization, and by internalization and lysosomal sorting. Desensitization of PAR1 and PAR2 requires GRKs and beta-arrestins. GRKs are serine-threonine kinases that phosphorylate activated receptors, usually within the carboxy terminus, that further disrupts their association with heterotrimeric G proteins and results in termination of the signal. Beta-arrestins serve as cofactors for GRKs. Recent studies carried out in mouse embryonic fibroblasts derived from beta-arrestin knock-out mice have shown the importance of beta-arrestin1 in mediating PAR1

desensitisation (9). Another mechanism controlling PAR signaling is the internalization and lysosomal sorting of activated PARs. PAR1 is rapidly internalized after activation and this occurs via a clathrin- and dynamin-dependent pathway. Beta-arrestins as well as other adaptor proteins, such as beta-adaptins, may also play a role in PAR1 internalization. Although internalized PARs are mainly targeted for endocytic degradation, a small proportion of internalized receptors recycle back to the plasma membrane (10).

Physiopathological role of PARs in the cardiovascular system

Both *in vitro* and *in vivo* studies provide evidence that PARs play critical roles in normal physiological processes as well as during diseased states. PARs couple to multiple signaling pathways and therefore mediate a wide range of functions relating to cardiovascular, respiratory, gastrointestinal, nervous and immune systems. This brief overview focuses on the role of PARs within the vasculature.

One of the most well-defined functions of PARs in the vasculature is the thrombin-mediated activation of PAR1 and PAR4 on platelets, which causes aggregation and induction of procoagulant activity and granular secretion contributing to haemostasis. Thrombin signals by activating PAR1 and PAR4 in human platelets but only PAR4 in murine platelets. *In vivo* studies using PAR antagonists and inhibitors have highlighted the relative importance of PAR1 in the formation of thrombi during vessel injury, whereas PAR4 seems to be more prominent in mice. Blockade of PAR4 prolongs bleeding time and protects against systemic platelet activation, consistent with the phenotype of PAR4-deficient mice (11). The role of PAR4 in cells other than platelets is relatively unknown but there is evidence that functionally active PAR4 is present in vascular smooth muscle cells and endothelial cells raising the possibility that this receptor has functional significance (12). PARs activation is important for controlling cell permeability and vascular tone. Thus, thrombin and selective PAR1 agonists cause relaxation of precontracted blood vessels in several species including humans (13, 14), and PAR1-induced relaxation is prevented by removal of the endothelium or by inhibition of nitric oxide (NO) synthase indicating that vasorelaxation is mediated in part by the release of NO from endothelial cells. Endothelial-derived hyperpolarizing factor as well as products of cyclooxygenases may also contribute to relaxation (13, 15, 16). Thus, PAR1 activators can modify vascular tone by both endothelium-dependent and -independent mechanisms.

Activators of PAR2 such as trypsin and PAR2-AP also induce arterial relaxation which depends on the presence of the endothelium and involves both NO-dependent and -independent mechanisms (14, 17). Data from *in vivo* studies also support the vasorelaxant effects of PAR1 and PAR2. In mice, intravenous injection of a PAR1-selective AP causes a rapid and sustained hypotension, which is not mediated by NO (18). Similarly, in rats and mice, PAR2 activators promote hypotension by NO-dependent and -independent mechanisms, which can be followed by a reflex hypertension (19). The effects of PAR2 activators on blood flow have recently been investigated in humans. Administration of PAR2-AP promotes dilation of forearm resistance vessels and increased blood flow through NO- and prostaglandin-dependent mechanisms (20).

Proliferative and proangiogenic effects of PARs activation have been reported in endothelial (21) and vascular smooth muscle cells (22). The proangiogenic effects of thrombin involve interactions with vascular endothelial growth factor (VEGF), which is a pivotal angiogenic factor. PAR1 activators stimulate expression of VEGF receptors by endothelial cells and potentiate the mitogenic effects of VEGF on endothelial cells (23) suggesting the existence of a mechanism for amplifying the angiogenic response involving PAR1 and VEGF receptors. Activation of PAR2 also stimulates proliferation of endothelial cells (21). In a murine model of limb ischemia, trypsin and PAR2-AP promote

angiogenesis and accelerate hemodynamic recovery of the limb, implying a role for PAR2 in angiogenesis (24). Similarly, activation of PAR4 by thrombin promotes proliferation of vascular smooth muscle cells (12).

Apart from their role in normal physiology, PARs play important roles during inflammation when there are increased levels of proteases derived from many sources including inflammatory cells, together with increased expression of PARs. *In vitro* studies in endothelial cells have shown upregulation of PAR2, but not PAR1, in response to inflammatory mediators such as TNFα and LPS (25). *In vivo* administration of endotoxin to rats also causes increased expression of PAR2 in the vasculature, thereby potentiating the PAR2-induced hypotensive response (26). Similarly, human coronary artery segments exposed to interleukin-1α or TNFα show upregulation of PAR2 and PAR4 and concomitant increases in PAR2- and PAR4-mediated relaxation (27). Activation of PAR2 also promotes the initial steps of the inflammatory process including leukocyte rolling, adhesion, and transmigration in rat mesenteric venules (28, 29). Indeed, PAR2 activation is associated with neurogenic inflammation (30, 31) and non-neurogenic inflammation (32) and is observed during acute as well as chronic inflammatory responses e.g. arthritis (33). A recent study has demonstrated that PAR2 expression is enhanced in human coronary atherosclerotic lesions, suggesting that PAR2-dependent events may be involved in atherogenesis (34). This emerging evidence for the pro-inflammatory role of PAR2 necessitates further understanding of the molecular mechanisms regulating these events. In other systems there is evidence for an anti-inflammatory role of PAR2 (35), which has yet to be defined in the vasculature.

