The Bulletin

of

The British Society for Cardiovascular Research

Registered Charity Number: 1011141

Vol. 21 No. 2

April 2008

www.bscr.org

The Bulletin

The Publication of The British Society for Cardiovascular Research

Contents

Editorial

Welcome to the April 2008 issue of *The* Bulletin!

Our review for this issue has been witten by Drs Dagmar Harzheim and Martin Bootman of the Babraham Institute. The authors provide a concise overview of the role of HCN channels in regulating the pacemaker activity of the mammalian heart with insight from their analyses of genetic mouse models.

We would like to draw your attention to the call for nominations for membership of the BSCR Committee. With four current members approaching the end of their terms, the search for their successors is underway. A nomination form is printed in this issue and we urge anyone wishing to play an active role in the running of the society to consider standing for election.

In this issue we bring you the first announcement of a BSCR workshop which will be held at the Hatter Cardiovascular Institute in early December. Dr Derek Hausenloy and Professor Derek Yellon have put together an outstanding programme of talks and discussion but places are limited for this exceptional workshop and early registration will be essential.

Our travel report for this issue is particularly interesting. Instead of a meeting report, David Martindill relates the experiences of a final year PhD student visiting a laboratory in the States to discuss common research interests and to explore the possibility of a longer term collaboration in the form of a post-doctoral position.

As we look forward to the Society's first venture in holding a joint meeting with the British Cardiovascular Society in June, a final programme giving full details of the symposia, keynote lectures and poster sessions is included within. See you in Manchester!

Helen Maddock and Nicola Smart

Physiology of HCN channels in the mammalian heart

by Dr Dagmar Harzheim and Dr Martin D. Bootman, Laboratory of Molecular Signalling, The Babraham Institute, Cambridge

The role of I_f in cardiac pacemaker depolarization

The sino-atrial node (SAN) is the primary pacemaker region of the heart. The SAN myocytes generate spontaneous action potentials that trigger the beating of the heart. These action potentials are characterized by a slow diastolic depolarization. The slope of the depolarization determines the time period between two action potentials and thus the heart-beat frequency. Therefore, the diastolic depolarization has also been termed pacemaker depolarization (**Figure 1**). One of the major ionic currents thought to contribute to the pacemaker depolarization is the hyperpolarization-activated (I_f) current [1]. It is activated during hyperpolarization of the membrane potential, providing a depolarizing inward current in the voltage range of the diastolic depolarization [2]. A striking feature of the I_f current is its regulation by autonomic stimuli; activation of β-adrenergic receptors increases, whereas activation of muscarinic receptors decreases, the I_f current [3]. It has been shown that this regulation is due to direct activation of I_f by intracellular cAMP [4]. Activation of β-adrenergic receptors increases the intracellular cAMP concentration leading to a shift in the voltage dependence of I_f towards more positive potentials, and thereby facilitating I_f activation. Conversely, activation of muscarinic receptor decreases the intracellular cAMP concentration, shifting the voltage dependence towards more negative potentials, and thereby reducing I_f activation at a given voltage. It has been proposed that the acceleration of the heart beat during β-adrenergic stimulation is due to direct cAMP-mediated stimulation of I_f [4].

Molecular basis of I_f

The channels underlying the I_f current were molecularly identified in the late 1990s [5-8]. They have been designated as hyperpolarization activated and cyclic nucleotide-gated channels (HCN channels), and so far four isoforms, namely HCN1-4, have been cloned. HCN channels contain six transmembrane domains (S1-S6), a voltage sensor in S4, cytosolic N- and C-termini, with the latter containing the cyclic nucleotide-binding domain (CNBD) (**Figure 2**). It has been proposed that functional channels consist of four HCN channel-subunits [9]. HCN1-4 differ in their voltage range of activation, their activation kinetics and their sensitivity to cAMP. For example HCN2 has a more negative activation threshold compared to HCN1 and HCN4 but the activation kinetics of HCN2 are faster than HCN4 and HCN3 but slower than HCN1 [10-12]. HCN4 shows the highest responsiveness to cAMP followed by HCN2 and HCN1 [8, 13, 14]. In contrast to the other HCN-channel isoforms, the activity of HCN3 is not enhanced by cAMP [12].The characteristics of I_f in the heart do not resemble those of a single isoform. Therefore, native I_f channels are unlikely to be homotetramers. Indeed, heteromeric channels exist *in vivo* [15] and heterologous expression of tandem constructs revealed that heteromultimers of HCN1 and HCN4, with a prevalence of HCN4, closely resemble the characteristics of the native I_f in the SAN [14]. Underlining these findings, HCN4 is the prevalent isoform in the SAN, accounting for ~80% of the total HCN message [16, 17]. HCN1 is highly expressed in the rabbit SAN (~20% of total HCN message) but can hardly be detected in the mouse SAN [16]. HCN2 compared to HCN4 is rather moderately expressed and shows a ubiquitous distribution throughout the whole heart, whereas HCN4 can be specifically found in regions that are spontaneously active [16-18].

Insights into HCN-channel function *in vivo*

The use of knockout and transgenic mice has shed light on the physiological role of HCN channels in the heart in more detail. So far, results for HCN1, 2

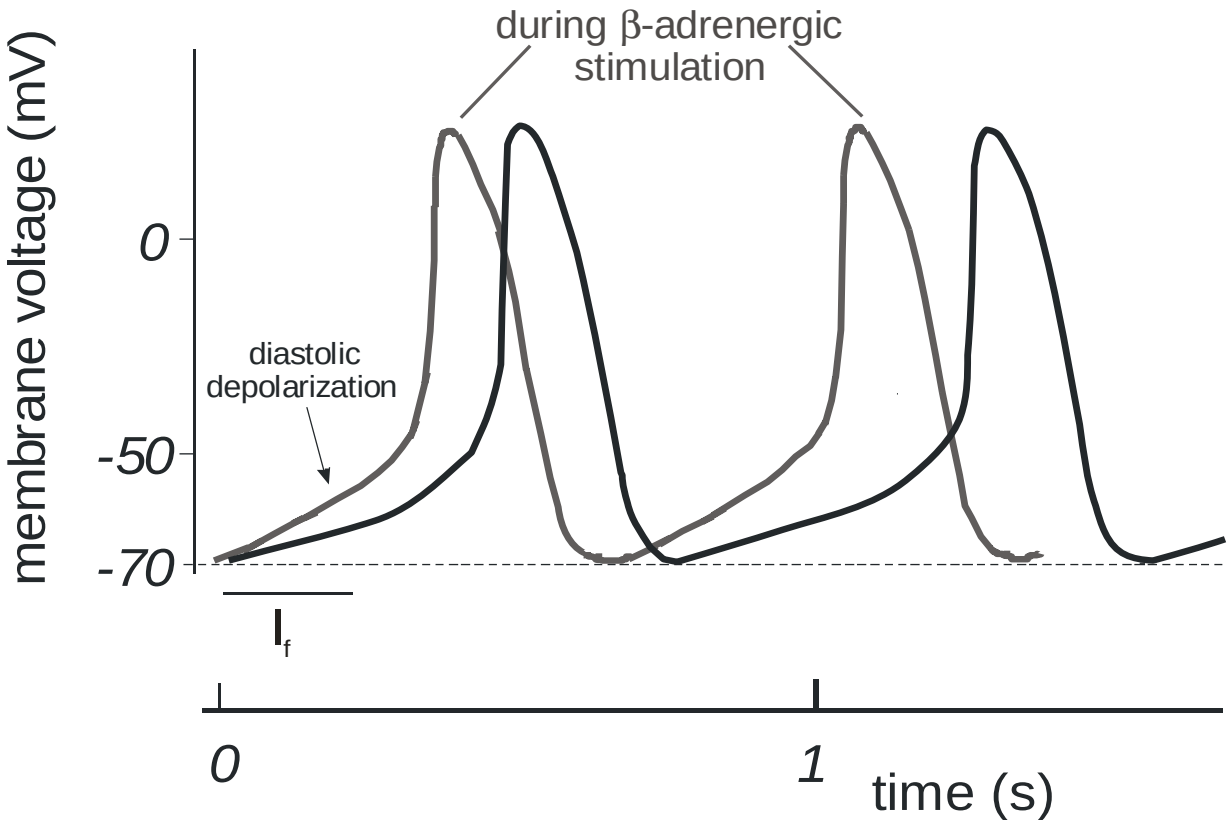


Figure 1. Generation of action potentials in the sino-atrial node (SAN) during basal conditions (black) and during β-adrenergic stimulation (grey). As indicated, the I_f current contributes to the diastolic depolarization and increases the slope of the diastolic depolarization during β-adrenergic stimulation.

and 4 knockout mice have been published [19-23]. Interestingly, mice lacking HCN1 globally show no cardiac phenotype whereas HCN2 and HCN4 knockout mice both show profound alterations in cardiac function. Mice lacking HCN2 either globally or specifically within the heart exhibit sinus arrhythmia, but show no alteration of the heart rate [23]. They are neither bradycardic at rest nor do they respond differently to sympathetic stimulation under stress or during administration of β-adrenergic agonists. The only difference to wild type mice is the variation of RR intervals in the electrocardiogram (ECG). Recordings from single SAN cells revealed that the I_f current in HCN2 deficient cells is reduced by ~25% and that the maximum diastolic potential is more hyperpolarized (~5mV). Ludwig and co-workers proposed the following model to explain these results; in wild type SAN cells, HCN2 stabilizes the generation of spontaneous activity by setting the diastolic potential to a more depolarized level. In HCN2 deficient cells, this influence is missing resulting in a delayed generation of action potentials after K^+ channel-dependent hyperpolarization. The delay is dependent on the magnitude of the hyperpolarization and the time needed to compensate the lack of depolarization by HCN2. In summary, HCN2 is not a cardiac pacemaker but rather is required for a regular heart rate.

