The Bulletin

of

The British Society for Cardiovascular Research

Registered Charity Number: 1011141

Vol. 15 No. 3

July 2002

www.kcl.ac.uk/bscr

The BSCR is sponsored by

Aventis

The Bulletin

The Publication of The British Society for Cardiovascular Research

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Contents

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Editorial

Welcome to the July 2002 issue of *The* Bulletin!

Our review article for this issue, *'Stimulus-trafficking of the* β_2*AR between G-proteins in human heart-* β*- blockers turn to agonists*', has been written by Dr Sian Harding of the Cardiac Medicine Department at the National Heart and Lung Institute, Imerial College, London. Dr Harding provides a fascinating insight into the role of G proteins in healthy and failing human heart.

In the Secretary's Column, Dr Barbara McDermott highlights the forthcoming election of Committee members and ballot forms are enclosed with this copy of *The* Bulletin. To assist with voting, biographical summaries and statements from the candidates are published within this issue. Please help to select the four candidates who you feel will benefit the society, by completing the ballot form and returning it to Barbara by 14th August.

Following the successful Spring 2002 meeting of the Society in Reading, an account of the proceedings has been provided by Jane Harper and Linda McLatchie of The University of Reading and Kings College London, respectively. Additionally, the organisers, Drs Gavin Brooks and Michael Shattock have provided a selection of abstracts presented at the meeting.

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 would like to thank Gaynor Dewsnap who has provided us with grant details on behalf of the BHF for many years. Gaynor has recently left the Foundation and we wish her well in her new career.

Helen Maddock and Nicola Smart

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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)

Stimulus-trafficking of the β_2AR between G-proteins in human heart - β-blockers turn to agonists

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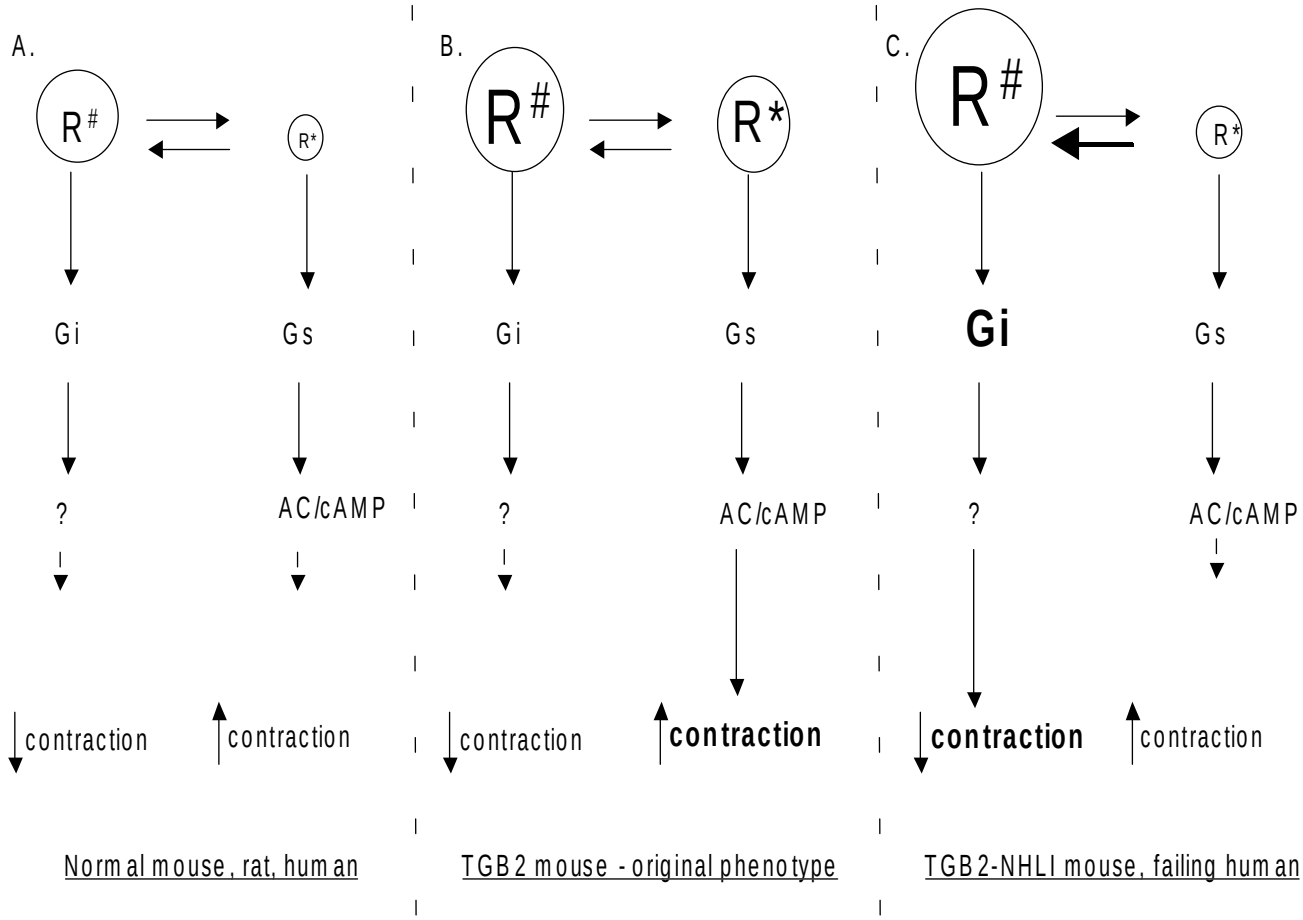
Why are human β_2-adrenoceptors so boring?

The β_1- and β_2-adrenoceptors (ARs) exist together on human ventricular myocytes and, despite being separate gene products, appear to have the same mechanism of action. Both stimulate adenylyl cyclase via coupling to a stimulatory guanine nucleotide binding protein (Gs) so increasing production of cyclic AMP. This dissociates the regulatory from the catalytic subunits of protein kinase A (PKA) and leads to phosphorylation of various targets within the myocyte, producing positive inotropic and lusitropic (relaxation) effects.

In animal heart, exciting data had been reported suggesting that the β_2AR could also activate contraction by a non-cyclic AMP-dependent mechanism. Contraction increases through the β_2AR occurred without speeding of relaxation, and without phosphorylation of phospholamban (1;2). Agents which specifically reduced cyclic AMP-dependent effects, such as the PKA antagonist RpcAMPS or the m2 muscarinic agonist carbachol, reduced β_1AR but not β_2AR-mediated contraction (3;4). Most strikingly, overexpression of β_1ARs caused a rapid early mortality in transgenic mice while equivalent overexpression of β_2ARs did not (5;6). The link through to Gi was made using pertussis toxin, an agent that specifically inhibits Gi-mediated effects. Pertussis toxin could make the β_2AR effects look like β_1AR, and could reveal cyclic AMP-dependent activation of contraction by previously silent β_2ARs (7). Toxin treatment also enhanced the apoptotic effects of dual β_1- and β_2AR stimulation, and it was found that β_2ARs acting through Gi could oppose the pro-apoptotic effect of β_1ARs acting via Gs (8;9). Down-stream pathways such as MAPKinase and PI3 kinase were identified as targets of β_2AR/Gi stimulation (8;10). The protection from early death in the transgenic mouse overexpressing the β_2AR was linked to a spontaneous up-regulation of Gi which decreased both the raised basal activity and the hyper-responsiveness to catecholamines, and may also have activated these protective pathways (11;12).

We turned to the human heart with keen anticipation since the conditions seemed ideal to display these novel β_2AR/Gi-coupling effects. Human ventricular myocytes have probably the strongest contribution of the β_2AR to contraction of any species (13). We have hunted through the animal kingdom to find a match; examining myocytes from mouse, rat, guinea-pig, rabbit, dog and sheep, but nothing comes close. In failing human heart, which comprises the majority of our samples, the β_1AR contribution is reduced (following prolonged sympathetic activation in these patients) while β_2AR numbers are preserved and therefore take on an even greater importance. Additionally, Gi is increased and acts to suppress the contractile effects of βAR stimulation (14). Disappointingly, however, most of the β_2AR-mediated stimulatory effects in human ventricular myocytes appeared to resemble the β_1AR and to be clearly linked to cyclic AMP. Relaxation velocity was accelerated equally by β_1- and β_2AR stimulation, and studies in whole muscle had shown phospholamban phosphorylation via either subtype (13;15). In fact, the β_2AR was calculated to be more efficiently coupled to adenylyl cyclase and produce four times more cyclic AMP than the β_1AR in human ventricle (16). Both RpcAMPS and carbachol were able to reverse β_2AR-mediated stimulation in human myocytes (17). It seemed clear that the positive inotropic and lusitropic cardiac effects of β_2AR activation were cyclic AMP-linked in man.