PAR-induced signaling pathways

PARs couple to multiple signaling pathways to mediate their effects. Signal transduction is initiated by coupling of PARs to heterotrimeric G proteins at the plasma membrane. The first signaling pathway characterized for PAR1 was coupling through Giα proteins inducing inhibition of cAMP and increased production of inositol-triphosphate (InsP3). The cAMP response was blocked by pertussis toxin indicating involvement of a Gi-dependent pathway, while phosphoinositide hydrolysis was insensitive to pertussis toxin (36). The Gqα pathway also plays a major role in coupling PAR1 signaling in response to thrombin in platelets and fibroblasts (37, 38). Platelets derived from Gqα-deficient mice exhibit markedly diminished thrombin-induced aggregation and degranulation that leads to prolonged bleeding times, probably due to impaired thrombin signaling in platelets (39). These pathways also mediate thrombin-induced activation of phospholipase C (PLC), leading to generation of $InsP_3$, which mobilizes intracellular calcium (Ca^{2+}), and diacylglycerol, which activates protein kinase C (PKC). Furthermore, activation of both PLC and PKC is required for thrombin-induced activation of phospholipase A_2 (PLA_2) and phospholipase D (PLD) (40). Together, Ca^{2+} and PKC activate numerous pathways, including Ca^{2+}-regulated protein kinases and mitogen-activated protein kinases (MAPKs). Other studies have reported coupling of PAR1 to Gq12/13 (41) and this pathway is involved in thrombin-induced control of cell shape and motility through Rho-guanine nucleotide exchange factors (42). In platelets, G12/13α induces activation of Rho-kinase and myosin light-chain kinase, which mediates thrombin-induced shape changes. Fibroblasts from G13α-deficient mice show reduced migratory responses to thrombin, and also have impaired vascular development resulting in premature death (43). In human umbilical vein endothelial cells (HUVEC), PAR1 activators induce stress fibre formation, accumulation of cortical actin and cell rounding (44). Inhibition of Rho partially attenuates thrombin-induced cell rounding, whereas dominant-negative Rac blocks the response to thrombin. These results suggest that Rho is involved in thrombin-induced

regulation of endothelial permeability while Rac mediates cytoskeletal remodeling. The extent to which PAR1 couples to each of these pathways may depend on the G protein sub-types expressed within the cells. A recent study has also revealed that thrombin inhibits eNOS phosphorylation and expression via the Rho/ROCK pathway in HUVEC. This pathway negatively regulates eNOS phosphorylation through inhibition of protein kinase B (PKB), whereas eNOS expression appears to be independent of PKB (45, 54). Activation of PAR1 also induces phosphorylation of the EGF receptor in endothelial cells (46). PAR1 stimulation mediates activation of $p38^{mapk}$ in cardiac fibroblasts by a mechanism involving EGF receptor transactivation by Src family kinases (47). Possible mechanisms mediating this transactivation include activation of the Ca^{2+}-dependent kinase Pyk-2, which shows strong PAR1-mediated regulation in endothelial cells (46, 48).

The involvement of the PI3K/Akt pathway in thrombin induced effects has been reported in platelets (49-51), vascular smooth muscle cells (52, 53) and endothelial cells (54), suggesting that this is likely to be an important component of PAR signaling in the vasculature. PAR1 signaling also involves JAKs (janus family of tyrosine kinases). These kinases tyrosine phosphorylate STAT proteins (signal transducers and activators of transcription), which dimerize and translocate to the nucleus to direct gene transcription. In vascular smooth muscle cells, thrombin activates JAK2, resulting in nuclear translocation of the transcription factors STAT2 and STAT3 (55). Inhibition of JAK2 reduces thrombin-induced ERK2 activity and cellular proliferation, suggesting that JAK2 is upstream of the Ras/Raf/MEK/ERK pathway. There is also recent evidence that thrombin-induced motility of vascular smooth muscle cells requires STAT3-dependent induction of cPLA2 (56).

PAR2 activators also strongly activate ERK1/2 and weakly stimulate the $p38^{mapk}$, but not JNKs (c-jun amino-terminal kinases) (57). There is also some recent evidence that beta-arrestins might play a role in modulating PAR2-induced activation of ERKs (58). It is suggested that beta-arrestins act as molecular scaffolds that promote the formation of an ERK1/2 module (containing beta-arrestins, raf-1, and activated ERK1/2) at the plasma membrane or in endosomes, which then retains the activated ERK-module and thus prevents further activation of ERK-dependent events. PAR2 and PAR4 agonists also activate the NFkB pathway emphasizing the importance of PARs in inflammation (59, 60). Despite these recent developments, further elucidation of the molecular mechanisms involved is essential to fully understand and control PAR-mediated effects in vascular cells.

