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Contents

Editorial

Weclome to a rather late 'October' 2008 issue of *The* Bulletin.

We bring you an absorbing review on the role of mitochondria in regulating macrophage cholesterol efflux, a process which has critical implications for atherolsclerosis, the underlying cause of coronary heart disease. The review is written by Dr Annette Graham and colleagues at Glasgow Caledonian University.

Following a busy conference season, this issue contains a number of entertaining travel reports, from the ISHR American Section in Ohio to the World Congress on Heart Disease in Toronto. Closer to home, Claire Schwartz reports on the very successful BSCR Autumn Meeting where the emphasis was placed on Young investigators, both in terms of organisation and the scientific programme.

From past meetings to forthcoming meetings. The first announcement of the BSCR Spring meeting, to be held in association with the British Atherosclerosis Society, is contained herein. You'll find a provisional programme within and all the relevant contact information on the back page.

Following the recent election of new Committee members, the Secretary's Column in this issue provides details of those who were successfully elected. As Bulletin editors, we would like to thank retiring Committee members, including the outgoing Chairman, David Eisner, for their assistance and cooperation with production of *The* Bulletin. It has been a great pleasure to work with them over the past few years.

Helen Maddock and Nicola Smart

Mitochondrial Regulation of Macrophage Cholesterol Efflux: Lessons from Steroidogenic Tissues?

by Janice M. Taylor, Faye Borthwick and Annette Graham, Vascular Biology Group, Biological and Biomedical Sciences, Glasgow Caledonian University

INTRODUCTION

Coronary heart disease (CHD) is responsible for over 100,000 deaths in the UK each year, and is the most common cause of premature death in the UK. Recent estimates suggest that 8% of men and 6% of women in Scotland are living with coronary heart disease, while in the UK as a whole it is estimated that there are just over 1.5 million men, and 1.1 million women, who have had suffered coronary heart disease in the form of either angina or myocardial infarction (www.heartstats.org). The primary cause of CHD, atherosclerosis, is characterised by the presence of arterial macrophage 'foam cells' (Gerrity, 1981) which influence both plaque stability and progression; these cells are laden with excess cholesterol and cholesteryl ester, derived from the unregulated uptake of pro-atherogenic lipoproteins, such as oxidized LDL (OxLDL) by macrophage scavenger receptors. Elimination of stored cholesterol from macrophage foam cells, by cholesterol efflux to (nascent) high-density lipoproteins (HDL) remains a key preventive strategy for CHD, particularly since decades of research have highlighted both the benefits and potential limitations of reducing plasma LDL levels alone. The importance of the reverse cholesterol transport pathway is supported by epidemiological studies in humans, indicating that high levels of HDL protect against the development of CHD, and from studies in transgenic mice in which components of the reverse cholesterol transport pathway have been deleted or over-expressed (Marcel *et al*., 2008; Rader and Maugeais, 2000; Pastzy *et al*., 1994; Rubin *et al*., 1991).

Macrophage cholesterol efflux is orchestrated, at least *in vitro*, via ATP binding cassette (ABC) transporters, such as ABCA1, ABCG1 and ABCG4, and lipid-poor 'acceptor apolipoproteins, such as apoAI, apoE and nascent HDL (Rader and Maugeais, 2000; Rubin *et al.*, 1991; Pastzy *et al*., 1994). ABCA1 promotes efflux of cholesterol to lipid-poor acceptors, such as apoAI and apoE, while ABCG1 and ABCG4 promote efflux of cholesterol, oxysterols and desmosterol to HDL (Cavalier *et al*., 2006; Tall, 2008), so that these transporters appear to work in concert to generate HDL which enters the reverse cholesterol transport pathway, delivering excess cholesterol to the liver for excretion in bile. Transcriptional regulation of ABCA1 transporter has focused attention on the role(s) of Liver X nuclear receptors (LXR): both synthetic and endogenous oxysterol LXR ligands potently up-regulate ABCA1 and ABCG1 gene expression in human monocyte-macrophages.

In this review, we summarise the evidence that trafficking of cholesterol to mitochondrial sterol 27-hydroxylase (CYP27A1) is a key determinant of the rate of production of endogenous oxysterol ligands for LXR, and in the regulation of macrophage cholesterol efflux via ABCA1 and ABCG1. Further, we propose that, in this regard, informative parallels may be drawn between the mitochondrial processes governing generation of 27-oxygenated sterols, and those regulating production of pregnenolone in steroidogenic tissues, revealing new targets for therapeutic exploitation.

LIGAND ACTIVATION OF LIVER X RECEPTORS

Ligand activation of Liver X nuclear receptors is pivotal to marshalling appropriate cholesterol homeostatic mechanisms leading to cholesterol efflux and nascent HDL generation. Macrophage cholesterol efflux mechanisms lie under the transcriptional control of liver X receptor (LXR)

and retinoic acid receptor (RXR) heterodimers, which bind at an imperfect direct repeat of the nuclear receptor half-site TGACCT separated by four bases (DR-4) (Schwartz *et al* 2000; Venkateswaran *et al.*, 2000). Liver X Receptors, LXRα and LXRβ, were first identified as 'orphan' members of the nuclear receptor superfamily (Janowski *et al.*, 1996), and subsequently 'deorphanised' following the demonstration that particular oxysterols potently activate LXR *in vitro* (Janowski *et al.*, 1996; 1999; Peet *et al.*, 1998), and X-ray crystallographic studies of the LXR ligand binding pocket showing that an hydroxyl group at positions -22, -24 or -27 in the cholesterol side chain is important for ligand binding (Svensson *et al.*, 2003).

LXRβ is expressed ubiquitously, whereas LXRa is highly expressed in tissues and cells with important roles in lipid homeostasis, including the liver, intestine, adipose tissue and macrophages: both isoforms act as 'sensors' of sterol accumulation within cells. Bone-marrow specific deletion of both LXRα and LXRβ accelerates atherosclerosis in both spontaneous (apoE$^{-/-}$) and diet-induced (LDL receptor$^{-/-}$) hypercholesterolaemic murine models of atherosclerosis (Tangirala *et al.*, 2002). Genetic deletion of either isoform alone does not reveal an obvious phenotype, suggesting that one LXR isoform can compensate for the loss of the other (Lund *et al.*, 2006). However, Bradley *et al* (2007) recently showed that deletion of LXRα in apoE$^{-/-}$ mice induced a striking accumulation of cholesterol in peripheral tissues and accelerated atherosclerosis, which could only be reversed following activation of LXRβ with the synthetic (non-sterol) LXR agonist T0901317, arguing that the level of LXRβ activation in macrophages achieved by endogenous ligands cannot maintain cholesterol homeostasis under hypercholesterolaemic conditions.

Activation of LXRα enhances transcription of genes encoding ABCA1 and ABCG1, and the endogenous apolipoprotein cholesterol acceptor, apoE, increases cholesterol efflux and stimulates uptake of cholesteryl esters from HDL (Geyeregger *et al.*, 2006; Beaven and Tontonez, 2006; Venkateswaran *et al.*, 2000; Bultel *et al.*, 2008). However, LXRα also regulates the cholesterol biosynthetic pathway, by directly silencing the expression of lanosterol 14α-demethylase (CYP51A1) and squalene synthase via novel negative LXR DNA response elements (nLXREs) located in each of these genes, suggesting coordinated repression of cholesterol synthesis accompanies up-regulation of cholesterol efflux from cells (Wang *et al.*, 2008). Pharmacological activation of LXR leads, via activation of SREBP-1c, to induction of lipogenesis, and hepatic production of large, triglyceride-rich very low density lipoprotein (VLDL) particles (Gefhorst *et al.*, 2002). This potentially pro-atherogenic 'down-side' of currently available (non-selective) LXR agonists may ultimately be resolved by the development of gene- or target-selective LXR modulators (Quinet *et al.*, 2004; Molteni *et al.*, 2007). Activation of LXRs can also induce trans-repression of other transcription factors, an indirect effect which can reduce macrophage inflammatory responses *in vitro* (Geyeregger *et al.*, 2006; Kaul, 2006; Millat *et al.*, 2006; Zelcer and Tontonez, 2006). Chen *et al* (2007) recently provided direct evidence for oxysterols as LXR ligands *in vivo*: adenoviral over-expression of cholesterol sulfotransferase, which catabolises oxysterols, inactivated LXR signalling in hepatic tissues of mice, whereas responses to T090317 remained intact. Further, 'triple-knockout' mice deficient in the synthesis of 24(S)-hydroxycholesterol, 25-hydroxycholesterol and 27-hydroxycholesterol, responded to dietary administration of LXR agonist T0901317 by inducing hepatic LXR target genes, but exhibited impaired responses to dietary cholesterol (Chen *et al.*, 2007).

Intriguingly, recent data suggest that the LXRβ/RXR heterodimer can interact directly with ABCA1 protein at the plasma membrane: when cholesterol levels within the cell increase, oxysterols bind to LXRb and the LXRβ/RXR complex dissociates from ABCA1, restoring ABCA1 activity and facilitating apoAI-dependent cholesterol efflux (Hozoji *et al.*, 2008). It has also now emerged that other cytoplasmic (oxy)sterol binding proteins can interact with the LXR pathway by sequestering or delivering substrates and ligands: over-expression of the STARD4 and STARD5 members of the START (steroidogenic acute regulatory protein related transfer) family of lipid trafficking proteins enhances LXR activation (Soccio *et al.*2005). By contrast, oxysterol binding protein (OSBP) negatively regulates ABCA1 protein stability (Bowden and Ridgway, 2008), and OSBP-related

protein-8 (ORP8) suppresses ABCA1 expression, and cholesterol efflux from macrophages (Yan *et al*., 2007).