The deletion of HCN4 either globally or specifically within the heart results in embryonic death between E10 and E11.5 [22]. At this developmental stage, HCN4 in wild type embryos is specifically expressed in the wall of the left and the right common cardinal vein at the orifice of the sinus venosus - the regions that develops into the SAN. HCN4 knockout embryos show a ~40% reduction of heart rate but no differences in cardiac morphology compared to wild type embryos. Moreover, embryos lacking HCN4 do not respond with an acceleration of the heart rate when increasing the intracellular cAMP concentration. Recordings from single embryonic cardiomyocytes revealed that the I_f current is reduced by 80% in HCN4 deficient cells. Most interestingly, no mature pacemaker-like action potentials could be detected in these cells, confirming the role of HCN4 as a pacemaker in the heart.

Recently, these results have been supported by results from our laboratory. We have generated HCN4 knock-in mice where the binding of cAMP to HCN4 has been abolished by a single amino-acid exchange (R669Q) [24] (**Figure 2**). In a heterologous expression system, it has been shown that the mutation does not influence the protein expression or the cAMP-independent voltage-dependent activation of the channel. But it completely abolishes the shift of the voltage-dependence towards positive potentials when the intracellular cAMP concentration is increased. Surprisingly, $HCN4^{R669Q/R669Q}$ knock-in mice die during embryonic development between days E11.5 and E12. These embryos also show a profound reduction in heart rate and do not respond to administration of β-adrenergic agonists demonstrating that HCN4 is a true pacemaker and the major, if not the only, target for cAMP during sympathetic stimulation in the embryonic heart. Recordings from single embryonic cardiomyocytes revealed that the voltage of half-maximal activation ($V_{1/2}$) of I_f in wild type cells is shifted by 13 mV towards positive potentials compared to $HCN4^{R669Q/R669Q}$ knock-in cells. Addition of cAMP shifted the $V_{1/2}$ of I_f in wild type cells by 6 mV whereas no shift could be observed in mutant cells. Decreasing the intracellular cAMP concentration by blocking adenylyl-cyclase activity negatively shifted the $V_{1/2}$ in wild type cells, thereby reaching the same $V_{1/2}$ as in $HCN4^{R669Q/R669Q}$ knock-in cells. These results strongly support the notion that, even under basal conditions, the I_f in wild type cardiomyocytes is significantly up-regulated by high cAMP concentrations, and that this regulation is crucial for the physiological function of HCN4 as a true cardiac pacemaker and therefore for the survival of the embryo. A further increase of the intracellular cAMP concentration during sympathetic stimulation accelerates the heart rate by shifting the voltage-dependence of I_f towards positive potentials, and thereby enhances the current at a given voltage. The fact that we could not only observe a significant decrease in the heart rate of $HCN4^{R669Q/R669Q}$ but also of $HCN4^{+/R669Q}$ embryos prompted us to study the cardiac phenotype of adult $HCN4^{+/R669Q}$ mice. They are viable and show no obvious difference compared to wild type mice. Surprisingly, neither the heart rate nor the electrophysiology of the atrio-ventricular node or the ventricles was different between genotypes. Only after exercise $HCN4^{+/R669Q}$ developed pauses and sino-atrial node block more often than their wild type littermates. Our findings are supported by those of Herrmann and co-workers [21]. They deleted HCN4 in a conditional manner specifically in the adult heart. The resulting mice display recurrent sinus pauses and show a 75% reduction of I_f in sino-atrial node cells with the remaining current displaying characteristics of HCN2 and, to a lesser degree, of HCN1. In line with our findings, neither basal nor β-adrenergic stimulated heart rate is different in adult HCN4 knockout mice compared to wild-type mice. Based on these results, it has been proposed that HCN4 is the major contributor to sino-atrial I_f. During embryonic development, HCN4 functions as a true pacemaker and is thought to be the major target for cAMP-dependent acceleration of heart rate. In the adult state, I_f seems to largely function as a backup mechanism providing stable cardiac rhythmicity rather than pacing the heart rate itself [21, 23].

What is striking about the results obtained using adult mice is that in humans mutations in the Hcn4 gene are associated with bradycardia as well as other cardiac arrhythmias ([25-28] (**Figure 2**). In a patient with idiopathic sinus-node dysfunction (SND), a heterozygous single base pair deletion in the Hcn4 gene has been found that resulted in a truncated HCN4 protein lacking the CNBD (HCN4-573X) [25]. Heterologous expression of the mutant channel revealed that protein expression and trafficking is not affected by the mutation. However, electrophysiological studies showed that the I_f is insensitive to stimulation with cAMP, that its deactivation kinetics are altered, and that both effects are dominant-negative when co-expressing the mutant channel with wild type channels. Thus, the mutation in the Hcn4 gene alters the I_f characteristics and results in sinus bradycardia *in vivo* underlining the pacemaker function of HCN4 in the human heart. This view is supported by findings from Milanesi and co-workers [26] who showed that in members of a large family sinus bradycardia was associated with a mutation in the Hcn4 gene. They found a single amino-acid exchange in the HCN4 CNBD (S672R) that resulted in a -8.4 mV shift of the $V_{1/2}$ in a heterologous expression system, but did not interfere with the cAMP-induced channel activation. The authors proposed that this effect decreased the depolarizing inward current during the diastolic potential, resulting in a slower basal heart rate. Ueda and colleagues [28] found in a patient with life-threatening sinus-node dysfunction associated with recurrent syncope, QT prolongation in the ECG, and polymorphic ventricular tachycardia, *torsade de pointes*, a missense mutation in the C-linker region between S6 and the CNBD in the Hcn4 gene (D553N).

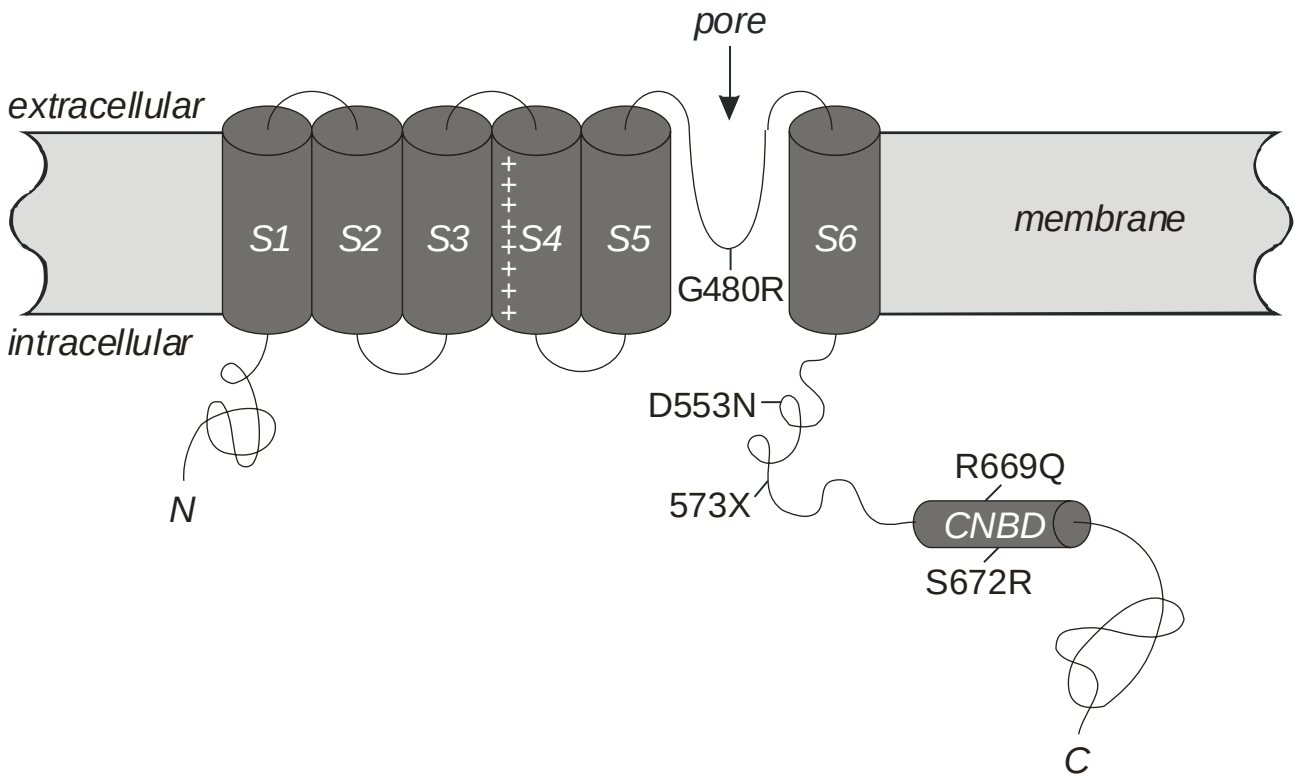


Figure 2. Proposed membrane topology of HCN channels. They consist of six transmembrane domains (S1-S6), a pore loop between S5 and S6 and a cyclic nucleotide-binding domain (CNBD) in the cytosolic C-terminus. The location of the HCN4 mutations found in humans [25-28] as well as the amino-acid exchange that has been used to generate HCN4R669Q knock-in mice [24] is indicated.