Endothelium and PARs

Endothelial cells (ECs) lining the blood vessels play a critical role in the maintainence of vascular homeostasis and express all known PARs. ECs respond to the activation of these PARs by promoting various cellular effects including secretion of von Willebrand factor, upregulation of IL8 and adhesion molecules (P-selectin, ICAM1, VCAM1), and increased expression of protective molecules (eg: decay accelerating factor) (61). During tissue injury the levels of circulating proteases such as thrombin and trypsin are increased and may alter the functions of endothelial cells as well as those of other surrounding cells. PAR stimulation strongly influences prostanoid production by ECs, particularly PGI_2. PGI_2 contributes to the inflammatory response by promoting vasodilation and increasing vascular permeability. This prostanoid is also a powerful antiplatelet agent, and has both anti-proliferative and anti-fibrotic effects. Thus, understanding EC production of PGI_2 and how this is regulated by proteases has significant implications for both normal and pathophysiological control of the vasculature.

We have previously shown that COX-2 expression is enhanced in response to thrombin as well as to the PAR1- and PAR2-selective agonist-peptides, TFLLRN and SLIGKV

respectively, in HUVEC (62). However, the mechanisms by which this upregulation is mediated remained unknown. In a recent study we investigated the molecular signalling mechanisms underlying PAR-induced COX-2 upregulation and PGI_2 release in HUVEC (63, 64). Thrombin and PAR2-AP strongly activated both ERK1/2 and p38 ^{mapk} and pharmacological blockade of MEK1/2 or p38^{mapk} markedly inhibited thrombin- and SLIGKV-induced COX-2 expression, as well as PGI_2 synthesis. In HUVEC transfected with an NF-kB reporter adenovirus, exposure to thrombin and SLIGKV resulted in increased transcriptional activity of NF-kB, whereas no change was observed in response to PAR4-AP(GYPGQV). Similarly, immunohistochemical studies showed that thrombin and SLIGKV, but not PAR4-AP, induced nuclear translocation of NF-kB in HUVEC. Consistent with these findings, PAR-induced COX-2 expression was markedly attenuated by triptolide (PG-490), an NF-kB inhibitor. These findings suggest that (i) activation of PAR1 and PAR2 in HUVEC enhances COX-2 expression and PGI_2 release, and (ii) PAR-driven COX-2 expression requires ERK1/2 and p38^{mapK} signaling, as well as NF-kB-dependent mechanisms. We are currently examining interactions between MAPKs and the NF-kB pathway in PAR-driven upregulation of COX-2, as well as studying other potential signaling mechanisms that could be involved in regulating mediator release from ECs.

Conclusion

In summary, proteases and PARs are emerging as critical regulators of biological functions in the vasculature. During the last decade much work has been directed towards understanding the cellular and functional roles of PARs and significant knowledge has been gained about the functioning of PAR1. However the signaling mechanisms of other PARs are not fully explored and remain to be defined. The development of selective and potent agonists and antagonists for all four PARs would be an essential requirement for enhancing our knowledge of PAR-specific functions but could also aid in controlling PAR-induced effects during disease. Finally, a full understanding of the potential roles played by specific proteases and their inhibitors in healthy and diseased vasculature would be helpful in developing PAR-targeted therapeutic strategies.

Acknowledgements

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64. F Syeda, R Houliston, R Keogh, J Grosjean, E Paleolog, T Carter and CPD Wheeler-Jones. Protease-activated receptors (PARs)-mediated up-regulation of Cyclooxygenase-2 (COX-2) by in human endothelial cells: involvement of ERK1/2, p38^{mapk} kinases and NF-kB. *Manuscript in preparation.*

Dr Farisa Syeda is a Post-Doctoral Research Assistant in the Laboratoy of Dr Caroline Wheeler-Jones at the Department of Veterinary Basic Sciences, The Royal Veterinary College.

Farisa may be contacted by e-mail: fsyeda@rvc.ac.uk

BSCR Autumn Meeting Report 9-10th September 2004

"Integrative Cardiovascular Physiology in Gene-Modified Models"

Organised by Professor Ajay Shah and Dr Alison Cave at King's College London

Over the last 10 years there has been a steady increase in the number of studies using transgenic mice (**Figure 1**). Given this almost 4 fold increase, we felt that a meeting focussing on the ability to assess integrative pathophysiology in murine gene modified models would be timely.