Strange effects of inverse agonists

Inverse agonism is a phenomenon that has been observed for various G-protein coupled receptors, and was described for the β_2AR in the transgenic mouse with 200- fold overexpression of this subtype (TGβ_2). Cardiac contractility and adenylate cyclase activity in these animals was constitutively activated in the absence of agonists, and basal levels were equal to that produced by maximal βAR stimulation in controls (18;19). Certain antagonists, termed inverse agonists, could reduce basal contraction by up to 80% while others, termed neutral antagonists, competitively inhibited the effects of both agonists and inverse agonists (19). The archetypal inverse agonist at the β_2AR is ICI 118,551, which is also one of the most specific blockers of the β_2AR-mediated stimulatory effect through Gs/adenylyl cyclase. It was hypothesised that the β_2AR existed in two conformations in equilibrium, active (R*) and inactive (R) and that, in normal animals, agonists bound to and stabilised R* which then activated adenylate cyclase via Gs. In TGβ_2 mice, overexpression of the β_2AR had increased proportionately the amount of R+R* such that levels of R* were sufficient to produce maximal contractile activation even in the absence of agonist. Inverse agonism was thought to be due to binding to R, the inactive form, shifting the equilibrium away from R*. Basal contraction amplitude decreased as R* levels declined and adenylate cyclase activity was reduced. Neutral antagonists bound approximately equally to both R and R*, leaving the equilibrium (and therefore basal contraction) undisturbed but blocking the action of either agonists or inverse agonists.

To our surprise, it was with the inverse agonists that we found the missing β_2AR/Gi link. ICI 118,551, at inverse agonist concentrations, produced a profound depression of contraction in myocytes from failing human heart, and this was pertussis toxin sensitive (20). The negative inotropic effect could not be due to blocking of catecholamine stimulation of the βAR, since the isolated, superfused myocyte preparation is free of endogenous noradrenaline or adrenaline. Importantly, this strong negative inotropic effect of ICI 118,551 was not seen in myocytes from non-failing heart (or from

normal animal heart) so that non-specific or membrane-stabilising effects seen with some β-blockers could also be excluded. The effect developed rapidly and was quickly and completely reversible. Using specific agonists/blockers we showed that it was the β_2AR, rather than β_1ARs or β_3ARs, that was responsible. We could also mimic the effect in rat or rabbit myocytes by using adenoviral vectors to overexpress either the human β_2AR or Giα2, and these new negative responses to ICI 118,551 were also pertussis toxin sensitive (20).

The observations were clear, but there was a problem with the theory: contraction is not constitutively activated through β_2ARs in the failing human heart. The human heart, unlike other species, has no "spare" βAR capacity even under normal conditions. The β_2ARs, while not lost in heart failure, are certainly not increased (14). High Gi levels damp the βAR responses and reduce cyclic AMP under both basal and catecholamine-stimulated conditions. We have challenged myocytes from human ventricle with either RpcAMPS or carbachol and it is clear that there is no tonic stimulation by cyclic AMP in these cells when the βARs have not been activated. Interestingly, we saw a parallel in the TGβ_2 mice. The sub-strain we studied in London (TGβ_2-NHLI) did not have high basal cyclic AMP or contraction either, even though the overexpressed β_2ARs were still in the membrane. Even the effect of direct βAR stimulation was markedly depressed compared to wild-type mice. Gi had up-regulated and damped down the β_2AR responses. Yet these animals still showed negative inotropic responses to ICI 118,551. The effect of ICI 118,551 cannot, therefore, be ascribed to a reduction of a constitutively active form of the β_2AR in either TGβ_2-NHLI mice or failing human heart.

Two active forms of the β_2AR?

We have proposed a modification to the original theory of inverse agonism. Binding is not to an inactive form of the β_2AR (R) but to another active form, coupled to Gi ($R^{\#}$). This occurs in parallel to the normal R*-Gs coupling which activates adenylyl cyclase. In normal mouse, rat or human levels of total β_2AR ($R^{\#}$+R*) are moderate and so are those of Gi (Fig 1A). In the absence of agonists, neither Gs nor Gi coupling has any tonic effect on basal contraction.

In TGβ_2 mice as originally described, the original theory of inverse agonism predominates. Total β_2AR levels ($R^{\#}$+R*) are massively increased, although the equilibrium between them is not necessarily altered (Fig 1B) and Gi levels are moderate. The excess R* is sufficient to activate the adenylate cyclase pathway to produce levels of cyclic AMP which will stimulate contraction above basal. Antagonists which bind preferentially to $R^{\#}$ (inverse agonists) have negative effects mainly by decreasing levels of R*, via a shift in equilibrium, reducing Gs activation of adenylyl cyclase and the raised basal contraction.

In failing human heart and TGβ_2-NHLI mice (Fig 1C) Gi has up-regulated. If $R^{\#}$ binds directly to Gi, the excess Gi will shift the equilibrium away from R*. This produces the damping of βAR responses seen in failing human heart and in the TGβ_2-NHLI mice, and the reversal of the raised basal activity in TGβ_2-NHLI. Inverse agonists bind to $R^{\#}$, and the increased amount of $R^{\#}$ and Gi is now sufficient to reveal a direct negative inotropic effect of β-blockers mediated through the β_2ARs. This kind of mechanism, where different effects can be mediated by the same receptor acting through different G-proteins, is known as stimulus-trafficking.

Characteristics of stimulus-trafficking

Evidence for ligand-specific receptor active states, or stimulus trafficking of receptors, has been obtained previously for several G-protein coupled receptors including the dopamine, tyramine, PACAP receptors and the β_2AR (21). When receptors can activate distinct subcellular pathways through two different G-proteins the rank order of potency of agonists differs for the two effects. For example, substance P is two-fold more potent than its synthetic analog for producing cyclic AMP through activation of Gs by the neurokinin-1 receptor, but 10-fold less potent for stimulating PI hydrolysis through Gq coupling to the same receptor (22). Further, kinetics of activation through different G-proteins can differ and mutations of a given receptor can preferentially affect responses through one pathway but not the other (21). We suggest that ICI 118,551 has effectively zero potency to activate through the R^{*}-Gs pathway but is a potent agonist at the $R^{\#}$-Gi form of the β_2AR. Furthermore, although isoprenaline is clearly a full agonist at R*-Gs we also suggest that it may be a partial agonist at $R^{\#}$-Gi. This latter effect could explain the β_2AR-Gi coupling by isoprenaline in animal myocytes described above, since high concentrations (1-10μM, 3 log units above the EC_{50}

for Gs activation) were often used in those experiments We have confirmed the observations of others that TGβ_2 mice with high Gi show negative inotropic responses to isoprenaline at similar high concentrations, and that these are pertussis toxin sensitive (23).

Mechanism of the negative inotropic effect of ICI 118,551

Identification of the final mechanism is not complete, but our preliminary experiments have eliminated various possible G-linked targets for the negative inotropic effect including the Na^+/H^+-exchanger, PI3 kinase, and the nitric oxide pathways. An abbreviation of contraction occurs, possibly related to a decrease in action potential duration, but Ik_{ACh} and Ik_{ATP} do not seem to be involved. Interestingly, the effect of ICI 118,551 is opposite to that of catecholamine stimulation through Gs, which often prolongs second phase of relaxation in human ventricular myocytes into a distinct aftercontraction (24). Catecholamine-induced aftercontractions have been linked to the torsades de pointes arrhythmia *in vivo*: stimulation through the β_2AR/Gi pathway may therefore oppose this effect and decrease the likelihood of arrhythmias.

