The Bulletin

of

The British Society for Cardiovascular Research

Registered Charity Number: 1011141

Vol. 16 No. 4

October 2003

www.bcs.com/affiliates/bscr.html

The BSCR is sponsored by

The Bulletin

The Publication of The British Society for Cardiovascular Research

Contents

Editorial

Welcome to the October 2003 issue of *The* Bulletin!

This issue includes a review article, written by Dr Sarah Calaghan of the School of Biomedical Sciences, University of Leeds. Dr Calaghan provides a comprehensive update of recent resaerch in the field of cardiac mechanotransduction.

Great news for student members! We would like to draw your attention to the notice on page 10 regarding free membership for student members. This is discussed, along with other society news, in the Secretary's Column by Professor Barbara McDermott.

Following another successful meeting of the society in Edinburgh, we can begin to look forward to next year's Spring meeting, to be held in Manchester. The organisers, Professor David Eisner and Dr. Cathy Holt 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. We are very grateful to Victoria Hodges for providing us with the BHF grant details over the past year. Victoria has recently left the fund and we wish her every success.

Helen Maddock and Nicola Smart

Mechanotransduction in the heart: Myofilaments and membrane proteins

Dr. Sarah Calaghan

School of Biomedical Sciences, University of Leeds, LS2 9JT, UK

Mechanotransduction describes the process by which mechanical stimuli are transformed to produce a cellular response. In the heart this is a vital process that allows the heart to respond to the demands of the circulation. For example, when ventricular filling is increased during exercise, the ventricles are dilated and the myocardium is stretched. This stretch of cardiac muscle leads to an increase in the force and rate of contraction of the heart, and enhanced cardiac output to meet raised metabolic requirements. However, in other circumstances, myocardial stretch can have negative consequences, and lead to potentially fatal changes in cardiac rhythm, or to cardiac hypertrophy which is a precursor to heart failure.

An interesting question is how stretch of cardiac muscle is translated into changes in force, rhythm, or protein expression within the heart. For this to occur there must be a pathway that allows the sensing, and the transduction, of the mechanical stimulus. This review does not aim to provide an exhaustive list of the mechanotransducing elements of the cardiac cell. Rather it will focus on the role of the myofilaments and selected membrane proteins in mechanotransduction, with particular regard to the effect of stretch on changes in the rate and force of contraction.

The myofilaments

Perhaps the most famous response of the myocardium to mechanical stimulation was first reported by Frank and Starling a century ago, who described how the output of the heart is equal to, and determined by, the amount of blood flowing into the heart. In essence, this means that stretch of the myocardium causes an immediate increase in its contractility. Since these early experiments it has been shown that the same rapid increase in contraction is seen upon stretch of isolated cardiac muscle, and even in the single cardiac myocyte (see **Figure 1**).

It is now known that the mechanotransductive elements that underlie the Frank-Starling response reside within the sarcomere, the basic contractile unit of the cardiac cell (see **Figure 2**). The increase in contractility, or active force, seen upon stretch is related to the change in the length of the individual sarcomeres, measured from Z-line to Z-line, within the myocyte. As muscle is stretched from resting length to the length at which maximum tension is generated, the degree of overlap between the thick myosin and thin actin filaments changes (see Gordon et al., 1966) and this increases the opportunity for force-producing actomyosin crossbridges to form. However, in cardiac muscle this change in myofilament overlap has been estimated to account for only 40% of the increase in force seen upon stretch (Kentish & Wrzosek, 1998). The main contribution to the Frank-Starling mechanism actually comes from changes in the activation of cardiac muscle, which has been shown to be due to a length-dependent increase in the sensitivity of the myofilaments to Ca^{2+} (Allen & Kurihara, 1982; Hibberd & Jewell, 1982).

So what is the sarcomeric component responsible for translating changes in muscle length to changes in myofilament Ca^{2+} sensitivity? The thin filament binding protein troponin C (TnC) has been suggested for this role. The affinity of TnC for Ca^{2+} is one way that myofilament sensitivity can be modulated, and it has been shown in bovine ventricular muscle that the binding of Ca^{2+} to TnC increases at longer sarcomere lengths (Hofmann & Fuchs, 1987). It has been suggested that the Ca^{2+} affinity of TnC may be determined by cross-bridge interactions (rather than muscle length; Hofmann & Fuchs, 1987). One idea that has been put forward is that a unique domain of the cardiac isoform of TnC possesses length-sensing properties (Babu et al., 1990), however, work in which a skeletal muscle isoform of TnC was expressed in the hearts of transgenic mice has questioned this hypothesis (McDonald et al., 1995). Furthermore, the idea that changes in TnC affinity are

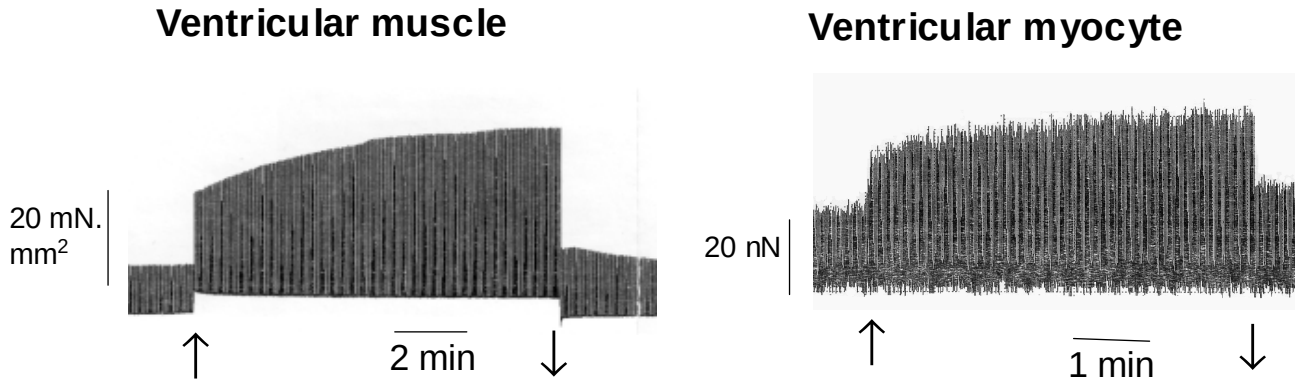

Figure 1. The biphasic increase in contractility seen upon stretch of cardiac muscle and the single ventricular myocyte. In muscle and myocytes (as in the intact heart), there is an immediate increase in force upon stretch (the Frank-Starling mechanism) which is followed by a further secondary increase in force which takes place over several minutes (the slow response). Rat papillary muscle was stretched from 88 to 98% of the length at which maximum tension is generated at - and released 10 min later. Rat ventricular myocytes were stretched using a pair of carbon fibres from a resting sarcomere length of 1.85 μm to 2.0 μm at - and released 5 min later (the trace is recorded through a sample-and-hold circuit so that changes in active force, but not resting force, are seen upon stretch).

the central player in length-dependent activation of cardiac muscle is not certain, as length dependence occurs even in the absence of Ca^{2+}, for example when muscle is activated by reducing [ATP] (Kajiwara et al., 2000).

