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Contents

Editorial

Welcome to the April 2009 issue of *The* Bulletin!

We are pleased to bring you a review discussing the cardioprotective properties of activating A3 adenosine receptors and involvement of Nitric oxide synthase in the myocardium by Dr Afthab Hussain.

Included in this issue is the meeting report by Laura Newell on the recent joint Spring Meeting of the British Atherosclerosis Society (BAS) and the British Society for Cardiovascular Research (BSCR) which took place in Oxford in the first week of April of this year.

In the Secretary's column by Dr Chris Jackson, he highlights your attention to the next BSCR meeting in September this year again in Oxford, organised by Barbara Casadei, Kieran Clark and Saadeh Sueliman, titled Myocardial Energetics and Redox in Health and Disease, details of which are on the back page of this Bulletin issue and also posted soon on the BSCR website.

Finally, details of the latest grants awarded to researchers in the Cardiovascular field by the British Heart Foundation are listed towards the back of this issue.

Helen Maddock and Nicola Smart

The role of Nitric oxide in A3 adenosine receptor-mediated cardioprotection

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Limiting the impact of ischemia reperfusion-related cell death is of vital importance given the enormous figures of heart related mortality in the world. 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 and as a whole it is estimated that there are just over 1.5 million men, and 1.1 million women, who have suffered coronary heart disease in the form of either angina or myocardial infarction (www.heartstats.org). In patients undergoing standard clinical reperfusion treatment today such as thrombolysis, percutaneous coronary angioplasty (primary PCTA), and bypass surgery, there remains an underscored need for novel therapies and strategies to reduce post-ischemic infarct size.

Significant advances have been made in the past decade in recognizing distinct intracellular pathways involved in the mechanisms that influence myocardial programmed cell death including the activation of signalling molecules and transcription factors. Given the considerable progress made in the field, including the more recent discovery from the laboratory of Vinten-Johansen et al. (2003) of ischemic postconditioning, an enhanced emphasis has been placed on the more clinically appealing alternatives of pharmacological interventions applied at the onset of reperfusion (Zhao et al., 2003). It is beyond the remit of this review to cover all aspects relating to myocardial preconditioning and postconditioning, for an extensive overview see Hausenloy & Yellon (2007). This review will concentrate on adenosine receptors and the cardioprotective intracellular signalling mechanisms triggered specifically by A3 adenosine receptors.

Adenosine Receptors and Cardioprotection

Mechanical interventions aimed at reducing reperfusion injury have gained rising interest however there are also many pharmacological interventions that have shown impressive potential. Using the adenosine pathway to protect the myocardium has been an ever increasing topic of investigation. Endogenous purine nucleoside adenosine was recognized as far back as 1929 by Drury & Szent-Gyorgyi for its effects on the cardiovascular system (Drury et al., 1929). Four decades

later, in 1970, the first pharmacological evidence of adenosine receptors emerged, based on studies by Sattin & Rall which showed that xanthines, theophylline and caffeine were adenosine receptor antagonists (Sattin et al., 1970).

Since those early adenosine studies, significant advancements in the understanding of the physiology, pharmacology and molecular biology of adenosine and adenosine receptors has been made. Adenosine has been documented to affect almost all mammalian organ systems with a diverse range of physiological functions including energy regulation. Specifically, adenosine is recognized for its ability to limit injury in a variety of tissues during an ischemic or hypoxic insult and has been dubbed the "retaliatory" metabolite (Newby et al., 1984). Research has shown that endogenous adenosine is released upon ischemic insult or de-energization and is responsible for decreasing infarction size and limiting cellular injury as well as restoring energetic homeostasis (Zhao et al., 1993, Headrick et al., 2003, Peart and Headrick 2007). Endogenous adenosine has been demonstrated to be released during the early phase of reperfusion and it is thought that adenosine receptors are activated during pre- and postconditioning making the use of adenosine as a pharmacological agent appealing. In the myocardium, adenosine is produced at basal levels during normoxia, however during ischemia there is an increase in adenosine which is caused by the breakdown of adenosine triphosphate (ATP). The primary function of adenosine is to undergo phosphorylation by adenosine kinase to form adenosine monophosphate (AMP) and subsequently phosphorylation to generate ATP. In the myocardium, adenosine has been shown to regulate heart rate, hypotension, coronary blood flow, bronchoconstriction and mast cell degranulation. Adenosine levels are significantly elevated during cellular stress playing a role in limiting necrosis and apoptosis during periods of ischemic injury (Van Wylen., 1994). The increase in production of adenosine then stimulates adenosine receptors on the surface of ventricular cardiomyocytes and endothelial cells (Sommerschild et al., 2000). Adenosine has a myriad of physiological effects, all of which are mediated by the activation of cell surface adenosine receptors (ARs). Since adenosine has a short half-life, it exerts those physiological effects in an autocoid manner. There are four known subtypes of adenosine receptors that exist: A1, A2a, A2b, and A3 receptors.

They are coupled via G proteins to multiple effectors including enzymes, channels, transporters and cytoskeletal components. All four subtypes have been recognized to have protective attributes in cardiovascular tissue, with the most research conducted on the A1 Adenosine receptor. All four subtypes were cloned and pharmacologically characterised between 1989 to 1994, and, with the exception of A2b, have been functionally expressed in rat ventricular cardiomyocytes (Fredholm et al., 2001).

The A3 Adenosine receptor (A3AR) is the most

recently identified receptor subtype and has generated growing interest, with many studies concerning the role of receptors in regulating cardiovascular injury and cell death. A3ARs are thought to be expressed in cardiomyocytes and may potentially be involved in apoptosis (Shneyvays et al., 2000). Studies have also supported their participation in the activation and translocation of protein kinase C which ultimately leads to an increased opening of K_{ATP} channels, thought to be the final mediators of cardioprotection (Zhao et al., 1993).

Maddock et al., were the first to demonstrate that activation of A3AR at reperfusion following ischemia improves myocardial functional recovery in a guinea-pig working heart model, reduces myocardial injury in a rat langendorff heart model and also helps protect isolated cardiomyocytes from cell death (Maddock et al., 1997, 2002 & 2003). Using a selective A3AR agonist, 2-Cl-IBMECA, administered at reperfusion in the perfused heart, a significant decrease in infarct size was observed.