Clinical relevance of the negative inotropic effects of β_2AR-Gi coupling

We have investigated the relationship between the clinical characteristics of the patients and the degree of negative inotropic effect of ICI 118,551. There is a clear increase in the magnitude of response with severity of symptoms, as defined by New York Heart Association Class, but little influence of the underlying aetiology (20). This pattern is reminiscent of the one observed for βAR desensitisation and Gi-upregulation (14). There is no relation to previous treatment with β-blockers, and the somewhat greater effects in patients receiving inotropes is most likely due to the greater severity of disease in those patients.

β-blockers, especially metoprolol and carvedilol, are now being introduced as standard treatment for heart failure because of unequivocal demonstrations of improvement in survival and ventricular function (25). Clearly, the unopposed β_2AR responses and high Gi levels in heart failure predispose to the demonstration of direct negative inotropic effects of β-blockers. We have so far discussed only results with the experimental compound, ICI 118,551. However, we have noted similar effects with alprenolol and propranolol in human myocytes, and effects were non-additive with ICI 118,551 suggesting a final common pathway. We could not complete experiments with carvedilol because of its tendency to inhibit electrical activity in these cells, probably because of its action on the HERG channel (26). A previous study (27) has shown negative inotropic effects of carvedilol in six out of seven muscle strips from failing human heart at concentrations between 0.01 and 0.1 μmol/l when the clinical concentrations can reach 0.1 to 0.6 μmol/. Interestingly, the same study also showed strong depression of contraction by metoprolol at submicromolar concentrations, although the subtype mediating the effect was not determined. Metoprolol, which is used in heart failure, is generally thought of as a β_1AR-selective agent. However, its relative selectivity for the β_1AR over the β_2AR can be as little as 5-fold (28) and it is therefore possible that metoprolol can act at ventricular β_2ARs in the clinical concentration range.

It is known that β-blockers were previously contraindicated for many years in heart failure patients because of an abrupt decline in cardiac function during the initial dosage period, and now must be titrated carefully (29). It has been assumed that the initial decrease in cardiac output (30) is a consequence of withdrawal of tonic sympathetic support. We now suggest that direct negative inotropic effects of β-blockers might contribute to this initial decline in contractility.

To be even more speculative, there is also the possibility that β_2AR-Gi coupling contributes to the longer-term recovery seen in these patients (30). As shown in the animal experiments, β_2AR-Gi signalling can offset the damaging effects of β_1AR-Gs stimulation. Two further observations may be of significance in this respect. First, a polymorphism of the β_2AR that decreases its activity is a strong negative prognostic indicator in heart failure, increasing the relative risk of mortality 5-fold (31). Second, trials using moxonidine (an agent which inhibits sympathetic drive) were discontinued due to an increase in mortality in heart failure patients (32). If β-blockade simply acts to prevent sympathetic stimulation of the heart then moxonidine and β-blockers should have equivalent effects. These two observations are consistent with our suggestion that an active effect of β-blockers through the β_2AR could contribute to the improvement they produce in the failing human heart.

Summary

The β_2AR in human ventricle may exist in two active forms, one coupled to Gs and one to Gi. Conventional agonists preferentially bind to the Gs coupled form, while agents previously described as inverse agonists direct coupling towards Gi. In failing human heart, where β_2ARs predominate and Gi is upregulated, the Gi coupling overshadows Gs and a direct negative inotropic effect of β-blockers is revealed. Activation of Gi by clinically used β-blockers has the potential for both short-term harm and long-term benefit in failing human heart.

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32. **Jones, C.G. and J.G. Cleland.** Meeting report—the LIDO, HOPE, MOXCON and WASH studies. Heart Outcomes Prevention Evaluation. The Warfarin/Aspirin Study of Heart Failure. *Eur J Heart Fail* 1: 425-431, 1999.

Dr Sian Harding is a reader in Cellular Pharmacology in the Cardiac Medicine Department at the National Heart and Lung Institute, Imperial College School of Medicine

Secretary's Column

The end of this year will see a number of significant changes on the BSCR Committee. Firstly, I am delighted to announce that Professor Mike Marber has been elected unanimously by the present Committee to succeed Professor Metin Avkiran as Chairman. Subject to approval by the membership at the next AGM to be held in Bristol on 6 September, he will take up the position in January 2003. Mike is an obvious choice. One of an increasingly rare breed of clinical scientists in cardiology, he would undoubtedly provide strong leadership as we move to interesting times in developing our impact in promoting basic cardiovascular research and its translation to clinical practice. Mike has a long standing commitment to the Society and recently has worked very successfully with Metin to secure major core funding to support the Society's activities. In addition to the vacancy left by Mike, there will be three further vacancies at the end of 2002 when Dr Adrian Brady, Dr Sarah George and Dr Lip Bun Tan will retire from the Committee. I am pleased to say that considerable interest has been shown in taking up these positions, in that five nominations have been received for the four vacancies. The biographies of the individuals are given in this issue of the Bulletin. It is necessary now to hold a postal ballot and a voting paper for the purpose has also been included. I would encourage you all to make your choice known, using only the official stamped form and by no later than 14 August. The result will be announced at the next AGM.

So far, this year has seen two very successful meetings and you can read the report and abstracts from the Reading meeting in this issue. The proceedings of the meeting held in Oxdord will be published later. The next one is the Autumn 2002 meeting, to be held at the University of Bristol. This is advertised again on the back cover, and registration and abstract forms are included as inserts. Dr Suleiman and Mr Caputo have put together an excellent programme, the details of which are also published here. They look forward to welcoming several eminent faculty and would appreciate a good attendance from the membership. I can give advance notice now of the Spring 2003 meeting, which will take place in Glasgow on 27-28 March. This is being organized by Dr Andy Baker and Dr Susan George on the subject of "Molecular therapy for cardiovascular diseases". The BSCR symposium on 'Magnetic resonance techniques in heart failure research' held at the recent BCS meeting in Harrogate generated good discussion from a sizeable audience. At the next BCS meeting in May 2003, the BSCR Symposium will be organized by Dr Andrew Grace from the University of Cambridge and Papworth Hospital on the theme of 'Ion channels and cardiac arrhythmias'. For up to date information on forthcoming meetings, workshops and symposia, please remember to check the BSCR Website (www.kcl.ac.uk.bscr). As a forward thinking Committee, we are now working on the programme for 2004, and would welcome proposals. If you would like to consider doing this, please refer to the guidelines for organization of meetings / workshops also published on the website, which gives details of how to go about it and the support that can be given.

Barbara McDermott

Nominations for Membership of the BSCR Executive Committee

KEITH CHANNON

I am currently a British Heart Foundation Clinical Reader in Cardiovascular Medicine at the University of Oxford, based at the John Radcliffe Hospital. My principal research interests are focused on the importance and mechanisms underlying endothelial dysfunction and oxidative stress in cardiovascular disease. This work encompasses endothelial cell biology, the generation and phenotyping of mouse models of cardiovascular disease, and patient-based clinical studies. As a part of these areas of interest, we have developed gene transfer techniques to investigate the function of individual targets and to provide a "proof of principle" for future therapeutic strategies.

I graduated from the University of Manchester in Medical Biochemistry in 1985 and in Medicine in 1988. Following post-graduate medical training, I was awarded a BHF Clinician Scientist Fellowship in 1993 which provided for an integrated seven year training programme in both basic science and clinical research. From 1993 – 1997, I was a Research Fellow in the Division of Cardiology at Duke University Medical Center in the USA where I developed my interests in endothelial cell biology, nitric oxide regulation of vascular function and gene transfer. I returned to a Clinical Lecturer position at the University of Oxford in 1997 and subsequently was appointed Clinical Reader in 1999. I continue to take an active role as a clinical cardiologist that provides me with valuable interactions and profile in clinical cardiology and greatly facilitates clinical and translational research. I would like to see the BSCR raise its profile as a national organisation representing those interested in integrating cardiovascular biology from basic mechanisms to clinical research. I would support its continued strong profile within the British Cardiac Society and would aim to extend this profile through interactions with European Societies.