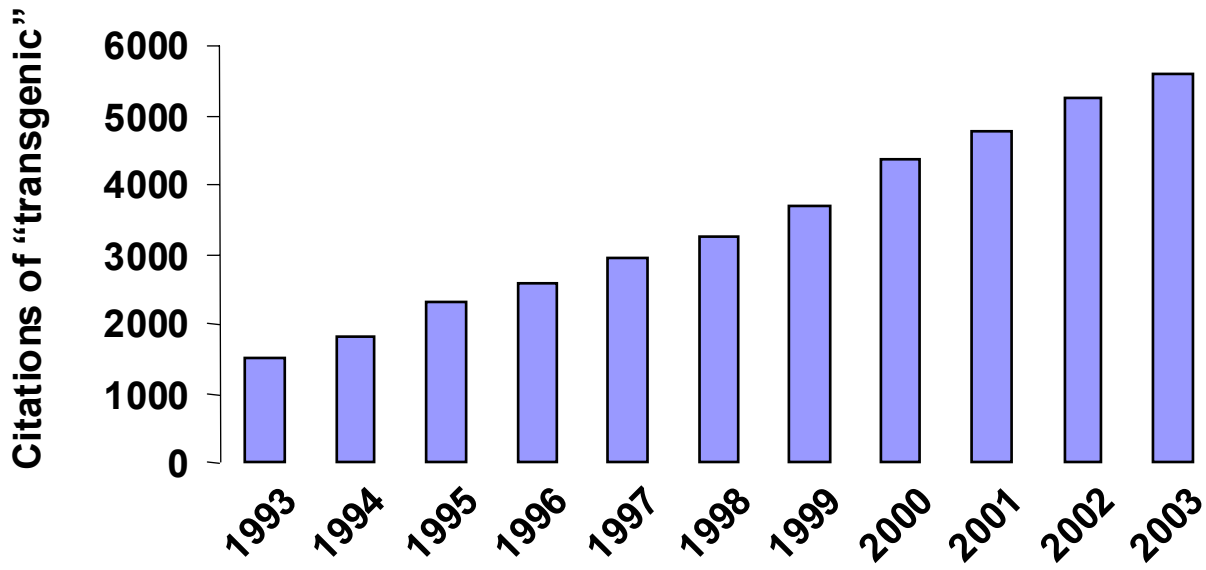


Figure 1: Increase in the number of articles citing transgenic over the last 10 years

The first session of the meeting was entitled cardiac disease and chaired by Professors Metin Avkiran (London) and Barbara McDermott (Belfast). The session was kicked off by Professor Michael Marber (London) who described the pitfalls of murine models of both reversible myocardial ischaemia and reperfusion (for the study of stunning, hibernation, preconditioning etc) and irreversible ischaemia (for the study of myocardial remodelling). He highlighted the difficulties in the assessment of cardiac function and the critical importance of using littermate controls since sensitivity to ischaemia varies widely both between strains and within strains of mice from different sources. Dr Alison Cave (London) continued the session by describing the murine models of cardiac hypertrophy developed in their laboratory

over the last 5 years. The potential of these models was illustrated by their studies performed in knockout mice with a non-functional Nox2 subunit of the NADPH oxidase. The third speaker of the session was Professor Andrew Grace from Cambridge who described some of the difficulties of studying electrophysiology in mice but emphasised that the ability to model ion channel mutations seen in patients in mice will help to resolve the complex functional consequences of such mutations. This was illustrated elegantly by an example where the consequences of gain-of-function mutations in the cardiac sodium channel gene, *SCN5A*, in patients with long-QT syndrome (LQT3) have been investigated by the construction of a gene-modified mouse. The last speaker in this session was Dr Christopher Loughrey (Glasgow) who described studies investigating the function of FK506-binding protein (FKBP12.6) using adenoviral-mediated gene transfer to over-express this protein in adult rabbit ventricular cardiomyocytes. FKBP12.6 has been shown to modulate cardiac excitation–contraction coupling by binding to the SR Ca^{2+} release channel (ryanodine receptor type 2). The results presented supported the idea that increasing FKBP12.6:RyR2 stoichiometry may, under some circumstances, increase Ca^{2+} transient amplitude and may be a possible therapeutic target in heart failure.

In the second session, we were privileged to receive the British Cardiac Society Lecture entitled "State of the Art assessment of murine LV haemodynamics" by Professor David Kass (Baltimore, USA). Professor Kass gave a superb lecture in which he emphasised that the utility of gene-modified mice as tools for investigating pathophysiological mechanisms of cardiovascular disease absolutely requires the ability to carefully and precisely measure and interpret the physiological consequences of genetic manipulation. His talk focussed on the assessment of *in vivo* cardiovascular haemodynamics and demonstrated that the use of left ventricular pressure-volume analyses (with microconductance) can provide very detailed and integrative information both on cardiac and arterial function as well as ventriculo-arterial coupling. The talk was illustrated by many examples of excellent integrative studies in mice from his laboratory, including a novel method for targeted *in vivo* gene delivery to the heart and the world's smallest biventricular pacemaker suitable for implantation in mice! Truly an outstanding and motivating talk!

The first day ended with a wine reception and poster session followed by a trip on the London Eye, for which the weather was thankfully perfect, and a very enjoyable dinner of steak frites at the nearby Chez Gerard.

On day 2, we moved to vascular disease in the first session chaired by Professors Qingbo Xu (London) and Giovanni Mann (London). Professor Keith Channon (Oxford) described murine models for the study of atherosclerosis and restenosis in mice. In addition, he showed elegant studies illustrating how ex-vivo high-resolution 3D MRI could accurately quantify the lipid-rich/necrotic core and cell-rich cap areas in atherosclerotic lesions in apoE-/- mice compared with histology. He also re-emphasised a familiar theme of the meeting that it is vital to use littermate controls for experiments in view of often substantial differences even within the same strain. Dr Alberto Smith (London) discussed animal