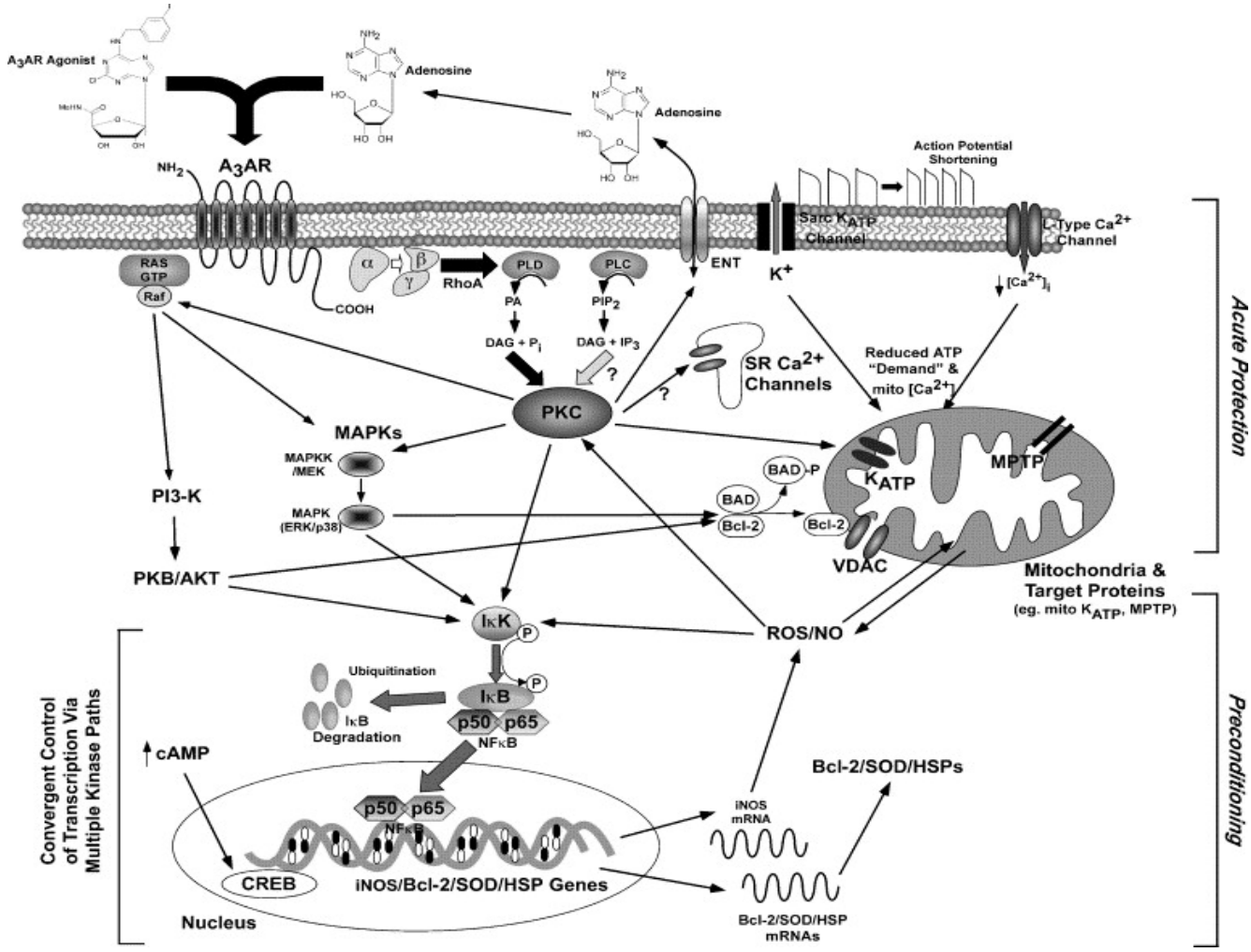

Figure 1: A3 Adenosine Receptor proposed mechanism of protection (Source: Headrick et al., 2005)

CREB, cAMP response element B; DAG, 1,2-diacylglycerol; ENT, equilibrative nucleoside transporter; HSPs, heat shock proteins; iNOS, inducible nitric oxide synthase; IP3, inositol-(1,4,5)-triphosphate; KATP, ATP-sensitive K+ channels; MPTP, mitochondrial permeability transition pore; NO, nitric oxide; PA, phosphatidic acid; Pi, inorganic phosphate; PIP2, phosphatidylinositol-(4,5)-diphosphate; PKC, protein kinase C; PLC, phospholipase C; PLD, phospholipase D; ROS, reactive oxygen species; Sarc KATP channels, sarcolemmal ATP-sensitive K+ channels; SOD, superoxide dismutase; SR, sarcoplasmic reticulum; VDAC, voltage-dependent anion channel.

Additionally, the A3AR agonist exerted anti-apoptotic and anti-necrotic effects when administered at reperfusion which was observed in isolated adult rat myocytes following simulated ischemia / reoxygenation (Maddock et al., 2002). An optimum sub-threshold of A3ARs needs to be achieved to elicit a protective effect since high doses have been shown to trigger cell-death (apoptosis and necrosis) in myocytes, (Shneyvays et al., 2000, Maddock et al.,2003).

Further research has recognized A3ARs as modulators of apoptotic and necrotic cell death as well as having a role in the enhancement of contractile function. Evidence suggests that A3ARs have very low cardiac expression and are minimally activated by endogenous adenosine during ischemia and therefore more susceptible to activation with an exogenous agonist. It has been suggested that the possible reason for its ability to generate different protected phenotypes is because it is efficiently coupled to powerful cell signalling pathways (Headrick et al., 2005). Our lab has looked extensively over the past 8 years at the intracellular signalling pathways involved with A3 adenosine receptor mediated reduction in reperfusion injury in various myocardial models of simulated ischemia / reperfusion (Maddock et al., 1997, 2002, 2003; Hussain et al., 2006; Karjian et al., 2006, 2008).

Research has indicated that adenosine receptors cause a cascade of events similar to those induced by preconditioning. They are thought to include the activation of protein kinase C and its downstream effectors such as MAP kinases, heat shock proteins and mitochondrial KATP channels (Zhao et al., 1993). The possibility of multiple signalling pathways converging to generate cardioprotection has been suggested (Headrick et al., 2005). **Figure 1** demonstrates the proposed mechanisms by which A3AR agonism improves ischemic tolerance:

One of the proposed mechanisms by which A3ARs reduce infarct size is by attenuating PMN activation and accumulation. Studies conducted by Vinten- Johansen et al. have shown that A3 receptor activation at reperfusion attenuates neutrophil-mediated reperfusion injury (Jordan et al., 1999). Their studies have also suggested that adenosine administered at reperfusion inhibits apoptotic cell death modulating the expression of Bcl-2 and Bax (Zhao et al., 2001). In a study by Budde et al. it was reported that multiple applications of adenosine (during early and late phase reperfusion) significantly protected the heart better than a single administration. This is thought to occur because late PMN recruitment is inhibited as well as early PMN accumulation (Budde et al., 2004). Another mechanism by which A3ARs are thought to protect is by stimulating the phosphorylation of Akt whose activation is known to inhibit apoptosis (Kennedy et al., 1999). It is also thought that A3AR activation causes the phosphorylation of extracellular regulated kinase 1/2 (ERK1/2) and the activation of the RISK pathway following both pre-conditioning and post-conditioning respectively (Germack

and Dickenson, 2005, Yellon et al., 1999, Hussain et al., 2006).

Furthermore, activation of A3AR has been indicated in a multitude of studies to show significant cardioprotection by limiting injury both during ischemia and following ischemia-reperfusion. The exact mechanisms associated with the effects of A3AR agonists continue to be investigated as there remains some ambiguity. Overall, therapeutic strategies using A3 AR agonists seem promising in reducing reperfusion injury.

Intracellular signaling pathways attributed to A3 Adenosine Receptor mediated cardioprotection

To date, a plethora of research has presented considerable evidence that exogenous A3AR activation leads to cardioprotection following ischemia reperfusion, although the precise mechanisms remain to be fully elucidated (Maddock et al., 2002; Kerendi et al., 2005; Shneyvays et al., 2005).

To date, several signalling pathways in A3AR mediated cardioprotection have been identified. However, it is important to note that while a variety of potential protective paths have been suggested, differences have been seen in acute vs. delayed responses to A3AR agonism. Lee at al. (2001) and Parsons et al. (2000) have found that the protection involves phosphatidylethanolamine formation and the conversion of phosphatidic acid to diacylglycerol (DAG). This attributes the response to a more prolonged protection of selective RhoA-dependent activations of phospholipase D (PLD) (Lee et al., 2001, Parsons et al., 2000). Multiple kinases have also been shown to be involved in A3AR dependent cardioprotection. Schulte and Fredholm (2003) have provided evidence of A3AR modulating mitogen activated protein kinase (MAPK) signalling (Schulte et al., 2003), Germack and Dickenson (2004) have shown a stimulation of ERK1/2 in neonatal cardiomyocytes following preconditioning (Germack and Dickenson, 2004) or postconditioning (Hussain et al., 2006) via activation of A3AR . Further research has suggested that the activation of ERK1/2 also involves both ROS signalling and ATP sensitive potassium (KATP) channel opening (Gross et al., 2003). Germack and Dickenson (2005) were the first to demonstrate that the protection afforded by A3AR activation also involved a phosphatidylinositol 3-OH- kinase (PI3-K) dependent pathway in neonatal cardiomyocytes (Germack and Dickenson, 2005). In this particular study, the role of adenosine receptor-induced cardioprotection was investigated in a preconditioning model and not, as in this present study, at the time of reperfusion.