In more recent years, the search for the mechanosensing element of the sarcomere has moved from the thin filament binding protein TnC to focus on the giant protein titin. Like TnC, titin binds to the thin filament (in this case at the Z-line), but its primary structural role is to link the thick filament and Z-line (see Figure 2). A role for titin in mechanotransduction is suggested by studies which have shown that digestion of titin from skinned muscle or cardiac myocytes reduces the stretch-dependent increase in myofilament sensitivity (Cazorla et al., 1999; Fukuda et al., 2001). There are two ways in which titin may alter myofilament Ca^{2+} sensitivity, and therefore force, upon stretch. The first of these concerns the spacing between the myofilaments. The closer the actin and myosin head are, the more likely a force-generating cross bridge is to form. It has been argued that titin exerts a radial stress that brings the myofilaments closer together as sarcomere length is increased. This is one way in which titin could translate changes in length into changes in force, although it should be borne in mind that the relevance of stretch-induced changes in interfilament spacing has been questioned (Konhilas et al., 2002). An alternative way in which titin could facilitate the Frank-Starling mechanism is by regulating thick filament structure and myosin crossbridge arrangement. Titin may increase the disorder of myosin heads within the thick filament which, in turn, increases the probability of actin and myosin interacting (Moss & Fitzsimons, 2002; Cazorla et al., 2001; Fukuda et al., 2001). Interestingly, in heart failure, titin expression is down-regulated (Morano et al., 1994), and this may limit the way in which the failing heart can improve its contractile performance.

Sarcolemmal channels and exchangers

When cardiac cells are stretched, not only is there a change in length of the sarcomeres, the cell membrane will also be subject to stresses. Large proteins, such as ion channels and exchangers, which are located within the sarcolemma will be subjected to these stresses (directly or indirectly) and if this changes their conformation, and thereby function, they are likely candidates for cardiac mechanotransducers.

Stretch-activated channels

In 1915, Bainbridge first described how an increase in filling (or stretch) of the right atrium causes an increase in heart rate. Although the 'Bainbridge effect' may, to some extent, be ascribed to autonomic influences, it is now clear that at least part of the mechanism responsible for the increase in heart rate upon stretch is intrinsic to the cardiac myocyte (Cooper

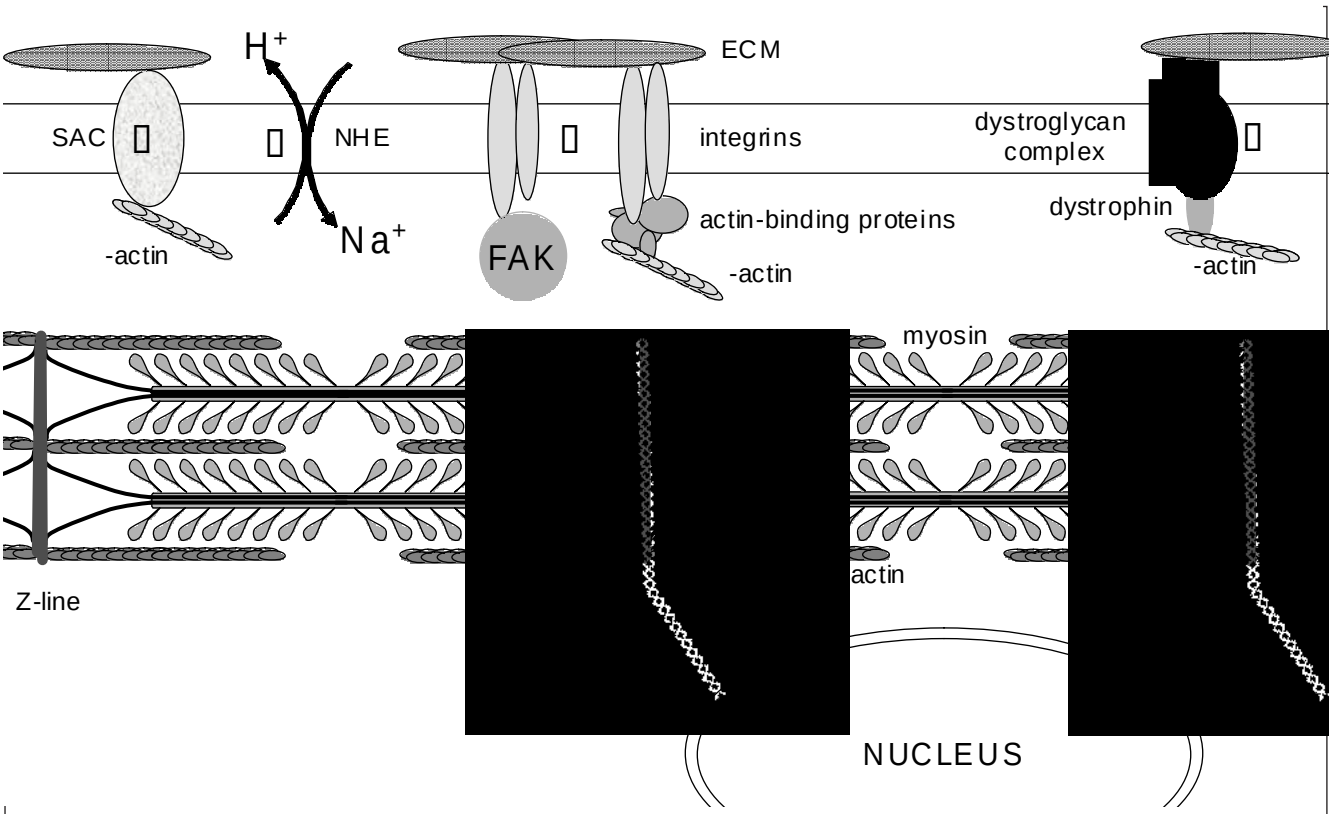

Figure 2. A simple schematic representation of some of the mechanotransducers within the cardiac cell. Some mechanotransduction appears to take place within the sarcomere; other relies on membrane-bound proteins. Evidence highlights the giant protein titin (1), which tethers the myosin filament to the Z-line, as a likely mechanotransducer for the Frank-Starling response. The sarcolemmal non-selective cationic stretch-activated channel (SAC; 2) has been linked with both changes in rate and force of contraction following stretch of cardiac muscle. The activity of membrane-bound exchangers such as the Na^+/H^+ exchanger (NHE; 3) has also been shown to be modulated by stretch. The membrane-spanning extracellular matrix (ECM) receptors are the integrins (4) and dystroglycan (5) complex, but of these it is the integrins which appear to form part of the major mechanotransductive pathway in the heart. Integrins turn on signalling pathways via focal adhesion kinase (FAK) and also by their interaction with components of the cytoskeleton such as γ-actin.