models in which venous thrombus resolution could be investigated. The talk was illustrated with studies in gene knockout mice in which either tissue-type plasminogen activator (tPA) or urokinase-type plasminogen activator (uPA) had been knocked out. Additional studies utilised bone marrow transplantation to dissect out the relative role of bone marrow–derived monocytes versus resident cells in thrombus resolution, and showed that uPA in marrow-derived cells was especially important. The third speaker of the session was Dr Mark Kearney (London) who talked about different murine models of obesity/insulin resistance. He demonstrated using mice heterozygous for a knockout for the insulin receptor that vascular NO production and blood pressure homeostasis are very sensitive to changes in insulin action in the endothelium. He then went on to demonstrate a novel anti-adipogenic action for IGF-BP2 in a transgenic mouse overexpressing this peptide in studies showing that these animals were protected against the development of age- and diet-induced insulin resistance. The last speaker of the session was Dr Jean-Sebastian Silvestre (Paris) who gave an impressive talk describing his group's work on angiogenesis. In particular, he described recent work evaluating the safety of bone marrow-derived mononuclear cell-based therapy in the setting of atherosclerosis. Bone marrow-derived mononuclear cells (BM-MNCs) enhance postischaemic neovascularization, and their therapeutic use is currently under clinical investigation. However, Dr Silvestre concluded that the use of bone marrow derived mononuclear cells could actually promote further atherosclerotic plaque progression in an ischemic setting.

The next session was chaired by Dr Gillian Gray (Edinburgh) and Professor Michael Shattock (London) and consisted of four 10 minute presentations that had been selected from the submitted abstracts. Dr K. Bicknell (Reading) started the session with a talk entitled *"The re-expression of a constitutively-active cyclin B1:CDC2 complex in adult rat cardiomyocytes is sufficient to re-initiate cell division"*; Dr D. Grieve gave a talk entitled *"A gp91^{phox}-containing NADPH oxidase contributes to the contractile dysfunction associated with pressure-overload cardiac hypertrophy"*; Dr J. Bendall (Oxford) gave a talk entitled *"Endothelial tetrahydrobiopterin regulates eNOS coupling/uncoupling independent of vascular disease: insights from targeted transgenic models"* and finally Dr A Bagnall finished the session with a talk entitled *"Hypertension and endothelial dysfunction in mice featuring endothelial cell specific knockout of endothelin B receptors."* All speakers gave excellent presentations.

After the Annual General Meeting and a break for lunch, Professor Michael Marber awarded the oral presentation prize to Dr K Bicknell from Reading and the poster presentation prize to Miss Ay Lin Kho from London. All abstracts from this meeting can be viewed on line on the following link:

http://heart.bmjjournals.com/cgi/reprint/90/12/e68

The first talk after lunch was the National Heart Research Fund lecture given by Dr Karen Svenson from Jackson Labs, USA. Dr Svenson is the Programme Manager at the Centre for

New Mouse Models of Heart, Lung, Blood and Sleep Disorders. She gave a fascinating lecture in which she explained that the goal of the centre was to link genetic variation to biological function and dysfunction – aiming to identify both single genes and interacting gene networks that underlie the pathophysiology of cardiovascular diseases using a phenotype-driven approach. The basic methodology is to perform high throughput comprehensive phenotypic characterisation of ENU-generated mutant mice as well as analyse inter-strain variations among established inbred mouse strains. Newly identified ENU phenotypic deviants are made available to the public for the cost of shipping only. Dr Svenson encouraged us to visit the web site (http://pga.jax.org) regularly for the latest listing of these new models of human disease.

The last session of the meeting on imaging was chaired by Professors Ajay Shah (London) and Keith Channon (Oxford). The session was kicked off by Dr Martin Denvir (Edinburgh) describing the pitfalls of echocardiography in mice. Dr Denvir showed some excellent images and discussed some of the technical difficulties of the technique. Professor Mathias Gautel (London) continued the session with a beautiful demonstration of in situ imaging in cardiac cells and again discussed some of the many difficulties with the technique and ways of overcoming these. After tea, we had the last two talks in this session. In the first, Professor Andre Constantinesco (Strasbourg) gave an excellent talk on functional nuclear imaging in mice in which he described the advantages micro SPECT (Single photon Emission Computed Tomography) in terms of the functional information collected and the large library of labelled molecules which can be exploited. The last speaker of the meeting, Professor Stefan Neubauer (Oxford) held everyone's attention with an excellent talk on murine magnetic resonance imaging emphasing the quality of the images and data which can be obtained and thus the ability to use the technique to accurately phenotype mice in terms of their cardiac anatomy, function, perfusion, viability and metabolism.

All in all, the meeting provided an excellent overview of the current state of the field and hopefully encouraged more groups to start utilising some of the models and methods presented.

Alison Cave and Ajay Shah

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

BSCR SPRING MEETING 2005
EMERGING CONCEPTS IN ATHEROTHROMBOSIS

Thursday 21 and Friday 22 April 2005

Stamford Hall, University of Leicester

Organisers: Professor NJ Samani & Professor AH Goodall

The theme of the meeting will be **Atherothrombosis**. The programme is designed to cover current ideas on the way in which atherosclerotic plaque rupture drives the thrombotic response.