The activation of these kinase cascades, termed Reperfusion Injury Salvage Kinase (RISK) pathway by Yellon et al. (2005), are regarded as important mediators in cardioprotection at the time of reperfusion (Hausenloy et al., 2005).

Our lab has recently investigated the role of the PI-3-kinase cell survival pathway in context of the

apoptotic second messenger signalling pathway elicited by administration of A3AR agonist, 2-Cl-IB-MECA, at reperfusion in an intact heart model and in isolated adult cardiomyocytes. The results of this study demonstrated that treatment with 2-Cl-IBMECA significantly reduced infarct size when administered at reperfusion. The results indicated the importance of recruitment of the PI-3 kinase/Akt pathway and involvement of ribosomal p70S6 kinase in the cardioprotection afforded by 2-Cl-IBMECA when administered at reperfusion (Hussain et al., 2006)

Another downstream target of PI-3 kinase and Akt, is phospho-Bad (Ser136). Bcl-2 family pro-apoptotic protein (BAD) is a pro-apoptotic member of the Bcl-2 family which causes cell death by displacing Bax from binding to Bcl-2. The apoptotic activity of BAD can be inhibited by activating intracellular signalling pathways that result in the phosphorylation of BAD at Ser112 and Ser136. The phosphorylation of these sites inhibits the binding of Bad to pro-apoptotic proteins Bcl-2 and Bcl-xL. Moreover, the activation of Akt has been shown to promote cell survival by its ability to phosphorylate BAD at Ser136 (Datta et al., 1997, del Peso et al., 1997). Our lab has also demonstrated that A3AR activation at reperfusion causes the upregulation of phospho-BAD (Ser136) which is suggested to contribute to the protective properties of A3AR activation. These findings provide additional evidence that A3AR activation at the onset of reperfusion is mediated via the PI3 kinase-Akt cell survival pathway as well as demonstrating the phosphorylation of downstream protein BAD at Ser136 (Hussain et al., 2006; Karjian et al., 2008). In reference to the PI3-kinase pro-survival signalling pathway, it is important to mention that a few recent studies have implicated its role in inhibiting the mitochondrial permeability transition pore (mPTP). Regulating the opening of the mPTP has been a target of modern cardioprotective strategies because the opening of the mPTP upon post-ischemic reperfusion has been suggested to be responsible for lethal reperfusion injury. Studies conducted by Yellon's group with rat cardiomyocytes has demonstrated a direct link between the PI3-K pathway and mPTP whereby overexpression of constitutively active Akt delayed the opening of the mPTP (Davidson et al., 2006). Bopassa et al. found the same relationship between PI3-K and mPTP in their studies with rat hearts reperfused with low pressure or postconditioning (Bopassa et al., 2006).

More recent findings by Park et al. (2006) have demonstrated that 1μM 2-Cl- IBMECA applied during reperfusion prevented reperfusion injury by inhibiting the mPTP opening through the inactivation of glycogen synthase kinase (GSK)3β. In addition, their studies suggest that 2-Cl-IBMECA-induced GSK-3β inhibition is mediated by the PI3-kinase/Akt signalling pathway (Park et al., 2006). The ability of the A3AR to prevent dissipation of the mitochondrial membrane potential in rat cardiomyocytes treated with sodium azide under hypoxic conditions has also been recenty reported (Shneyvays et al., 2005). We are currently investigating the role of the mitochondria in A3AR mediated

cardioprotection which promises to yield interesting research implications.

Role of nitric oxide in A3AR mediated cardioprotection

A role for nitric oxide in another stage of the cardioprotective response elicited by A3ARs has also been implicated in various studies. The induction by kinase-dependent activation of a range of protein mediators of protection including inducible and endothelial nitric oxide synthase (iNOS, eNOS respectively) have both been suggested in models of late phase ischemic preconditioning with A3ARs. Research conducted by Bolli (2000) and Stein et al.(2004) have both suggested a role of iNOS (Bolli 2000, Stein et al., 2004) and similarly, Zhao and Kukreja (2002) have demonstrated that activation of A3ARs in delayed preconditioning cause an induction of iNOS activity (Zhao and Kukreja 2002). Research from our lab supports the role of nitric oxide in A3AR mediated cardioprotection, and we have shown for the first time the involvement of iNOS as a downstream effector of the PI-3 kinase signalling cascade after activation of A3ARs at reperfusion (Karjian et al., 2007). The role of eNOS has also been proven in several research studies as being a downstream target of phosphorylation by Akt. This has been demonstrated in research by Bell and Yellon (2003) conducted with Atorvastatin (Bell and Yellon, 2003) and Bradykinin (Bell and Yellon, 2003), both administered at the onset of reperfusion to cause upregulation of the PI3-kinase, Akt and eNOS. Initial studies in our lab at present rule out eNOS involvement in A3AR mediated cardioprotection, although further studies are currently underway to confirm these results (unpublished data).

Our lab has recently demonstrated that activation of A3AR throughout reperfusion following an ischemic insult caused upregulation of a PI3-K-Akt and iNOS mediated pathway (Karjian et al., 2006, 2008). This concept is supported by many recent findings that iNOS plays an important role in pharmacologically mediated cardioprotection. A number of studies have also suggested the role of Akt-stimulated NO production, where the majority have linked the recruitment of the PI3-K-Akt pathway to the phosphorylation of eNOS (Gao et al., 2002). Yellon et al. (2004) have shown that postconditioning activates prosurvial kinases PI3K-Akt inducing phosphorylation of downstream targets eNOS and p70S6K which is abrogated by PI3-kinase inhibition (Tsang et al., 2004). Studies by Yang et al. (2005) have found that PI3-kinase activation during postconditioning is blocked by NOS inhibition (Yang et al., 2005). However, recent studies have also revealed the importance of the PI3-K-Akt pathway in controlling the expression of iNOS. The study by Hattori et al. (2004) in lipopolysaccharide- and cytokine-stimulated vascular smooth muscle cells demonstrated that activation of Akt directly increased iNOS and increased NO production (Hattori et al., 2004). In accordance with those findings, Smart et al. found that pre-treatment of neonatal rat

cardiomyocytes with interleukin-6 also resulted in activation of the PI3-K-Akt pathway and induction of iNOS (Smart et al., 2006). A mild increase in iNOS is thought to be significant enough to generate NO for signal transduction, increasing second messenger cGMP which would then activate mitochondrial K_{ATP} channels and, furthermore, a mechanism of cardioprotection (Wang et al., 2001). The paradigm linking adenosine receptor activation and iNOS has been found in several recent studies in late preconditioned models. Studies by Zhao and Krukeja demonstrated that A3AR delayed preconditioning triggers transcription of iNOS and synthesis of NO (Zhao and Kukreja., 2001). The same group also found evidence using iNOS knockout mice that the delayed protective effect of A1AR activation is mediated by a mild upregulation of iNOS (Zhao and Kukreja, 2000). Guo et al. also demonstrated the obligatory role that iNOS plays in cardioprotection induced by late preconditioning with A1AR using iNOS knockout mice (Guo et al., 2005).Based on these and other results in the field of A3AR mediated cardioprotection, Figure 2 below demonstrates a proposed schematic diagram of the pathway of protection.