et al., 2000). This is an example of mechanoelectric feedback (MEF; Lab, 1996), the process by which changes in mechanical activity influence the electrical activity of the heart. Opening of stretch-activated channels (SACs) is a popular mechanism to explain how mechanical stimuli are transduced into changes in electrical activity. There are several types of stretch-sensitive channels in the heart, one of the most common is the non-selective cationic SAC which has a reversal potential between 0 and –30 mV. It has been shown that axial stretch of sino-atrial node cells increases the rate of spontaneous beating, associated with a decrease in the maximum diastolic and systolic membrane potentials (Cooper et al., 2000). This is consistent with activation of a non-selective cationic current I_{ns}. However, I_{ns} also has the potential to cause cardiac arrhythmia as a result of diastolic depolarisation, and shortening of early repolarisation and lengthening of the later phases of repolarisation of the action potential (Franz & Bode, 2003). Diastolic depolarisation and early after-depolarisations may trigger spontaneous activity. Changes in action potential duration, refractory period and excitability can produce re-entrant arrhythmias (Lab, 1996). There is evidence to support the involvement of SACs in the generation of arrhythmia in both the atria and ventricle (Hansen et al., 1991; Franz & Bode, 2003).

SACs have not only been assigned a role in chronotropy; they also appear to be important for length-dependent changes in force. When cardiac muscle is stretched the force of contraction increases immediately (the Frank-Starling mechanism, as described above). However, there is a further secondary increase in force which takes place over

several minutes following stretch. This slow response is seen in the intact heart (Tucci et al., 1984), and also in isolated muscle and the single ventricular myocyte (see **Figure 1**). Unlike the Frank-Starling mechanism, the slow response is associated with an increase in intracellular $[Ca^{2+}]_i$ ($[Ca^{2+}]_i$) and although several mechanisms have been suggested to explain this, no consensus has been reached (see Calaghan et al., 2003a for a recent review). It has been suggested that SACs may be important for this mechanically induced increase in $[Ca^{2+}]_i$ (Lab, 1996). Indeed we have recently shown the first direct evidence of this in the ventricle. Streptomycin, which selectively blocks stretch-activated currents (Belus & White, 2003), significantly attenuates the slow response to stretch in rat ventricular myocytes (Calaghan & White, 2002). In support of a role for the SAC in the slow response to stretch, Tavi et al. (1998) have mimicked the biphasic increase in force in a model of stretched rat atrial muscle with an increase in TnC Ca^{2+} affinity, and entry of Ca^{2+} through non-selective cationic SACs.

Na^+/H^+ exchanger

Another sarcolemmal protein which has been shown to be important for the slow inotropic response to cardiac stretch is the Na^+/H^+ exchanger (NHE). Inhibitors of NHE reduce the magnitude of the slow response in cardiac muscle from several species (Alvarez et al., 1999; Perez et al., 2001; von Lewinski et al., 2003). From studies using rat and feline ventricular muscle, it has been proposed that it is endothelin 1 released upon stretch that is responsible for increased NHE activity (Alvarez et al., 1999; Perez et al., 2001). However, more recent work in the rabbit has suggested that stretch may have a more direct effect on NHE function (von Lewinski et al., 2003). The mechanism by which stretch could modulate NHE activity is not known. It is possible that bilayer deformation associated with stretch could directly affect exchanger function, or this may be mediated through its interaction with accessory proteins, the cytoskeleton, or through phosphorylation of its regulatory C-terminal domain (Goss et al., 1994; Hayashi et al., 2002).

Integrins

Aside from ion channels and exchangers, there are other sarcolemmal proteins that play a pivotal role in cardiac mechanotransduction. These are the membrane spanning extracellular matrix (ECM) receptors. There are two main ECM receptors in the cardiac cell; integrins, and dystroglycan (see Figure 2). Through its links with dystrophin, actin, and the Z-line it appears that the primary role of the dystroglycan complex is in stabilisation of the sarcolemma and lateral force transmission (Kaprielian & Severs, 2000; McNally et al., 2003). Of the ECM receptors it is the integrins that play an important role in mechanotransduction in the heart.

Membrane spanning integrins are heterodimers of α and β integrin, which bind to components of the ECM (laminin, fibronectin, collagen) which sheath the cardiac myocyte. They are concentrated in specialised regions of the sarcolemma at or near the Z-line (Borg et al., 2000). Integrins do not have enzymatic activity of their own. Instead their short cytoplasmic tails transduce signals by associating with other proteins such as tyrosine kinases, G proteins and components of the cytoskeleton (see reviews by Borg et al., 2000; Ross & Borg, 2001). In this sense, integrins may be seen more as *part* of a mechanotransductive pathway than mechanotransducers in their own right.

There appear to be two ways in which mechanotransduction can occur via integrins. A mechanical stimulus may be transduced into a chemical signal via integrin-activation of intracellular signalling pathways. The association of integrins with components of the ECM causes clustering of integrins in the cell membrane, which results in activation and autophosphorylation of focal adhesion kinase (FAK), a nonreceptor protein tyrosine kinase. The continuing phosphorylation of FAK creates docking sites to which other kinases can bind (Schlaepfer et al., 1994). Many signalling pathways have been shown to be activated by the ECM-integrin axis: Tyrosine kinases; Ser and Thr kinases; phosphatidyl inositol metabolism; the NHE (Samuel et al.,2000; Simpson et al., 1998; Cybulsky et al., 1990; Ingber et al., 1991). For example, stretch of single cardiac myocytes encased within an agarose gel has been shown to activate nitric oxide signalling, leading to an increase in Ca^{2+} spark frequency and the global $[Ca^{2+}]_i$ transient (Vila-Petroff et al., 2001). The enzyme phosphatidyl inositol-3-OH kinase has been shown to be important in the stimulation of endothelial nitric oxide synthase following stretch, and phosphatidyl inositol-3-OH kinase has been shown to associate with FAK only minutes after induction of pressure-overload in the intact rat heart (Franchini et al., 2000).