Programme

Thursday 21st April

12.30 – 14.00	Registration and lunch
14.00–17.00	**Session 1: Plaque and Vessel Wall**
14.00–14.10	Introduction and welcome
14.10-14.45	Raffaele De Caterina (Chieti, Italy) Endothelial cell function, oxidative stress and atherosclerosis
14.45-15.20	Andrew Newby (Bristol) Plaque stability: the role of metalloproteinases
15.20-15.55	Martin Bennett (Cambridge) The role of apoptosis in atherosclerosis
15.55-16.15	Tea
16.15-17.00	**Keynote Lecture:Lina Badimon (Barcelona) Plaque thrombogenicity**
17.00-18.00	Poster viewing and wine reception
19.30	Dinner

Friday 22nd April

09.00–10.45	**Session 2: Current Insights in Platelet Biology**
09.00-09.35	Steve Watson (Birmingham) Intracellular signalling pathways in platelets
09.35-10.10	Richard Evans (Leicester) $P2X_1$ receptors, platelets and calcium signalling
10.10-10.45	Johan Heemskerk (Maastricht) Platelets and the procoagulant response
10.45 – 11.15	Coffee
11.15–12.45	**Free communications (6)**
12.45-14.00	Lunch
14.00-16.00	**Session 3: Current clinical perspectives in atherothrombosis**
14.00-14.35	Peter Grant (Leeds) Factors affecting fibrin clot formation
14.35-15.10	Alison Goodall (Leicester) Variability in platelet reactivity
15.10-15.45	Rob Storey (Sheffield) Current and future perspectives for antiplatelet and antithrombotic therapy
15.45-16.30	**Keynote lecture**: **Gordon Lowe (Glasgow) New insights into the epidemiology of atherothrombosis**
16.30	Tea and close of meeting

Cardiovascular Related Meetings

Molecular Biology of Cardiac Diseases and Regeneration (D2) Apr 3 - 8, 2005 Steamboat Springs, Colorado. For further information: Phone: (800) 253-0685 or (970) 262-1230; Fax: (970) 262-1525; info@keystonesymposia.org; Website: http://www.keystonesymposia.org/

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/

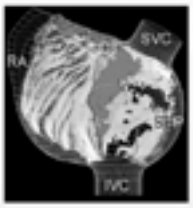
CHANNELS: Trafficking & Biophysics
W. Catterall (USA), I. Cohen (USA), D. Roden (USA), M. Sanguinetti (USA), D. Yue (USA)

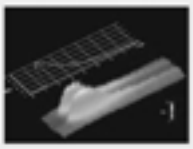
CELL & TISSUE ELECTROPHYSIOLOGY
A. Kleber (Switzerland), D. Paterson (UK), R. Winslow (USA)

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 August 2004

Programme Grants

Prof Q Xu et al, St George's Hospital, London. "Impact of progenitor cells in the pathogenesis of arteriosclerosis" 5 years £993,292

Prof A C Newby et al, Bristol Royal Infirmary. "Mechanisms of neointima formation and role of extracellular proteolysis" 5 years (renewal) £843,592

Special Project Grants

Prof J Scott et al, Imperial College London. "Human genetic variation underlying risk of insulin resistance and type 2 diabetes in Indian Asian and Northern European men" 4 years £1,593,681

Project Grants Committee September 2004

DEFERRED APPLICATIONS AWARDED

Dr M C P Glyn & Dr P Clark, Imperial College London. "Examining the cellular events regulating endothelial cell responses to hypoxia, ischaemia and reperfusion in the heart" (3 years) £175,498

Professor D S Latchman, Institute of Child Health (UCL). "Role of specific serine residues in CBP and p300 in cardiac development and hypertrophy" (3 years) £120,521

NEW APPLICATIONS AWARDED

Dr J Brittenden et al, University of Aberdeen. "A randomised controlled trial of omega-3 fatty acid on platelet and endothelial function in patients with peripheral arterial disease" (2 years) £96,281

Professor A F Dominiczak et al, Western Infirmary, Glasgow. "Functional characterisation of the *Gstm1* deficiency in the stroke prone spontaneously hypertensive rat: *in vitro* and *in vivo* studies" (3 years) £153,686

Ms A J Orrell et al, University of York. "Validation of a brief questionnaire to measure activity levels in people with heart disease" (1 year) £20,240

Professor R C Trembath, University of Leicester. "Investigating the role of SREBP1 in familial partial lipodystrophy using a knock-in mouse model" (3 years) £169,243

Professor H S Markus et al, St George's Hospital Medical School, London. "Investigating cognitive function in hypertension using diffusion tensor imaging" (2 years) £83,820

Professor J Adgey, Royal Victoria Hospital, Belfast. "Identification of posterior AMI with non-diagnostic ECGs using body surface mapping and radionuclide imaging" (2 years) £80,777

Dr R M A Sitsapesan & Dr K Venkateswarlu, University of Bristol. "Role of the cardiac ryanodine receptor carboxyl-terminal tail region in subunit assembly and single-channel function" (3 years) £163,880

Professor M R Bennett, Addenbrooke's Hospital, Cambridge. "Control of human atherosclerotic plaque vascular smooth muscle cell senescence" (3 years) £151,316

Prof L M Machesky & Prof S Watson, University of Birmingham. "Signalling to platelet actin assembly via integrins: the role of Rac, Scar/WAVE and Arp2/3 complex" (3 years) £127,199

Dr J N Townend et al, Queen Elizabeth Hosp, Birmingham. "Is spironolactone safe and effective in the treatment of cardiovascular disease in mild chronic renal failure?" (2 years) £189,622

Prof P J Talmud & Prof S Humphries, University College London. "*In vivo* and *in vitro* studies of Apolipoprotein AV and its relation to other genes in the *APOA5-A4-C3-A1* gene cluster" (3 years) £150,199