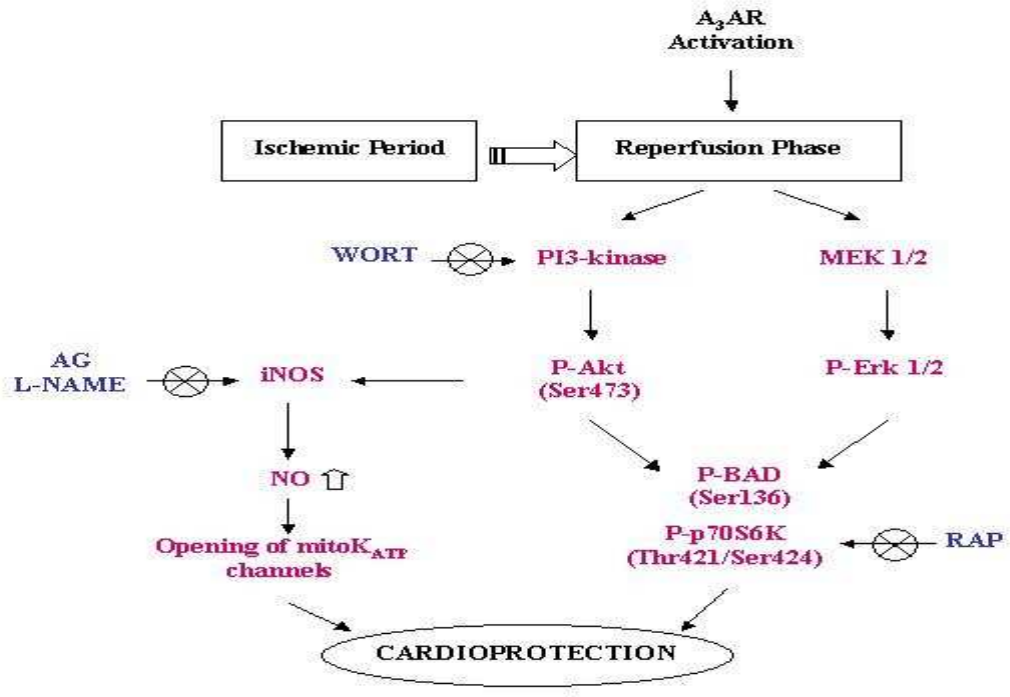

Figure 2: Proposed schematic pathway of A3 Adenosine receptor-mediated cardioprotection following activation at the onset of post-ischemic reperfusion (Karjian et al., 2006,2008).

WORT = Wortmannin, L-NAME= N_w-Nitro-L-arginine methyl ester hydrochloride, AG = Aminoguanidine, RAP = Rapamycin, PI3-K= hosphatidylinositol 3-OH-kinase, NO= Nitric Oxide, NO= Nitric oxide, iNOS = Inducible nitric oxide synthase, BAD = Bcl-2 family pro-apoptotic protein, ERK = Extracellular regulated kinase, mitoK_{ATP}= mitochondrial ATP sensitive potassium, p70S6K = 70S ribosomal protein, RAP = Rapamycin

Future research implications for reperfusion-induced injury

In summary, slowing the progression of heart failure is vital in prolonging a person's life given the fact that the adult myocardium has a very limited ability for self-renewal after injury. We have gained significant knowledge as to the importance of critical events that occur at the time of reperfusion and continue to acquire a clear focus of methods to modify them. Research has shown that myocyte survival can be influenced by either pharmacological or mechanical interventions applied at the time of post-ischemic reperfusion. Ongoing progress in the field is aimed at understanding the pivotal role that apoptosis plays in myocardial injury and investigating the cellular factors and signalling pathways that regulate apoptosis. This will ultimately enable the development of methods to suppress apoptotic cell death and overall myocardial injury. Additional research is also needed to investigate the release of death promoting factors from the mitochondria which could expose other complex pathways in the development of apoptosis. Research in the field has demonstrated that it is feasible to attenuate ischemic-reperfusion injury and significant advancements have been made in the last decade with the ultimate goal of obtaining beneficial applications for the clinical setting.

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References

Bell RM, Yellon DM. (2003) 'Atorvastatin, administered at the onset ofreperfusion, and independent of lipid lowering, protects the myocardium by up regulating a prosurvival pathway' J Am Coll Cardiol (41) 508-515

Bell RM, Yellon DM. (2003) 'Bradykinin limits infarction when administered asan adjunct to reperfusion in mouse heart: the role of PI3K, Akt and eNOS' J Mol Cell Cardiol (35) 185-193

Bolli R. (2000) 'The late phase of preconditioning' Circ Res (87) 972-983

Bolli R. (2001) 'Cardioprotective function of inducible nitric oxide synthase and role of nitric oxide in myocardial ischemia and preconditioning: an overview of a decade of research' J Mol Cell Cardiol (33) 1897-918

Bopassa JC, Ferrera R, Gateau-Roesch O, Couture-Lepetit E, Ovize M. (2006) 'PI 3-kinase regulates the mitochondrial transition pore in controlled reperfusion and postconditioning.' Cardiovascular Research (69) 178-85

Budde JM, Morris CD, Velez DA, Muraki S, Wang NP, Guyton RA, Zhao ZQ. (2004) 'Reduction of infarct size and preservation of endothelial function by multidose intravenous adenosine during extended reperfusion.' Journal of Surgical Research (116) 104-115

Datta SR, Dudek H, Tao X, Masters S, Fu H, Gotoh Y, Greenberg ME. (1997) 'Akt phosphorylation of BAD couples survival signals to the cell-intrinsic death machinery' Cell (91) 231-241

Davidson SM, Hausenloy D, Duchen MR, Yellon DM. (2006) 'Signalling via the reperfusion injury signalling kinase (RISK) pathway links closure of the mitochondrial permeability transition pore to cardioprotection.' The International Journal of Biochemistry & Cell Biology (38) 414-419

Drury AN, Szent-Gyorgyi A. (1929) 'The physiological activity of adenine compounds with special reference to their action upon the mammalian heart' J Physiol (68) 213-237

Fredholm B, Ijzerman A, Jacobson K, Klotz KN and Linden J. (2001) 'International Union of Pharmacology. XXV. Nomenclature and Classification of adenosine receptors' Pharmacol Rev (53) 527–552

Freude B, Masters TN, Robicsek F, Fokin A, Kostin S, Zimmermann R, Ullmann C, Lorenz-Meyer S, Schaper J. (2000) 'Apoptosis is initiated by myocardial ischemia and executed during reperfusion.' J Mol Cell Cardiol (32)197-208

Gao F, Gao E, Yue T-L, Ohlstein EH, Lopez BL, Christopher TA, Ma YL. (2002) 'Nitric oxide mediates the antiapoptotic effect of insulin in myocardial ischemia-reperfusion: The roles of PI3-kinase, Akt and endothelial nitric oxide synthase phosphorylation' Circulation (105) 1497-1502

Germack R, Dickenson J. (2004) 'Characterization of ERK/1/2 signalling pathway induced by adenosine receptor subtypes in rat cardiomyocytes' Br J Pharmacol (141) 329-339

Germack R, Dickenson JM. (2005) 'Adenosine triggers preconditioning through MEK/ERK1/2 signalling pathway during hypoxia/reoxygenation in neonatal rat cardiomyocytes.' J Mol Cell Cardiol (39) 429-442

Gross ER, Peart JN, Hsu AK, Grover GJ, Gross CJ. (2003) 'KATP

opener induced delayed cardioprotection: involvement of sarcolemmal and mitochondrial KATP channels, free radicals and MEK1/2' J Mol Cell Cardiol (35) 985-992

Guo Y, Stein A, Wu W-J, Zhu X, Tan W, Li Q, Bolli R. (2005) 'Late preconditioning induced by NO donors, adenosine A1 receptor agonists, and ä1-opioid receptor agonists is mediated by iNOS' Am J Physiol Heart Circ Physiol (289) H2251-H2257

Hattori Y, Hattori S, Kasai K. (2004) 'Lipopolysaccharide activates Akt in vascular smooth muscle cells resulting in induction of inducible nitric oxide synthase through nuclear factor-kappa B activation' Euro J of Pharm (481) 153-8

Hausenloy D, Tsang A, Yellon D. (2005) 'The reperfusion injury salvage kinase pathway: a common target for both ischemic preconditioning and postconditioning.' Trends Cardovasc Med (15) 69-75

Hausenloy DJ & Yellon DM (2007). Preconditioning and postconditioning: United at reperfusion. *Pharmacol Thera* 116, 173-191.