Joined Society: 2000 **Proposed by**: Michael Marber **Seconded by**: Metin Avkiran

DAVID EISNER

Born 1955. BA (Physiology, Cambridge, 1976). D. Phil (Physiology, Oxford, 1979). 1980-1990 Department of Physiology, University College London. 1990-1999, Department of Veterinary Preclinical Sciences Liverpool. 1999- BHF Professor of Cardiac Physiology, University of Manchester. Fellow of the Academy of Medical Sciences, Fellow of the International Society for Heart Reasearch.

I have previously been Chairman of the Editorial Board of The Journal of Physiology. Currently on the Editorial Boards of Circulation Research, The Journal of Cellular and Molecular Cardiology and Cell Calcium. I am a member of the Council of the European Section of the International Society for Heart Research. I have organized a BSCR –sponsored symposium – "The Mammalian Myocardium". My research interests are centered around the control of calcium and other ions in cardiac cells. My main reason for wishing to join the Committee of the BSCR is to try to improve links between basic and clinical cardiovascular research in the UK. I feel that (at least outside a few centres) these links are weak and are certainly less well established than in the USA. I would see the BSCR collaborating with both basic and clinical societies to put on meetings to consolidate these links.

Joined Society: 1983 **Proposed by**: C.M. Holt **Seconded by**: Barbar McDermott

CHRIS JACKSON

I spent my early research career working at Rhône Poulenc Rorer, and then was fortunate enough to be able to study part-time for my PhD with Dr David Bowyer at the University of Cambridge, investigating the effects of calcium channel blockers on smooth muscle cell proliferation in injured arteries. I took up a postdoctoral fellowship with Professor Michael Reidy at the University of Washington in Seattle, looking at plasminogen activators and smooth muscle cell migration and proliferation. After two brief further stints in industry, at Pfizer in Kent and DuPont Merck in Pennsylvania, I joined Professor Gianni Angelini's team at the University of Bristol in 1995. During my 7 years at Bristol I have developed animal models of endothelial regrowth, homocysteinaemia, and plaque rupture, and have been successful in obtaining generous funding from the BHF and from industry. My lab is now entirely focussed on our murine plaque rupture model, which is beginning to yield unique insights into plaque destabilisation. I would like to serve on the BSCR committee because I think my experience of both academia and industry would provide useful links. Also, I think it is important that the vascular aspects of cardiovascular science continue to be an important part of the Society's efforts, and I would like to do what I can to support efforts in this area.

Joined Society: 1995 **Proposed by**: Sarah George **Seconded by**: Andrew Newby

NILESH SAMANI

I qualified from the University of Leicester Medical School in 1981 having spending some initial period doing research during an intercalated BSc year. Between 1985-1988, I spent three years on an MRC Training Fellowship with Professor Bill Brammar in the Department of Biochemistry at the University of Leicester, learning molecular biology techniques (something relatively new for a clinician) and having fun investigating tissue renin-angiotensin systems. I returned to the Department of Medicine as a Lecturer in 1988 and over the last 14 years have continued to undertake both clinical and basic research with a strong molecular biology theme. I have a team of over 20 clinical and basic scientists working with me and the main focus of the group's research is around the molecular genetic basis of hypertension and coronary heart disease and the pathogenesis of left ventricular hypertrophy. There is a strong interface between clinical and basic research. The work is funded through both project and programme grant support from the BHF and MRC and recently (with other colleagues) under the Wellcome Trust Functional Genomics Initiative. I was appointed to a Chair of Cardiology at the University of Leicester in 1997, and work as a Consultant Cardiologist with interventional interest at Glenfield Hospital. I am currently on the BHF Project Grants Committee and Associate Editor (Cardiovascular) for Clinical Science.

I strongly believe in and support the concept of scientists and clinicians working together. I think the BSCR embodies this and provides an excellent forum for dialogue between basic and clinical scientists. If appointed, I hope to bring my experience in promoting this important function of the Society, and raising its profile, particularly among clinical colleagues.

Joined Society: 1995 **Proposed by**: Metin Avkiran **Seconded by**: Michael Marber

PETER WEINBURG

After graduating from Cambridge in 1979 with a Natural Sciences degree, I moved to Imperial College where I completed an MSc and then a PhD. Following the award of a Lady Davis fellowship to study in Israel and further postdoctoral work at Imperial College, I was appointed Lecturer and then Reader in the School of Animal & Microbial Sciences, University of Reading, where I remain. My main research interest is to understand why some regions of arterial wall are prone to atherosclerosis whilst others are resistant. The long-term aim is to reduce disease by inducing in susceptible areas of the wall the key properties found in protected regions. We have shown that variations in the permeability of the arterial wall can explain the pattern of adult human disease, and that these variations are determined by nitric oxide synthesis and blood flow. I head the Vascular Permeability and Atherosclerosis Group at Reading, which has accommodated 18 staff and students and has received funding from the BHF, Wellcome Trust, MRC, BBSRC, Royal Society and smaller charities. I am an active member of the British Atherosclerosis Society and the Physiological Society (for whom I recently organised a symposium on Vascular Cells in Health and Disease), and I have served as a committee member for the London Microcirculation Group. I am keen to serve on the BSCR committee to participate in its valuable and effective support of UK cardiovascular research, to increase representation of Universities which have not traditionally been regarded as cardiovascular centres but which now have nationally-significant cardiovascular groupings (Reading's is described in Bulletin vol 13, No. 1), and to promote links with researchers and societies in disciplines (atherosclerosis, microcirculation, hypertension, etc.) that come under the broad cardiovascular umbrella but are not currently involved in the BSCR

Joined Society: 1998 **Proposed by**: Jeremy Pearson **Seconded by**: Gavin Brooks

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

www.kcl.ac.uk.bscr

Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
15(4)	***October 2002***	*September 1st*
16(1)	***January 2003***	*December 1st*
16(2)	***April 2003***	*March 1st*
16(3)	***July 2003***	*June 1st*

BSCR Autumn Meeting 2002

THE DEVELOPING HEART: BIOLOGY AND PROTECTION

Dates: 6th and 7th September, 2002

Venue: The Education Centre, Marlborough Street, Bristol BS2 8AE

Organisers: Saadeh Suleiman and Massimo Caputo

Friday 6th September

13.45 **Professor Gianni D Angelini, Cardiac Surgery, University of Bristol**
Why the developing heart?

14.00 **Professor Anton F M Moorman , Academic Medical Centre, Amsterdam**
Cardiac chamber formation

14.30 **DrStevenCoppen , Imperial College, London**
Connexin distribution during myocardial development

15.00. **Dr Sarah George , Bristol Heart Institute, Bristol**
Changes in myocardial cadherins during development

16.00. **Professor Jürgen Hescheler , University of Cologne, Germany**
Embryonic stem cells for cardiovascular research and cardiomyoplasty

16.30. **Dr Elinor Griffiths, Biochemistry, University of Bristol**
Mitochondrial calcium mobilisation during cardiac development

Saturday 7th September

09.00. **Professor Michael Artman MD, New York University Medical Centre**
Excitation-contraction coupling during cardiac development
(Nominated Speaker for British Cardiac Society Lecture)

09.30. **Dr Massimo Caputo, Cardiac Surgery, University of Bristol**
Cardiac pathologies in paediatric heart surgery

10.00. **Dr Marianne Thoresen MD , Institute of Child Health, University of Bristol**
Cardiovascular changes after global hypoxia in the piglet: effect of hypothermia

11.00. **Dr Andrew Parry, Children's Hospital, University of Bristol**
Foetal intervention in cardiac disease

11.30. **Dr Gavin Brooks, Cardiovascular Research Group, University of Reading**
Targeting the cell cycle machinery for the treatment of aberrant cardiovascular cell growth

13.30. **Dr John E Baker, Wisconsin College of Medicine, Milwaukee**
Protection of the infant heart during surgical repair of congenital defects: prospects for future therapies

14.00. **Dr Mike Shattock, St Thomas' Hospital, London**
Developmental changes in preconditioning

14.30. **Dr Hajime Imura, Nippon Medical School, Tokyo, Japan**
"Hot Shot" and multidose cardioplegia in cardioprotection of immature hearts

15.30. **Dr Pedro del Nido, Harvard University, Boston**
Myocardial Protection in Hypertrophied and Immature Myocardium
(Nominated Speaker for National Heart Research Fund Lecture)

16.00. **Dr Paul Modi, Cardiac Surgery, University of Bristol**
Crystalloid vs. blood cardioplegia during paediatric cardiac surgery

16.30. **Professor Sir Magdi Yacoub, National Heart & Lung Institute, London**
Age dependence of heat stress mediated cardioprotection

This meeting is supported from grants by Wellcome Trust, British Heart Foundation, National Heart Research Fund, ADInstruments and Beckman Coulter

BSCR Spring 2002 Meeting:
ION CHANNELS AND TRANSPORTERS IN CARDIOVASCULAR CELL GROWTH
The University of Reading, 11-12th April

A report by Jane Harper (The University of Reading) and Linda McLatchie (King's College London)

This meeting, which was held on the Whiteknights campus of The University of Reading, was attended by nearly 100 delegates from all over the UK, parts of Europe and also the USA. The organisers, Gavin Brooks (The University of Reading) and Michael Shattock (King's College London) had organised a very interesting and stimulating programme of presentations over the day and half period.

