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Contents

Editorial

Welcome to the July 2005 issue of *The* Bulletin!Our review for this issue has been written by Drs Mehregan Movassagh and Anna Philpott of the Department of Oncology at the Hutchison/MRC Research Centre, University of Cambridge. The authors present a comprehensive review of the transcriptional regulation and signalling pathways involved in heart development in *Xenopus laevis*, highlighting the versatility of this organism and the advantges that it offers to the study of cardiac morphogenesis.

Once again, there are vacanices to be filled on the Executive Committee of the BSCR and, as five candidates have been nominated, an election is required. To assist you with voting, biographical summaries and statements from the candidates are included within this issue. Members are urged to make their preferences known by completing the enclosed ballot form and returning it to the Secretary, Professor Barbara McDermott, by the 9th of September.

Following the recent meeting of the Society at the University of Leicester, we are pleased to include a summary of the proceedings, written by the organisers, Professors Nilesh Samani and Alison Goodall. We then look ahead to an exciting Autumn meeting in London under the organisation of our current Chairman, Professor Michael Marber and former Chairman, Professor Metin Avkiran. A full programme and registration details are included herein and on the new BSCR website: www.bscr.org.

As is customary, we finish by bringing you the latest details of grants awarded to Cardiovascular researchers, by the British Heart Foundation and the Wellcome Trust.

Helen Maddock and Nicola Smart

Xenopus laevis as a Model for Heart Development

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Introduction

In man, congenital heart malformation is the most common form of birth defect in the Western industrialized world, which affects nearly 1% of all live born infants, whereas the incidence of fatal pre-natal congenital malformation leading to spontaneously aborted pregnancies has been estimated to be much higher (1,2). However, despite recent significant progress in the field, including use of techniques such as catheters for treatment of septal defects in conjunction with improved imaging and surgical techniques in diagnosis and treatment of congenital defects in new-borns, the rate of congenital heart disease has risen over the last 30 years (1).

The molecular pathways involved in normal heart development and in congenital heart disease have not as yet been fully elucidated and remain largely undetermined. Thus, a deeper understanding of the molecular and cellular mechanisms involved in the development of the normal heart will provide a more comprehensive understanding of this process and pave the way for development of novel therapeutic opportunities to alleviate, prevent and even potentially cure this disease.

Why Xenopus?

Xenopus laevis is a species of aquatic South African frog. Females injected with human chorionic gonadotropin hormone ovulate and lay hundreds of relatively large eggs, which can easily be fertilised, *in vitro*. Thus, *Xenopus* has been extensively utilised as a model system to investigate early embryonic development. It has become evident that, despite significant anatomical and morphological differences amongst vertebrates, the majority of the genes, signalling pathways and mechanisms involved in heart development are conserved in all vertebrates (3). Hence, a number of model organisms such as mouse, chick, zebrafish and *Xenopus* have been used and have significantly contributed towards our understanding of vertebrate heart development. The mouse has served as the preferred model for investigating mammalian heart development as its genome has been sequenced, and transgenic knockout mice can be generated and used to unravel the role of specific genes in heart development. However, it has been demonstrated that even the specific cardiac knockdown of a number of genes that play a role in the very early stages of heart development results in early embryonic death, thus making further analyses difficult. On the other hand, alternative model organisms such as *Xenopus* are not hampered by this significant problem, as these aquatic embryos do not depend on the heart's physiological pumping function for survival; small embryos obtain sufficient oxygen through simple diffusion across their body and thus heart function is not required until the later stages of development (4).

The heart of *Xenopus* laevis is adapted to suit its life in an aquatic and amphibious environment and observed superficially, an adult *Xenopus* heart looks different from an adult mammalian heart with significant anatomical dissimilarities. In comparison to the mammalian four-chambered asymmetrical heart, the adult heart of *Xenopus* contains a partially septated atrium that separates the pulmonary from the venous returns with only a single highly trabeculated ventricle and an atrioventricular inflow valve (5). However, despite these anatomical differences, there are striking molecular and embryological similarities by which the

Xenopus and mammals undergo cardiogenesis. Indeed, molecular analyses have revealed that many of the mechanisms and processes such as transcriptional regulation and signalling pathways involved in driving heart development are ancient and highly conserved amongst vertebrates.