Headrick JP, Hack B, Ashton KJ. (2003) 'Acute adenosinergic cardioprotection in the ischemic reperfused heart' Am J Physiol Heart Circ Physiol (285) H1797-H1819

Headrick JP, Peart J. (2005) 'A3 adenosine receptor-mediated protection of the ischemic heart.' Vascular Pharmacology (42) 271-279

Hussain A., Al-Rajaibi H., Karjian P., Maddock, H. L. (2006) Post-ischaemic administration of A3 adenosine receptor agonist ameliorates myocardial ischaemia-reperfusion injury via ERK 1/2. J of Mol and Cell Cardiol 40 (6): 974-974

Hussain A, Al-Rajaibi H, Maddock HL. (2006) Post ischaemic administration of A3 adenosine receptor agonist ameliorates myocardial ischaemia-reperfusion injury via PI3-kinase. Heart, 92, (2): 014, FEB.

Jennings RB, Sommers HM, Smyth GA, Flack HA, Linn H. (1960) 'Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog.' Arch Pathol (70) 68-78

Jordan JE, Thourani VH, Auchampach JA, Robinson JA, Wang NP, Vinten Johansen J. (1999) 'A3 adenosine receptor activation attenuates neutrophil function and neutrophil-mediated reperfusion injury.' Am J Physil Heart Circ Physiol (277) H1895-H1905

Karjian P., Al-Rajaibi H., Hussain A., Maddock, H. L. (2006) Activation of A3 Adenosine Receptors Protects the Ischemic Reperfused Myocardium Via Recruitment of PI3K-AKT- iNOS Cell Survival Pathway. Circulation. 2006;114:II_1204.

Karjian P., Al-Rajaibi H., Hussain A., Maddock, H. L. (2008) A3 adenosine receptor activation via 2-Cl-IBMECA protects the myocardium via recruitment of PI3K-AKT-iNOS intracellular signalling pathway during reperfusion. Journal of Molecular and Cellular Cardiology. Vol. 44, Issue 4, Page 738

Kerendi F, Kin H, Halkos ME, Jiang R, Zatta AJ, Zhao ZQ, Guyton RA, Vinten-Johansen H. (2005) 'Brief renal ischemia and reperfusion applied before coronary artery reperfusion reduces myocardial infarct size via endogenous activation of adenosine receptors' Basic Res Cardiol (100) 404-412

Lee JE, Bokoch G, Liang BT. (2001) 'A novel cardioprotective role of RhoA: new signalling mechanism for adenosine' FASEB J (15) 1886-1894

Maddock, H.L. Broadley, K.J., Bril, A & Khandoudi, N. (1997) Cardioprotection from ischaemic insult in isolated working hearts by an A3 receptor agonist. *Br.J. Pharmacol*., 120, 19P.

Maddock HL, Mocanu M, Yellon D. (2002) 'Adenosine A3 receptor activation protects the myocardium from reperfusion/reoxygenation injury.' Am J Physiol Heart Circ Physiol (283) H1307-H1313

Maddock HL, Gardner NM, Khandoudi N, Bril A, Broadley KJ. (2003) 'Protection from myocardial stunning by ischaemia and hypoxia with the adenosine A3 receptor agonist, IB-MECA.' European Journal of Pharmacology (477) 235-245

Newby, AC. (1984) 'Adenosine and the concept of retaliatory metabolites' Trends Biochem Sci (9) 42-44

Parsons M, Young L, Lee JE, Jacobson KA, Liang BT. (2000) 'Distinct cardioprotective effects of adenosine mediated by differential coupling of receptor subtypes to phospholipases C and D' FASEB J (14) 1423-1431

Park S-S, Zhao H, Jang Y, Mueller R, Xu Z. (2006) 'N6-(3-Iodobenzyl)-adenosine-5'-N-methylcarboxamide confers cardioprotection at reperfusion by inhibiting mitochondrial permeability transition pore opening via glycogensynthase kinase 3â' J Pharmacol Exp Ther (318) 124-131

Peart JN, Headrick JP (2007). Adenosinergic cardioprotection: multiple receptors, multiple pathways. *Pharmacol Therapeutics* **114,** 208-221.

del Peso L, Gonzalez-Garcia M, Page C, Herrera R, Nunez G. (1997) 'Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt' Science (278) 687-689

Sattin A, Rall TW. (1970) 'The effect of adenosine and adenine nucleotides on the cyclic adenosine 3', 5'-phosphate content of guinea pig cerebral cortex slices' Mol Pharmacol (6) 13-23

Schulte G, Fredholm BB. (2003) 'Signalling from adenosine receptors to mitogen activated protein kinases' Cell Signal (15) 813-827

Shneyvays V, Jacobson A, Li AH, Nawrath H, Zinman T, Isaac A, Shainberg A. (2000) 'Induction of apoptosis in rat cardiocytes by A3 adenosine receptor activation and its suppression by Isoproterenol.' Experimental Cell Research (257) 111-126

Shneyvays V, Lesham D, Zinman T, Mamedova LK, Jacobson KA & Shainberg A (2005) Role of adenosine A1 and A3 receptors in regulation of cardiomyocyte homeostasis after mitochondrial respiratory chain injury. *Am J Physiol Circ Physiol* 288, H2792-H2801.

Smart N, Mojet MH, Latchman DS, Marber MS, Duchen MR, Heads RJ.(2006) 'IL-6 induces PI-3-kinase and nitric oxide-dependent protection and preserves mitochondrial function in cardiomyocytes' Cardio Res (69) 164-77

Sommerschild HT, Kirkeboen KA. (2000) 'Adenosine and cardioprotection during ischaemia and reperfusion – an overview' Acta Anaesthesiol Scand (44)1038-55

Stein AB, Tang XL, Guo Y, Xuan YT, Dawn B, Bolli R. (2004) 'Delayed adaption of the heart to stress: late preconditioning'

Stroke (35,11 Suppl.1) 2676-2679

Tsang A, Hausenloy D, Mocanu M, Yellon D. (2004) 'Postconditioning: a form of "modified reperfusion" protects the myocardium by activating the phosphatidylinositol 3-kinase-Akt pathway.' Circ Research (95) 230-232

Vinten-Johansen J, Kin H, Sun HY. (2003) 'Post-Conditioning Reduces Myocardial injury by inhibiting reactive oxygen species during reperfusion.' Circulation (108) suppl IV 219

Wang Y, Kudo M, Xu M, Ayub A, Ashraf M. (2001) 'Mitochondrial KATP channel as an end effector of cardioprotection during late preconditioning:triggering role of nitric oxide' J Mol Cell Cardiol (33) 2037-2046

Yang XM, Philipp S, Downey JM, Cohen MV. (2005) 'Postconditioning's protection is not dependent on circulating blood factors or cells but involves adenosine receptors and requires PI3-kinase and guanylyl cyclase activation' Basic Res Cardiol (100) 57-63

Yellon DM, Baxter GF. (1999) 'Reperfusion injury revisited: is there a role for growth factor signalling in limiting lethal reperfusion injury?' Trends Cardiovasc Med (9) 245-249

Zhao T, Xi L, Chelliah J, Levasseur E, Kukreja R. (2000) 'Inducible nitric oxide synthase mediates delayed myocardial protection induced by activation of adenosine A 1 receptors: evidence from gene-knockout mice' Circ (102) 902-907

Zhao TC, Kukreja RC. (2002) 'Late preconditioning elicited by activation of adenosine A3 receptor in heart: role of NF-kappa B, iNOS and mitochondrial KATP channel' J Mol Cell Cardiol (34) 263-277