In vitro studies revealed that this amino-acid exchange affects trafficking of the channel to the plasma membrane in a dominant-negative manner resulting in reduced I_f currents. Recently, a mutation in the HCN4 ion channel pore leading to sinus bradycardia has been found [27]. Expression of the mutated channel (HCN4G480R) in HEK293 cells revealed that the mutant channels are activated at more negative voltages compared with wild type channels. Moreover, the mutation reduces protein synthesis and trafficking. Taking all these data together, HCN4 seems to be a major contributor to cardiac pacemaking in humans. One reason for the discrepancy between the findings in humans and mice might be the difference in the beating rate of the heart in these two species (60-200 bpm in humans vs. 500-1000 bpm in mice). HCN4 may only serve as a pacemaker at low beating frequencies, as observed in humans, as well as in embryonic mice where the beating frequency is close to that in humans. At higher frequencies, the properties of HCN4 might not be suitable to support the generation of cardiac rhythmicity and therefore, other components take over to generate spontaneous rhythmic activity [29, 30].

Heart rate-reducing agents

Being one of the major pacemakers in the human heart, I_f is an obvious target in the search for drugs that are able to interfere with the generation of cardiac rhythmic activity. The development of HCN channel-specific blockers to selectively influence the heart rate has been one of the goals of pharmacological research over the last few years. These blockers are expected to specifically alter the slope of the diastolic depolarization and therefore, the frequency of the heart rate without affecting other cardiac parameters. The drugs that have been developed to block the I_f current have been named "heart rate-reducing agents". Members of this family are ST567 (alinidine) , UL-FS49 (zatebradine), ZD-7288, and S16257 (ivabradine) [31]. Only one of these substances, ivabradine, has completed clinical development for the treatment of stable angina. Its heart rate-reducing action is specifically due to inhibition of I_f [32]. Ivabradine inhibits the maximal conductance of I_f without modifying the voltage-dependence of activation [33]. The block of HCN channels by ivabradine is "current-dependent"

as well as use-dependent [34, 35]. This means that the effect of the drug is dependent on the ion flow across the membrane and that the effect accumulates during repetitive activity. Therefore, the block is more efficient at higher beating frequencies. HCN channels are the first and so far the only class of ion channels underlying cardiac pacemaking for which a specific blocker has been developed that is in use as a therapeutically active drug.

Biological pacemakers

Recently, efforts have been made to create biological pacemakers as an amendment of, or even substitute for, electronic pacemakers in the treatment of cardiac rhythm disorders. The biggest potential advantage of a biological pacemaker compared to an electronic pacemaker is that they are expected to exhibit autonomic regulation of the rhythm *in vivo*. Therefore, HCN channels are the perfect molecular basis for the generation of a gene-based biological pacemaker because they fulfill both major requirements: 1) they are exclusively activated during the maximum diastolic potential, 2) they are strongly modulated by cAMP, the second messenger that conveys autonomic regulation. At first, the utility of HCN2 as a biological pacemaker has been explored [36]. An adenoviral construct of HCN2 has been generated, which was previously characterized in isolated neonatal and adult ventricular cardiomyocytes [37]. The same construct has been used for injection into the canine left atrium. After sinus arrest, the overexpression of HCN2 was able to restore a normal sinus rhythm [36]. To test the autonomic responsiveness of this biological pacemaker, the HCN2 virus was injected into the left bundle brunch of the Purkinje system, a permanent AV block was induced and an electronic pacemaker was inserted at an escape rate of 46 bpm [38]. Epinephrine increased the idioventricular rate in HCN2-injected animals from 56 to 86 bpm. This shows that HCN2 has the potential to function as a biological pacemaker that even responds to autonomic stimulation. Another approach used human mesenchymal stem (hMS) cells that stably expressed HCN2 [39]. hMS cells have been shown to electrically couple to cardiomyocytes *in vitro* [40]. HCN2-expressing hMS cells are not spontaneously active but generate an I_f current when the adjacent cardiomyocyte is hyperpolarized. The current from the cardiomyocyte flows through gap junctions to the hMS cell and opens the HCN2 channels. The resulting I_f current induces the generation of an action potential in the adjacent myocyte that then propagates throughout the heart [41]. HCN2 expressing hMS cells have been injected into the ventricular myocardium of the dog heart. Most of the animals sustain cardiac pacemaker function after suppression of SAN automaticity and AV node conduction [42]. In the future, gene-based and cell-based assays need to be optimized and safety issues need be addressed before these approaches can be applied for therapeutic use.

References

1. DiFrancesco, D., Pacemaker Mechanisms in Cardiac Tissue. Annual Review of Physiology, 1993. 55(1): p. 455-472.

2. DiFrancesco, D., The contribution of the 'pacemaker' current (If) to generation of spontaneous activity in rabbit sino-atrial node myocytes. J Physiol, 1991. 434(1): p. 23-40.

3. DiFrancesco, D. and C. Tromba, Muscarinic control of the hyperpolarization-activated current (If) in rabbit sino-atrial node myocytes. J Physiol, 1988. 405(1): p. 493-510.

4. DiFrancesco, D. and P. Tortora, Direct activation of cardiac pacemaker channels by intracellular cyclic AMP. Nature, 1991. 351(6322): p. 145-147.

5. Santoro, B., et al., Interactive cloning with the SH3 domain of N-src identifies a new brain specific ion channel protein, with homology to Eag and cyclic nucleotide-gated channels. Proceedings of the National Academy of Sciences, 1997. 94(26): p. 14815-14820.

6. Santoro, B., et al., Identification of a Gene Encoding a Hyperpolarization-Activated Pacemaker Channel of Brain. Cell, 1998. 93(5): p. 717-729.

7. Ludwig, A., et al., A family of hyperpolarization-activated mammalian cation channels. Nature, 1998. 393(6685): p. 587-591.

8. Seifert, R., et al., Molecular characterization of a slowly gating human hyperpolarization-activated channel predominantly expressed in thalamus, heart, and testis. Proceedings of the National Academy of Sciences, 1999. 96(16): p. 9391-9396.

9. Kaupp, U.B. and R. Seifert, Molecular diversoty of pacemaker ion channels. Annual Review of Physiology, 2001. 63(1): p. 235-257.

10. Altomare, C., et al., Integrated Allosteric Model of Voltage Gating of HCN Channels. J. Gen. Physiol., 2001. 117(6): p. 519-532.

11. Qu, J., et al., Functional comparison of HCN isoforms expressed in ventricular and HEK 293 cells. Pflügers Archiv European Journal of Physiology, 2002. 444(5): p. 597-601.

12. Mistrik, P., et al., The Murine HCN3 Gene Encodes a Hyperpolarization-activated Cation Channel with Slow Kinetics and Unique Response to Cyclic Nucleotides. J. Biol. Chem., 2005. 280(29): p. 27056-27061.

13. Wainger, B.J., et al., Molecular mechanism of cAMP modulation of HCN pacemaker channels. Nature, 2001. 411(6839): p. 805-810.

14. Altomare, C., et al., Heteromeric HCN1-HCN4 channels: a comparison with native pacemaker channels from the rabbit sinoatrial node. J Physiol, 2003. 549(2): p. 347-359.

15. Much, B., et al., Role of Subunit Heteromerization and N-Linked

Glycosylation in the Formation of Functional Hyperpolarization-activated Cyclic Nucleotide-gated Channels. J. Biol. Chem., 2003. 278(44): p. 43781-43786.

16. Moosmang, S., et al., Cellular expression and functional characterization of four hyperpolarization-activated pacemaker channels in cardiac and neuronal tissues. European Journal of Biochemistry, 2001. 268(6): p. 1646-1652.

17. Shi, W., et al., Distribution and Prevalence of Hyperpolarization-Activated Cation Channel (HCN) mRNA Expression in Cardiac Tissues. Circ Res, 1999. 85(1): p. e1-6.

18. Dobrzynski, H., et al., Site of Origin and Molecular Substrate of Atrioventricular Junctional Rhythm in the Rabbit Heart. Circ Res, 2003. 93(11): p. 1102-1110.