Integrins may also work as part of a mechanotransductive pathway in the heart by forming physical links with components of the cardiac cell

cytoskeleton (see the review by White et al., 1998 in *The* Bulletin of the BSCR). The actin cytoskeleton appears to be the major player in this, as it is actin binding proteins, such as vinculin, talin and α-actinin, that associate with integrins on the inner surface of the sarcolemma (Borg et al., 2000; Samuel et al., 2000). Interestingly, however, although the actin cytoskeleton is well visualised in the neonatal cardiac cell, there is little direct information on its structure in the adult cardiac cell (see Calaghan et al., 2003b for a recent review). Pulling on surface integrin receptors has been shown to trigger cytoskeletal organisation in endothelial cells (Maniotis et al., 1997). Propogation of mechanical force through the cytoskeleton may be sensed by signalling molecules which are anchored to the cytoskeleton, changing their molecular conformation and thereby activity (Shafrir & Forgacs, 2002). Autophosphorylation of FAK may also promote association of cytoskeletal elements with the focal adhesion complex (Schlaepfer et al., 1994).

Pathophysiologically, integrin activation of intracellular signalling pathways has been implicated in the development of cardiac hypertrophy. For example, in neonatal myocytes, the ECM-integrin axis has been shown to be vital for the hypertrophic response to mechanical stretch (Ruwhof & van der Laarse, 2000), providing an example of how a mechanical stimulus may be transduced into a change in gene expression and protein synthesis in the heart.

Conclusions

It is clear that there are many elements of the cardiac cell that may be involved in the process of mechanotransduction. This review has compartmentalised these elements into sarcomeric proteins, membrane bound channels and exchangers, and the membrane spanning ECM receptors. However this somewhat simplistic approach does not give credit to the potential complexity of the mechanotransductive process. For example, SACs and NHE function may be controlled by tethered cytoskeletal components (Isenberg et al., 2003; Goss et al., 1994), and anchoring of SACs to the ECM has been suggested (Liu et al., 1996). Furthermore, there are myriad cytoskeletal links between the myofilaments and the sarcolemma of the cardiac cell which may be important not only in lateral force transmission from cell to cell, but also in mechanotransduction.

Acknowlegements

My work is sponsored by the British Heart Foundation. Thanks to Tim Lee for help with preparation of Figure 2.

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Dr Sarah Calaghan is a Senior Research Fellow in the laboratory of Dr. Ed White at the School of Biomedical Sciences, University of Leeds

E-mail: s.c.calaghan@leeds.ac.uk

**** 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

Edinburgh is always a lovely place to visit and particularly so in early autumn, when the evening sun reflects so well the glory of the magnificent granite buildings. It was such a scene when we made our way to the BSCR dinner held at the National Trust for Scotland, the social highlight of what was a very valuable joint meeting with the Scottish Cardiovascular Forum organized by Gillian Gray and colleagues. The meeting also provided the opportunity of taking forward the business of the BSCR, firstly with a meeting of the Committee and then later, the AGM.

Undoubtedly the most interesting discussion at the Committee meeting focused on the question, 'Are the strengths of the Society being exploited optimally'? Yes, we do know that the BSCR has a broad specialty base covering research interests in the heart and vasculature, and provides a forum for in depth examination of specific themes with state-of-the-art contributions by prominent researchers, all this being set in an environment to foster the participation of more junior scientists. It is evident, however, that the younger people are not taking full advantage of what is on offer, since the numbers attending are less than might be expected and there is no great demand for the bursary scheme. It might be hoped that postgraduate students would attend meetings outside their own specific research topic, in order to pursue a more comprehensive grounding in cardiovascular science. It has been decided, therefore, that to foster greater involvement in the Society, the membership fee for postgraduate students will be waived. It should be noted also that there is no limit on the number of bursaries for which students can apply during their postgraduate training and most applications will be successful, although preference will be given to those who intend to present their research. A letter from the Chairman giving further details of this initiative is included here as an insert.

At the AGM, the Chairman reported on a previous also highly successful meeting which took place during 2002/3, in Glasgow, and gave notice of future main meetings to be held in Manchester (Spring 2004) and London (Autumn 2004). A total of nine travel bursaries were awarded for attendance at the Glasgow or Edinburgh meetings, and the Chairman reflected on the Committee enterprise to encourage greater student participation as above. A BSCR symposium on 'Ion channels and cardiac arrhythmias' was held at the 2003 BCS meeting in Glasgow and one is scheduled for the Manchester meeting in May 2004. Finally, the continued sponsorship from Aventis was highlighted as a significant contribution to the strength of the Society, along with the support given for invited speakers by the British Cardiac Society and the National Heart Research Fund. This was taken up in the Treasurer's report, which showed the total reserves to be in good shape, largely as a result of the core sponsorship and also contributions raised by meeting organizers from major charities and commercial companies. The Secretary's report concerned mostly a consideration of the current committee membership. There would be no retirements at the end of 2003, but a maximum of six replacements would be needed to take up office in January 2005. As such, there would be a call for nominations in April of next year.

There is an exciting and broadly appealing scientific programme planned for 2004. The next BSCR main meeting will be held for the first time at the University of Manchester. It is being organized by Professor David Eisner and Dr Cathy Holt on 1-2 April 2004 on the subject of 'Frontiers in cardiovascular signalling'. This meeting is advertised on the back cover and further details are given in the programme printed in this issue. The Autumn meeting 2004 is scheduled for 9-10 September and marks a return to a London venue after more than three years 'out of town'. This is being organized by Professor Ajay Shah, who plans to focus on 'Integrative cardiovascular physiology in gene-modified models'. Professor Shah is also organizing the next BSCR – BCS Symposium, at the end of May 2004 in Manchester, on the theme 'Repairing the broken heart – the promise of stem cells'. Ideas for events for 2005 are developing well, but more of that in the next issue . . .