Zhao ZQ, McGee DS, Nakanishi K, Toombs CF, Johnson WE, Ashar MS, Vinten-Johansen J. (1993) 'Receptor mediated cardioprotective effects of endogenous adenosine are exerted primarily during reperfusion after coronary occlusion in the rabbit.' Circulation (88) 709-719

Zhao ZQ, Budde JM, Morris C, Wang NP, Velez DA, Muraki S, Guyton RA, Vinten-Johansen J. (2001) 'Adenosine attenuates reperfusion-induced apoptotic cell death by modulating expression of Bcl-2 and Bax proteins.' J Mol Cell Cardiol (33) 57-68

Zhao ZQ, Corvera JS, Halkos ME, Kerendi F, Wang NP, Guyton RA, Vinten-Johansen, J. (2003) 'Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning.' Am J Physiol Heart Circ Physiol (285) H579-H588

Zhao ZQ, Morris CD, Budde JM, Wang NP, Muraki S, Sun HY, Guyton RA. (2003) 'Inhibition of myocardial apoptosis reduces infarct size and improves regional contractile dysfunction during reperfusion.' Cardiovascular Research (59) 132-142

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Articles for *The* Bulletin

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

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

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

Secretary's Column

According to Margaret Atwood, "In the spring, at the end of the day, you should smell like dirt." Fortunately, given the rather crowded poster session at our recent Spring Meeting, few attendees had followed this dictum to the letter. I'm very pleased instead to report that the conference, held jointly with the British Atherosclerosis Society in Oxford, went very well. The topic, Atherosclerotic Plaque Rupture, attracted so much interest that we had to disappoint some late registrants because we reached the maximum capacity for the venue. We had two late and unavoidable changes of speaker, but Professors Coulton and Thompson who stood in for them both did excellent jobs and made the last session of the meeting a real highlight. The meeting was also graced during the conference dinner by the reminiscences of Professors Gustav Born and Peter Richardson of their time working with the late and much-missed Michael Davies. There were both a Young Investigator session and a Free Communications session, thus maintaining the Society's tradition of providing opportunities for the stars of the future to speak. Congratulations again to our prizewinners: Dr Ayman Al Haj Zen (University of Bristol) won the BSCR Prize for his talk on "Inactivation of EphB2 Gene Promotes Pathogenesis of Saccular Aneurysms in ApoE Knockout Mice", and Miss Anna Elena Pepe (King's College, London) won the Clinical Science Prize for her poster entitled "NRF3 Mediates Stem Cell Differentiation into Smooth Muscle Cells Through Increased ROS Generation and PLA2G7 Production". A full meeting report can be found on page 16 in this issue of the Bulletin.

Our next meeting will be on September 7th and 8th, again in Oxford. Organised by Barbara Casadei, Kieran Clarke and Saadeh Suleiman, the topic will be "Myocardial Energetics and Redox in Health and Disease". Full details will appear on the BSCR website soon, and I look forward to seeing many of you at the conference.

Chris Jackson

BSCR Meeting Report

"Atherosclerotic Plaque Rupture"

Joint Spring Meeting BAS/BSCR 2009

A report by Laura Newell

Bristol Heart Institute, University of Bristol

The joint Spring Meeting of the British Atherosclerosis Society (BAS) and the British Society for Cardiovascular Research (BSCR) took place in the beautiful city of Oxford in the first week of April of this year. This meeting was the 2nd joint meeting between the two societies, and focused upon the substantial, and somewhat controversial, topic of "Atherosclerotic Plaque Rupture".

Atherosclerotic plaque rupture is implicated in the advanced stages of ischaemic heart disease, and is the most frequent cause of acute coronary syndromes such as unstable angina, acute myocardial infarction, and sudden coronary death. The joint Spring Meeting showcased a variety of recent advances in the field of atherosclerotic plaque rupture, as well as innovative new diagnostic techniques to image the vulnerable plaque.

The meeting was opened by Chris Newman, Treasurer of the BAS and Chair of the BSCR, who set the scene for an informative first session titled "What is a vulnerable plaque?". This was chaired by Dr Mark Kearney and consisted of two talks. The first was by Dr Hector Garcia (Cardialysis, The Netherlands) who discussed the concepts of virtual histology and palpography in defining a 'vulnerable plaque'. This talk was followed by Dr Allard van der Wal (University of Amsterdam, The Netherlands) who eloquently described the scientific basis behind the observation that thrombus age, as studied from thrombosuction specimens in pathology, correlates with long-term mortality as a result of distal embolisation.

The second session, chaired by Dr Cathy Holt and titled "Do we have an animal model of plaque rupture?", was another thought-provoking session commenced by Dr Florian Bea (Universität Heidelberg, Germany). Dr Bea raised the issue of whether plaque rupture actually occurs in apoE$^{-/-}$ mice – an issue of considerable debate in recent literature – and proposed that disturbances in the Receptor for Advanced Glycation End-products (AGEs) coupled with the ultralipidaemia induced by the fat-feeding method may cause the membrane disturbances observed in the atherosclerotic lesions of fat-fed apoE$^{-/-}$ knockout mice.

The lecture theatre, Medical Sciences Teaching Centre, Oxford University.

Following on from this, Dr Erik Biessen (Maastricht University Medical Centre, The Netherlands) discussed the influence of leukocytes and their associated chemokines in atherosclerosis. His extensive data showed not only a correlation between plasma levels of the atheroprotective chemokine, SDF-1, in stable and unstable angina, but in addition showed that if the receptor for SDF-1 (CXCR4) was blocked, neutrophils became more adhesive; this is a characteristic of unstable angina.

The third session of the day, chaired by Professor Peter Weinberg, concentrated on events inside the unstable atherosclerotic plaque and was opened by Professor Rob Krams (Imperial College London, UK) who provided an interesting discussion of the 'chicken

and egg' conundrum of inflammation and instability inside unstable plaques and detailed the cellular effects of different shear stresses on the atherosclerotic endothelium. Next to present was Dr Isabelle Gorenne (University of Cambridge, UK) whose talk concentrated on the fascinating topic of cell senescence and apoptosis and in particular detailed the shorter telomere length of smooth muscle cells in the fibrous cap, an observation which Dr Gorenne suggested could be as a result of increased oxidative stress or hypercholesterolaemia. This was seen in apoE$^{-/-}$ATM$^{+/-}$ mice, which display accelerated atherosclerosis. The final talk of the session was given by Professor Allen Burke (University of Maryland, USA) who articulately detailed the presence of healed ruptures in atherosclerotic lesions using a series of histological specimens, and described how acute coronary syndromes can occur at almost any stage of atherosclerotic lesion development, from pathological intimal thickening to the unstable thin cap fibroatheroma. Furthermore, Prof Burke described the importance of plaque repair relative to the prevention of plaque rupture.

The penultimate session of the first day, chaired by Dr Sarah George, comprised four young investigators who each gave short presentations of their research. The standard was impeccably high, and it must have been a tough job for the judges to choose the recipient of the prestigious 'Michael Davies Young Investigator Award'. The first speaker was Dr Afroze Abbas (Leeds Institute of Genetics, Health and Therapeutics, UK) who competently presented his recent work into the role of the IGF-1 receptor on endothelial cells and suggested a role for decreased IGF-1 in producing a favourable effect on the bioavailability of nitric oxide via insulin signaling. The second talk, by Dr Ayman Al Haj Zen (Bristol Heart Institute, UK), gave an interesting account of his research into EphB2 gene regulation in the maintenance of vascular integrity in atherosclerosis, and in addition detailed the presence of saccular aneurysms in regions of high shear stress in apoE$^{-/-}$EphB2$^{-/-}$ double knockout mice. The next talk, given by Dr Matthew Gage (Leeds Institute of Genetics, Health and Therapeutics, UK), focused on the controversial topic of whole-body glucose regulation by the endothelium. Dr Gage used SHIP-2 deficient mice to show that endothelial insulin signaling could be a critical target in the control of whole-body glucose levels. The final talk from the young investigators was given by Dr Mat Kahn (Leeds Institute of Genetics, Health and Therapeutics, UK) who studied a cohort of South Asian men with a naturally low endothelial progenitor cell (EPC) count, as observed in type II diabetes, to show that endothelial regeneration after injury by EPCs was impaired by mild insulin resistance. This finding shows that the balance between endothelial damage and repair in atherosclerosis may be adversely affected in diabetics.