The meeting began on Thursday 11th April in beautiful sunshine with the British Cardiac Society Lecture presented by Sir Michael Berridge (Babraham, Cambridge) on the spatial and temporal aspects of calcium signalling. He described the mechanisms for calcium release in cells and discussed differences between "calcium sparks" that are mediated via ryanodine receptors, and "calcium puffs", that are mediated through IP_3 receptors. He also described the role of calcium in contraction and proliferation of cardiovascular cells and in hypertrophy.

Bernd Nilius (Leuven, Belgium) then followed with a talk on volume regulated anion channels (VRACs). He gave an overview of the channel's properties and its role in endothelial cell proliferation and discussed the fact that VRAC current increases during proliferation but decreases during differentiation. Lucie Clapp (UCL) gave the final presentation in this first session discussing potassium channels and their role in mediating vascular smooth muscle cell (VSMC) growth. She described how VSMC proliferation is associated with a decrease in potassium channel activity and also discussed possible mechanisms that might modulate this decrease in activity.

The second session of the first day consisted of four free communications that were selected from submitted abstracts. Richard Heads (KCL), who discussed calcium-induced protection and iNOS expression in isolated myocytes, gave the first of these. Simon Bryant (Oxford) followed with a presentation describing superoxide production under both control conditions and during hypertrophy. In the third presentation, Harry Witchel (Bristol) presented evidence that the potassium channel, $Kir_{2.1}$, could decrease proliferation when expressed in HEK cells. This included the interesting observation of 'dancing' cells whereby some of his transfected HEK cells separated after touching. Finally, Linda McLatchie (KCL) addressed the question of whether T-type calcium channels play a causal role in proliferation of A10 VSMCs.

The conference dinner that evening was held on the New Orleans Paddle Steamer that travelled up the Thames from Henley-On-Thames to Sonning and back. More than 70 delegates enjoyed good food and free wine (due to the generosity of Jencons PLS and Endocrine Pharmaceuticals Ltd.) whilst listening to the on-board Jazz band and admiring all the large houses along the river. At one point we were chased by two large dragon boats, just two of the other craft on the river enjoying an early summers' evening.

Back in Reading and Friday 12th April, emphasis shifted to hypertrophy and began with a session considering 'Ion transporters as *initiators* of cardiomyocyte hypertrophy'. Ole Petersen (Liverpool) began with a talk about calcium transport within the cell. This included nuclear transport, 'calcium tunnelling' through the endoplasmic reticulum and 'belts' of mitochondrial restricted calcium movement within the cell. Guy Vassort (Montpellier, France) then provided evidence that aldosterone, production of which increases during infarct, could increase L-type calcium currents and decrease the potassium I_{TO} current modifying action potentials thereby suggesting a role in left ventricular hypertrophy. Metin Avkiran (KCL) then gave an elegant overview of the Na^+/H^+ exchanger and presented evidence for a causal role in hypertrophy.

The second session 'Ion transporters in *response* to hypertrophy' began with Karin Sipido (Leuven, Bel-

gium) who summarised changes in potassium and calcium channels during hypertrophy. Ken MacLeod (KCL) followed this with a description of experiments that modified calcium handling in cardiac myocytes by altering SERCA 2a (calcium uptake) and Na/Ca exchanger (calcium efflux) expression levels. The effects of this were species and state of hypertrophy dependent due to changes in internal sodium. We then had a nice walk across the very rural campus, still in the sunshine, all the umbrellas (kindly provided by Legal and General) obviously doing their job, for lunch.

After lunch the final session, 'Signalling through ion channels' began with Max Lab (Imperial College London) who described his scanning ion conductance microscope allowing, not only exploration of the surface of living cells, but accurate mapping of channels and positioning of patch pipettes. He was followed by Michael Whitaker (Newcastle) who gave us a nice introduction to the world of calcium signalling and cell cycle control in sea urchin and *Drosophila* embryos. The large size of these cells allows easy visualisation of mitosis and calcium waves with a clear visual demonstration of the effects of blocking the cell cycle. Gary Baxter (Royal Veterinary College) followed this with an overview of ischaemic preconditioning, emphasising the areas of controversy and the question of whether, and at what stage, mitochondrial K_{ATP} channels play a role.

The meeting ended with the National Heart Research Fund Plenary Lecture given by Jeffrey Molkentin (USA) on the role of calcineurin in myocyte hypertrophy. He described a range of experiments using both transgenic and knock-out mice to modulate calcineurin levels and demonstrated that the increase in calcineurin during hypertrophy is a causal factor. He also described knock-out experiments implicating NFAT3 in the signalling pathway activated by calcineurin.

This was followed by votes of thanks to the Organisers and apologies to Godfrey Smith (Glasgow) who was to have talked about 'E-C coupling in cardiac hypertrophy and failure' but unfortunately was the victim of AV problems.

This meeting would not have been possible without sponsorship from the following organisations, to whom the Organisers and the BSCR are very grateful; Aventis, who provided core sponsorship, The British Heart Foundation, The National Heart Research Fund, The Wellcome Trust, Endocrine Pharmaceuticals Ltd., Jencons-PLS and Legal and General.

Spring 2002 BSCR meeting: abstracts

ARE T-TYPE CALCIUM CHANNELS CAUSALLY INVOLVED IN SMOOTH MUSCLE CELL PROLIFERATION?

McLatchie LM, *Harper JV, *Brooks G and Shattock MJ. Centre for Cardiovascular Biology and Medicine, King's College, St Thomas' Hospital, London, and *School of Animal and Microbial Sciences, University of Reading, PO Box 228, Reading, UK.

Aberrant smooth muscle cell growth is a major component of in-stent stenosis and vascular remodelling. T-type calcium channel expression has been linked with cell proliferation but it remains unclear whether it is a causal factor. We have addressed this question in rat A10 VSMC's by modulating T-type calcium channel expression through pharmacological blockade and stable over-expression. Mibefradil, nickel, TH1177 and verapamil blocked proliferation in these cells with IC_{50} values of 8.6 ± 0.5 μM, 428 ± 14 μM, 17.5± 0.5μM and 70 ± 3 μM respectively. Eliminating differences due to the presence of serum, calcium concentration etc. Mibefradil, nickel, TH1177 and verapamil block T-type current measured using whole-cell voltage clamp with IC_{50} values of 0.4 ± 0.1 μM, 1500 ± 300 mM, 1.2 ± 0.3 μM and 17 ± 2 μM respectively. These values for mibefradil, TH1177 and verapamil are all slightly lower than the anti- proliferative values but there is a correlation between the amount of T-type current block and block of proliferation. Nickel was anti-proliferative at concentrations well below those required to block the T-type current suggesting an alternative site of action.

Over-expression of the T-type calcium channel α_{1H} led to the production of a stable clone with T-type calcium current 20 fold higher than vector controls. This clone also demonstrated an increased proliferative capcaity of 2.6 fold at 72 hours as compared to our first vector control. However, comparing a number of stable clones revealed no correlation between T-type current magnitude and rate of proliferation. Although not ruling out a role for T-type calcium channels in proliferation these results suggest that T-type calcium current magnitude is not a primary causal factor in the rate of A10 smooth muscle cell proliferation. The drugs used in this study do clearly modulate proliferation and it remains to be seen where they act and whether these represent possible therapeutic target(s) for the treatment of instent stenosis or vascular remodelling.