19. Nolan, M.F., et al., The Hyperpolarization-Activated HCN1 Channel Is Important for Motor Learning and Neuronal Integration by Cerebellar Purkinje Cells. Cell, 2003. 115(5): p. 551-564.

20. Nolan, M.F., et al., A Behavioral Role for Dendritic Integration: HCN1 Channels Constrain Spatial Memory and Plasticity at Inputs to Distal Dendrites of CA1 Pyramidal Neurons. Cell, 2004. 119(5): p. 719-732.

21. Herrmann, S., et al., HCN4 provides a 'depolarization reserve' and is not required for heart rate acceleration in mice. EMBO J, 2007. 26(21): p. 4423-32.

22. Stieber, J., et al., The hyperpolarization-activated channel HCN4 is required for the generation of pacemaker action potentials in the embryonic heart. Proceedings of the National Academy of Sciences, 2003. 100(25): p. 15235-15240.

23. Ludwig, A., et al., Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2. EMBO J, 2003. 22(2): p. 216-24.

24. Harzheim, D., et al., Cardiac pacemaker function of HCN4 channels in mice is confined to embryonic development and requires cyclic AMP. EMBO J, 2008. 27(4): p. 692-703.

25. Schulze-Bahr, E., et al., Pacemaker channel dysfunction in a patient with sinus node disease. J. Clin. Invest., 2003. 111(10): p. 1537-1545.

26. Milanesi, R., et al., Familial Sinus Bradycardia Associated with a Mutation in the Cardiac Pacemaker Channel. N Engl J Med, 2006. 354(2): p. 151-157.

27. Nof, E., et al., Point Mutation in the HCN4 Cardiac Ion Channel Pore Affecting Synthesis, Trafficking, and Functional Expression Is Associated With Familial Asymptomatic Sinus Bradycardia. Circulation, 2007. 116(5): p. 463-470.

28. Ueda, K., et al., Functional Characterization of a Trafficking-defective HCN4 Mutation, D553N, Associated with Cardiac Arrhythmia. J. Biol. Chem., 2004. 279(26): p. 27194-27198.

29. Couette, B., et al., Physiological and pharmacological insights into the role of ionic channels in cardiac pacemaker activity. Cardiovasc Hematol Disord Drug Targets, 2006. 6(3): p. 169-90.

30. Lakatta, E.G., et al., The Integration of Spontaneous Intracellular Ca2+ Cycling and Surface Membrane Ion Channel Activation Entrains Normal Automaticity in Cells of the Heart's Pacemaker. Ann NY Acad Sci, 2006. 1080(1): p. 178-206.

31. Baruscotti, M., A. Bucchi, and D. DiFrancesco, Physiology and pharmacology of the cardiac pacemaker ("funny") current. Pharmacology & Therapeutics, 2005. 107(1): p. 59-79.

32. DiFrancesco, D. and J.A. Camm, Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. Drugs, 2004. 64(16): p. 1757-65.

33. Bois, P., et al., Mode of action of bradycardic agent, S 16257, on ionic currents of rabbit sinoatrial node cells. Br J Pharmacol, 1996. 118(4): p. 1051-7.

34. Bucchi, A., M. Baruscotti, and D. DiFrancesco, Current-dependent Block of Rabbit Sino-Atrial Node I_f Channels by Ivabradine. J. Gen. Physiol., 2002. 120(1): p. 1-13.

35. Van Bogaert, P.P. and F. Pittoors, Use-dependent blockade of cardiac pacemaker current (If) by cilobradine and zatebradine. European Journal of Pharmacology, 2003. 478(2-3): p. 161-171.

36. Qu, J., et al., Expression and Function of a Biological Pacemaker in Canine Heart. Circulation, 2003. 107(8): p. 1106-1109.

37. Qu, J., et al., HCN2 Overexpression in Newborn and Adult Ventricular Myocytes: Distinct Effects on Gating and Excitability. Circ Res, 2001. 89(1): p. e8-14.

38. Plotnikov, A.N., et al., Biological Pacemaker Implanted in Canine Left Bundle Branch Provides Ventricular Escape Rhythms That Have Physiologically Acceptable Rates. Circulation, 2004. 109(4): p. 506-512.

39. Potapova, I., et al., Human Mesenchymal Stem Cells as a Gene Delivery System to Create Cardiac Pacemakers. Circ Res, 2004. 94(7): p. 952-959.

40. Valiunas, V., et al., Human mesenchymal stem cells make cardiac connexins and form functional gap junctions. J Physiol, 2004. 555(3): p. 617-626.

41. Robinson, R.B., et al., If and the biological pacemaker. Pharmacological Research, 2006. 53(5): p. 407-415.

42. Plotnikov, A.N., et al., Xenografted Adult Human Mesenchymal Stem Cells Provide a Platform for Sustained Biological Pacemaker Function in Canine Heart. Circulation, 2007. 116(7): p. 706-713.

Dr. Dagmar Harzheim and Dr. Martin Bootman

may be contacted at:

The Laboratory of Molecular Signalling,

The Babraham Institute

Babraham

Cambridge

CB22 3AT UK

dagmar.harzheim@bbsrc.ac.uk

martin.bootman@bbsrc.ac.uk

Secretary's Column

Normally at this time of year I would be able to report on the Society's Spring Meeting, but this year things are different as the meeting has been replaced by a joint effort with the British Cardiovascular Society which will not take place until June. Plans for the meeting are progressing well and an excellent programme has been put together, but a report will have to wait until the next issue of the Bulletin in July.

Therefore I will instead introduce you to our new Committee members: Yvonne Alexander, Alison Cave and David Grieve. Yvonne adds to the already strong representation from the University of Manchester; having now met Alison for the first time, she has started sending me manuscripts to review as part of her editorial role at the British Journal of Pharmacology - I don't mind really, no honestly I don't; and David continues the link with Queen's University Belfast that started with Barbara McDermott. It is a pleasure to work with them all and I look forward to the next 3 years.

At the end of this year four vacancies will arise on the Committee as Barbara Casadei, Andrew Grace, Cathy Holt and Nicola King will all come to the end of their 3-year stints. A nomination form has been included with this issue of the Bulletin so that, if necessary, an election can be held prior to the Annual General Meeting, which will be in Bristol in September. Please send your nominations to me at the address on the form.

I hope to see as many of you as possible in Manchester.

Chris Jackson

Heart Research UK/BSCR Session at the Joint BSCR/BCS Meeting

Wednesday 4th June, 10.45 - 12.15

Exchange Hall, Manchester Central Convention Centre

'Translational research in cardiac electrophysiology'

Chairs:
Prof David Eisner, University of Manchester
Dr Andrew Grace, University of Cambridge

Atrial electrophysiology - role of tissue preparations
Prof Nicholas Peters, St Mary's Hospital, London

AV nodal electrophysiology - new insights
Prof Mark Boyett, University of Manchester

Ventricular arrhythmias in heart failure - cellular studies
Dr Luigi Venetucci, University of Manchester

Ventricular arrhythmias in heart failure - animal models
Dr Rachel Myles, University of Glasgow

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Vacancies on Executive Committee

At the end of 2008 the following members will retire from the Committee, having completed a 3-year term of service: Barbara Casadei, Andrew Grace, Cathy Holt and Nicola King. Thus there will be vacancies for 4 new members of the Committee.

Nominations are therefore required for these posts, to be taken up for 3 years from January 2009. Nominations of both clinically-qualified investigators and basic scientists are encouraged.

If the number of nominees exceeds the number of vacancies, elections will take place by postal ballot before the AGM. Clause 7b of the Constitution stipulates that "nominations for members of the Committee must be made by full members of the Association in writing and must be in the hands of the Secretary at least 60 days before the Annual General Meeting". This year the AGM will be held at the BSCR Meeting to take place at the University of Bristol during September 2008. To allow time for a postal ballot (if required) prior to the AGM, nominations must be received by 31 May 2008.

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

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Nomination Form for Committee Membership

Name of proposed Committee Member:

Year of first joining the Society:

Please provide brief biographical details and a statement of reasons for wanting to serve on the Committee (please do not exceed the space provided below). In the event that a postal ballot is required, these details will be printed in the BSCR Quarterly Bulletin. For this purpose, please e-mail an electronic copy of the following statement and a photograph to chris.jackson@bristol.ac.uk.

I agree to stand for election to the BSCR Committee

Signature: Date:

Proposed by: Signature:
(BLOCK CAPITALS)

Seconded by: Signature:
(BLOCK CAPITALS)

Please return the completed form (by post) by 31 May 2007 to the Secretary:

Dr Christopher Jackson
Bristol Heart Institute
University of Bristol
Level 7, Bristol Royal Infirmary
Bristol BS2 8HW

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

WINTER BSCR WORKSHOP 2008

A joint workshop with the British Heart Foundation

"NEW FRONTIERS IN CARDIOPROTECTION"

DATE: Monday 1st December, 2008

VENUE: The Elias Library,
3rd Floor, The Hatter Cardiovascular Institute,
University College London,
London, WC1E 6HX.