Thus, oxysterols exert pleiotropic functions in regulating cellular cholesterol homeostasis. Some oxysterols can suppress sterol regulatory element binding proteins (SREBPs) by binding to Insig, a sterol sensing protein in the endoplasmic reticulum, and some can accelerate the degradation of the enzyme catalysing the rate-limiting step for cholesterol biosynthesis, HMG CoA reductase (recently reviewed by Gill *et al.*, 2008). The production of oxysterols within cells is therefore of key importance in coordinating both cholesterol biosynthetic and effluxing mechanisms, although the precise identities of the oxysterol(s) implicated *in vivo* remain uncertain. Potential sources of oxysterols within the arterial wall include those provided by the uptake and hydrolysis of oxidized LDL (Brown and Jessup, 1998; Bjorkhem and Disczfalusy, 2002), oxysterols derived by trafficking cholesterol to mitochondrial sterol 27-hydroxylase (CYP27A1) (Fu *et al.* 2001), or those generated via the cholesterol biosynthetic pathways, such as 24(S), 25-epoxycholesterol (Rowe *et al.*, 2002; Yang *et al.*, 2006; Wong *et al*., 2008). Synthesis of 24(S), 25-epoxycholesterol is thought to provide protection against cellular accumulation of newly-synthesized cholesterol (Wong *et al*., 2007). Blockade of the cholesterol biosynthetic pathway by statins reduced the synthesis of 24(S), 25-epoxycholesterol, down-regulated expression of ABCA1 and ABCG1 transporters, and reduced cholesterol efflux from THP-1 macrophages in culture (Wong *et al*., 2004). This effect was lost in cells loaded with acetylated LDL, reflecting the fact that active cholesterol biosynthesis is profoundly repressed in cholesterol-enriched macrophage 'foam' cells, and strongly suggesting an alternate source of oxysterol ligands for LXR in cholesterol 'foam cells'. The major oxysterols present in oxidized LDL, non-enzymically generated 7-keto and 7-β-hydroxycholesterol, do not bind LXRα (Janowski *et al*.,1999), and oxidized LDL down-regulates the expression of ABCA1 in human vascular endothelial cells by inhibiting LXR ligand binding (Zhu *et al.* 2005). By contrast, human macrophages exhibit high levels of expression of sterol 27-hydroxylase (CYP27A1) (Brown *et al*., 2000) which produces 27-hydroxycholesterol and 3β-hydroxy-5-cholestenoic acid. 27-Hydroxycholesterol acts as an endogenous ligand for LXRα in human macrophage foam cells (Fu *et al*., 2001) despite *in vitro* studies suggesting this molecule to be a fairly weak ligand for LXRα (Janowski *et al*., 1999). Several lines of evidence support the concept that CYP27A1 may be an important defence mechanism preventing macrophage cholesterol accumulation.

MACROPHAGE MITOCHONDRIAL STEROL 27-HYDROXYLASE (CYP27A1)

Macrophage sterol 27-hydroxylase (CYP27A1), is a cytochrome P450 enzyme located on the inner mitochondrial membrane, involved in bile acid production in liver (Cali and Russell, 1991; Dubrac *et al*., 2005), but also expressed in a number of extra-hepatic tissues, where it aids removal of excess cholesterol (Babiker *et al.*, 1997; Bjorkhem *et al*., 1994; Brown *et al*., 2000; Westman *et al.*, 1998; Szanto *et al*., 2004). High levels of sterol 27-hydroxylase activity are found in the vascular endothelium (Reiss *et al*., 1994; 1997), and a marked induction of CYP27A1 activity and mRNA occurs during differentiation of human monocytes into macrophages (Hansson *et al*., 2003). Sterol loading of macrophages also markedly induces the expression of CYP27A1 (Llaverias *et al*., 2005), and the cellular content of 27-hydroxycholesterol increases in proportion to the cholesteryl ester content of human monocyte-macrophages (Westman *et al*, 1998). CYP27A1 is markedly up-regulated, and colocalises with macrophages, in human atherosclerotic lesions (Reiss *et al*., 1994; Crisby *et al*., 1997; Shanahan *et al*., 2001), and 27-hydroxycholesterol is the major oxysterol present in human atheroma (Garcia-Cruset *et al*., 2001).

Regulation of CYP27A1 expression appears to display some tissue specificity: in hepatic tissues, CYP27A1 mRNA and/or activity is repressed by sitosterol (Nguyen *et al*., 1998), cafestol (Post *et al.*, 1997), bile acids (Twisk *et al.*, 1995; Vlahcevic *et al*., 1996; Chen and Chiang, 2003), thyroxine and phorbol ester (Araya *et al*., 2003), and up-regulated by glucocorticoids (Tang *et al*., 2008), growth hormone and insulin-like growth factor-1 (Araya *et al*., 2003), while in the intestine, ligation of the steroid and bile acid-activated pregnane X receptor (PXR) stimulates CYP27A1 gene transcription, increases intracellular 27-hydroxycholesterol levels and induces ABCA1 and ABCG1 gene transcription (Li *et al.*, 2007). Immune complexes and interferon

γ decrease the expression of sterol 27-hydroxylase in human arterial endothelium and macrophages (Reiss *et al*., 2001), impeding reverse cholesterol transport and promoting foam cell formation (Reiss *et al*., 2004), while transforming growth factor β1 upregulates CYP27A1 (Hansson *et al.*, 2005), as does the RXR ligand, 9-*cis*-retinoic acid, in partnership with peroxisome-proliferator-activated receptor γ (PPARγ), in human monocyte-macrophages (Szanto *et al*., 2004; Quinn *et al*., 2005). Indeed, Szanto *et al* (2004) have suggested that CYP27 acts as a link between retinoid, PPARγ and LXR signalling, and demonstrated that human macrophage-rich atherosclerotic lesions have increased levels of retinoid, PPARγ and LXR-regulated gene expression, and enhanced CYP27 levels.

Forced over-expression of sterol 27-hydroxylase in cultured cells enhances cholesterol efflux to apoAI or human plasma (Escher *et al*., 2003), reduces the expression of HMG CoA reductase, and significantly increases bile acid synthesis in HepG2 cells (Hall *et al.*, 2001). CYP27A1, by oxidizing cholesterol to more polar metabolites which tend to efflux more readily from cells, also provides an alternative route by which macrophages and other peripheral cells rid themselves of excess cholesterol in the absence of (apo)lipoprotein acceptors (Bjorkhem *et al*., 1994; Babiker *et al*., 1997; Westman *et al*., 1998). Sterol 27-hydroxylase can act on other oxysterols, such as 7-ketocholesterol derived from oxidized LDL, which are rather more recalcitrant to efflux and tend to accumulate within macrophage foam cells (Lyons and Brown, 2001; Brown *et al*., 2000). Hydroxylation aids the conversion of such oxysterols to more soluble products, facilitating their removal from cells and tissues (Brown *et al*., 2000). A significant daily flux of 27-oxygenated cholesterol products proceeds from extra-hepatic tissues to the liver where they are catabolised further and excreted in bile (Babiker *et al*., 1997; Bjorkhem *et al*., 1994; Bjorkhem *et al*., 1999).

The importance of CYP27A1 in regulating macrophage cholesterol accumulation is highlighted by the rare autosomal recessive disorder cerebrotendinous xanthomatosis (CTX), an inherited lipid storage disease caused by inactivity or absence of this enzyme, which is localised on the long arm of chromosome 2. CTX features the accumulation of cholestanol and cholesterol in most tissues, and is characterised clinically by tendon xanthomas, slowly progressive neurological deterioration, and accelerated atherosclerosis (despite normal circulating levels of cholesterol), and pathologically by lipid granulomata, with foamy histiocytes, and cholesterol clefts (Kuriyama *et al*., 1991; Brown *et al*., 2000; Bjorkhem and Leitersdorf, 2000; Gonzalez-Cuvar *et al*., 2007). Genomic and proteomic analyses have shown that the expression of vinculin, ABP-280, talin and vimentin change significantly in leukocytes derived from CTX patients, reflecting the changes in membrane dynamics due to cholestanol accumulation (Wang *et al.*, 2006). More than 300 patients with CTX have been reported worldwide, with over 50 different mutations identified in the CYP27A1 gene (Gallus *et al*., 2006). A unique CTX patient was recently described, who possessed a defect in a gene not identical to sterol 27-hydroxylase: this individual had extremely low sterol 27-hydroxylase activity, and proved to be heterozygous for two mutations affecting one allele of the CYP27A1 gene, and with at least one additional, as yet unidentified, gene of critical importance for the activity of this enzyme (Hansson *et al*., 2007).

CHOLESTEROL TRAFFICKING TO MITOCHONDRIAL STEROL 27-HYDROXYLASE: LESSONS FROM STEROIDOGENIC TISSUES?

Trafficking of cholesterol to mitochondrial sterol 27-hydroxylase, from the outer to the inner (cholesterol-poor) mitochondrial membrane, across the inter-membrane space, is the rate-limiting step governing the activity of this enzyme, and generation of 27-oxygenated derivatives of cholesterol (Pandak *et al*., 2002). Despite the potential importance of this process in activation of LXRs, and regulation of cholesterol efflux via both 'classical' efflux to apoAI and HDL, and the 'alternate' oxidative pathway, the mechanisms involved remained largely uncharacterised (Figure 1). However, decades of work in steroidogenic tissues have shed light on some of the proteins involved in trafficking cholesterol to the mitochondrial P450 side chain cleavage enzyme (P450scc), which has proved to be the rate-limiting step in production of pregnenolone, the common precursor for synthesis of all steroid hormones.