ECDYSONE ANALOGUE SPECIFIC INDUCTION OF K_{IR}2.1 EXPRESSION LEADS TO SLOWING OF PROLIFERATION IN AN HEK 293 BASED CELL LINE

H.J. Witchel, O. Crociani, J.T. Milnes, M. Belsey, R. Kozlowski, J.C. Hancox and A. Arcangeli
University of Bristol, England and University of Firenze, Italy; harry.witchel@bristol.ac.uk

Recent studies have presented evidence that K^+ channels are important regulators of cell proliferation [Wonderlin and Strobl, 1996], and that a switch in major activity from HERG K^+ currents to inward rectifier K^+ currents is associated with neuronal maturation and the change from dividing to "differentiating" modes in cultured quail neural crest cells [Arcangeli et al., 1997]. Here we examine whether the association is causal using a stably transfected HEK 293 cell line with an inducible Kir2.1 transcript under the control of an ecdysone responsive element. This cell line shows electrophysiological evidence of inward rectifier current that is inducible by the ecdysone analogue ponasterone A. Ponasterone A induction was also associated with a decrease in cell growth as estimated by total protein, BrdU incorporation and cell counts. These experiments add selective molecular gain-of-function evidence to the theory that a switch to inward rectifier K^+ channel expression may be causally related to a reduction in proliferation.

Arcangeli A, Rosati B, Cherubini A, Crociani O, Fontana L, Ziller C, Wanke E, Olivotto M (1997). Eur. J. Neurosci. 9:2596-2604.
Wonderlin WF, Strobl JS (1996). J. Membr. Biol. 154:91-107.

CALCIUM-INDUCED PROTECTION AND iNOS EXPRESSION IN ISOLATED CARDIOMYOCYTES IS MEDIATED BY CALCINEURIN.

R.J Heads, K. Obasanjo and M.S. Marber, Department of Cardiology, GKT School of Medicine and Biomedical Sciences, The Rayne Institute, St Thomas's Hospital, London, UK.

To investigate the mechanism of delayed calcium-dependent protection in cardiomyocytes, isolated neonatal rat cardiomyocytes were treated for 3 hours with simulated ischaemia/reperfusion (SI/R). Injury was assessed by creatine phosphokinase (CPK) release and MTT bioreduction. Calcium-induced preconditioning (CIPC) was elicited by pretreatment with ionomycin (1.3 μM), cyclopiazonic acid (CPA:30μM) or ryanodine (1μM) to elevate cytosolic Ca^{++}, (CPK:50±10%, 58±12% and 45±14% vs SI/R [normalised to 100%], $p<0.001$). Pretreatment of cardiomyocytes with ionomycin or CPA was associated with expression of inducible nitric oxide synthase (iNOS) and protection was blocked by the selective iNOS inhibitor amino guanidine (200μM). The role of the Ca^{++}/calmodulin-dependent protein phosphatase 2B (calcineurin) was determined. Western blots demonstrated iNOS induction in hearts isolated from transgenic mice overexpressing calcineurin A catalytic subunit (CnA) but not non-transgenic mice. Furthermore, both protection and iNOS expression were recapitulated by transfection of cardiomyocytes with a constitutively active mutant of CnA (ΔCamAI). CnA has been reported to modulate p38-MAPK signalling through induction of MAPkinase phosphatase-1 (MKP-1)/CL100. In cotransfection experiments ΔCamAI abolished the activation of NFkB-luc reporter by MEKK1. Furthermore, transfection of cardiomyocytes with a truncated active CL100 cDNA selectively downregulated p38-MAPK phosphorylation and protected against SI/R. Therefore, calcium-dependent protection in cardiomyocytes involves calcineurin, iNOS and MKP-1-mediated downregulation of p38-MAPK activation.

SUPEROXIDE PRODUCTION BY LEFT VENTRICULAR MYOCYTES IN CONTROL AND HYPERTROPHIED HEARTS.

Simon M. Bryant, Claire Sears, Young M. Kim, Keith Channon, Barbara Casadei. Department of Cardiovascular Medicine, John Radcliffe Hospital, Oxford.

Oxidative stress induced by an increase in vascular superoxide anion ($O2\cdot^-$) production has been implicated in the pathogeneses of cardiac hypertrophy and failure. However it is unknown whether $O2\cdot^-$ is generated from within ventricular myocytes themselves and whether an increase in its production is an early feature of myocardial pathology. We have measured NADPH-stimulated $O2\cdot^-$ production in left ventricular myocytes isolated from age matched (8 week) Wistar (WKY) and spontaneously hypertensive rats (SHR), using lucigenin-enhanced chemiluminescence, at 37ºC. NADPH elicited $O2\cdot^-$ production in a dose-dependent manner that was not attenuated by oxypurinol or rotenone but was abolished by the flavoprotein-oxidase inhibitor DPI. NADPH-derived $O2\cdot^-$ production was increased by ~58% in hypertrophy (from 1.43±0.27 in WKY to 2.46±0.28 $RLU.sec^{-1}$ per myocyte in SHR, $P < 0.05$).

Conclusion: These data show for the first time that $O2\cdot^-$ is produced within rat ventricular myocytes and is increased in hypertrophy. These findings suggest a putative autocrine role for $O2\cdot^-$ in the control of cardiac function.

Cardiovascular Related Meetings

Translational Approaches to Cardiovascular Disease, the 24th Annual Meeting, ISHR, North American Section, will be held in Madison, Wisconsin, July 24-27, 2002. The abstract deadline is February 1, 2002. Organizer: Richard L. Moss, Ph.D., Director, UW Cardiovascular Research Center, Professor and Chair, Department of Physiology, Telephone: 608-262-1939, Fax: 608-265-5072, email: rlmoss@physiology.wisc.edu

22nd Meeting of the European Society for Microcirculation: 'The Microcirculation and Vascular Biology' will be held at the University of Exeter, Devon, 28th-30th August, 2002. For further information, please contact Hampton Medical Conferences Ltd. (ESM202650), 127 High Street, Teddington, Middlesex TW11 8HH UK Tel: +44 (0) 20 8977 0011; Fax: +44 (0) 20 8977 0055; E-mail: esm@hamptonmedical.com www.hamptonmedical.com; www.medizin.fu-berlin.de/esm Main announcement and Call for Abstracts now available

Congress of the European Society of Cardiology, 31 August - 4 September, 2002, Berlin, Germany. For further information concerning registration, hotels, exhibition, satellite symposia, write to: ESC- The European Heart House 2035, Route des Colles, Les Templiers, BP 179, 06903 Sophia Antipolis Cedex, France. www.escardio.org. General enquiries: +33 -(0)4 92 94 76 00; Fax: +33 -(0)4 92 94 76 01. E-mail: webmaster@escardio.org; Registration: registration@escardio.org; Scientific Programme: scientific@escardio.org; Exhibition: exhibition@escardio.org; Hotels: hotels@escardio.org. On-line registration and abstract submission is available on-line at: www.escardio.org.

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

XXIII Congress of the European Society of Cardiology, together with Heart Failure 2003 (ESC). Strasbourg, France. Enquiries: ESC, 2035 Route des Colles, BP 179 - Les Templiers, 06903 Sophia Antipolis Cedex, France. Tel: +33 4 9294 7600; Fax: +33 4 9294 7601; Website: www.escardio.org

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

Travel Reports for *The* Bulletin

The Bulletin regularly publishes travel reports written by members. These are up to 3 pages in length, may include photographs and can be on any conference, course or laboratory visit of interest to other members. 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!

BRITISH HEART FOUNDATION GRANTS

Chairs and Programme Grants Committee, February 2002
Programme Grant

Prof R H Anderson, Institute of Child Health, London. "The fate and function of extracardiac cell populations in heart development and malformation" (5 years). £806,913

Prof H Tunstall-Pedoe, Ninewells Hospital, Dundee. "Scottish heart health and MONICA cardiovascular epidemiology programme group: Dundee" (5 years). £500,560

Prof J Bradley & Dr E Bolton, Addenbrooke's Hospital, Cambridge. "Antigen recognition pathways in cardiac allograft rejection and tolerance" (5 years). £913,851.