Xenopus laevis embryos are not only less labour intensive and cheaper alternative to amniote model systems, but also provide an attractive model for investigating the steps, molecules and signaling pathways involved in heart development for a number of other reasons. Since *Xenopus* embryos are optically translucent, the vascular system and heart are easily observable with the light microscope, making them ideal for non-invasive investigation of the circulatory system during embryonic development, (Use of *Xenopus* as a model to determining cardiovascular parameters using a variety of micro-techniques, has been reviewed by Schwerte and Fritsche (6)). Embryos are available in large numbers that are relatively large in size and develop for a considerable period without growth using nutrients from yolk proteins stored within each cell. Furthermore, since fertilization occurs externally, *all* stages of development are accessible for study, thus providing a significant advantage especially for investigating *earlier* stages of heart development when compared to amniote counterparts. Since in *Xenopus* embryos cardiac function is not required until very late stages of embryonic development (swimming tadpole) (7), experimental manipulations leading to heart abnormalities, malformation or even disruptions leading to *complete ablation* of heart development are feasible as embryos can, by and large, continue to develop normally. Other significant advantages which have contributed to the wide use of *Xenopus* as a suitable model for investigation of heart development include the ability to use microsurgery to generate explants, which will undergo lineage specific tissue differentiation *ex vivo*. This provides a powerful model system, which has proved useful for investigating the role of individual genes and determining the role of various signaling pathways in heart development. Embryos of *Xenopus* are also robust enough to be exploited for microinjection and their relative large size makes this procedure easy. Thus, microinjection of capped RNA has been employed to investigate the effects of overexpression of various molecules. Conversely, microinjections of specific anti-sense "morpholino" oligonucleotides are utilized to investigate the consequences of knockdown in the expression of genes on heart development. Use of these methods will be described in more detail below.

Heart Development in Xenopus and Other Vertebrates

In all vertebrate embryos, the heart is the first organ to become functional (8, 9). The origin of cardiac tissue has been traced to bilateral patches of cardiogenic mesoderm (3). Sater and Jacobson mapped the putative heart forming region in gastrulation stage of *Xenopus* embryos, to the marginal zone between 30°-45° lateral to either side of dorsal midline flanking the "Spemann Organizer" which contains the cardiac progenitor cells (Figure 1A) (10). Interestingly, however, further microsurgical studies by these investigators demonstrated that by the end of neurulation (Nieuwkoop and Faber (NK) (11) stage 20) the heart "morphogenic field" has relocated to the opposite side of the embryo i.e. to the dorsal region and is at the site of heart morphogenesis (Figure 1B). This region does not then undergo any further significant large-scale movement (Figure 1C & 1D) (12).

They demonstrated that when explants from anterior-ventral segment (just posterior to the cement gland) were cultured, they led to formation of well formed beating hearts, whereas this ability was absent in explants dissected from the more posterior regions of the ventral side of stage 20 embryos (12). Hence the prospective heart region was shown to be localised to the anterior-ventral segment of the *Xenopus* embryo (12, 13).

Development of linear heart tube

The discovery of the homeobox gene Tinman (Tin) in Drosophila in the early 1990s was a major step to elucidating the origin of cardiac progenitor cells, since the mammalian ortholog of this gene (Nkx or Csx) was found to be expressed in cardiac cells right from the onset of embryonic heart formation until adulthood (14, 15). Embryological and fate mapping studies in vertebrates have revealed that these genes are amongst the earliest molecular markers whose expression precedes morphological differentiation. Thus, their expression profile helped to confirm that the heart precursor cells originate from a bilateral population of mesodermal cells, localised in the anterior primitive streak, which give rise to bilaterally symmetrical heart primordia, in response to signals from the underlying endodermal cells (3, 16). In situ hybridisation analyses of the *Xenopus* Tinman homologs, Nkx2-3 (17) and Nkx2-5 (18) allowed visualisation of these events in *Xenopus* embryos. These genes are initially expressed in the bilateral regions of the cardiac mesoderm that arise below the anterolateral edges of the neural plate