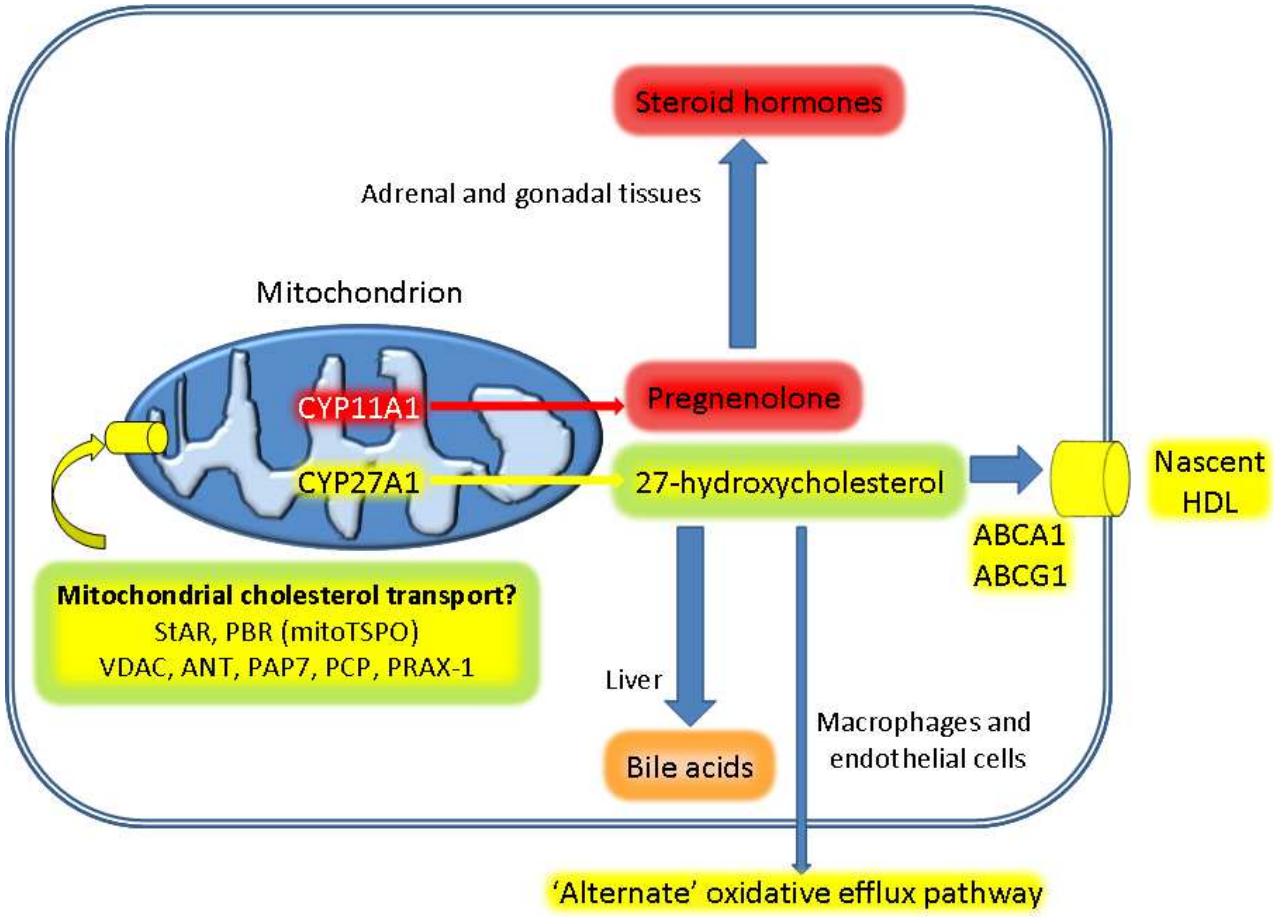

Figure 1: Mechanisms involved in the regulation of cholesterol efflux via both 'classical' efflux to apoAI and HDL, and the 'alternate' oxidative pathway.

Thus, putative components of the mitochondrial cholesterol trafficking machinery may include steroidogenic acute regulatory protein (StAR), the peripheral benzodiazepine receptor (PBR) and PBR-associated protein complex (Lacapere and Papadopoulos, 2003; Papadopoulos *et al*., 2007).

StAR, the prototypic member of the START family of lipid trafficking proteins (Soccio and Breslow, 2003), is a critical regulator of the synthesis of adrenal and gonadal steroids, facilitating the rate-limiting step in steroidogenesis: the movement of cholesterol from the outer to the inner mitochondrial membrane (IMM) where P450scc is located (reviewed in Christenson and Strauss, 2001; Jo *et al*., 2005; Miller, 2006, Miller 2007). StAR is a nuclear encoded, mitochondrially targeted protein which is expressed in the cytoplasm as a 37kDa protein, phosphorylated, and processed to a 32kDa intermediate, and imported into mitochondria where it is cleaved to a 30kDa protein (Granot *et al*., 2003). Phosphorylation of human StAR on Ser^{195} by protein kinase A (PKA), combined with rapid induction of StAR biosynthesis, explains the acute regulation of steroid formation in response to trophic hormones (Arakane *et al*., 1997). Mutations in the StAR protein cause congenital lipoid adrenal hyperplasia, an autosomal recessive disorder characterised by impaired adrenal and gonadal steroid synthesis and massive cholesteryl ester deposits within the adrenal cortex (Caron *et al*., 1997). Significantly, the cholesterol-binding 'START' domain of StAR interacts exclusively with the OMM, and physical restriction of StAR to the OMM does not reduce its functionality (Bose *et al*., 2002; reviewed by Miller, 2006) suggesting that other proteins are involved in forming 'contact sites' between the OMM and IMM, channelling cholesterol to CYP27A1.

StAR interacts with the peripheral benzodiazepine receptor (PBR) complex, which is widely distributed in a number of tissues, and which

plays an established role in mitochondrial cholesterol trafficking in steroidogenic cells (Krueger and Papadopoulos, 1990), but which is also functional in non-steroidogenic tissues (Caselles *et al*., 2002). PBR is a key component of a multimeric 140-200 kDa complex located at the OMM and enriched at contact sites between outer and inner mitochondrial membranes (Culty *et al*., 1999). Other members of the PBR protein complex include a 30kDa adenine nucleotide carrier (ANC), PBR associated protein (PRAX-1) (Galiegue *et al*., 1999), both of undefined function within the PBR complex at present, VDAC, the voltage dependent anion channel (McEnery *et al*., 1992), the phosphate carrier protein (PCP) and PAP7, a 56kDa PBR and protein kinase A regulatory subunit RIα (PKA-RIα) associated protein (Liu *et al*., 2003a, b). Hormone- and cAMP-dependent formation of a macromolecular signalling complex, composed of PBR, PAP7, PKA-R1α and STAR, was recently demonstrated in steroidogenic tissues, and non-steroidogenic COS cells engineered to metabolise cholesterol (Liu *et al*., 2006), and Bose *et al* (2008) VDAC as a necessary component of a protein complex influencing mitochondrial membrane cholesterol distribution, and influencing the rate of oxidative phosphorylation.

The peripheral benzodiazepine receptor is an 18kDa protein (recently renamed mitochondrial translocator protein: mitoTSPO), with five alpha-helical transmembrane domains (Murail *et al*., 2008), located in the OMM, and enriched at contact sites between the outer and inner mitochondrial membranes. PBR possesses a high-affinity cholesterol recognition amino acid (CRAC) binding domain in its cytosolic C-terminus, which is essential for its cholesterol transport function (Li *et al*., 2001; Jamin *et al*., 2003). Synthetic PBR ligands bind at a site distinct from the CRAC domain, induce cholesterol transport to the inner mitochondrial matrix, enhance steroidogenesis (Lacapere and Papadopoulos, 2003) and stabilise the PBR tertiary structure (Murail *et al*., 2008). Falchi *et al*. (2007) also noted that PBR ligands induced changes in the cellular distribution of intracellular cholesterol in astrocytes and fibroblasts. Successful PBR knockout, antisense and silencing RNA protocols induce arrest of cholesterol transport into mitochondria, and blockade of steroidogenesis (Hauet *et al*., 2005), while transfection with PBR cDNA rescues both cholesterol transport and steroidogenesis (Papadopoulos *et al*., 1997). Knockout studies in mice have shown that genetic deletion of the PBR gene (*Bzrp*) induces an early embryonic-lethal phenotype (Lacapere and Papadopoulos, 2003). A close association between StAR and PBR exists at the OMM (West *et al*., 2001; Hauet *et al*., 2005), and treatment of cells with antisense oligonucleotides to PBR, or a transducible peptide antagonist to PBR, results in reduction of mature mitochondrial StAR, strongly suggesting that PBR is required for StAR import into mitochondria (Miller, 2006). A number of other functions have also been assigned to this protein, which is widely expressed in cells and tissues, including porphyrin transport and haem biosynthesis, ion transport, immunomodulation, and regulation of cellular respiration (reviewed by Papadopoulos *et al*, 1997, 2004, 2006, 2007). Intriguingly, an autoradiographic study recently demonstrated increased expression of peripheral benzodiazepine receptors in the arterial plaque of patients in atherosclerosis, using [^{3}H]PK11195 as a ligand for PBR, as an indicator of macrophage infiltration within lesions (Fujimura *et al*., 2008); Laitinen *et al* (2008) have also demonstrated increased uptake of [^{11}C]PL11195 into highly inflamed atherosclerotic plaques in LDL receptor/apoB48 atherosclerotic mice.