Fellowships Committee October 2004

DEFERRED APPLICATIONS AWARDED

Intermediate Research Fellowship

Dr S Wildman, Royal Free Campus - (UCL). "Extracellular ATP, renal P2 receptors and the epithelial sodium channel: implications for renal Na^+ excretion and blood pressure control" (3 years) £153,001

Dr K Bradley, University of Glasgow. "Regulation of the calcium-dependent transcription factor NFAT in native vascular smooth muscle" (3 years) £127,368

NEW APPLICATIONS AWARDED

International Fellowship

Dr J H F Rudd, Addenbrooke's Hospital, Cambridge; Mount Sinai Medical Center, New York. "An evaluation of multi-modality imaging (FDG- PET/CT/ HRMR) to detect and characterise atheroma in the carotid artery thoracic aorta and coronary arteries" (1 year) £45,688

Senior Research Fellowships

Dr D P Francis, Imperial College, London. "Optimisation, regulation and stabilisation of cardiopulmonary physiology in chronic heart failure: maximising current pacemaker therapies, potential for new dynamic therapies" (5 years) £467,223

Dr C M Shanahan Addenbrooke's Hospital, Cambridge. "The role of nesprins in cardiovascular cell function" (5 years) £300,820

Intermediate Research Fellowships

Dr Y Sun, Guy's Hospital, London. "Molecular mechanism of cardiac muscle regulation: role of changes in the conformation of Troponin C in situ" (3 years) £184,079

Junior Research Fellowships

Dr R G Assomull, Royal Brompton Hospital, London. "Accuracy and cost effectiveness of cardiovascular magnetic resonance versus x-ray coronary angiography to determine the aetiology of heart failure" (2 years) £105,345

Dr A J Hogarth, St James's University Hospital, Leeds. "Differences in sympathetic neural activation between men and women following acute myocardial infarction" (2 years) £86,844

Clinical PhD Studentships

Mr M B Will, Glasgow Royal Infirmary. "Generation of cardiomyocytes from mesenchymal stem cells derived from adult human sternal bone marrow" (3 years) £149,478

Dr G E Marshall, Royal Infirmary Glasgow. "Pharmacological remodelling in human atrium: electrophysiological and molecular mechanisms of action potential prolongation by b-adrenoceptor antagonist therapy" (3 years) £136,523

PhD Studentships

Ms H Jundi, University of Wales College of Medicine. "Elucidating ryanodine receptor domain interaction in sudden cardiac death (SCD): towards the development of novel therapeutic strategies" (3 years) £74,418

Unnamed & Dr C L Shovlin Hammersmith Hospital, London. "Identification of a further gene for hereditary haemorrhagic telangiectasia" (3 years) £84,533

Unnamed & Dr D Bates, University of Bristol. "Regulation of angiogenic and anti-angiogenic isoforms of VEGF" (3 years) £75,351

Unnamed & Dr S J Tucker, University of Oxford. "A structural and functional analysis of heteromeric inwardly rectifying (Kir) potassium channels" (3 years) £78,933

Mr A F Catchpole, University of Oxford. "Cardiac inflammation and insulin resistance in the chronically infarcted rat heart" (3 years) £78,273

Travelling Fellowship

Dr A V Vorotnikov, Cardiology Research Center, Moscow. To: Royal Brompton Hospital, London. "Caldesmon control by MAP-kinase" (3 months) £10,160

Cardiovascular Related Wellcome Trust Grants

September to November 2004

Senior Research Fellowships In Clinical Science

Dr Penelope E Stein, Department Of Haematology, Cambridge Institute For Medical Research, University Of Cambridge. Structural Studies Of Non-Inhibitory Serpins. 24 Months £158,990

Dr Paul N Bishop, Wellcome Trust Cent Cell-Matrix Research, School Of Biological Sciences, University Of Manchester. Functional Analysis Of The Anti-Angiogenic Glycoprotien Opticin. 24 Months £381,115

Wellcome - South African Senior Research F'ships

Dr Edward D Sturrock , Department Of Medical Biochemistry, Medical School, University Of Cape Town Observatory South Africa. Angiotensin-Converting Enyme: Crystallographic Studies, Structure-Guided Inhibitor Design, And Ectodomain Shedding. 36 Months £21,108

Wellcome - Indian Senior Research Fellowships

Dr S V Ramanan, Au-Kbc Center For Internet And, Telecom Technologies, MIT Campus, Chennai India. Intercellular Messengers That Couple Intercellular Cascades: From Permeability And Gating Of Gap Junction Channels To A Model Of Coordinated Tissue Response. 48 Months £8,799

Senior Central European Fellowships

Dr Alicja Jozkowicz, Institute Of Molecular Biology, Jagiellonian University, Krakow Poland. Protective Role Of Heme-Oxygenase-1 In Endothelial Cells - Construction Of Helper-Dependent Adenoviral Vectors For A Long-Term Heme Oxygenase Expression. 60 Months £230,810

Research Training Fellowship

Dr Simon T Macdonald, Department Of Cardiology, John Radcliffe Hospital, University Of Oxford. Genetic And Molecular Mechanisms In Coronory Artery Development. 36 Months £192,752

Cardiovascular Research Initiative

Miss Christine Mulford, Molecular Physiology Laboratory, Wilkie Building, University Of Edinburgh Medical School, Scotland. Role Of Two Transcription Factors In Early Heart Patterning. 36 Months £77,451