Barbara McDermott

BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

SPRING 2004 MEETING

"Frontiers in Cardiovascular Signalling"

1st and 2nd April, 2004

Manchester University, Hulme Hall

Organising Committee: David Eisner and Cathy Holt, University of Manchester

Thursday 1st April

1.00 – 2.00 Registration and Lunch

2.00 – 2. 05 Welcome

Keynote lecture

2.05 – 2.50	**EDHF & Vascular Function**	Arthur Weston (*Manchester)*
2.50 – 5.00	**Session 1: Calcium**	
	Chair : Susan Wray	
2.50	Localised Ca fluxes in cardiac myocytes	Clive Orchard (*Leeds*)
3.15	Ca signalling in vascular smooth muscle	Ted Burdyga (*Liverpool*)
3.40 – 4.10	Coffee/Tea	
4.10	Mitochondria and cardiac muscle	Michael Duchen (*London*)
4.35	**Mitochondria & Ca in vascular smooth muscle**	Tomoko Kamishima (*Liverpool*)

5.00 – 5.45 **British Cardiac Society Lecture**

Calcium signalling in the heart: basic mechanisms to heart failure
W J Lederer *(Baltimore, USA*)

5.45 – 7.00 **Poster Session** (wine reception)

7.30	Dinner	
9.00	Postprandial reflections on signalling	Austin Elliot *(Manchester*)

Friday 2nd April

9.00 – 10.40	**Session 2: Phosphorylation Signalling Pathways** Chair: Cathy Holt	
9.00	G proteins in cardiac myocytes	Angela Clerk (*London*)
9.25	Ras signalling in cardiac myocytes	Chris Proud (*Dundee*)
9.50	NFkB in vascular cells	Robin Plevin (*Glasgow]*
10.15	SAPKs in small arteries	Jaqui Ohanian (*Manchester*)
10.40 – 11.10	Coffee/Tea	
11.10 – 12.10	**Selected Abstracts** Chair: Stephen O'Neill	
12.10 – 12.55	**National Heart Research Fund Lecture** **Targeting signalling for restenosis** Robert Wilensky *(Philadelphia,USA)*	
12.55 – 2.00	Lunch	
2.00 – 4.30	**Session 3: Signalling out-of-control** **Chair: David Eisner**	
2.00	Ca signalling in heart failure	Andrew Trafford *(Manchester)*
2.25	MAPKs in ishaemia-reperfusion	Michael Marber *(London)*
2.50	**Smooth muscle signalling in atherosclerosis**	Quingbo Xu (*London*)
3.15 – 3.45	Coffee/Tea	
3.45 – 4.30	**Keynote Lecture** NO in heart failure	Jean Luc Ballingand *(Belgium)*
4.30 – 4.45	**Abstract Prizes and Meeting Close**	

BRITISH HEART FOUNDATION GRANTS

CHAIRS AND PROGRAMME GRANTS COMMITTEE FEBRUARY 2003

Programme Grants

Prof PJ Kemp & Prof C S Peers, University of Leeds. "Hypoxic remodelling of ion channels in cardiorespiratory disease: a functional proteomics approach". £567,587

CHAIRS AND PROGRAMME GRANTS COMMITTEE MAY 2003

Programme Grants

Prof A P Halestrap et al., University of Bristol. "Mitochondria in the life and death of the heart - from molecule to man" 5 years. £670,712

Prof A J Williams, Imperial College London. "Structures and mechanisms involved in cation translocation and discrimination in the cardiac sarcoplasmic reticulum Ca2+-release channel" 5 years (renewal). £798,039

Prof P J Grant et al., Leeds General Infirmary. "Molecular analysis of factor XIII/fibrinogen interactions in the regulation of fibrin assembly" 3 years. £240,122

Basic Science Lectureships

Dr A Kitmitto, University of Manchester. "Structural and functional studies of ion channels in cardiovascular disease" 5 years (renewal) £272,262

Dr D S Gardner, University of Nottingham. "Fetal programming of blood pressure control: The effects of nutritional manipulation during fetal and/or postnatal development in the sheep on the dynamics of cardiovascular control" 5 years. £245,475

PROJECT GRANTS COMMITTEE MARCH 2003

DEFERRED APPLICATIONS AWARDED

Dr P J Kemp & Professor C S Peers , University of Leeds. "The molecular basis of ion channel modulation by hypoxia: a study of recombinant and native human K^+ channels" (3 years). £154,707

Professor B Henderson et al, Eastman Dental Institute, London. "Circulating human chaperonins and susceptibility to coronary heart disease: is there a relationship between psychological and cellular stress?" (3 years). £201,111

Dr G F Baxter, The Royal Veterinary College, London. "Elucidation of autocrine and paracrine roles of adrenomedullin in myocardial infarction" (3 years). £133,922

Dr AH Baker et al,University of Glasgow. "Development of a novel adenovirus-based, targetable vector for selective in vivo gene delivery" (2 years). £99,152

Dr D R Greaves & Prof S Gordon, University of Oxford. "Transcriptional regulation of the gene encoding the CC chemokine MDC/CCL22" (2 years). £102,175

NEW APPLICATIONS AWARDED

Mr M Caputo et al, Bristol Royal Infirmary. "Effects of epidural anaesthesia on inflammatory and stress responses, and clinical outcomes in patients undergoing off pump coronary surgery: a prospective randomised trial" (2 years). £110,529

Dr S C Langley-Evans, University of Nottingham. "Fetal undernutrition, lifespan and mechanisms of ageing" (3 years).£120,738

Dr G C Brown, University of Cambridge. "Nitric oxide and S-nitrosothiols actions on mitochondria in heart ischaemia" (3 years). £151,933

Dr T L Shaw et al, University College London. "Frequency and molecular characterisation of desmosomal gene mutations in families with arrythmogenic right ventricular cardiomyopathy" (3 years). £135,434

Professor W J McKenna, University College London. "Sarcomere protein gene mutations in familial dilated cardiomyopathy" (1 year). £111,211

Dr F Lyall, University of Glasgow. "The placental hemeoxygenase/carbon monoxide system in normal pregnancy, pre-eclampsia and fetal growth restriction" (3 years). £142,716

Professor F A Lai & Dr L M Blayney, University of Wales College of Med, Cardiff. "Mechanism of intrinsic association of the human cardiac ryanodine receptor" (2 years). £110,798

Prof P N Baker & Professor S Gaskell, St Mary's Hospital, Manchester. "The characterisation of the vasoactive circulating factor(s) in pre- eclampsia" (2 years). £103,995

Dr A E Munsterberg et al, University of East Anglia. "The molecular mechanisms controlling cardiac precursor cell movements in chick embryos" (3 years). £123,711

Professor A J Williams, NHLI, London. "Elucidation of the mechanisms governing ryanodine binding and modified function of cardiac SR Ca^{2+}-release channels" (3 years). £125,687