Expression of StAR mRNA and protein have previously been found in non-steroidogenic tissues, such as the liver, where StAR is thought to increase synthesis of bile acids by the 'alternative' pathway; certainly StAR enhances the activity of CYP27A1 by stimulating cholesterol trafficking to the IMM (Sugawara *et al*., 1995). Over-expression of CYP27A1, or direct administration of 27-hydroxycholesterol, increased StAR protein levels in HepG2 cells (Hall *et al*., 2005), while over-expression of StAR and, indeed, other cholesterol transporters such as STARD3 (MLN64) and sterol carrier protein-2 (SCP-2) led to marked increases in cholesterol metabolism via this route (Ren *et al*., 2004a, b). Ma *et al* (2008) recently found cAMP induces StAR expression in murine macrophages, and evidence for the expression of StAR mRNA and protein in aortae of apoE$^{-/-}$ mice; expression of macrophage StAR was also down-regulated by inflammatory cytokines, which may be significant

within the inflammatory milieu of the artery wall. Our own work has found expression of StAR in human monocytes, THP-1 macrophages (Borthwick *et al*., 2007) and human aortic tissue, along with other components of the PBR protein complex (unpublished data). In October 2007, we presented data to the XVI Drugs Affecting Lipid Metabolism (DALM) meeting in New York, demonstrating that over-expression of StAR in murine (RAW 264.7) macrophages enhances LXR activation, induces expression of LXRα, and increases [^{3}H]cholesterol efflux to apoAI via induction of ABCA1 mRNA and protein (Taylor *et al.* 2007); notably, this effect was not observed with mutated (R181L) StAR, which retains cholesterol-binding but not mitochondrial transporting functionality.

Evidence linking StAR, the PBR complex, and cholesterol metabolism in non-steroidogenic tissues, and with regulation of macrophage cholesterol efflux is lacking at present, and forms the focus of our current studies funded by the British Heart Foundation. However, PBR ligands apparently exert anti-atherosclerotic effects in rabbits and roosters, decrease circulating cholesterol concentrations, liver cholesterol content and acyl CoA: cholesterol acyltransferase (ACAT) activity in cholesterol-fed rats, and alter the pattern of circulating lipoproteins in man (Balasubramaniam *et al*., 1986; Bell, 1986; Horak *et al*., 1997; Hunninghake *et al*, 1981). The mechanisms are not fully understood, and caution must be used in interpreting these studies, as benzodiazepine drugs can exert pleiotropic, drug-specific and PBR-independent effects in cells and tissues (Kletsas *et al*., 2004).

CONCLUSIONS

Oxysterol ligation of Liver X receptors is fundamental to coordination of macrophage cholesterol homeostasis, and removal of excess cholesterol via ABCA1 and ABCG1 transporters. Sterol 27-hydroxylase is an important source of endogenous oxysterol ligands for LXR in macrophage foam cells, with its activity limited by the supply of cholesterol to the inner mitochondrial membrane wherein it resides. Based on studies in steroidogenic tissues, we propose that proteins involved in trafficking cholesterol to CYP27A1, and in regulating macrophage cholesterol, may include the steroidogenic acute regulatory protein, peripheral benzodiazepine receptor (mitoTSPO), VDAC1, the phosphate carrier protein and other components of the PBR protein complex.

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Dr Annette Graham may be contacted at:
Vascular Biology Group,
Dept Biological and Biomedical Sciences,
Glasgow Caledonian University,
Cowcaddens Road,
Glasgow G4 0BA.
Tel: +44(0)141 331 3722;
Fax: +44(0) 141 3208;
E-mail: Ann.Graham@gcal.ac.uk

Articles for *The* Bulletin

Would you like to write a Review or Laboratory Profile for the BSCR Bulletin? These articles provide an excellent opportunity to let BSCR members know about your research activities and also provide an insight into your research field.

We are keen to hear from anyone in cardiovascular research who would be willing to write for *The* Bulletin.

If you are interested, please contact the Bulletin editors with your ideas:
Helen (h.maddock@coventry.ac.uk) or Nicola (N.Smart@ich.ucl.ac.uk)

Submission Deadlines for *The* Bulletin:

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

Secretary's Column

It is a particular pleasure to report on a very successful meeting in Bristol on September 15-16. The theme was "Cell signalling in cardiovascular disease: life or death" and there was a strong emphasis on young investigators: no fewer than 12 of the oral presentations were selected from submitted abstracts. The BSCR has historically been very active in providing opportunities for cardiovascular scientists in the early stages of their careers, and it was nice to see this tradition carried on in such a successful way. The University of Bristol generously supported the initiative with extra prize money, so all of the Young Investigator Award finalists received a prize. Details of prize winners on page 20 and on the website (www.bscr.org).

The Annual General Meeting of the Society took place during the Bristol meeting. It was well attended and there was lively discussion (those are two things you don't often hear said about AGMs). The nomination of Chris Newman as the new Chair of the Society from January 2009 was ratified, as were the elections of Derek Hausenloy and Richard Heads and the re-elections of Barbara Casadei, Andrew Grace and Cathy Holt. A number of constitutional changes were also agreed.

Chris Newman had an important Chair-Elect job to do at the conference dinner in Bristol – he gave a very nice short speech of thanks to David Eisner, the outgoing Chair, at the last main meeting of the BSCR under his leadership. He also presented David with a gift on behalf of the Society. Chris highlighted David's negotiation of closer links with the British Cardiovascular Society, in particular at the 2008 Spring Meeting. It is likely that this will be repeated in 2010, and indeed may become the standard model for our Spring meetings.

We have two BSCR Workshops coming along. The first, "Targeting myocardial reperfusion injury: a new frontier in myocardial protection" will be held on December 1st at the Hatter Institute at UCL and is organised by Derek Hausenloy and Derek Yellon. A Workshop on "Studying vascular biology using the zebrafish", organised by Tim Chico and sponsored jointly with the British Atherosclerosis Society, will be held at the University of Sheffield on January 30th.

Our next main conference will be the Spring Meeting in 2009, to be held jointly with the British Atherosclerosis Society on the topic of "Atherosclerotic Plaque Rupture". The meeting will take place in Oxford on April 2nd-3rd. Further details can be found on the back page and on the website. I hope to see as many of you as possible at what promises to be an absolutely superbly fantastically brilliant meeting (just look at the organisers).

Chris Jackson

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

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Joint Spring Meeting 2009: Provisional Programme

St. Catherine's College, Oxford

Atherosclerotic Plaque Rupture

Thursday 2nd April

09.30 **Registration** (Medical Sciences Teaching Centre)

09.50 **Introduction and Welcome**

Session 1: Pathology of Atherosclerotic Plaque Rupture

a. Why are only some plaque ruptures lethal?

10:00 What is a Vulnerable Plaque? *Patrick Serruys (Erasmus Medical Center, Rotterdam)*

10:35 Discussion

10:50 How Representative are "Culprit" Plaques? *Allard van der Wal (AMC, Amsterdam)*

11:10 Discussion

b. Do we have an animal model of plaque rupture?

11:25 Spontaneous Plaque Rupture in Mice: Real or Imaginary? *Chris Jackson (Bristol Heart Inst.)*

11:45 Discussion

12:00 Induced Plaque Rupture in Mice: Quick but Dirty? *Erik Biessen (University of Maastricht)*

12:20 Discussion

12:35 **---- Lunch ----**

Session 2: Inside the Unstable Atherosclerotic Plaque

13:15 Inflammation and Instability: Which is Chicken and Which is Egg? *Rob Krams (Imperial College London)*

13:35 Discussion

13:50 Cell Death and Cell Senescence: Root Causes or Collateral Damage? *Martin Bennett (University of Cambridge)*

14:10 Discussion

14:25 Plaque Repair: More Important Than Plaque Rupture? *Allen Burke (CVPath Institute, Maryland)*

14:45 Discussion

15:00 **---- Tea ----**

Session 3: Young Investigators: Michael Davies Award and BSCR Award

15:30 Presentation 1

15:40 Discussion

15:45 Presentation 2

15:55 Discussion

16:00 Presentation 3

16:10 Discussion

16:15 Presentation 4

16:25 Discussion

16:30 **British Atherosclerosis Society John French Lecture**

17:15 **BAS AGM (Medical Sciences Teaching Centre)**

18:00 **Poster Session and Drinks Reception** (St Catherine's College)

19:45 **Conference Dinner and announcement of the winners of the Young Investigator awards**

Friday 3rd April

08:00 **BAS Committee meeting (Medical Sciences Teaching Centre)**

Session 5: Free Communications

09:30 Presentation 1

09:40 Discussion

09:45 Presentation 2

09:55 Discussion

10:00 Presentation 3

10:10 Discussion

10:15 Presentation 4

10:25 Discussion

10:30 Presentation 5

10:40 Discussion

10:45 **---- Coffee ----**

Session 6: Diagnosis and Treatment of the Vulnerable Plaque

11:15 Imaging the Wall, Not the Lumen *Andreas König (Ludwig-Maximilians-Universität, Munich)*

11:35 Discussion

11:50 Do Biomarkers Tell You Any More Than You Already Know? *Juan Carlos Kaski (St Georges, London)*

12:10 Discussion

12:25 Drugs For Primary And Secondary Prevention: From Statins To Beyond *Andrea Mezzetti (University of Chieti)*

12:45 Discussion

13:00 **Presentation of the Clinical Science award for best poster**

13:05 **Concluding remarks**

13:15 **Close of meeting, poster removal, and lunch**

14:00 **BSCR Committee meeting** (Medical Sciences Teaching Centre)

BSCR Young Investigators Meeting–Autumn 2008

"Cell Signalling in Cardiovascular Disease: Life or Death"

15th-16th September, 2008, Merchant Venturers Building, University of Bristol

A meeting report by Claire Schwartz

A new season and a new meeting and this year the change in season was mirrored by a change to the usual BSCR meeting, aiming it for the first time at young investigators. Mixing speakers who were more experienced and those who were fresh to the field gave a unique perspective to the meeting, allowing the participants to see the new directions that established theories and models were taking, whilst having the experts on hand to give their valuable insights. It proved to be a great success and gave both young investigators and more experienced investigators an opportunity to learn from the other. Part of the meeting's success was down to its smooth running and this is thanks to the organisers: Dr Jason Johnson, Dr Cressida Lyon, Joanne Ferguson, Oliver Stone and Dr Elinor Griffiths.