ORGANISORS: Dr Derek Hausenloy & Prof Derek Yellon

STRUCTURE: This BSCR Winter Workshop will be a one day symposium comprising presentations from National and International speakers interspersed with plenty of time for discussion.

PROGRAMME (with confirmed speakers)**:**

1. Cardioprotection: Lost in translation	Prof Lionel Opie	Cape Town, South Africa
2. Ischaemic Postconditioning	Prof Michel Ovize	Lyon, France
	Prof Michael Marber	London, UK
3. Remote Ischaemic Pre/Postconditioning	Prof Hans Bøtker	Copenhagen, Denmark
	Dr Rajesh Kharbanda	Oxford, UK
	Mr Michael Gaunt	Cambridge, UK
4. Adenosine and its agonists	Prof James Downey	Alabama, US
5. Metabolic Modulation in AMI	Prof Lionel Opie	Cape Town, S Africa
6. The RISK Pathway-Erythropoietin	Dr Derek Hausenloy	London, UK
7. The RISK Pathway-Natriuretic Peptides	Prof Gary Baxter	Cardiff, Wales
8.The Mitochondrial Permeability Transition Pore	Prof Andrew Halestrap	Bristol, UK
	Prof Michel Ovize	Lyon, France
9. Imaging Cardioprotection using Cardiac MRI	Dr Stuart Cook	London, UK
10. Comorbidites and Cardioprotection	Prof Derek Yellon	London, UK
11. Adipocytokines and Cardioprotection	Dr Chris Smith	London, UK

Attendance is limited to BSCR members only (www.bscr.org) and places are strictly limited to the first 50 interested participants. *Please contact:* Dr Derek Hausenloy E-mail – d.hausenloy@ucl.ac.uk

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

JOINT MEETING WITH

British Cardiovascular Society

DATES: Mon 2nd and Tues 3rd June, 2008

VENUE:
Manchester Central Convention Centre (Charter 2)

"CAUSES AND CONSEQUENCES OF MYOCARDIAL INFARCTION: NEW CONCEPTS"

Monday 2nd June

11.00 – 11.15h **Welcome and introduction**

11.15 – 12.45h **BSCR Symposium (1)**

Unstable Plaque: To Inflammation and Beyond

Chairpersons: Cathy Holt, Chris Jackson

Erik Biessen (Maastricht, The Netherlands): 'Inflammatory mediators and plaque destabilisation'.
Juan Kaski (London): 'Biomarkers of inflammation'.
David Grainger (Cambridge): 'Chemokines as therapeutic targets in plaque rupture'.
Mark Pepys (London): 'C-reactive protein and plaque stability'.

12.45 – 14.00h **LUNCH**

14.00 – 15.30h **BSCR Symposium (2)**

Targeting Acute and Chronic Remodelling Post-myocardial Infarction

Chairpersons: Gillian Gray, Nicola King

Allan Struthers (Dundee): 'Cardiac remodelling - mechanisms and clinical implications'.
Nicola Smart (London): 'Thymosin β4, angiogenesis and cardiac remodelling'.
Johann Bauersachs (Wurzburg, Germany): 'Role of aldosterone in acute and chronic cardiac remodelling'.
Emma Birks (London): 'Reversing cardiac remodelling in the failing heart'.

15.30 – 16.30h **TEA**

16.30 – 17.30h **BCS Keynote Lecture – Nilesh Samani (Leicester)**

17.30 – 19.00h **WINE RECEPTION**
BSCR posters / BCS Basic Science posters

20.00h **BSCR DINNER**
@ Manchester Museum of Science and Industry (MOSI)

Tuesday 3rd June

08.45 – 10.15h **BSCR *Free Communications* -** Early Career Investigator Prize

Chairpersons: Barbara McDermott, Michael Curtis

Cressida Beeching (Bristol): 'Reduction of plaque instability by suppression of VSMC apoptosis with soluble N-cadherin'.
Agnieszka Kozak (Edinburgh): 'Characterization of the role of dimethylarginine dimethylaminohydrolases in murine heart post-myocardial infarction'.
Sara McSweeney (Edinburgh): 'Deficiency of 11β-hydroxysteroid dehydrogenase type 1 augments the inflammatory response during myocardial infarct healing'.
Kirsten Riches (Leeds): 'Hypoxia inhibits MMP-2 activation and invasion in human cardiac myofibroblasts'.
Youyou Zhao (Belfast): 'Role of NADPH oxidase-derived reactive oxygen species in cardiac dysfunction associated with doxorubicin chemotherapy'.

10.15 – 11.15h **COFFEE**

11.15 – 12.45h **BSCR Symposium (3)**

Electrophysiological Consequences of Myocardial Ischaemia and Remodelling

Chairpersons: Barbara Casadei, Andrew Grace

Gerd Hasenfuss (Göttingen, Germany): 'The myocardial response to injury: stretching the role of calcium'?
David Eisner (Manchester): 'The impact of ischaemia and remodelling on the myocardium – alternating contraction and sparking arrhythmias'.
Nicholas Peters (London): 'Cellular and electrophysiological remodelling and ventricular arrhythmogenesis'.
Arthur Wilde (Amsterdam, Netherlands): 'Genetic basis of malignant ventricular arrhythmias'.

12.45 – 14.00h **LUNCH**
BCS Young Research Workers Prize (Basic Science)

14.00 – 15.30h **BSCR Symposium (4)**

Novel Therapeutic Developments in Gene and Cell Therapy

Chairpersons: Andrew Baker, Chris Newman

Sian Harding (London): 'Adeno-associated virus-6 SERCA2a as a therapy for heart failure'.
Keith Channon (Oxford): 'HIF1α: a promising therapeutic approach for peripheral and myocardial ischemia'.
Paolo Madeddu (Bristol): 'Gene and cell therapy for angiogenesis'.
Anthony Mathur (London): 'Clinical trials using autologous stem cells for cardiac disease'.

15.30 – 15.45h **Presentation of *Clinical Science* and BSCR prizes**

15.45 – 16.30h **TEA**

16.30 – 17.30h **BCS keynote lecture – Michael Schneider (London)**

Travel Report: A visit to the Cardiovascular Development Unit at the Herman B. Wells Centre for Paediatric Research, University of Indiana, Indianapolis, U.S.A.

4th-6th February 2008

By David Martindill, Molecular Medicine Unit, UCL Institute of Child Health

Weather-wise, luck wasn't on my side during my visit to the Herman B. Wells Centre for Paediatric Research at the University of Indiana (UI) in Indianapolis. My host for the trip, Dr. Anthony Firulli, had advised me to wrap up warm but I was still under-prepared for the particularly harsh Midwest winter. Tony is one of the group leaders from the Wells Centre's Cardiovascular Development Unit (CDU). We met at a symposium in Kyoto last year and decided to remain in close contact in light of our common interest, the Twist subfamily of bHLH transcription factors. My trip therefore served an obvious purpose, namely to forge a better understanding of the work carried out in our labs. However, it also enabled me to receive critical feedback of my work a couple of months before my PhD viva examination.

The location of Indianapolis (top) and the view of the city skyline from the University Place Hotel (bottom).

Indianapolis, referred to by the locals as 'Indy', has had a hard time shaking off nicknames such as 'India-no-place'. That it is the capital of a state famed for little more than growing corn and soybean doesn't help matters. This is despite its hosting of the impressive Indianapolis 500 race each spring. Personally, I enjoyed my time in the city. It was clean, felt very safe and had some great places to eat (I especially recommend the Brussels sprout soup at the 'Bugs Temple' restaurant on the UI campus!).

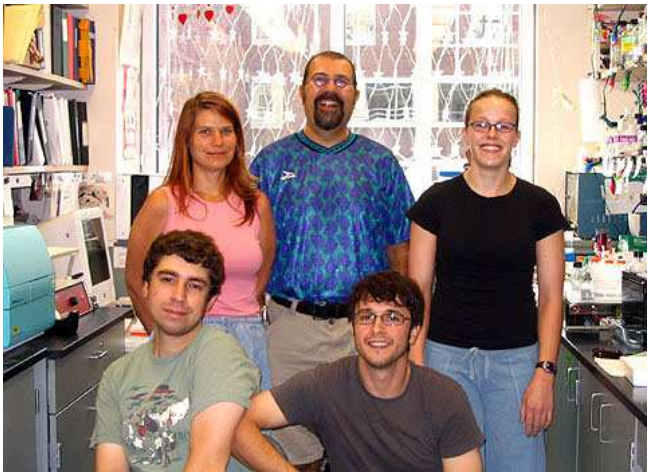
The Herman B. Wells Centre (the 'Wells Centre') was opened in 1991 and is named after a long-standing UI president. Presently the centre accommodates 32 investigators and over 200 staff members but is expanding rapidly. Its situation within the IU School of Medicine, the second largest medical school in America, provides excellent opportunities for collaborations between scientists and physicians. Professor Loren Field is the head of the CDU at the Wells Centre. This unit comprises seven investigators whose teams research the molecular biology of heart morphogenesis (Dr. Tony Firulli and Dr. Simon Conway), adult heart function (Dr. Mark Payne and Dr. Lei Wei) and the regeneration of the diseased heart (Prof. Field, Dr. Michael Rubart and Dr. Weinian Shou). The group is therefore unique in that it comprehensively analyses mammalian heart function from the fetal stage to the diseased adult state. The CDU hosted the very successful 14th Annual Weinstein Cardiovascular Development Conference in May 2007. Not long afterwards, Loren and his team secured a whopping $11.5 million grant from the NIH. These funds have made expansion of the CDU possible and Loren's team is looking to recruit at least three more investigators in the near future.