Dr T Burdyga et al, University of Liverpool."Ca^{2+} signals in the smooth muscle and endothelial cells of in *in situ* terminal arterioles" (3 years). £128,657

Dr K J Linton et al, Hammersmith Hospital, London. "Structure and function analysis of the fatty acid translocase CD36" (3 years). £173,586

Dr M J Rayner et al, University of Oxford. "Environment and physical activity study" (1 year 8 months). £74,893

Mr D P Taggart & Prof A Galione, John Radcliffe Hospital, Oxford. "An investigation of 'novel' intracellular and extracellular calcium antagonists to prevent radial artery vasospasm in CABG" (2 years). £75,834

Professor R F Heller et al, University of Manchester. "The population impact of cardiovascular interventions" (2 years). £89,390

Professor N Chaturvedi et al, St Mary's Hospital, London. "Cardiovascular morbidity and mortality in an ethnically diverse cohort" (1 year). £36,165

Prof M S Gautel & Prof E Solomon, Guy's Hospital, London. "Characterisation of NBR1, a novel link of titin to stress-related signalling in a muscle" (3 years). £171,963

Dr I B Wilkinson et al, Addenbrooke's Hospital, Cambridge. "Do phenotypic and haemodynamic differences in cardiac output and arterial stiffness predict the development of hypertension?" (3 years). £144,686

Dr M F Scully & Dr X Lu et al, Thrombosis Research Institute, London. "Structural and functional analysis of the zinc binding site of factor IXa" (2 years). £88,024

PROJECT GRANTS COMMITTEE MAY 2003

DEFERRED APPLICATIONS AWARDED

Professor D J Paterson & Dr S Golding, University of Oxford. "Use of gene transfer to modulate cardiac vagal function in pathophysiological states" (3 years). £168,152

NEW APPLICATIONS AWARDED

Professor M Avkiran et al, St Thomas' Hospital, London. "Phosphorylation of cardiac troponin I by protein kinase D: a novel regulatory pathway in myofilament contraction?" (3 years). £170,702

Dr M J Curtis & Professor D J Hearse, St Thomas' Hospital, London. "Neutrophils: mediators of ventricular arrhythmias during evolving infarction?" (1 year). £44,243

Professor R E Collins et al, Radcliffe Infirmary, Oxford. "Long-term efficacy and safety in the MRC/BHF heart protection study of cholesterol-lowering therapy and antioxidant vitamin supplementation" (3 years). £233,316

Dr I C Wood & Professor D J Beech, University of Leeds. "Repressor element-1 silencing transcription factor (REST) in blood vessels" (1 year 5 months). £60,150

Professor J R Cockcroft et al, University of Wales College of Med, Cardiff . "Arterial stiffness and cardiovascular risk prediction, association with risk factors in a well described Welsh population" (2 years). £183,171

Professor J M Marshall, University of Birmingham. "Factors underlying changes in the vasoconstrictor effects of muscle sympathetic nerve activity in acute and chronic systemic hypoxia" (1 year). £35,009

Dr S V Smirnov & Dr K A Dora, University of Bath. "Chronic hypoxia-induced changes in mechanisms controlling calcium homeostasis in rat pulmonary arterial smooth muscle" (3 years). £120,464

Professor A D Struthers et al, Ninewells Hospital Med Sch, Dundee. "Mechanistic insights and therapeutic opportunities arising from allopurinol improving endothelial dysfunction" (2.5 years). £173,194

Dr C M Moran et al, University of Edinburgh. "Optimisation of a targeted antibody-linked microbubble for ultrasonic imaging of arterial plaque" (2 years). £175,680

Dr L H Clapp, University College London. "Molecular and biophysical properties of inward rectifier potassium channels in human pulmonary artery and their modulation by growth: role of Kir2.4" (3 years). £133,507

Dr S Nourshargh, Hammersmith Hospital, London. "Role of $\alpha 6\beta 1$ in monocyte transmigration in vivo: regulation of expression by PECAM-1 (CD31) and ICAM-2 (CD102)" (3 years). £168,785

Dr G F Clunn & Prof A D Hughes, St Mary's Hospital, London. "Control of the p38 stress response pathway in human vascular smooth muscle cells" (2 years). £107,437

Dr A M Evans, University of St Andrews. "Mechanisms of vasodilation by cyclic adenosine diphosphate-ribose" (3 years) £117,262

Professor R K Patient, University of Nottingham. "Establishing the transcriptional regulatory network controlling development of the myocardium" (3 years). £189,304

Professor H S Markus et al, St George's Hospital Medical School, London. "Evaluation of GSNO as a novel treatment to reduce thromboembolism in man" (3 years). £137,573

Dr A Philpott, Addenbrooke's Hospital, Cambridge. "Division versus differentiation in the embryonic heart:

the role of CDK inhibitors" (3 years). £145,804

Dr K S Authi, Guy's Hospital, London. "Expression and role of TRPC proteins in human platelets and related cells" (2 years). £124,675

Professor H S Markus et al, St George's Hospital Medical School, London. "Inherited inflammatory responses and environmental interactions in the pathogenesis of carotid atherosclerosis: a prospective evaluation in 2 independent populations" (2 years). £128,363

Dr G A Gray et al, University of Edinburgh. "Elafin overexpression and myocardial protection" (1 year). £46,400

PROJECT GRANTS COMMITTEE JULY 2003

DEFERRED APPLICATIONS AWARDED

Dr J C Oldroyd et al, University of Manchester. "Do maternal glycaemic status, diet and growth from birth to 2 years influence coronary risk factors in Pakistani and European infants?" (3 years). £203,256

Dr A F James et al., University of Bristol. "Atrial electrical remodelling in spontaneously hypertensive rats" (2 years) £134,390

Dr D Birchall et al., Newcastle General Hospital. "Computer modelling of haemodynamic patterns in the atherosclerotic carotid artery using computational flow dynamic technology" (1 year). £58,713

Dr P C Hindmarsh et al., Middlesex Hospital, London. "Effects of intrauterine and postnatal growth on blood pressure in childhood" (3 years). £289,933

NEW APPLICATIONS AWARDED

Dr P G Browning, The Cardiothoracic Centre, Liverpool. "The acute effects of testosterone on human vascular tissue and the significance of in situ conversion to oestrogen via aromatase" (3 years). £96,065

Dr N A Turner & Dr K E Porter, University of Leeds. "Identification of autocrine growth factors required for beta- adrenergic receptor-mediated proliferation of human cardiac fibroblasts" (2 years). £87,017