Miss Linsay Macdonald, Molecular Physiology Laboratory, Wilkie Building, University Of Edinburgh Medical School, Scotland. The Influence Of Glucocorticoid Metabolism On The Vascular Response To Injury. 36 Months £49,877

Miss Katrin Buerger, Molecular Physiology Laboratory, Wilkie Building, University Of Edinburgh Medical School, Scotland. Functional Characterisation Of Mospd3: A Novel Msp Domain Containing Protein Implicated In Right Ventricle Development. 36 Months £90,539

Project Grant

Professor Michael S Marber, Department Of Cardiology, Rayne Institute, Gkt School Of Medicine, King's College London. The Role Of P38 Mitogen-Activated Protein Kinase In Left Ventricular Remodelling. 36 Months £292,063

Professor Chris J Garland, Department Of Pharmacy And Pharmacology, University Of Bath. An Investigation Of The Physiological Mechanisms Regulating Diameter In Mesenteric And Cerebral Small Resistance Arteries. 36 Months £513,963

Dr W Martin, Department Of Pharmacology, Institute Of Biomed And Life Sciences, University Of Glasgow. Flow And Endothelium-Derived Hyperpolarising Factor (Edhf). 36 Months £198,015

Dr Kathleen M Botham, Department Of Veterinary Basic Sciences, Royal Veterinary College, London. Dietary Fats And Atherosclerosis: Role Of Sterol Regulatory Element-Binding Proteins In The Modulation Of Hepatic Very Low Density Lipoprotein Secretion By Dietary Fats Carried In Chylomicron Remnants. 36 Months £180,382

Professor Kevin Moore, Centre For Hepatology, Upper Third Floor, Royal Free And University College School Of Medicine, London. Dynamic Assessment Of Nitration, Chlorination And Bromination Reactions In Vivo. 36 Months £206,410

Dr Yuri V Kotelevtsev, Department Of Biomedical Sciences, University Of Edinburgh, Scotland. Derivation Of Endothelial Progenitor Cell Lines From Differentiating Human Embryonic Stem Cells And Embryonal Tissue Based Stem Cells. 12 Months £49,380

Equipment

Dr Valerie B O'donnell, Department Of Medical Biochemistry, , University Of Wales College Of Medicine, Cardiff Wales. Application For Part-Funding Of Liquid Chomatograph-Tandem Mass Spectrometer (Lc/Ese/Ms/Ms) For Studies On Lipid Signalling In Inflammation. 36 Months £233,090

University Translation Awards

Dr Adrian J Hobbs, Wolfson Institute For Biomedical Research, University College London. Design And Development Of Novel Non-Peptide Agonists At The Natriuretic Peptide Receptor-C And Evaluation Of Therapeutic Potential For Cardiovascular Disease. 12 Months £50,000

PhD Studentships

Mr Francisco C Villafuerte, University Laboratory Of Physiology, University Of Oxford. Effects Of Intracellular Ph On Calcium Signalling In Mammalian Myocytes. 36 Months £68,089

Miss Winifred Idigo, Department Of Cardiovascular Medicine, John Radcliffe Hospital, University Of Oxford. Interaction Of Reactive Oxygen Species With Ion Transport Mechanisms In The Chronically Infarcted Myocardium Of nNOS Mice. 36 Months £124,161

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

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

BSCR Spring Meeting 2005

Emerging Concepts in Atherothrombosis

Dates: Thursday 21st and Friday 22nd April, 2005

Venue: Stamford Hall, University of Leicester, Leicester.

Organisers: Professor Nilesh J Samani and Professor Alison H Goodall

Objectives: Atherothrombosis is the underlying mechanism for the majority of clinical cardiovascular events. There is increasing evidence that factors in both the vessel wall and the blood contribute to atherothrombotic risk. This symposium will cover current and emerging concepts regarding the molecular, cellular and genetic mechanisms that underlie atherothrombosis and their potential impact on future therapeutic strategies.

Programme: The programme will consist of state-of-the-art presentations by leaders in the field. Part of the meeting will be devoted to oral presentation of selected abstracts and poster presentations. Prizes will be awarded for the best oral and best poster presentations given by young investigators.

Travel & Accommodation: Stamford Hall is located about 2 miles from the Centre of Leicester and the train station, and is easily accessible by bus or taxi. Accommodation will be available at the Hall or in hotels nearby (if required). Logistics for the meeting will be handled by Fiona Legate, Millbrook Medical [fionalegate@millbrookconferences.co.uk]

Registration (excluding accommodation): Free to BSCR members, £40 for non-members.

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

A full programme, the abstract pro-forma, meeting registration / accommodation forms and forms for application for student bursaries are available for downloading from the BSCR website (www.bcs.com/affiliates/bscr.html).

Deadline for submission of abstracts, registration and application for student bursaries: 28th February, 2005.

Further enquiries: Enquiries about the programme should be directed to Professor Nilesh Samani, Cardiology Group, Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences Wing, Glenfield Hospital, Groby Road, Leicester, LE3 9QP, Leicester. Tel: 0116 2563021; Fax: 0116 2875792;
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Enquiries about registration and accommodation should be directed to Fiona Legate, Millbrook Conferences Ltd, Suite 13, Devonshire House, Bank Street, Lutterworth, Leicestershire LE17 4AG. Tel: 01455 552559; Fax: 01455 550098;
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