Dr. Tony Firulli is becoming increasingly recognised

The Wells Centre

as the leading expert on the Twist subfamily of bHLH transcription factors. This small family of proteins plays important roles during embryogenesis, particularly during placentation and cardiac, limb and craniofacial morphogenesis. Tony acquired his PhD at Buffalo University in New York, but has spent the majority of his research career in Eric Olson's lab in Texas. In 1998, Tony and my supervisor, Dr. Paul Riley, independently published studies that characterised the phenotype of mice deficient for another developmentally important bHLH transcription factor, Hand1. Tony's interest in bHLH factors subsequently broadened and in 2003 his group published a study that illustrated the importance of site-specific phosphorylation in modulating the function of the Twist subfamily bHLH factors. Two years later, his group published an article in Nature Genetics that showed that mutations of two phosphoresidues in Twist1 are associated with Saethre-Chotzen syndrome, a disorder affecting several tissues derived from the neural crest. My work is related in this regard to Tony's. Last year we published data that implicate the phosphorylation of Hand1, at the two conserved residues identified by Tony's group, in its release from the nucleolus as a critical step in the giant cell differentiation programme during rodent placentation.

Tony employs a small but very efficient group of people. His most senior post-doc is his wife, Beth, who has the envious reputation among the unit of being the hardest worker! This fantastic husband-and-wife team is supported by Josh Vincentz, a post-doc who is currently preparing a manuscript for Developmental Biology, and Ralston Barnes, a PhD student who arrived after his previous lab in New Orleans was destroyed by Hurricane Katrina. Their lab technician, Ellen Gunn, completes the group. During my visit, Beth showed me in detail how to conduct phosphopeptide mapping, a process by which the position of phosphorylated residues in proteins can be inferred. Tony also revealed some unpublished *in vitro* and mouse phenotype data that supported my work and prompted an insightful discussion regarding the mechanism and function of bHLH post-translational modification. Additionally, the team shared with me details of the unpublished cardiac phenotype of a mouse carrying Hand2 knocked into Hand1. This shed some light on the degree of functional redundancy between the Hand factors during cardiac morphogenesis.



The Firulli group. Clockwise from top left: Beth Firulli, Tony Firulli, Ellen Gunn, Ralston Barnes and Josh Vincentz.

Although Prof. Field and Dr. Shou were away during my visit, I had the privilege of meeting the remaining CDU group leaders on a one-to-one basis. My first appointment was with Dr. Mark Payne. Mark's work investigates how aberrant mitochondrial function results in heart failure in children and recently delineated the co-translational model of protein import into mitochondria. This involves the recruitment of ribosomes to mitochondria, which facilitates efficient mitochondrial import of nuclear-encoded proteins. Mark has also investigated the link between mutations in mitochondrial tri-functional protein (MTP), an enzyme that catalyses long chain fatty acid oxidation, and a subset of metabolism disorders. Recessive mutations in MTP are associated with sudden infant death syndrome (SIDS). Often the basis of this is cardiomyopathy, which is due to the heart switching its energy source from glucose to fatty acids in times of stress or poor nutritional intake. Mark's group has developed a technique of delivering MTP to the mitochondria of affected individuals. This is achieved by fusing to the MTP protein the transactivator of transcription (TAT) peptide from HIV, which delivers proteins to mitochondria. Importantly, the fusion protein can cross the placenta and

Dr. Mark Payne

is detectable in the fetus and newborn pups. Current treatment of patients with MTP defects is fasting avoidance and a low fat diet. Mark's team is hoping that their work will strengthen the possibility of gene therapy being used to treat the condition and reduce the incidence of SIDS.

I was next introduced to Dr. Michael Rubart. Michael recently set up his own group after many successful years as a post-doc in Loren's lab. Michael is interested in the possibility of repairing the damaged heart by cellular transplantation. To investigate this he uses two-photon laser scanning microscopy (TPLSM), a process by which calcium transients in donor and host cardiomyocytes are simultaneously measured within recipient hearts, to assess the level of functional coupling of transplanted cells. In 2003, Michael and Loren's team transplanted EGFP-expressing fetal cardiomyocytes into the hearts of non-transgenic adult mice. Incredibly, the donor cardiomyocytes formed a functional syncytium with host cardiomyocytes in the myocardium and their calcium transients were synchronous. More recently, in collaboration with a group in Los Angeles, Michael showed that human embryonic stem cell-derived cardiomyocytes can also survive and mature in rat hearts. On the other hand, a Nature paper that Michael and Loren published in collaboration with another group showed that skeletal myoblasts were, on the whole, functionally isolated from host myocardium. Michael's work therefore supports the possibility that donor cardiomyocytes, but probably not skeletal myoblasts, can stably engraft into recipient hearts when injected directly into the myocardial wall.

Dr. Michael Rubart

Next on my itinerary was an appointment with Dr. Simon Conway, who moved to the U.S.A. as a post-doc from Britain in the mid-90s. Simon and I actually had more in common than a British passport; his first post-doctoral position was at the Institute of Child Health in London. Simon was able to give me some valuable insights into what it is like for a fellow countryman living in the States, most memorably the claim that "most Americans think us Brits are smarter than we really are!". Simon's team is investigating the roles during cardiac morphogenesis of the neural crest-expressed transcription factor Pax3 and the adhesive glycoprotein Periostin. Simon's team have shown that loss of Pax3 in mice leads to mid-gestational lethality, caused by insufficient mesenchymal cells that normally septate the OFT. Simon's group have cloned the proximal promoter of Periostin and showed that it drives tissue-specific expression in a subpopulation of cells in the cardiac OFT and endocardial cushions. Appropriately, mice deficient for Periostin have cardiac OFT and atrioventricular valve defects. These findings are therefore hoped to shed some light on the pathogenesis of cardiac outflow tract (OFT) and valve defects.

Dr. Simon Conway

I finally had the pleasure of meeting Dr. Lei Wei. Lei is the most recent addition to Loren's team and most recently worked with Bob Schwartz at Baylor College of Medicine in Houston. Lei's work is advancing our understanding of the functions of Rho kinases in cardiac morphogenesis and adult heart function. Over a cup of tea, Lei described to me how she became interested in these factors. Nearly ten years ago, she found that treating mouse embryos with a Rho kinase inhibitor blocked the migration and fusion of the bilateral cardiac primordia. More recently, work by Lei's team has shown that one of these kinases, Rho-associated coiled-coil containing protein kinase-1 (Rock-1), is activated by Caspase-3-dependent cleavage. Moreover, ectopic Rock-1 cleavage is associated with many cases of human heart failure characterised by cardiomyocyte apoptosis. Rock-1 has previously been implicated in modulating cardiomyocyte hypertrophy. This is initially a compensatory response as a result of pressure overload but, if persistent, can lead to heart failure. Lei's team has shown that in a transgenic mouse model of cardiac hypertrophy, Rock-1 deficiency does not attenuate the hypertrophic response. This is despite these mice exhibiting attenuated left ventricular dilation and contractile dysfunction. Thus deletion of Rock-1 is thought to protect the heart against pressure overload.

Dr. Lei Wei

The CDU at the Wells Centre thoroughly deserve their reputation and my trip to meet them was an illuminating and enjoyable experience. Happening just after submitting my PhD, it also gave me a valuable insight into the benefits of gaining experience in the U.S. Finally, the trip dispelled - at least in my mind - the myth that Indy is merely just a stopover on the way to somewhere else!

Cardiovascular Meetings

Weinstein Cardiovascular Development Conference will this year take place in Houston, Texas on 15th-18th May, 2008. Please visit http://www.weinsteinmeeting.org/ for further information and registration.