Dr R J MacAllister et al, University College London. "Inflammation-induced endothelial dysfunction in humans; role of COX isoforms" (1.5 years). £60,757

Dr D R Poyner, Aston University. "Photoaffinity probes for CGRP and adrenomedullin receptors" (3 years). £120,420

Dr R J Pease et al, Leeds General Infirmary. "Is factor XIIIA actively secreted from haemopoietic cells?" (3 years). £131,594

Dr B J Wojciak-Stothard et al, University College London. "Role of Rho GTPases in the remodeling of pulmonary artery endothelial cells in response to hypoxia and shear stress" (2 years). £174,107

Dr M Wheatley & Dr G E Rainger, University of Birmingham. "Regulation of human vascular smooth muscle cells by oxytocin receptors" (3 years). £139,794

Professor D A Eisner et al, University of Manchester. "What produces stability and alternans of the systolic calcium transient?" (3 years). £135,010

Professor Sir P J Lachmann, University of Cambridge. "Investigations on the "Streptococcal Inhibitor of Complement": a unique polyfunctional inhibitor of the mucosal innate immune response" (2 years). £133,284

Dr I Greenwood & Dr S Prestwich, St George's Hospital Medical School. "Characterisation of ion channels encoded by KCNQ and *ether-a- go-go- related* genes in vascular smooth muscle" (3 years). £177,202

Dr N Sattar et al, Glasgow Royal Infirmary. "Pathways to cardiovascular risk: the role of leptin and adiponectin"(1 year 9 months). £83,004

Dr A F Mackintosh, St James's University Hospital, Leeds. "The magnitude of sympathetic neural hyperactivity following acute myocardial infarction in hypertensive patients" (3 years). £23,402

Dr S Pyner et al, University of Durham. "A selective role for oxytocin and vasopressin controlling the heart and kidney" (3 years). £145,796

Dr G E Jarvis & Dr R W Farndale, University of Oxford. "GPVI-independent platelet activation and signalling induced by collagen and collagen-related peptides" (3 years). £149,099

Dr I Hopkinson et al, Institute of Child Health. "The identification and management of familial cardiovascular disease in primary care - a pilot study" (1 year). £34,443

Dr K Barnes et al, University of Leeds. "Nucleoside transporters and adenosine-mediated regulation of cardiovascular function" (3 years). £157,372

Dr D P Ramji, Cardiff University. "The role of the c-Jun NH_2-terminal kinase/stress-activated protein kinase signal transduction pathway in the regulation of genes in macrophages implicated in stimulating cholesterol efflux" (3 years). £133,574

Professor K Clarke et al, University of Oxford "Cardiomyogenesis from stem cells in haemopoietic tissues: cellular therapeutics for myocardial infarction and heart failure" (3 years). £295,961

Dr N P J Brindle, University of Leicester. "Role of the ABIN family of proteins in control of endothelial activation by the receptor tyrosine kinase Tie2" (3 years). £122,363

Professor A D Struthers et al, Ninewells Hospital Med Sch, Dundee. "Near patient BNP and portable echocardiography in general practice" (2 years). £124,670

Professor G D Holman, University of Bath. "Investigation of insulin-induced alkalinisation of membrane compartments of heart cells" (3 years). £126,674

Professor M R Cowie et al, NHLI, London. "The early high risk period for patient with heart failure: a population-based study" (2 years). £151,484

Professor R J P Lewin et al, University of York. "Patients and carers: a self-management programme for people with heart failure and their carers" (3 years). £155,798

Professor J J V McMurray et al, University of Glasgow. "Can guiding medical treatment by measurement of blood N- terminal pro-BNP concentration improve outcome in chronic heart failure?" (2 years) £181,451

Dr R F Storey, Northern General Hospital, Sheffield. "Functional studies of the platelet $P2Y_{12}$ receptor" (1 year). £59,029

Professor S Harding & Dr S Fuller, NHLI, London. "Interactions between host and engrafted myocytes in models of cardiac disease" (3 years). £211,449

Dr R Clayton & Professor A Holden, University of Sheffield. "Initiation of re-entry and fibrillation in the ventricle: a mechanistic investigation using computational models" (3 years). £97,443

Dr M J Taggart et al, Manchester Royal Infirmary. "Investigation of the relationship between sub-cellular CA^{2+} dynamics, Ca^{2+}-sensitisation of tone and pressurised small artery diameter" (2 years). £88,855

Dr F Marelli-Berg & Dr K Okkenhaug, Hammersmith Hospital, London. "Phosphoinositide 3-kinases P110delta subunit as a pharmacological target for the regulation of TCR-dependent allospecific T cell recruitment" (3 years). £152,370

Professor D A Lane et al, Hammersmith Hospital, London. "*In vivo* analysis of the human EPCR gene promoter - transgenic analysis of a transcriptional enhancer" (3 years). £185,584

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

Cardiovascular Related Meetings

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

Keystone Symposia: 'Molecular Biology of Cardiac Disease' and 'Cardiac Development and Congenital Heart Disease'. March 7-12, 2004, Keystone Resort, Colorado, USA. For further information: www.keystonesymposia.org; 221 Summit Place #272, Drawer 1630, Silverthorne, CO 86498; Tel: +1 970 262 1230; info@keystonesymposia.org.

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

Cardiovascular Related Wellcome Trust Grants

May 2003 to August 2003

Project Grant

Professor M J S Langman, Department Of Medicine, Queen Elizabeth Hospital, University Of Birmingham. Sudden Death In The Community. An Examination Of Drug Exposure As An Antecedent Factor. 36 Months, £18,944

Dr Sergey Kasparov, Department Of Physiology, School Of Medical Sciences, University Of Bristol. Central Phosphatidylinositide 3-Kinase (PI3k) Signalling Pathway In Genetically Pre-Programmed Hypertension. 36 Months, £169,894

Professor K Ravi Acharya, Department Of Biology And Biochemistry, University Of Bath. Structure-Function Studies On Human Angiotensin Converting Enzyme And The Design Of Novel Structure-Based Inhibitors. 36 Months, £145,160

Dr Stefan P Hoppler, Department Of Biomedical Sciences, Institute Of Medical Sciences, University Of Aberdeen, Scotland. Wnt Signalling In Xenopus Organogenesis: Myocardium Specification. 36 Months, £245,401

Dr Bridget M Lumb, Department Of Physiology, School Of Medical Sciences, University Of Bristol. Functional Anatomical Studies Of The Descending Control Of Nociceptive Inputs To Autonomic Control Centres In The Brain Stem And Its Behavioural Significance. 36 Months, £204,530