66 participants registered in all for the two day event, which included seven sessions, each with a different theme. After a warm welcome from Dr Johnson, highlighting the importance of young investigators, we began with the first session. This covered smooth muscle cells and was chaired by Professor David Eisner and Oliver Stone. There was a very smooth start to the session by Martin Bennett, (University of Cambridge), covering the causes and consequences of smooth muscle cell death in atherosclerosis. He gave a very comprehensive overview of apoptosis in smooth muscle cells, highlighting the importance of the IGF-1 pathway in regulating cell death by its presence in plaque cells. Following him was Dr Cressida Lyon, (University of Bristol), presenting her work on smooth muscle cell proliferation and migration with soluble cadherin, a smaller more therapeutic-friendly form of N-cadherin. She showed very eloquently that soluble cadherin affected migration through ß-catenin signalling, whilst it influenced proliferation via the FGF-receptor signalling pathway. After Dr Lyon was Kelly Farrell, (University of Manchester), who introduced us to the transcription factor C-Myb. She has convincingly shown the presence of C-Myb in the smooth muscle cells of atherosclerotic plaques and is now investigating its role as a potential signalling molecule in the process of atherosclerosis. The final speaker of this session was Dr Sarah George, (University of Bristol), who neatly tied together cadherin signalling and its effect on smooth muscle cell regulation, highlighting the importance of the smooth muscle cell apoptosis in the unstable atherosclerotic plaque.

After this very informative session, came a well-earned break and a chance to discuss concerns or suggestions at the BSCR annual general meeting.

Session 2 had four presentations from the candidates nominated for the Young Investigators Award and was chaired by Drs Yvonne Alexander and David Grieve. The audience were treated to a glimpse into some of the most cutting edge research currently taking place in the cardiovascular field. The first presentation was by Dr Vivek Sivaraman, (Hatter Cardiovascular Institute, University College London). He described how protein kinase C epsilon can be activated at the onset of reperfusion to give protection to the myocardium, whilst protein kinase C delta needs to be inhibited. The research showed huge therapeutic potential for treating human hearts with ischaemic injury. Dr Sapna Thakur gave the next presentation on the A_2A receptor in endothelial cells and its important role in the regulation of angiotensin II induced endothelial ROS production. She showed that by giving the A_2A antagonist, SCH 58261, Angiotensin II stimulated ROS production could be reduced by 47% showing the importance of the A_2A receptor in the functioning of the endothelium. The third speaker was Dr Aikaterini Tsaousi from the University of Bristol, who presented her work on the relationship between ß-catenin and WNT and the effects this has on the endothelial cells lining the intima. Upregulation of Wnt4 activates ß-catenin signaling, which drives a proliferation pathway resulting in

intimal thickening, a problem in many cardiovascular clinical applications such as stenting. Elucidation of this process could have many therapeutic benefits. This excellent session was completed by Sarah Withers (University of Manchester); she is investigating the effects of aldosterone on vascular tone in the presence of adipocytes. Perivascular adipose tissue has anti-contractile effects but this is lost with the addition of aldosterone. Following experiments with the aldosterone antagonist, eplerenone, and hypoxic conditions, Dr Withers elegantly showed that aldosterone has a largely non-genomic effect on the anticontractile effects of perivascular adipose tissue. This research could be an important finding to help understand the vascular dysfunction of the metabolic syndrome.

Posters were displayed earlier in the day and with the completion of the session 2 there was the chance to properly discuss the work over a glass of wine. There were 18 posters to view, covering many aspects of cell signalling including: the electrophysiology of calcium channels and the myocardium, factors activated by shear stress, changes in development of cardiac myocytes and how they respond to protection and regeneration and of course vascular smooth muscle cells. The relaxed informal setting, allowed discussion to flow a bit more freely and gave the judges a good opportunity to speak to the poster presenters. It also meant that the delegates had a chance to get to know each other before dinner.

The conference dinner was held on Monday evening in the beautiful orangery of Goldney Hall, which provided a warm, intimate setting. Whilst this was the first young investigators meeting, it was also the last meeting for Professor David Eisner as chairman of the BSCR. This special occasion warranted a break in tradition and therefore a fitting goodbye speech and presentation were made. David has been Chairman of the BSCR for 3 years and he will be very hard to follow.

Despite the unfortunate absence of Professor Andrew Baker, day 2 began in fine form with Dr Stuart Nicklin, (University of Glasgow), doing an excellent job of standing in. He provided an in-depth overview of where gene transfer started in cardiovascular research and how the limitations of early vectors have been overcome to successfully use AAU6 via a systemic delivery. Next were two presentations highlighting the importance of the mitochondria to myocytes and subsequently the myocardium. Sang Bing Ong, (University College London), presented his work on mitochondrial fusion. Using HL1 cardiac cells as an experimental model, he showed how the overexpression of fused mitochondria made the cells more resistant to hypoxic injury and promoted their survival. Dr Derek Hausenloy also from University College London continued the theme of mitochondria by telling us about reversible mitochondrial transition pore opening and its requirement in ischaemic preconditioning. Opening of the pore generates reactive oxygen species, which are able to mop up damaging free radicals produced during ischaemia. Dr Hausenloy provided evidence of the importance of the pore for cell survival. Neatly moving on to the role of reactive oxygen species in heart failure was Professor Barbara Casadei, (University of Oxford, John Radcliffe), who braved an early start to give us an animated presentation on this complex area. Dr Casadei talked about nitric oxide and the important role of eNOS and nNOS in the myocardium to regulate calcium fluxes. The session was chaired by Drs Cathy Holt and Elinor Griffiths.

Session 5 had the theme of Inflammatory Cells and was chaired by Drs Katrina Bicknell and Jason Johnson. It began with an enchanting presentation by Dr David Greaves, (University of Oxford), talking about magical macrophage modifying peptides and their role in reducing vascular inflammation in atherosclerosis. Particularly significant was the Chemerin 15 protein, which appears to have many anti-inflammatory actions *in vivo*. Following Dr Greaves was Dr Nicolle Kraenkel, (University of Bristol), who presented data on the altered signalling of circulating progenitor cells in type I diabetes. Usually signalling and recruitment of pro-angiogenic progenitor cells is mediated by kinins, but Nicolle's work shows that impaired peripheral vascularization in diabetic patients may be due to a reduced sensitivity of the progenitor cells to kinins. Dr John Sinfield, (University of Leeds), covered the role of p38 MAP kinase subtypes in cytokine-induced IL6. Pro-inflammatory cytokines are elevated in the heart following myocardial infarction and are important in stimulating cardiac fibroblasts for remodelling. John used cardiac fibroblasts as an experimental model to show that the p38α subtype has a pivotal role in upregulating IL-6, data which may have useful therapeutic potential. Completing the session was Professor Dorian Haskard, (Impe-

rial College London), who elegantly compared the flow patterns of arteries with the corresponding signalling molecules, to give a holistic perspective of homeostatic and inflammatory responses.

Following this was lunch and the second poster session, giving the judges a final chance to look through some of the high quality data displayed and grill the presenters before the prize was awarded.

The final session of the meeting started with a dazzling 3D image of blood vessels. Dr Holger Gerhardt, (London), used this to illustrate the importance of sprouting patterns in angiogenesis. He eloquently showed how the simple idea of stalk cells and tip cells could be used to investigate a complex problem and could create some very cool animations. Dr Gerhardt may have been a tough act to follow, but Vinoj George, (University of Surrey), rose to the challenge to deliver an interesting presentation on the different targets that apocynin and tiron act on during ROS signalling and endothelial cell cycle regulation. The last oral abstract of the meeting was presented by Dr Nishith Patel, (University of Bristol), who brought to our attention acute kidney injury post cardiac surgery. This is a neglected but very important area of clinical research that affects 30% patients for whom mortality rates have remained unchanged for the last two decades. Dr Patel has successfully created an animal model in pigs that mirrors the effects seen in humans, in order to provide a way of investigating this. The final presentation of the day was a tour-de-force from Professor David Bates, (University of Bristol), on vascular endothelial growth factor and cardiovascular disease, a very fitting end to the endothelial cell theme of this session. Dr Chris Jackson and Joanne Ferguson chaired.

The meeting was rounded off by the prize giving. Marco Meloni from the University of Bristol took the first prize for his poster on, "Protective and Regenerative Actions on Nerve Growth Factor in the Post-Infarct Heart". This prize was kindly sponsored by Clinical Science. Gemma White from the University of Manchester took the second prize with her poster titled, "35K-FC: A Novel Therapeutic Strategy for CC Chemokine Blockade". In the Young Investigators Award; Dr Vivek Sivaraman, (University College London), was awarded the BSCR prize for his work looking at the "Opposing Roles of Protein Kinase C epsilon and delta in Simulated Ischaemia-reperfusion Injury in Human Myocardium". Second was Dr Aikaterini Tsaousi from the University of Bristol, third, Sarah Withers from the University of Manchester and fourth was Sapna Thakur from the University of Surrey. Congratulations to all the winners.

BSCR Young Investigators Meeting – Autumn 2008

Prize Winners

Young Investigators Award (BSCR Prize for Oral Presentation):

1st Dr Vivek Sivaraman (University College London) "*Opposing Roles of Protein Kinase C epsilon and delta in Simulated Ischaemia-reperfusion Injury in Human Myocardium*".