XXVIII European Section Meeting of the ISHR will be held on 28-31 May 2008, Athens, Greece. Further information can be obtained from www.ishr-greece2008.gr. Panos Travel Ltd - Attn: ISHR 2008 Phone: +30/2109962500; Fax: +30/2109969245 E-mail: ishr2008@panos-travel.gr

Heart Failure 2008 Congress, 14th - 17th June 2008 Milano Convention Centre, Milan, Italy. Further Information is available from: Heart Failure 2008 Secretariat, ESC - European Heart House, 2035 Route des Colles, Les Templiers - BP 179, 06903 Sophia Antipolis Cedex, France Tel: +33 (0)4 92 94 76 00; Fax: +33 (0)4 92 94 76 01

XXX Annual Meeting of the North American Section of the ISHR. Hilton Cincinnati, Netherlands Plaza, Cincinnati,OH. 17th-20th June , 2008. Enquiries: Dr Litsa Kranias, litsa.kranias@uc.edu; Dr Jeffrey Robbins, jeff.robbins@cchmc.org

AHA Basic Cardiovascular Sciences Conference 2008 - Heart Failure: Molecular Mechanisms and Therapeutic Targets will be held at Keystone Conference Center - Keystone, CO on 28-31 July, 2008. For further information: E-mail: scientificconferences@heart.org; Phone: (888) 242-2453 or (214) 570-5935

ESC Congress 2008, 30th August 2008 - 3rd September 2008 Messe München, Germany. Further information can be found at: http://www.escardio.org/

Keystone Symposium: Metabolism and Cardiovascular Risk will take place in Breckenridge, Colorado on 23-28 September, 2008. For details of this and other Keystone Symposia, visit: www.keystonesymposia.org

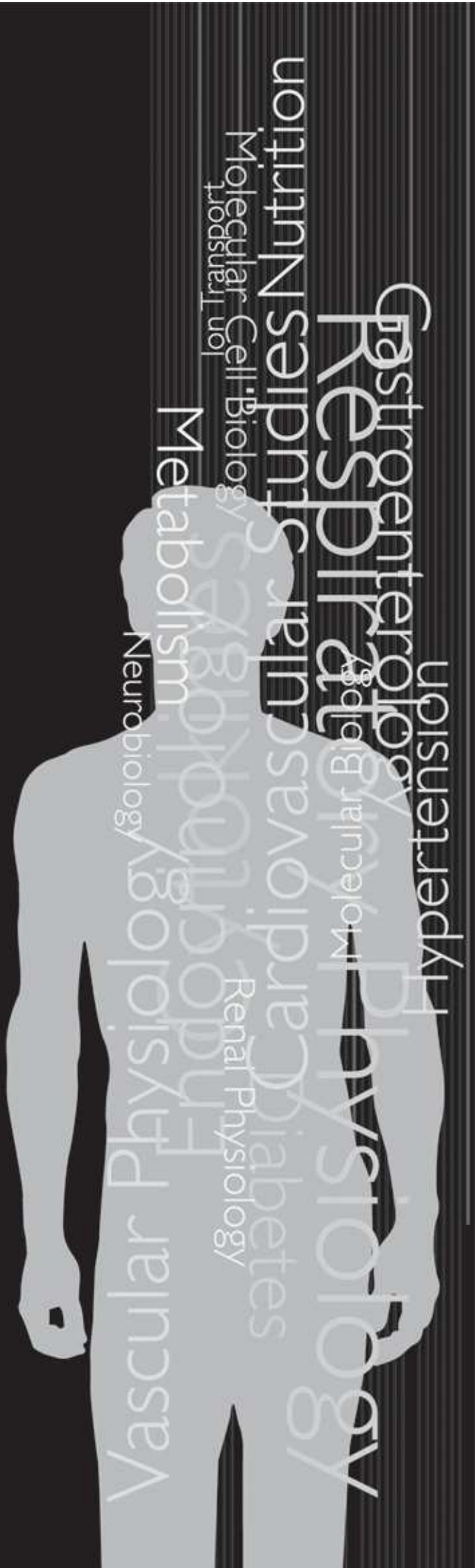
Mitochondrial Biology in Cardiovascular Health and Disease Conference to be held at the National Institutes of Health, Bethesda, Maryland on 6th-7th October, 2008. Further information regarding the programme, registration and abstract submission can be obtained from http://www.mitochondrial2008.com/

2008 Scientific Sessions of the American Heart Association will be held at the Ernest N. Morial Convention Center, New Orelans, Louisiana on 8th-12th November. All details including key dates can be found at: http://scientificsessions.americanheart.org/portal/scientificsessions/ss

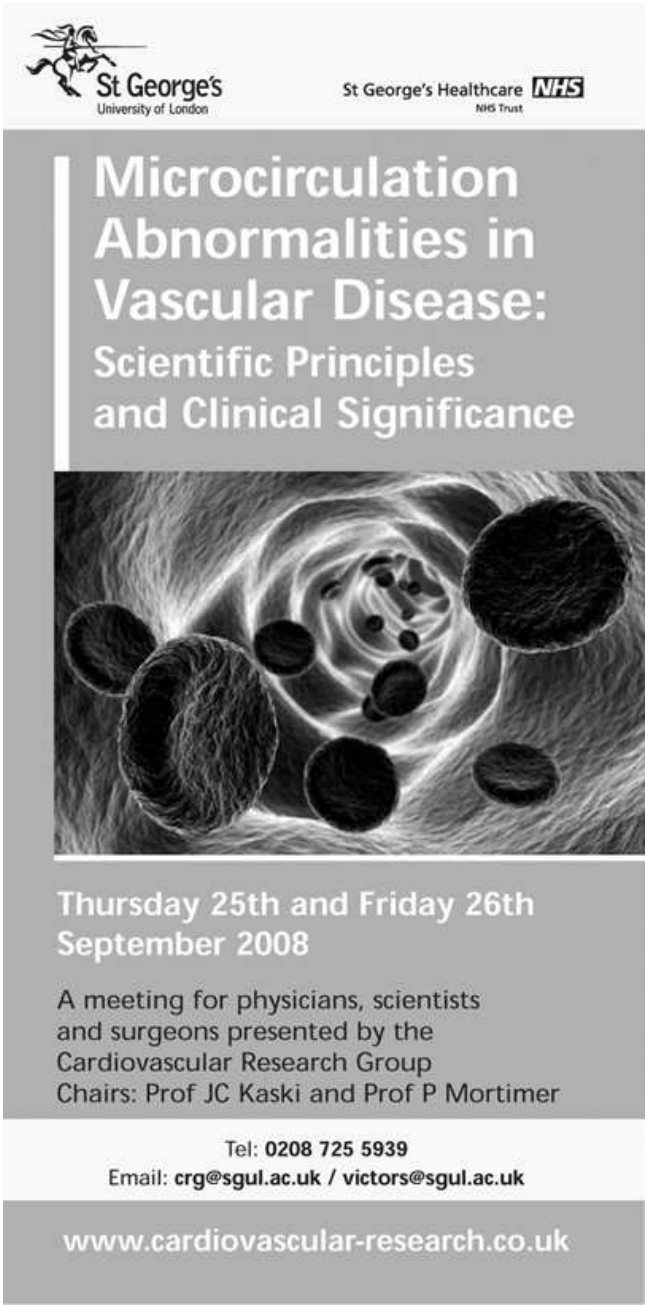
Travel Reports for *The* Bulletin

The Bulletin editors look forward to publishing travel reports written by BSCR members. These can be on any conference, course or laboratory visit of interest to other members and could perhaps contain photographs. If you are planning to travel to a relevant cardiovascular meeting and would like to write a report for *The* Bulletin, please contact the editors beforehand. A bursary of **£300** is available towards the cost of your visit which will be provided on receipt of the report.

Bon voyage!



Clinical SCIENCE



Submission Deadlines for *The* Bulletin:

Volume	*Date*	*Deadline*
21 (3)	***July 2008***	*1st June*
21 (4)	***October 2008***	*1st September*
22 (1)	***January 2009***	*1st December*
22 (2)	***April 2009***	*1st March*

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)

Visit the BSCR Website: www.bscr.org

- Information on forthcoming meetings, workshops and symposia
- All the latest BSCR News
- Job and Study Opportunities
- Download *The* Bulletin in pdf format
- Contact details and profiles of BSCR Committee Members

British Heart Foundation Grants

Chairs and Programme Grants Committee November 2007

Special Project Grants

Professor A M Buchan, University of Oxford. "Clinical Research Infrastructure Initiative: Clinical Research Imaging Centre" £3,000,000

Professor D E Newby, University of Edinburgh. "Clinical Research Infrastructure Initiative: Clinical Research Imaging Centre" £3,000,000

Professor D A Lawlor et al, University of Bristol. "Obstetric, lifestyle and genetic determinants of atherosclerosis, fat mass, insulin, glucose and lipid levels in women in early middle-age" 3 years £882,350

Programme Grants

Professor M A Hanson et al, University of Southampton. "Maternal and epigenetic determinants of cardiovascular structure and function" 5 years (renewal; years 6-10) £822,366

Professor J D Brook et al, University of Nottingham. "A gene regulatory network for the developing heart and congenital heart disease" 5 years (renewal; years 11-15) £1,095,435

Professor FGR Fowkes et al, University of Edinburgh. "Randomised controlled trial of low dose aspirin in the prevention of cardiovascular events and death in subjects with asymptomatic atherosclerosis" 3 years £241,464

Professor H C Watkins et al, University of Oxford. "Downstream mechanisms in hypertrophic cardiomyopathy: the importance of primary and secondary changes in energetics, angiogenesis and calcium handling" 5 years (renewal; years 11-15) £1,256,586