The final session of the day was the British Atherosclerosis Society John French Lecture, which this year was given by Dr Robin Choudhury (John Radcliffe Hospital, UK) on the emerging imaging techniques developed in response to the need to image the wall, rather than the lumen, of an atherosclerotic vessel. Dr Choudhury elegantly summarised his extensive research into imaging techniques, and described a promising new facet to diagnostic imaging in arterial disease.

Following a short break, the evening's entertainment began in the form of a poster session at St. Catherine's College. There was a selection of 40 posters with topics ranging from using targeted ultra-small super-paramagnetic particles of iron oxide to visualize endothelial adhesion molecules on MRI (J Chan, Imperial College London, UK), to reduction of early vein graft thrombosis by locally-derived tissue plasminogen activator gene transfer (A Thomas, Bristol Heart Institute, UK), each presenting a captivating new concept in cardiovascular research.

St Catherine's College, Oxford where both the poster session and the conference dinner were held.

The 5 course conference dinner followed on from the poster session, and the audience was treated to a talk by Professors Gustav Born and Peter Richardson (pictured), who detailed the advances in atherosclerosis research over the years, and also the importance of collaboration between different disciplines. The

Professor Gustaf Born

professors were both contemporaries of the late Michael Davies. The BAS Young Investigator award, named in honour of Michael Davies, was won by Dr Mat Kahn (Leeds Institute of Genetics, Health and Therapeutics, UK). The BSCR Young Investigator Award was won by Dr Ayman Al Haj Zen (Bristol Heart Institute, UK).

Professor Peter Richardson

The second day of the meeting began with a 'free communication' session, chaired by Dr David Grieve, which showcased more young investigators. Marianna Prokopi (King's College London, UK) opened the session by detailing her interesting research into thymidine phosphorylase in angiogenesis, and this was followed by Julie Lees (University of Sheffield, UK) who gave an engaging talk about her work into the role of parathyroid hormone receptor 1 in aortic occlusion studied in zebrafish embryos. Karina Di Gregoli (Bristol Heart Institute, UK) then described her novel work into the role of MT1-MMP in murine monocyte migration, and was followed by Sandrine Vessillier (Queen Mary University of London, UK) who gave an innovative insight into the therapeutic potential of IL-4 targeted to atherosclerotic plaques. The free communication session ended with a talk by Anna Zampetaki, who adeptly described her research into the role of HDAC3 in maintaining vascular integrity at arterial disease-prone branch points.

The final session, chaired by Dr Yvonne Alexander, focused on the important topic of diagnosing and treating the vulnerable plaque and was opened by Dr Andreas König (Ludwig-Maximilians-Universität, Germany). Dr König reinforced Dr Choudhury's proposal that imaging the wall rather than the lumen is critical in detecting high risk lesions, and furthermore favoured the use of intravascular ultrasound radiofrequency analysis of vessel walls. The second of three talks was given by Dr Gary Coulton (St George's Hospital Medical School, UK), in place of Professor Juan Carlos Kaski, and was an intriguing overview of his extensive work into biomarkers which raised valuable points surrounding the identification of potential biomarkers for atherosclerosis. The final talk of the meeting was given by Professor Gil Thompson (Hammersmith Hospital, UK) who graciously stepped in at the last moment in place of Professor Andrea Mezzetti. Professor Thompson's overview of current therapeutics and future therapeutic targets in atherosclerosis was both informative and absorbing, and was a fitting end to an inspiring Spring Meeting.

Congratulations to the prize winners of both the Young Investigator awards, and also to Anna Elena Pepe (King's College London, UK) who was the recipient of the Best Poster prize, generously sponsored by Clinical Science.

Congratulations should also go to the organisers of the meeting, Chris Newman, Chris Jackson and Martin Bennett, who provided an excellent array of speakers and topics within cardiovascular research which contributed to the indisputable success of the Spring Meeting 2009.

The meeting was generously supported by educational grants from Takeda, Pfizer, and the BHF.

Cardiovascular Related Meetings

The 2009 Weinstein Cardiovascular Development Conference will be held at the Hyatt Regency Hotel, San Francisco, California on 7th-9th May, 2009. Further details on registration, abstract submission and accommodation can be obtained from www.weinsteinmeeting.org

7th-9th May 2009, Focused Meeting: New Drugs in Cardiovascular Research. Joint Meeting with the German Societies for Pharmacology & Clinical Pharmacology.Dresden, Germany. 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

British Cardiovascular Society Annual Conference & Exhibition will be held at ExCeL, London on 1st - 3rd June, 2009. For more information, please visit: http://www.bcs.com/pages/conference.asp American Heart Association Basic Cardiovascular Sciences Annual Conference 2009 - Molecular

Mechanisms of Cardiovascular Disease will take lace at The Ritz Carlton, Lake Las Vegas, Nevada from 20th - 23rd July, 2009. More information is available from http://www.americanheart.org; E-mail: scientificconferences@heart.org; Phone: (888) 242-2453 or (214) 570-5935

European Society of Cardiology Congress 2009 will be held in Barcelona, Spain 29th August - 2nd September 2009. Further details are available at: http://www.escardio.org/congresses/esc-2009/Pages/welcome.aspx; Tel: +33 (0)4 92 94 76 00

Keystone Symposium: Advances in Molecular Mechanisms of Atherosclerosis. Organizers: Russell A. DeBose-Boyd and Christopher K. Glass 12th - 17th February, 2010 Fairmont Banff Springs, Banff, Alberta. Further details are available from: info@keystonesymposia.org; Tel: 800-253-0685 http://www.keystonesymposia.org/

Keystone Joint Symposia: 'Cardiovascular Development and Repair' and 'Angiogenesis in Health and Disease'. Organizers: Doris A. Taylor and Brian Annex. 28th February - 5th March, 2010 Keystone Resort, Colorado. Further details are available from: info@keystonesymposia.org; Tel: 800-253-0685 http://www.keystonesymposia.org/

XX World Congress of the International Society for Heart Research Kyoto 13-16 May 2010. For further details, please visit: http://www.ishrworld.org/

Submission Deadlines for *the Bulletin*

Volume	*Date*	*Deadline*
22 (3)	***July 2009***	*1st June*
22 (4)	***October 2009***	*1st September*
23 (1)	*January 2010*	*1st December*
23 (2)	***April 2010***	*1st March*

British Heart Foundation Grants

Non-Clinical Fellowships

Senior Basic Science Research Fellowship

Dr Y Sun, King's College London. "Control of myofilament calcium-sensitivity: a key determinant of the physiology and pathology of heart muscle". 5 years, £761,184

Intermediate Basic Science Research Fellowships

Dr K M Dibb, University of Manchester. "Integrating Ca^{2+} homeostasis and T-tubule function in the atria: normal physiology and dysfunction in ageing and disease". £476,690, 4 years.

Dr K J Woollard, King's College London. "Role of monocyte subsets in atherogenesis and the mechanisms of monocyte recruitment and migration in atherothrombosis" . £330,374, 4 years.

Dr M Nandi, University College London. "The role of GTP cyclohydrolase 1 feedback regulatory protein in the regulation of tetrahydrobiopterin synthesis in vivo". £331,960, 4 years.

Dr M Clarke, University of Cambridge. "Inflammatory consequences of vascular smooth muscle cell death in atherosclerosis" . £406,597, 4 years.