2nd Dr Aikaterini Tsaousi (University of Bristol)

3rd Sarah Withers (University of Manchester)

4th Sapna Thakur (University of Surrey)

***Clinical Science* Poster Prize:**

1st Marco Meloni (University of Bristol) "Protective and Regenerative Actions of Nerve Growth Factor in the Post-infarct heart"

Travel Report: American Section meeting of the ISHR, Cincinnati, Ohio

Interviews with the Organisers by Dr Anita Hoskins, King's College London

Cincinnati, Ohio

'It was the most satisfying moment of my career.' At the recent ISHR conference in Cincinnati, I interviewed Dr. Jeff Robbins, co-organiser of the American Section meeting, and asked him about his decision to give away the murine cardiac-specific inducible promoter, the technology developed in his laboratory, and allow it to be freely available to researchers. The murine α-myosin heavy chain (α-MyHC) promoter was developed in the Robbins lab in the early 90's, and has since been used to generate countless transgenic and gene-targeted animals in laboratories all across the world. 'I refused to licence it and refused to patent it. I just gave it away. After that, things clamped down and it became much harder to exchange reagents.' To this day, the Robbins lab still receives an average of seven requests per week for the promoter. 'A third to a half of all talks here have used this promoter. It was huge to give it away.' And it was indeed huge to give it away. In allowing researchers free access to the inducible promoter, Jeff has given us the freedom to side-step the mountain of paperwork that comes with the patent process, saving us from many headaches. And time. 'This way researchers can have the promoter in three or four days, instead of three or four months. We encourage labs to contact us so to avoid problems and to avoid mutations in the promoter. However, I have had refusals from other labs to share mice made from this promoter.'

The American Section meeting of the ISHR was held at the Hilton Cincinnati Netherland Plaza in downtown Cincinnati from the 16th to 20th June. This year's meeting was a broad scientific program that focused on translational research into cardiovascular disease, linking basic research to modern therapies at the bedside. The eleven symposia included topics such as cardiac signalling, cellular therapy for heart disease and genetics of congenital diseases. One particular symposium stood out for me. It was the fifth symposium, covering mechano-chemical signal transmission and transduction by cardiac sarcomeres which included talks by Pieter de Tombe, John Solaro, Jeff Walker, and a very topical talk on stretch activation by Rick Moss. Each year, the international council selects a speaker to deliver the Pfeffer distinguished lecture. The lectureship is designed to acknowledge the advances to the field of cardiac remodelling, as well as remember the early pioneering work of Dr. Janice Pfeffer. This year's recipient of the Pfeffer award was Howard Rockman for his work on G-protein-coupled receptors.

It was in Cincinnati that I set up interviews with Jeff and his co-organiser, Dr. Litsa Kranias. I wanted to discuss with them their thoughts on the direction of their research and the ups and downs

The Organisers - Jeff Robbins and Litsa Kranias

of organising an international conference. It was Thursday afternoon when I managed to catch Jeff for a few minutes. During the interview I asked Jeff what impact the development of the α-MyHC promoter has had on cardiovascular research. 'The α-MyHC promoter has given cardiac research a powerful new tool to ask cause and effect questions. It has allowed us to establish causality which gives insight into mechanisms. So it was very important.'

Jeff studied at the University of Rochester, New York, before completing his Ph.D. at the University of Connecticut. In 1993, Jeff was awarded Professor of Paediatrics and Division Director of Molecular Cardiovascular Biology before taking up the position of Associate Chair for Research at the Children's Hospital in 1999. The main goal of the Robbins lab is to define potential therapeutic targets. One of the current focuses in the lab is the contractile protein myosin and the hypothesis that MyHC isoform switching during heart disease has a direct effect on the developing pathology. Given that the healthy human ventricle contains predominantly α-MyHC and only 7-10% α-MyHC, I asked Jeff if he thought that the α-MyHC protein is a legitimate target for therapeutic intervention. 'Cytogenics definitely think so. They are currently undergoing clinical trials. In the lab, we have moved onto rabbit studies, which have similar hearts to human hearts, and these have answered 'sometimes' to the question as to whether MyHC isoforms can affect heart disease.' Jeff's lab has recently studied MyHC expression in three different rabbit models of human heart disease and found that myosin isoform switching had an impact in only one. 'We have shown that MyHC in tachycardia can make a big difference, but in myocardial infarction or a pressure overload rabbit model, MyHC isoform expression made no difference. So therapeutic intervention may be helpful in some diseases, but not in as many as we had hoped.'

Jeff said to me, 'Litsa is a people person' and when I sat down with Dr. Litsa Kranias, it did not take me long to discover that he was right. Despite the craziness of conference organisation going on around her (Litsa was signing cheques when I first met her), Litsa was immediately friendly, patient and willing to discuss her latest work. Litsa is the Chair of Pharmacology & Cell Biophysics and Director of Cardiovascular Biology at the University of Cincinnati, whose lab currently focuses on key Ca^{2+}-handling proteins with the aim to determine their physiological and pathophysiological significance *in vivo*. A particular favourite protein of Litsa's is phospholamban and I asked Litsa how this came to be. 'I did a post-doc purifying protein kinases and phosphatases. I then started in the cardiac field and a new protein called phospholamban had just been discovered. It was first called 'stimulator of cardiac function' but we later discovered it was an inhibitor. John Solaro and I were the first to discover that phospholamban was phosphorylated *in vivo*. Ten years later it was shown to be an inhibitor (of SERCA-2A).' Does phospholamban remain a serious target for therapeutic intervention in heart failure? 'Yes. Modulation of phospholamban itself, its inhibitor, or any process involved in Ca^{2+} uptake remains a good target.'

Welcoming remarks by Litsa Kranias

Using genetically-engineered mouse models, the Kranias Lab has helped to elucidate the role of phospholamban in the regulation of contractility. Their work has shown that the protein is a major determinant of the Ca^{2+} affinity of the SR Ca^{2+}-ATPase and an important regulator of Ca^{2+} homeostasis and contractility, as well as being pivotal in mediating β-adrenergic responses in the heart. Given their large focus on animal models, I asked Litsa how important and how relevant it is to use small animal models to study human heart disease. 'It is an important first step, especially the mouse. Currently, genetic manipulation is unavailable in stem cells of larger species. It is an advantage to use larger animals but it is much more expensive and difficult. Mouse models may serve as the basis for studies in heart disease which can then be expanded to higher species, but there must be concerted efforts in the human and the mouse. For example, we can first identify a mutation in human heart failure and then mimic it in the mouse

to understand its mechanism of action.'

Litsa emigrated to America from Greece after being awarded full scholarship following high school. She studied at the University of Chicago and received her Ph.D. from Northwestern University. Litsa developed a successful academic career in Cincinnati before establishing a second lab back in her home country of Greece. 'This lab is a biochemistry and clinical lab, where we derive some of our clinical material. We work on DCM (Dilated cardiomyopathy) and perform genetic testing. So I get to go back to Greece often. We are also establishing a lab in Alexandria, Egypt. We have the theory that most mutations in Ca^{2+}-cycling genes originate from this area.'

The conference was impeccably organised. I think this stemmed from the friendship that Jeff and Litsa have had for almost 20 years. Because of this friendship, they have a long history of collaboration and I asked them the importance of collaborators to their work. 'Extremely important' Litsa said, 'They are the biggest fun. We have 15-20 collaborators at one time. We are currently running clinical trials in the UK with Magdi Yacoub and Sian Harding. Collaborators are the biggest fun.' Jeff agreed. 'They are critical. We are applying to start a heart institute, merging basic sciences and cardio-thoracic surgery, which will be the first institute of its kind.' Jeff laughed when I asked him if he enjoyed organising an international meeting. 'It is a mixed blessing. I have enjoyed setting standards and living up to them. The downside is people's egos and technical hitches.'

My final question was a little self-indulgent but as a young post-doc in the beginnings of her career, I was curious to see how science has changed since Jeff and Litsa were starting out. I asked them if it is now more or less difficult for a young scientist to get established. I was surprised to find out that Litsa's stance was on one side, while Jeff's was firmly on the other. 'It is more difficult' Jeff said, 'The bar is continually being raised. But it doesn't mean a young scientist would not get ahead today. We are now given more tools to work with. I had an idea to isolate individual mRNAs by hybridising to a specific probe. To do this, I rang the NIH (National Institute of Health) to get serum from leukaemia patients. Using columns in cold rooms, I isolated the enzyme, reverse transcriptase, and I then used

Cincinnati Sights

the enzyme to make probes. This was a major experiment back then but this experiment is trivial now as we can just order the enzyme.' Litsa's career began when science was predominantly dominated by male scientists. 'I think it is easier to get

Delegates from the Rayne Institute,

King's College London

established as a scientist now. First, the role of women has opened up. It is much easier for a female to be accepted and integrated. It was difficult back then. I think it is very important to integrate young scientists, especially women. This makes them more comfortable and opens up possibilities to young researchers.' Litsa reflected on her first scientific conference. 'I stayed in my room and ordered room service as all the senior researchers were unwelcoming.' Thankfully, this was not the case in Cincinnati.

I very much enjoyed talking to Litsa and Jeff and am grateful to them for sharing their insights.

14th World Congress on Heart Disease: Annual Scientific Sessions of the International Academy of Cardiology, Toronto, Canada 26th-29th July, 2008

by Muhammad Nabeel Ghayur, McMaster University, Ontario, Canada

For the past 19 years, the International Academy of Cardiology (IAC) has been serving physicians and scientists alike in the area of cardiology and cardiovascular sciences with organizing meetings, publishing state-of-the-art literature and increasing awareness not only in the medical circle but also within the community. Founded, and presently Chaired, by A. Kimchi of University of California Los Angeles, USA, the IAC has now come a long way from being just a handful of clinicians and researchers to a forum now constituting world renowned professionals in the area of cardiology and cardiovascular sciences.

Each year, the IAC with endorsement from American College of Cardiology (California Chapter), organizes an annual meeting called the World Congress on Heart Disease (WCHD). This year in 2008, the 14th WCHD took place in Toronto, Canada, at the historic Fairmont Royal York Hotel in downtown Toronto. Built in 1929, the hotel is right across the street from Toronto's Union Station. The hotel is a favourite location for the British Royal family, including Queen Elizabeth II, when they visit Toronto and have a whole floor reserved for them. The meeting was spread over 3 days of scientific sessions consisting of plenary and invited talks, free presentations and posters. In total, more than 700 people participated in the meeting representing 60 countries while collectively around 565 orals and posters were presented.