Project Grants Committee November 2007

Dr A F James & Professor C H Orchard, University of Bristol. "Remodelling of Ca^{2+} handling in left atrial and pulmonary vein cardiomyocytes from spontaneously hypertensive rats: a basis for arrhythmogenesis?" (2 years) £133,134

Dr L Smith et al, University of Edinburgh. "Genetic mapping of a novel, spontaneous, early-onset mouse model of aortic aneurysm with acute dissection (AAD)" (2 years) £98,018

Professor R S Bonser et al, University of Birmingham. "Can enhanced glycaemic control in Type II diabetics improve myocardial protection during coronary artery bypass grafting?" (3 years) £261,172

Dr C M Moran et al, University of Edinburgh. "Quantification of the binding dynamics of ultrasonic targeted contrast microbubbles using intravascular ultrasound, laser Doppler anemometry and optical projection tomography" (3 years) £239,395

Dr R J F Loos et al, University of Cambridge. "Investigating the genetic determinants of daily physical activity" (3 years) £279,688

Dr S Pyner, University of Durham. "Do nucleus tractus solitarius neurones signal plasma volume status to spinally projecting paraventricular hypothalamic neurones to regulate sympathetic activity?" (3 years) £143,068

Professor R J MacAllister & Dr M Lythgoe, University College London. "Neuroprotection by remote ischaemic preconditioning and remote ischaemic postconditioning in experimental stroke" (3 years) £152,795

Dr A Stephanou & Dr S Jayasinghe, University College London. "Bio-electrospraying: a novel approach in cardiac tissue engineering" (2 years) £126,082

Dr N M Storey et al, University of Leicester. "The role of sarcolemmal K_{ATP} channel subunits in the protective response of cardiac muscle to metabolic stress and ischaemia" (3 years) £154,760

Dr E Gherardi, University of Cambridge. "Protein engineering of HGF/SF for stem cell-mediated repair of myocardial infarction" (2 years) £99,662

Professor S A M Thom & Professor N Poulter, Imperial College London. "Polypill Pilot - a randomised placebo-controlled trial of fixed-dose combination medication in people at raised risk of cardiovascular disease" (1 year) £58,206

Dr M E Werner, University of Manchester. "cGMP-mediated regulation of potassium channels in the corpus cavernosum" (3 years) £167,771

Professor S P Watson, University of Birmingham. "Dissection of the proximal events in the CLEC-2 signalling cascade" (3 years) £151,283

Professor A S Hall et al, University of Leeds. "An evaluation of the clinical utility of routine measurement of H- FABP in NHS patients presenting with either suspected or confirmed ACS" (1 year) £76,267

Professor A W Poole, University of Bristol. "The role of PKD in platelet function and thrombus formation" (3 years) £217,813

Dr A G Ramage, University College London. "Midbrain-hypothalmic 5-HT containing pathways mediating stress-related and DOCA-salt hypertension" (3 years) £198,353

Professor M Umpleby et al, University of Surrey. "Investigation of endogenous and exogenous postprandial TRL kinetics in the metabolic syndrome" (2 years) £120,862

Dr R J Tapp et al, Imperial College London. "Impact of size at birth and early childhood growth patterns on the microvasculature: the Avon Longitudinal Study of Parents and Children (ALSPAC)" (1 year) £44,515

Dr N J Mutch, University of Leeds. "Polyphosphate as a physiological surface for contact activation" (3 years) £153,479

Dr J A Huntington, University of Cambridge. "Serpin recognition, inhibition and clearance of thrombin" (3 years) £164,835

Dr A W Trafford et al, University of Manchester. "Probing the role of the putative intra-luminal calcium sensor in dysfunctional excitation contraction coupling and arrhythmogenesis in heart failure" (2 years) £129,077

Dr C L Jackson & Dr P D Weinberg, University of Bristol."Vessel wall dynamics and plaque rupture" (3 years) £169,649

Dr L M Work et al, University of Glasgow. "A combined approach targeting oxidative stress and apoptosis in stroke" (3 years) £186,911

Dr I A Greenwood & Dr D L Baines, St George's, University of London. "Contribution of bestrophins to calcium-activated chloride channels in vascular myocytes" (3 years) £158,653

Dr A Kitmitto & Dr A W Trafford, University of Manchester. "Characterisation of the molecular interactions between the luminal domain of triadin, the cardiac ryanodine receptor and calsequestrin" (2 years) £98,453

ILLUMINA APPLICATIONS AWARDED

Dr P B Munroe et al, Queen Mary, University of London."High throughput collaborative analysis of cardiovascular genes in 6000 hypertensives and 6000 controls" (1 year) £314,874

Professor H C Watkins et al, University of Oxford. "Genotyping CAD cases and controls from the PROCARDIS collection on the IMAT/Broad/CARE 50K vascular disease SNP array" (1 year) £207,170

Dr T R Gaunt et al, University of Bristol. "Genetic risk factors for cardiovascular disease in the British Women's Heart and Health Study and the Caerphilly Prospective Study" (3 years) £163,757

Professor N J Samani et al, University of Leicester. "Identifying and comparing genetic determinants of coronary artery disease in European Caucasians and South Asians using the 50K Illumina array" (1 year) £266,078

Dr A D Hingorani et al, University College London."Utilising genetic tools to dissect causal pathways in cardiovascular disease: deployment of a 50K high density SNP array in the Whitehall II prospective study" (1 year) £207,174

Cardiovascular Related Wellcome Trust Grants

November 2007 to February 2008

Project Grants

Prof Adrian Renton, School of Health and Bioscience, Stratford Campus, University of East London. A randomised cluster controlled trial of community level interventions to address social and structural determinants of physical activity, diet and mental well being. 48 months £740,092

Dr Julia Gorelik, National Heart & Lung Institute,London. Localisation of beta-adrenoceptor-dependent cyclic AMP signalling to surface structures on the cardiomyocyte. 24 months £189,810

Dr Valerie B O'Donnell, Dept of Medical Biochemistry, Cardiff University. Nitroarachidonate and Cholesteryl nitrolinoleate as Novel Anti-inflammatory Nitrated Lipids: Detection, Synthesis, Characterization and Biological Properties. 36 months £201,696

Research Training Fellowships

Mr Hutan Ashrafian, Division of Surgery, Oncology and Reproductive Biology, St Mary's Campus, Imperial College London. Investigating the mechanisms for the beneficial effects of bariatric surgery on cardiac function. 36 months £299,747

Dr Catherine Kyobutungi, African Population & Hlth Res Centre, (APHRC), Nairobi Kenya. Assessing the linkages between socioeconomic status, perceived personal risk, and risk factors for cardiovascular and related non-communicable diseases in a population of slum dwellers in Nairobi, Kenya. 36 months £307,949

Biomedical Resources

Dr Willem H Ouwehand, Division of Transfusion Medicine, East Anglian Blood Transfusion Ctr, University of Cambridge. The UK Blood Services Common Controls DNA Collection. 60 months £594,356

LATE SPRING MEETING 2008

A joint meeting with the

British Cardiovascular Society

"CAUSES AND CONSEQUENCES OF MYOCARDIAL INFARCTION: NEW CONCEPTS"

DATES: Monday 2nd and Tuesday 3rd June, 2008

VENUE: Manchester Central Convention Centre

STRUCTURE: The BSCR Spring Meeting will tale place over 1½ days in parallel with sessions held as part of the BCS Annual Meeting (2nd - 4th June).

PROGRAMME: The programme will consist of state-of-the-art presentations by leaders in the field and will include two keynote lectures and four symposia. Free communications of already accepted abstracts will be presented in oral and poster sessions.

Full programme details are contained in this issue of the Bulletin and are downloadable from the BSCR website (www.bscr.org).

Free Communications: Part of the programme will be devoted to oral presentation of selected abstracts and others will be presented in a poster exhibition. Submission of abstracts in any area of cardiovascular science is welcomed. There are two prizes of £250 each: the Clinical Science Early Investigator Award and the BSCR Early Investigator Award.

Student Bursaries: The BSCR will consider awarding travel grants of up to £200 to BSCR members who are bona fide students and application forms are available from the BSCR website (www.bscr.org).

BSCR Dinner / Hotel Accommodation: The BSCR Dinner will be held at the Manchester Museum of Science and Industry (MOSI) on the evening of 2nd June. The cost is £25 and a booking form is available for downloading from the BSCR website (www.bscr.org). A limited number of reasonably-priced rooms in nearby hotels can be booked for the night of 2nd June through a link on the BSCR website to Marketing Manchester.

REGISTRATION for this meeting is made through the BCS website and it is necessary to register with the BCS (https://secured.bcs.com/pages1/register.asp) before BSCR / BCS meeting registration can be completed. The pre-registration fee payable before/on 16 May is £60 (basic scientist / researcher) or £100 (clinically qualified scientist / researcher). There is a link from the BCS website for hotel bookings covering the nights 1st, 2nd, 3rd and 4th June.

FURTHER INFORMATION:

Professor Barbara McDermott, Email - b.mcdermott@qub.ac.uk; Phone - 02890 972242

Professor David Eisner, BSCR Chairman: Email - eisner@man.ac.uk; Phone - 0161 275 2702