Travel Fellowship

Dr S Pyner, University of Durham. "The role of the brain and renal sympathetic nerve activity in the development of heart failure". £6,800, 4 months

Dr T Salukhe, Imperial College London. "Critical endpoints for chronic AF ablation: a prospective randomized study". £59,145, 1 year

PhD Studentships

Unnamed and Dr S O'Sullivan University of Nottingham. "An investigation into the pharmacological effects of phytocannabinoid and endogenous cannabinoids in human arteries". £90,939, 3 years

Mr C Capelli, University College London (ICH). "Outflow tract rapid prototyping models for preclinical testing of percutaneous valve implantation devices". £95,156, 3 years

Mr J S Savage, University of Bristol. "Mechanisms underlying paradoxical thrombosis in patients treated with platelet integrin $\alpha_{IIb}\beta_3$ antagonists: adhesion receptor cross-talk in platelets" . £95,166, 3 years

Ms K Di Gregoli University of Bristol"The role and regulation of matrix metalloproteinase, MMP-14, in monocytes, macrophages and foam cells". £63,222, 21 months

Mrs L Lloyd , University of Nottingham"The effect of a maternal low protein diet on renal development and function in sheep" . £103,918, 3 years

Mr B C Lechtenberg University of Cambridge . "NMR studies on thrombin allostery and interactions". 3 years, £101,583

Unnamed and Dr A Munsterberg, University of East Anglia. "The role of KIhI31, a novel Wnt antagonist, in cardiogenesis". 3 years, £95,491

Unnamed and Prof D Henderson University of Newcastle. "Interaction of planar cell polarity and inversin signalling in congenital heart disease". £97,956, 3 years

Unnamed and Dr S Bamforth University of Newcastle. "Cardiovascular development following loss of Tcfap2a from the neural crest". £97,925, 3 years

Clinical Fellowships

Intermediate Clinical Research Fellowship

Dr E M Freel, University of Glasgow "Cardiovascular disease: investigating the expanding role of aldosterone". £461,562, 4 years

Clinical Research Training Fellowship

Dr T L Gatheral, Imperial College London "Mechanisms of NOD1 induced inflammation in vascular tissue". 3 years, £179,383

Dr G D Barnes, University of Edinburgh"Cardiovascular effects of apelin in heart failure: *interaction with the rennin-angiotensin system*". £179,912, 3 years

PROJECT GRANTS

DEFERRED APPLICATIONS AWARDED

Dr R J Schilling et al, Queen Mary University of London. "Comparison of catheter ablation with medical therapy for atrial fibrillation in heart failure". 2 years, £245,801

Dr J W G Yarnell et al, Queen's University, Belfast. "Early detection and determinants of stroke, coronary heart disease and congestive heart failure: the Caerphilly Prospective Study. Phase 5 follow-up". 3 years, £180,077

Dr B A Fielding et al, University of Oxford "Hepatic fatty acid partitioning in pre- and post-menopausal women in relation to risk factors for cardiovascular disease". 3 years, £254,894

Dr C Loughrey & Prof E Cameron, University of Glasgow. "Investigating the expression and function of RUNX£1 in cardiac tissue during myocardial infarction". 2 years, £104,723

NEW APPLICATIONS AWARDED

Dr J T B Crawley et al, Imperial College London. "Cytoprotective activated protein C and stroke". 2 years, £185,388

Professor M P Frenneaux et al, University of Birmingham. "Randomised double blind placebo controlled trial of perhexiline in heart failure with preserved ejection fraction syndrome". 2 years, £199,298

Professor D J Beech et al, University of Leeds. "TRPM3 and sulphated steroid responses of vascular smooth muscle cells". 2 years, £23,360

Dr S Plein et al, King's College London. "Three-dimensional whole heart myocardial perfusion MR imaging". 2 years, £194,732

Dr B J Wojciak-Stothard, University College London. "Role of RhoB in the regulation of pulmonary vascular contractility and remodelling in response to hypoxia". 3 years, £238,828

Professor G L Smith et al, University of Glasgow. "Cellular basis for alternating T-wave morphology in isolated rabbit hearts" . 3 years, £206,403

Prof N J Severs & Dr K T MacLeod, Imperial College London. "Heteromeric gap junction channels: correlation of electrical properties with connexin make-up". 3 years, £183,485

Prof C S Peers & Dr D S Steele, University of Leeds. "An investigation into the pro-arrhythmic actions of carbon monoxide". 3 years, £163,094

Professor B Henderson et al, University College London. "Circulating cell stress proteins, lymphocyte function, and cardiovascular disease". 3 years, £239,385

Dr K M O'Shaughnessy et al, University of Cambridge. "Molecular genetics of large artery stiffening". 2 years, £427,614

Dr S J Tucker, University of Oxford. "Functional validation of a structural gating model for the Kir potassium channel". 3 years, £191,042

Professor A H Baker et al, University of Glasgow. "Induced pluripotent cells: analysis of cell reprogramming of dermal fibroblasts derived from patients with cardiovascular disease vs age-matched healthy controls". 3 years, £190,903

Visit the BSCR Website: http://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

Cardiovascular Related Wellcome Trust Grants

Project Grant

Dr Willem H Ouwehand, Division of Transfusion Medicine, East Anglian Blood Transfusion Ctr, University of Cambridge. Replication for blood cell indicies associations. 12 months, £29,568

Dr Matthew K Lancaster, School of Biomedical Sciences, Medical School, University of Leeds. Why does ageing encourage the cardiac pacemaker to fail? 12 months, £74,993

Dr Jonathan G Hanley, Dept of Anatomy, MRC Centre for Synaptic Plasticity, University of Bristol. AMPA receptor endosomal sorting during ischaemia . 36 months, £248,202

International Senior Research Fellowship

Dr K Kacperski, Medical Physics Dept, Centre of Oncology, Warsaw. Optimal collimators for nuclear medicine functional imaging. 60 months, £400,902

Collaborative Projects

Prof Peter J Ratcliffe, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, University of Oxford, Headington. Role of 2-oxoglutarate dependent dioxygenases in oxygen and metabolic sensing: A genetic approach in Drosophila. 36 months, £162,937

Biomedical Resources

Dr Timothy J Mohun, Lab of Developmental Biochemistry, National Institute for Medical Res. London. An Imaging pipeline for screening mouse embryos. 36 months, £384,986

Programme Grant

Prof Jeremy Patrick T Ward, Dept of Physiology, St Thomas's Hospital Medical School, UMDS of Guy's & St Thomas's Hospital, London. Modulation of Vasomotor Tone by Hypoxia in the Pulmonary Circulation. 60 months, £1,022,784

Travel Reports for *The* Bulletin

The Bulletin editors are happy to publish travel reports written by BSCR members. These can be on any conference, course or laboratory visit of interest to other members and could perhaps contain photographs.

If you are planning on travelling to a cardiovascular-related meeting and would like to write a report for the Bulletin, please contact the editors. A bursary of **£300** is available towards the cost of your visit, and this will be provided on receipt of the report.

Bon voyage!

THE BRITISH SOCIETY FOR CARDIOVASCULAR RESEARCH

Autumn Meeting 2009

Myocardial Energetics and Redox in Health and Disease

Dates: Monday September 7th and Tuesday September 8th, 2009

Venue: Medical Sciences Teaching Centre/Trinity College, Oxford

Organisers: Barbara Casadei, Kieran Clarke and Saadeh Suleiman

Programme

The programme will consist of state-of-the-art presentations by leaders in the field. Speakers will include: Fran Ashcroft (Oxford), Dave Carling (London), Antonio Vidal-Puig (Cambridge), Phil Eaton (London), Peter Ratcliffe (Oxford), Andrew Halestrap (Bristol), Michael Murphy (Cambridge), Michael Frennaux (Birmingham) and Ivor Benjamin (Salt Lake City).

Free Communications

There will be 12 oral presentations of selected abstracts, one of which will win the BSCR Prize. There is also a Clinical Science Early Career Investigator Award for the 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 July 10th, 2009

Registration: Friday July 31st, 2009