Day-1 began with distribution of IAC 2008 Awards. These awards are established by IAC in memory of distinguished clinicians and researchers who contributed to the overall advancement of cardiology. Out of a number of applications, only five people were selected for these coveted awards and another three who received the Distinguished Fellowship Awards. The Awards Selection Committee consisted of 130 eminent cardiovascular medicine professionals who chose the following for these awards: H. Boudoulas of Ohio State University, Columbus,

The Fairmont Royal York Hotel in downtown Toronto

A scientific session in progress

USA; R. Roberts of University of Ottawa Heart Institute, Ottawa, Canada; P.R. Liebson of Rush University Medical Center, Chicago, USA; S.F. Nagueh of Weill Cornell Medical College, Houston, USA; U. Thadani of University of Oklahoma, Oklahoma City, USA; M. Alpert of University of Missouri, Columbia, USA; N.S. Dhalla of University of Manitoba, Winnipeg, Canada; and J.A. Elefteriades of Yale University, New Haven, USA.

The first talk on day-1 was by E.L. Barrett-Connor of University of California, San Diego, USA, who was invited to give the 3rd H.J.C. Swan Memorial Lecture. The speaker talked about 'women and heart disease in the post-WHI era'. She discussed cardiovascular diseases (CVD) in men and women and how the sex hormones play their role for the observed difference. The first session on day one focused on 'new therapeutic targets in cardiovascular medicine'. W. Koenig of University of Ulm, Ulm, Germany, talked about the role of oxidative stress in atherogenesis and how the two different types of phospholipase A_2 namely a) lipoprotein associated and b) secretory, can lead to atherosclerosis and increase in CVD. He pointed out that leading clinical research in this area is showing that using respective antagonists can result in decreased inflammation and lowered cholesterol thus proving better for prevention of CVD. The other presenters in the session were: C. Patterson of University of North Carolina, Chapel Hill, USA, who talked about the multiple roles of ubiquitin ligases such as atrogin -1, MURFs 1-3 and CHIP in the heart to regulate cardiomyocyte function and cardiac hypertrophy; A.H.J. Danser of Erasmus Medical Centre, Rotterdam, The Netherlands, discussed the advantage of renin inhibition in order to control blood pressure and thus protect the organs; L. Kuo of Texas A&M Health Science Centre, Temple, USA, explained the mechanism of biphasic activity of angiotensin II (Ang II) in coronary microvasculature and its deleterious effect on endothelium-dependent nitric oxide (NO)-mediated dilation; G.D. Lopaschuk of University of Alberta, Edmonton, Canada, discussed the upcoming use of malonyl CoA decarboxylase inhibitors to shun fatty acid oxidation in an attempt to permit the heart to produce energy more efficiently during and following cardiac ischemia; S.C.Tyagi of University of Louisville, USA, presented data on the cardioprotective role of sodium thiosulfate in chronic heart failure in mice

Poster Session in progress at the meeting

by a mechanism involving increased ventricular H_2S generation; H.K. Saini-Chohan of University of Manitoba, Winnipeg, Canada, showed the role of sarcoplasmic reticulum (SR) Ca^{2+} stores in eliciting ouabain-induced elevation of $[Ca^{2+}]i$ in cardiomyocytes; and finally B.C. Blaxall of University of Rochester, USA, claimed to have identified different genes like NOGO, Mena and protease activated receptors that might have a role in development and regression of CVD.

The second session on day-1 was about 'vascular biology: basic research'. The session began with a talk from A. Schaefer of University

of Wurzburg, Germany, who talked about the chemokine fractalkine and its role in congestive heart failure (CHF). The speaker showed that in lab rats induced with experimental CHF, there is increased vascular fractalkine and that the presence of fractalkine further deteriorates endothelial dysfunction and increases platelet aggregation in these animals. This talk was followed by: P. Pignatelli of University of Rome, Italy, who showed how TNF-α up-regulates the pro-inflammatory protein CD40L in CHF patients via a mechanism involving cyclooxygenase-1 independent of arachidonic acid-mediated oxidative stress; H. Yang of Meharry Medical College, Nashville, USA, presented how Apo-E deficient lipoproteins inhibit lysosomal hydrolase synthesis and transform macrophages into foam cells; J. Soria of Centre de Recherche des Cordeliers, Paris, France, presented data for the antithrombotic effect of rivaroxaban, an oral factor XA inhibitor, on clot structure and degradability through a dual mechanism involoving modification of clot structure and decrease in thrombin-activated fibrinolysis inhibitor activation by thrombomodulin-thrombin complex; J.E. Toblli of Hospital Aleman, Buenos Aires, Argentina, showed data of comparative studies for cardiovascular toxicity between different IV iron preparations in rats and showed ferric-carboxymaltose and iron-sucrose-complex to be the safest; P.Y. Cheung of University of Alberta, Edmonton, Canada, showed the deleterious effects of postresuscitation administration of an NO inhibitor on systemic, pulmonary and cardiac hemodynamic recovery in newborn piglets with hypoxia-reoxygenation (HR) insults; and lastly Y.Y. Bai of Chinese Academy of Medical Sciences, showed data from a meta-analysis of completed trials that L-arginine supplement therapy does repair but does not enhance endothelial function and clinical outcome in humans.

Day-2 started with a session on 'endothelial biomedicine: new opportunities for diagnosis and treatment'. The first talk was delivered by A.A. Knowlton of University of California, Davis, USA, who briefed the audience on the cardioprotective effects of estrogen. He claimed

Canadian symbol: CN Tower, pictured from in front of the hotel

that estrogen not only protects adult cardiomyocytes against HR but also protects adult human coronary artery endothelial cells against HR. According to the speaker, in the backdrop of unexpected negative findings of some clinical trials, there is a need to carefully study the effects of estrogen. The other presenters in the session were: C.F. Sanchez-Ferrer of University of Autonoma, Madrid, Spain, who reviewed the area of vascular endothelial dysfunction with particular reference to its link with vascular aging and how this leads to diminished vasodilation and exaggerated vasoconstriction with the increasing age of the patient; R.C. Austin of McMaster University, Hamilton, Canada, reviewed the etiology of atherosclerosis and the different mechanisms via which ER stress can cause atherosclerosis; S.B. Wheatcroft of University of Leeds, UK, summarised the results of his studies showing elevated fasting insulin levels and decreased vasodilatory scores in South Asians compared to Caucasians in the UK. To end the session, K. O from the University of Manitoba, Winnipeg, Canada, showed that

hyperhomocysteinemia induced superoxide anion production in vessels is mediated via activation of NADPH oxidase which as a result reduces NO availability and leads to endothelial dysfunction.

Session-2 on day-2 was titled 'atherogenesis, inflammation and oxidative stress'. The opening talk of the session was by N.S. Dhalla of University of Manitoba, Winnipeg, Canada. The speaker very nicely talked about the problems of $[Ca^{2+}]_i$ overload in reperfused ischemic hearts and the possible mechanisms that might be involved in this. Using the isolated rat heart technique, Dhalla showed that the depressed activity of the Na^+-Ca^{2+} exchanger and the SR Ca^{2+} pump coupled with increased sarcolemmal Ca^{2+} entry into the cell, may play a role. This interesting talk was followed by: P.R. Liebson of Rush Medical College, Chicago, USA, who reviewed the relationship between oxidative stress and atherosclerotic plaque formation; P.K. Singal of University of Manitoba, Winnipeg, Canada, who talked about the data from his lab detailing the involvement of TNF-α induced oxidative stress and cardiomyocytes apoptosis produced via p38 and ERK 1/2 leading to CHF; R. Touyz from University of Ottawa, Ottawa, Canada, who spoke about resistance arteries and how targeting different NOXES (non-phagocytic NADPH oxidases) can reduce oxidative stress and inflammation in these arteries and prevent end organ damage; and lastly S. Amar of Boston University, Boston, USA, presented interesting findings on unrecognized risk factors for atherosclerosis and CVD such as periodontal disease and pulmonary disease (longstanding and low grade infections) and how these pathologies can induce inflammatory mediators into the bloodstream thus causing atherogenesis.

The one session on the final day entitled 'Ischemic heart disease/risk assessment/new treatment strategies' opened with a talk by U. Thadani of University of Oklahoma, Oklahoma City, USA, who summarized the advantages and limitations of different anti-anginal treatment options including a) drugs like β- blockers, nitrates, Ca^{2+} antagonists, Na+ channel blockers, metabolic modulators and sinus node blockers and b) procedures like percutaneous coronary revascularization, external counterpulsation therapy, direct transmyocardial laser revascularization, sympathectomy, angiogenic gene therapy and heart transplant. This very extensive review talk was followed by: P.A. McCullough William Beaumont Hospital, Royal Oak, USA, who talked about the link between vascular calcification in chronic kidney disease patients; G.W. Barsness from Mayo Clinic, Rochester, USA, talked about treatment options (like spinal cord stimulation) for angina patients who are not candidates for standard revascularization procedures due to anatomical or comorbidity reasons; M. Madjid of Texas Heart Institute, Houston, USA, talked about an interesting yet neglected area of concern, that of influenza triggering acute coronary syndromes and how it can easily be tackled by increasing influenza vaccination; and finally M. Imazio of Maria Vittoria Hospital, Torino, Italy, reviewed the clinical potential of colchicine for recurrent pericarditis and also presented recommendations for its use.

The meeting, as far as the science was concerned, was very thorough. In particular, the speakers were all very well chosen and came from many countries of the world to reflect the global nature of this meeting. But apart from this, there were some flaws as well. The scientific program was too cluttered and at times didn't allow the listeners to even take a coffee break. The parallel sessions were not always synchronized which meant that if you are taking a session up to the end then you miss the start of the next session. Breaks between sessions were also not properly given which limited networking opportunities among delegates, otherwise a vital part of any meeting. At most times, the session chairs were at least careful to be punctual. No meals were served throughout the meeting which detracted from the character of the meeting and deprived the delegates of a chance to mingle and chat with each other. Next year the 15th WCHD will take place in Vancouver, Canada, from 18th to 21st Jul 2009 (deadline for abstract submission is 27th Feb 2009).