Project Grants Committee, March 2002
DEFERRED APPLICATIONS AWARDED

Dr H E Montgomery et al, University College London. "Angiotensin converting enzyme as a mediator of human left ventricular hypertrophy: a pharmacogenomic investigation of mechanisms" (3 years). £267,211

Dr J Higgins, University of Sheffield. "Investigation of the mechanisms which regulate the size, composition and structure of very low density lipoproteins secreted by the liver" (3 years). £138,624

Dr A A Grace et al, University of Cambridge. "Molecular physiology of cardiac sodium channel mice" (2 years). £128,609

Professor M R Wilkins & Prof A Aldeshev, Hammersmith Hospital, London. "Randomised, placebo controlled study of the effect of sildenafil on hypoxia-induced pulmonary hypertension" (2 years). £19,104

Dr J Ostberg & Dr G S Conway, University College London. "Characterisation of cardiovascular risk in adult women with Turner Syndrome" (2 years). £101,141

Dr D J Chambers, St Thomas' Hospital, London. "Comparison of ischaemic, mechanical and pharmacological preconditioning as interventions to protect lungs from damage during long-term preservation or cardiopulmonary bypass" (3 years). £138,175

Dr M Gatzoulis, Royal Brompton Hospital, London. "The effect of ACE inhibitors on pulmonary regurgitation, biventricular volume, mass and function, integrated cardiopulmonary exercise and cardiac autonomic reflexes late after Tetralogy of Fallot repair. The appropriate study (ACE inhibitors for prevention of the effects of pulmonary regurgitation in adults with tetralogy)." (2 years) £150,020

Dr L Swan, Royal Brompton Hospital, London. "The influence of aortic pulsatile haemodynamics on the development of left ventricular hypertrophy and atherosclerosis in patients with repaired coarctation" (1½ years). £30,794

Professor E D Saggerson, University College London. "Regulation of AMP-activated protein kinase activity in heart by long-chain fatty acids" (3 years) £201,253

NEW APPLICATIONS

Dr S J George & Prof A C Newby, Bristol Royal Infirmary. "The role of β-catenin in vascular smooth muscle cell proliferation and migration" (3 years). £106,495

Dr P R Kemp et al, University of Cambridge. "SRF and YY1 transcriptional regulation of vascular smooth muscle gene expression in vitro and in the developing pulmonary vasculature" (2 years). £92,361

Dr A A Harper, University of Dundee. "Towards an understanding of the development changes in integration of neuronal signalling in intracardiac ganglia" (3 years). £124,183

Dr K E Porter et al, University of Leeds. "The intracellular mechanisms underlying the anti-invasive properties of statins in human saphenous vein smooth muscle cells" (2 years). £48,318

Professor Q Xu, St George's Hospital Medical School, London. "Mechanical stress-initiated signalling in smooth muscle cell apoptosis: role of p53" (3 years). £131,088

Dr D J Henderson, University of Newcastle upon Tyne. "Lpp1 in myocardialisation and alignment of the proximal outflow tract" (3 years). £162,088

Dr S P Watson et al, University of Oxford. "The use of snake venom toxins to identify novel platelet surface receptors" (2 years). £107,061

Dr M K Patel et al, St Mary's Hospital, London. "The antisense AT_1 spontaneously hypertensive rat - a model to explore the molecular basis of 'heparin resistance'" (2 years). £126,309

Dr L Smeeth et al, London School of Hygiene & Trop Med. "Acute inflammation and the risk of vascular events" (1.5 years). £86,416

Dr M S Suleiman et al, Bristol Royal Infirmary. "An investigation into the expression and activity of the cystine-glutamate exchanger in relation to glutathione's role in myocardial protection" (2 years). £84,270

Professor C G Proud, University of Dundee. "Regulation of protein synthesis by MAP kinase signalling in cardiomyocytes" (3 years). £142,932

Dr A Tinker & Professor A J Williams, University College London. "Using ion channel reconstitution to understand the regulation of the G-protein gated inwardly rectifying K^+ channel" (3 years). £129,023

Prof J M Marshall & Dr D M Stroka, University of Birmingham. "Interdependence of genomic and vascular responses to chronic systemic hypoxia" (3 years). £105,024

Dr M P Burnham & Prof A H Weston, University of Manchester. "Role of Ca^{2+} - activated K^+ channels in diabetic microangiopathy" (3 years). £136,797

Mr M Caputo et al, Bristol Royal Infirmary. "Low or high magnesium concentration in intermittent warm blood cardioplegia in patients undergoing coronary artery surgery: a prospective randomised study" (3 years). £104,189

Dr S M Hampton et al, University of Surrey. "Circadian rhythm of endothelial function: a study using constant routine methodology in pre and postmenopausal women" (1 year). £38,102

Dr P D Weinberg, University of Reading. "Does the atheroprotective effect of dietary L-arginine disappear with age?" (3 years). £149,499

Dr S C Langley-Evans, University of Nottingham. "Fetal programming of blood pressure: interactions of glucocorticoids and renin-angiotensin system" (3 years). £120,025

Professor M P Frenneaux et al, University of Wales College of Medicine. "The effect of conjugated linoleic acid on body fat mass, endothelial function, platelet aggregation, and insulin sensitivity in obesity in man" (1.5 years). £82,222

Dr C Korbmacher & Dr H M Charlton, University of Oxford. "Adenovirus-mediated gene transfer to study the regulation of the epithelial sodium channel (ENaC) important for blood pressure control" (2 years). £90,029

Professor R A Lawrenson et al, University of Surrey. "Creating an evidence base for primary and secondary cardiovascular disease prevention in patients with diabetes using the genera practice research database" (1 year). £58,493

Prof D A Eisner & Dr A W Trafford, University of Manchester. "Role of SR Ca content in the inotropic effects of catecholamines" (3 years). £125,662

Dr S Ponnambalam et al, University of Leeds. "Intracellular trafficking and signalling by VEGFR-1 and VEGFR-2 in endothelial cells" (3 years). £123,647

Dr S S Ye, Southampton General Hospital. "Molecular genetic and functional analyses of ABCA 1 gene variants" (3 years). £117,549

Professor J M Squire, Imperial College, London. Myosin filament ultrastructure in health and disease" (3 years). £144,715

Professor M R Bennett, University of Cambridge. "Manipulation of cell death in vivo" (3 years). £146,084

Dr G K Dhoot, The Royal Veterinary College, London. "The relationship of slow skeletal muscle troponin T expression with coronary vasculoangiogenesis in normally developing and pathological heart" (3 years). £121,115

Dr D S Steele, University of Leeds. "Atrioventricular differences in sarcoplasmic reticulum Ca^{2+} regulation" (3 years). £151,535

Fellowships Committee: April 2002
DEFERRED APPLICATIONS AWARDED

Junior Research Fellowship

Dr K. Chitkara, Glenfield Hospital, Leicester. "Pre-clinical assessment of antithrombotic and antiproliferative action of stents eluting eptifibatide (integrilin)". (2 years) £95,622.

PhD Studentship

Dr R Motterlini, Northwick Park Hospital. "Pharmacological activities of cardon monoxide-releasing molecules (Co-RMs) in the cardiovascular system". (3 years) £63,432.

PhD Studentship (Clinical)

Dr C.J. Redpath, University of Glasgow. "The effects of neurohumoral activation on the electrophysiology of human isolated atrial myocytes". (2.5 years) £101,127

NEW APPLICATIONS AWARDED

Intermediate Research Fellowships

Dr M.J. Coffey, University of Wales College of Medicine. "Mechanisms and consequences of platelet 12-lipoxygenase of activation by collagen in the vasculature". (3 years) £124,819.

Junior Research Fellowship

Dr A.M. Ross, University of Aberdeen. "The role of MTHFR genotypes and dietary folate in the development of ventricular septal defects". (2 years) £84,944.

Dr K.J. Hogg, University of Glasgow. "Characterisation of patients with heart failure despite preserved left ventricular systolic function: a prospective, descriptive, cohort study". (2 years) £75,011.