Dr S A Thom, Department Of Clinical Pharmacology, St Mary's Hospital Medical School, Imperial College School Of Medicine, London. Retinal Microvascular Abnormalities And Risk Of Cardiovascular Disease. 9 Months, £38,291

Dr David L Buckley, Imaging Science And Biomed Engineering, University Of Manchester. Kidney Perfusion And Glomerular Filtration In Renovascular Disease:Development Of A Comprehensive Single-Visit Renal Examination Using Mri. 24 Months, £115,367

Dr David Bates, Department Of Physiology, New Veterinary School, University Of Bristol. Regulation Of Vascular Permeability By Shear Stress. 24 Months, £87,758

Dr Jonathan M Gibbins, School Of Animal And Microbial Science, University Of Reading. Study Of The Peripheral Tachykinins Endokinin A And B In The Regulation Of Platelet Function. 36 Months, £195,879

Travelling Research Fellowships

Dr Tetsuya Koyama, Department Of Anatomy And Dev Biology, University College London. Long-Term Effects Of Shear Stress On Atp Release And The Expression And Function Of P2 Receptors In Vascular Endothelial Cells. 24 Months, £106,724

Dr M A Esteban, Renal Section, Division Of Medicine, Imperial College School Of Medicine, Hammersmith Hospital, London. Characterization Of Enzyme-Substrate Interactions Underlying The Regulation Of Hypoxia-Inducible Factor By Oxygen Sensitive Hydroxylases. 24 Months, £91,638

South African Senior Research Fellowships

Dr Edward D Sturrock, Department Of Medical Biochemistry, Medical School, University Of Cape Town Observatory South Africa. Angiotensin-Converting Enzyme: Crystallographic Studies, Structure-Guided Inhibitor Design, And Ectodomain Shedding. 60 Months, £451,105

Indian Senior Research Fellowships

Dr S V Ramanan, Au-Kbc Center For Internet And, Telecom Technologies, Mit Campus, Chennai India. Intercellular Messangers That Couple Intercellular Cascades: From Permeability And Gating Of Gap Junction Channels To A Model Of Coordinated Tissue Response. 48 Months, £261,140

Senior Central European Fellowships

Dr Maris Laan, Institute Of Molecular And Cellular Biology, University Of Tartu, Tartu Estonia. Haplotype Structure Of The Human Genome And Its Implications For Mapping And Understanding The Evolution Of Common Disease: Using Extensive Estonian Population Sample As A Model. 60 Months, £566,031

Advanced Fellowships For Medical Graduates

Dr Bernard Khoo, Department Of Endocrinology, St Bartholomew's And Royal London School, Of Medicine And Dentistry, London. Mechanisms Of Splicing Inhibition In Apolipoprotein B Exon 26. 36 Months, £241,240

Dr Roger S-Y Foo, Clinical Pharmacology Unit, Addenbrooke's Hospital, University Of Cambridge. The Role Of Cardiac Myocyte Apoptosis In The Transition From Compensated Hypertrophy To Dilated Cardiomyopathy. 36 Months, £273,323

Advanced Training Fellowship

Dr G D Batty, MRC Social And Public Health Science Unit Glasgow. Cognition And Health: Analysis Of Data From A Series Of Population-Based Studies. 36 Months, £157,991

Collaborative Research Initiative Grants

Professor A J Llanos, Department Of Physiology, University Of Cambridge, Cambridge. Effects Of Chronic Hypoxia On Fetal Cardiovascular And Endocrine Functions In The Sheep. 36 Months, £184,328

Dr Johanna C Moolman-Smook, Department Of Cardiovascular Medicine, John Radcliffe Hospital, University Of Oxford. Exploration Of N-Terminal Interactions Of Cardiac Myosin Binding Protein C (Mybpc) And Their Influence On Mybpc Quaternary Structure And The Regulation Of Cardiac Contractility. 36 Months, £108,131

Prize Studentships

Miss Catherine Panayiotou, Wolfson Institute For Biomedical Research, University College London. Role Of Soluble Guanylate Cyclase In Regulating An Inflammatory Response. 36 Months, £97,191

Miss Cassandra Farthing, Department Of Cardiovascular Medicine, John Radcliffe Hospital, University Of Oxford. Cardiovascular Initiative - Genetic Mechanisms In Heart Development. 36 Months, £105,371

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(1)	***January 2004***	*December 1st*
17(2)	***April 2004***	*March 1st*
17 (3)	***July 2004***	*June 1st*
17 (4)	***October 2004***	*September 1st*

BSCR Spring Meeting 2004

Frontiers In Cardiovascular Signalling

Dates: 1st and 2nd April, 2004

Venue: Hulme Hall, University of Manchester

Organisers: David Eisner and Cathy Holt

Overall Aims:
The aim of the meeting is to cover a wide variety of signalling pathways in both cardiac and vascular muscles. These include: calcium; phosphorylation signalling pathways and signalling out of control. As well as discussing current concepts and results, speakers will be encouraged to relate their findings to both normal physiology and disease.

Speakers include: Arthur Weston (*Manchester*), Clive Orchard (*Leeds),* Ted Burdyga (*Liverpool*), Michael Duchen (*London*), Tomoko Kamishima (*Liverpool*), W J Lederer (*Baltimore)*, Angela Clerk (*London)* Chris Proud (*Dundee),* Robin Pleven *(Glasgow*), Jacqui Ohanian (*Manchester*), Robert Wilensky (*Philadelphia*), Andrew Trafford (*Manchester*), Michael Marber (*London)*, Quingbo Xu (*London*), Jean Luc Ballingand (*Belgium*).

Travel & Accommodation: Hulme Hall, Oxford Place, Victoria Park, Manchester
The conference centre is located 1.5 miles for Manchester City Centre, 10 minutes walk from the main University Campus, with good public transport links. En-suite rooms and parking are available on site.

Communications: Part of this meeting will be devoted to oral presentation of selected abstracts, and posters. Prizes will be given for the best oral and best poster presentation 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: 16th February, 2004.

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*:** Ros Poulton, University of Manchester, Room 1.305 Stopford Building, Oxford Road, Manchester M13 9PT; Tel: 0161 275 1628; Fax: 0161 275 5669; Email: rpoulton@fs1.scg.man.ac.uk.

Or: Barbara McDermott, BSCR Secretary, Department of Therapeutics and Pharmacology, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL; Tel: 02890-272242; Fax: 02890-438-346; Email: b.mcdermott@qub.ac.uk.