Cardiovascular Meetings

JOINT BSCR/ BAS WORKSHOP:

"Studying Vascular Biology using the Zebrafish"

5th February, 2009

Venue: MRC Centre for Developmental and Biomedical Genetics, University of Sheffield

Organisers: Dr Tim Chico and Dr Martin Denver

For further details, visit the BSCR website or contact t.j.chico@sheffield.ac.uk

British Pharmacological Society 2008 Winter Meeting, 18 December 2008, Brighton, UK. Mending a broken heart: Advances and challenges of stem cell therapy. Further information regarding the programme can be obtained by contacting Prof. Anwar Baydoun (University of Hertfordshire, UK) or online at http://www.bps.ac.uk

Keystone Symposium on Cardiac Disease: Development, Regeneration and Repair, organised by Michael D. Schneider and Nadia A. Rosenthal, will be held at Grove Park Inn, Asheville, NC on March 15 - 20, 2009. Further details can be found at http://www.keystonesymposia.org/

7-9 May 2009, Focused Meeting: New Drugs in Cardiovascular Research. Joint Meeting with the German Societies for Pharmacology & Clinical Pharmacology.Dresden, Germany. Early bird registration deadline: 31 January 2009. Further information regarding the programme, registration and abstract submission can be obtained http://www.bps.ac.uk

ESC 'Heart Failure Congress 2009' joint meeting with XIX Annual Meeting of the ISHR European Section will take place in Palais Acropolis, Nice, France on 30th May - 2nd June, 2009. Further details can be obtained from http://www.escardio.org/congresses/Pages/welcome.aspx

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!

British Heart Foundation Grants

Fellowships Committee July 2008

Senior Basic Science Research Fellowship

Dr K Dora, University of Oxford. "Novel integrative signalling mechanisms for endothelial cell control of microvascular tone" (3 years) £374,199

Intermediate Basic Science Research Fellowships

Dr Y A Senis, University of Birmingham. "Investigating the functional roles of SH2 domain-containing protein tyrosine phosphatases in platelets" (4 years) £384,053

Dr A M Miller, University of Glasgow. "Interleukin-33: a novel cytokine in the inflammation of atherosclerosis and obesity?" (4 years) £252,946

Advanced Training Award

Dr R Akhtar, University of Manchester. "Quantifying arterial stiffness as a function of glucose tolerance: from the nano to macro scale" (3 years) £133,816

PhD Studentships

Unnamed and McBride, University of Glasgow. "Dissecting microRNA regulation of gene expression in cardiac hypertrophy in the SHRSP" (3 years) £92,848

Unnamed and Kitmitto, University of Manchester. "Molecular investigations into the interaction between caveolin-3 and cardiac L-type voltage-gated calcium channels" (3 years) £89,838

Unnamed and Halestrap, University of Bristol. "The identification, role and regulation of the mammalian mitochondrial pyruvate carrier" (3 years) £81,043

Miss L C Elson, University of Oxford. "Regulation of calcium dynamics and contractility of cardiac ventricular myocytes by cyclic ADP-Ribose phosphate in health and disease" (3 years) £98,938

Unnamed and Plevin, University of Strathclyde. "Characterising the role of inhibitory kappa B kinase a in human endothelial cell function" (3 years) £92,327

Miss C Mill, University of Bristol. "Diversion of -catenin from TCF - to FoxO-mediated transcription by oxidative stress promotes VSMC apoptosis" (3 years) £91,600

Miss P Datta-Nemdharry, University College London."Food nutrient profiling and cardiovascular disease related outcomes: the Whitehall II study" (3 years) £77,039

Ms K Garner, University College London. "Angiotensin-II mediated signalling: is phosphatidylinositol transport an essential component for signal transduction?" (3 years) £100,911

Mr Y Bhagatte, University of Leicester. "Cellular regulation of mitochondrial permeability transition pore opening during cardiac muscle stress" (3 years) £86,578

Ms R Fujita, Institute of Child Health (UCL). "Analyzing the co-expression and effects of POU4F1/Brn-3a transcription factor and p53 family in the heart" (3 years) £108,718

Unnamed and Littlewood, University of Cambridge. "Regulation of vascular smooth muscle cell survival by the Akt pathway" (3 years) £96,150

Unnamed and Talmud, University College London. "Genetic architecture of secretory PLA2 (sPLA2) genes and their impact on sPLA2 activity and mass and association with CHD risk" (3 years) £100,291

Mr C Davies, University of Birmingham. "The role of oxygen-dependent substances in exercise" (3 years) £92,518

Unnamed and Jackson, University of Bristol. "Roles of blood clotting factor XIIIA and of fibrin in the stabilization and repair of atherosclerotic plaques" (3 years) £90,665

Unnamed and Oakey, King's College London. "Epigenetic mechanisms in heart development and disease" (3 years) £98,039

Mr M McArdle, University of Leeds. "Regulation of the gene expression in vascular proliferative disease" (3 years) £94,877

Mr G Mangialardi, University of Bristol. "Diabetes impairs bone marrow endothelial barrier function and trans-endothelial migration of stem cells" (3 years) £93,033

Unnamed and Zachary, University College London. "Role of Stanniocalcin in VEGF regulation of endothelial cell function" (3 years) £99,139

Mr R Endrighi, University College London. "Physical activity, adiposity, stress-induced inflammation and cardiovascular disease risk" (3 years) £98,112

Unnamed and Dash, University of Reading. "The regulation of cytoskeleton and adhesion complex dynamics in migrating trophoblast cells by nitric oxide" (3 years) £93,430

Unnamed and Aaronson, King's College London. "The

role of reactive oxygen species in the EDHF response" (3 years) £96,791

Clinical Research Training Fellowships

Dr T P E Lockie, King's College London. "Post conditioning in acute myocardial infarction: a randomised control trial" (2 years) £160,682

Dr M Kahn, University of Leeds. "Investigating the effects of insulin resistance on endothelial progenitor cells and vascular repair" (3 years) £162,526

Dr T T Biss, University of Newcastle. "Inter-individual variability in response to warfarin in children: analysis of environmental and pharmacogenetic factors" (2 years) £125,655

Dr A G Hameed, University of Sheffield. "Dissecting the role of TRAIL in the pathogenesis of pulmonary hypertension" (3 years) £172,627

Marian and Christina Ionescu Fellowship

Miss A P Barker, University of Cambridge. "Ex-vivo perfusion strategies for optimization of donor heart and lung function in intra-thoracic organ transplantation" (2 years) £67,388

Cardiovascular Related Wellcome Trust Grants

June to August 2008

Project Grants

Professor Caroline Fall, MRC Environmental Epidemiology Unit, Southampton General Hospital, University of Southampton. Early-life antecedents of type 2 diabetes and polycystic ovary syndrome in young Indian adults. 36 months £472,265

Prof Harry Hemingway, Dept of Epidemiology & Public Health, Univeristy College London. Higher resolution cardiovascular epidemiology: unique insights from linking the national cardiac event register with primary care records and highly phenotyped cohorts. 60 months £1,302,711

Dr Laila Jal Tata, Div Epidemiology & Public Health, Clinical Sciences Building, Nottingham City Hospital. Assessment of drug safety and the impact of illness in pregnancy: Establishing a routinely updated maternal-child linkage system in The Health Improvement Network database. 36 months £149,866

Dr M C Gulliford, Dept of Public Health Medicine, St Thomas's Campus, UMDS of Guy's & St Thomas's Hospital. Cluster randomised trials using a primary care database: utilising electronic patient records for intervention research. 36 months £338,335

Technology Development Grant

Dr Carl Paterson, The Blackett Laboratory, Imperial College London. Complete polarisation-sensitive confocal scanning laser ophthalmoscope. 36 months £217,680

Research Training Fellowships

Miss Helen Petersen, Dept of Oral and Dental Science, Bristol Dental Hospital, University of Bristol. Streptococcus Induced Thrombus Formation. 30 months £132,269

Dr John Cain, Imaging Sciences Research Group, University of Manchester. Combining Lower Body Negative Pressure With Magnetic Resonance Imaging To Investigate Cerebral Vascular Autoregulation. 36 months £176,118

Equipment Grant

Prof Dorian O Haskard, Cardiovascular Medicine Unit, Hammersmith Hospital, Imperial College School of Medicine. Mechanisms of leukocyte trafficking and differentiation in vascular inflammation. 60 months £65,280

Technology Development Grant

Prof Brian Derby, Manchester Materials Science Centre, UMIST. Quantitative measurement of tissue elastic properties using acoustic microscopy. 36 months £331,376

Clinical SCIENCE

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Spring Meeting 2009

A joint meeting with the British Atherosclerosis Society

Atherosclerotic Plaque Rupture

Dates: Thursday 2nd and Friday 3rd April, 2009

Venue: Medical Sciences Teaching Centre/St Catherine's College, Oxford

Organisers: Martin Bennett, Chris Jackson and Chris Newman

Programme: The programme will consist of state-of-the-art presentations by leaders in the field. Speakers will include: Patrick Serruys (Rotterdam), Allard van der Wal (Amsterdam), Chris Jackson (Bristol), Erik Biessen (Maastricht), Rob Krams (London), Martin Bennett (Cambridge), Allen Burke (Gaithersburg), Andreas König (Munich), Juan Carlos Kaski (London) and Andrea Mezzetti (Chieti)

Free Communications: A full session will be devoted to oral presentation of selected abstracts. There will also be a Young Investigator Award session, with the Michael Davies and BSCR Prizes to be won. There is also a Clinical Science Early Career Investigator Award for best poster.

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

Deadlines: **Submission of abstracts** Friday 6th February

Registration Friday 13th March