Dr G.C. Auld, University of Aberdeen. "Tissue transglutaminase (tTG) expression in endothelial cells: role for tTG in atherosclerotic plaque". (2 years) £65,511.

Dr C. Deighan, University of Glasgow. "Identification and characterisation of adventitial alpha 1- adrenoceptors on murine blood vessels from wildtype and adrenergic knockout mice". (2 years) £61,144.

PhD Studentships

Dr K M Naseem, University of Bradford. "Characterisation of the biomedical and physiological mechanisms regulating nitric oxide synthesis in blood platelets". (3 years) £62,147

Miss D. Paul, Imperial College. "Single particle analysis of muscle regulatory proteins and myosin on actin filaments" (3 years) £70,430.

Dr I Sabroe, Royal Hallamshire Hosp, Sheffield. "Toll-like receptors: the reguation of their expansion and signalling in atheroma". (3 years) £65,442.

Dr S J Harper, University of Bristol. "The mechanisms of increased vascular permeability of single mesenteric microvessels in diabetes". (3 years) £68,532.

Mr J. McCormick, Institute of Child Health , London. "The role of the C-terminal of STAT-1 in ischaemia/ reperfusion injury in cardiac cells ". (3 years) £70,885.

Miss S. Pitt, University of Cambridge. "A study of the factors responsible for voltage modulation of IP3-dependent Ca 2+ release in cardiovascular cells". (3 years) £74,850.

Ms J. Auger, University of Birmingham. "Signalling by von Willebrand factor in platelets". (3 years) £65,502.

Dr R Sitsapesan, University of Bristol. "Inactivation of cardiac ryanodine receptor channels". (3 years) £67,432

PhD Studentship (Clinical)

Mr M. Baghai, St Thomas' Hospital, London. "Develpmental changes in the cellular mechanisms underlying ischaemic preconditioning in the human nenatal myocardium". (3 years) £151,660.

Dr R.P. Weerackody, Western Infirmary, Glasgow. "Pulmonary hypertension: the improtance of cellular phenotype switching in remodelling and vascoconstriction in response to hypoxia" (3 years) £120,662.

Dr V. Reddy, University of Hull. "The effect of carnitine supplementation on myocardial function and energy provision in experimental uraemia" (3 years) £127,188.

Dr S. Johar, Kings College Hospital, London. "Role of reactive oxygen species in development of interstital fibrosis and diastolic dysfunction in the hypertensive heart" (3 years) £138,383.

Mr D.E. Pontefract, Southampton General Hospital. "The effects of gene expression in endothelial cells by the arterialisation of saphenous vein with comparison to internal mammary artery" (3 years) £138,235.

Mr M. Kanani, Institute of Child Health, London. "The surgical management of the left atrioventricular valve in atrioventricular septal defects" (3 years) £136,879.

Travelling Fellowship

Dr D. Ashby from Lennox Hill Hospital, New York to Freeman Hospital, Newcastle."The role of spiral multi-slice computed tomography in assessing changes in vascular structure and plaque morphology in aortocoronary vein grafts" (6 months) £3,400.

Book reviewer required

The following book has been received for the Book Review feature in *The* **Bulletin**. If you would like to review this title, please contact the Editors as soon as possible.

• From the *Developments in Cardiovascular Medicine* series: *"Exercise Testing, New Concepts for the New Century"*, edited by Myrvin H Ellestad and Ezra A Amsterdam (Kluwer Academic Publishers) ISBN 0-7923-7378-2, September 2001

The reviewer may keep the book after reviewing it.

Cardiovascular Related Wellcome Trust Grants

February 2002 to April 2002

Wellcome Programme Grant

Dr Martin Bobak, Dept of Epidemiology & Public Hth, University College London. Determinants of cardiovascular diseases in Eastern Europe: a multi-centre cohort study. 60 months £1,117,563

Project Grants

Dr Graeme F Nixon**,** Dept of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Scotland. The role of sphingosine 1-phosphate in vascular smooth muscle contractility: relationship to EDG receptor expression. 36 months £141,331

Prof Jeremy D Pearson**,** Cardiovascular Biology & Medicine, School of Biomedical Sciences, King's College London. ICAM-1 expression and regulation in systemic sclerosis. 36 months £184,050

Prof Constantino Pitzalis**,** Rheumatology Unit, Guy's Hospital, UMDS of Guy's & St Thomas's Hospital, London. Targeting the synovial tissue microvasculature with peptides from phage display in vivo using the human-synovium/scid-mouse transplantation model. 24 months £206,912

Prof Godfrey L Smith**,** Dept of Physiology, Institute Biomedical & Life Science, University of Glasgow, Scotland. The role of FK binding proteins in the modulation of excitation-contraction coupling in cardiac muscle. 36 months £205,626

University Awards

Dr Valerie B O'Donnell, Wales Heart Research Institute, Univ of Wales Coll of Medicine, Cardiff, Wales. Regulation of nitric oxide by lipoxygenases: role of lipoxygenase in modulating nitric oxide bioactivity in the vasculature. 60 months £332,792.

Health Services Research Projects Grant

Dr Steven M Thomas, Sheffield Vascular Institute, Vascular Office, Firth 4, Northern General Hospital, Sheffield. Cost effectiveness of fast track diagnostic services for stroke or threatened stroke. 12 months £4,068

Training Fellowship In Health Services Research

Dr Karen Rees, Dept of Social Medicine, Canynge Hall, University of Bristol. Prevention and treatment of cardiovascular disease in British women. 12 months £49,996

Travelling Research Fellowships

Dr Jan-Peter Koch**,** Laboratory of Physiology, University of Oxford. Functional characterisation of the amiloride-sensitive Na+ channel in microdissected cortical collecting duct (CCD) of normal and transgenic mice. 5 months £17,377

Clinician Scientist Fellowship

Dr Catherine L M Sudlow, Dept of Clinical Neurosciences, Western General Hospital, University of Edinburgh, Scotland. Revisiting the lacunar hypothesis: are lacunar strokes really different?

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

BSCR Autumn Meeting 2002

THE DEVELOPING HEART: BIOLOGY AND PROTECTION

Dates: 6th and 7th September, 2002

Venue: The Education Centre, Marlborough Street, Bristol BS2 8AE

Organisers: Saadeh Suleiman and Massimo Caputo

Overall aims:

1. To improve our understanding of the biology of cardiac development.
2. To compare different techniques of myocardial protection in experimental models and during paediatric open heart surgery.

Invited Speakers include: Sir Magdi Yacoub (London), Anton Moorman (Amsterdam), Steven Coppen (London), Sarah George (Bristol), Jürgen Hescheler (Cologne), Michael Artman (New York), Gavin Brooks (Reading), Elinor Griffiths (Bristol), Marianne Thoresen (Bristol), Andrew Parry (Bristol), John Baker (Milwaukee), Mike Shattock (London), Hajime Imura (Tokyo), Pedro del Nido (Boston), Paul Modi (Bristol).

Please visit website www.bris.ac.uk/bhi/meeting.htm

Communications: Part of this meeting will be devoted to the presentation of posters. **Abstract deadline: 6th August 2002.**

Travel & Accommodation: Bristol is ideally situated for travel by car, rail, bus or air. Further details are available on www.bristol.ac.uk/directions.html Accommodation will be available at local hotels. For details contact Jan Wild on address below.

Registration: Free to BSCR members, £50 for non-members. For further information contact: Saadeh Suleiman or Jan Wild, Bristol Heart Institute, University of Bristol, Bristol Royal Infirmary, Bristol BS2 8HW. Tel: 0117 928 3519 or 3582; Fax: 0117 928 3581; Email: M.S.Suleiman@bristol.ac.uk or J.Wild@bristol.ac.uk. Deadline for registration is August 6th, 2002.

Bursaries: The Society will consider awarding travel grants of up to £150 to *bona fide* PhD students. Application forms are available from Dr Barbara McDermott at the address below.

Applications for membership and student bursaries are available from Dr Barbara McDermott, Secretary of the BSCR, Department of Therapeutics and Pharmacology, The Queen's University of Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL. Tel: 02890-272242/33577o; Fax: 02890-438346; E-mail: b.mcdermott@qub.ac.uk