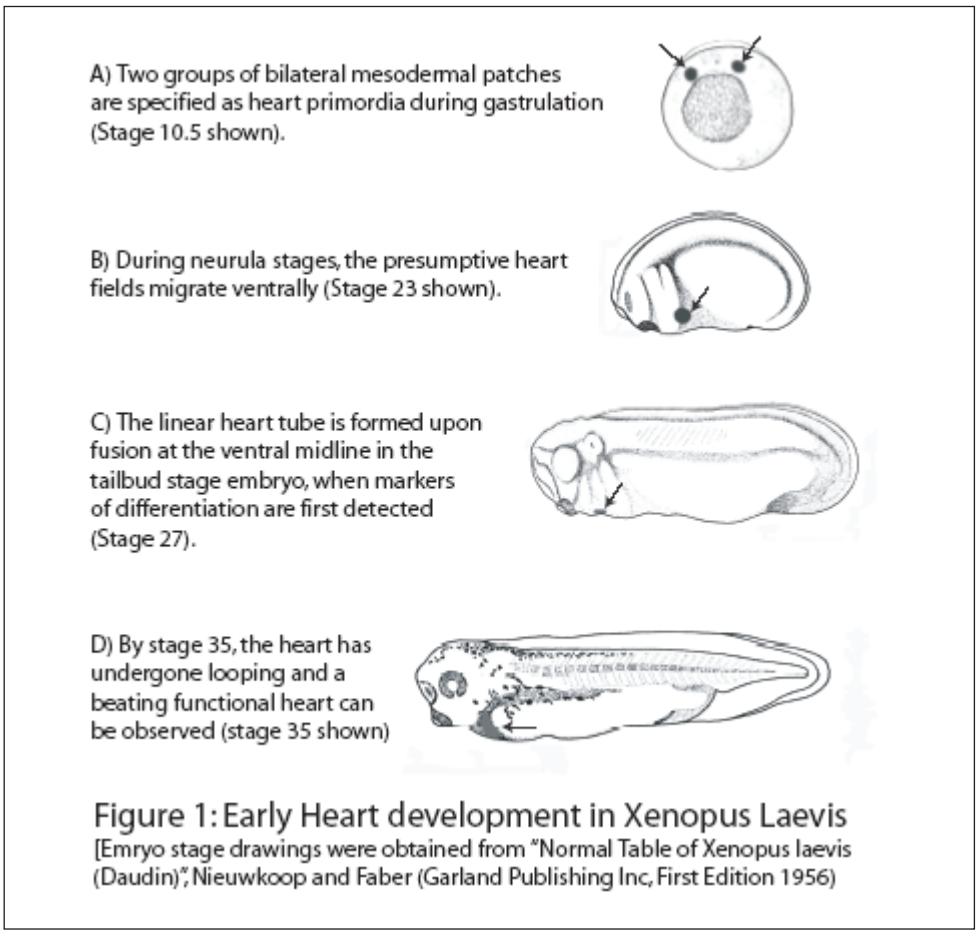

Figure 1: Early Heart development in Xenopus Laevis
[Emryo stage drawings were obtained from "Normal Table of Xenopus laevis (Daudin)", Nieuwkoop and Faber (Garland Publishing Inc, First Edition 1956)

on either side of embryo, and their expression corresponds exactly with the migration of the cardiac progenitor patches described above. These bilaterally symmetrical patches of mesodermal cardiac progenitor cells migrate and extend laterally during gastrulation to the anterior region of embryo, eventually fusing on the ventral midline to form a primitive linear heart tube (8) (Figure 1).

It remains undetermined whether the progenitor cells are already specified, or the specification occurs along the migration path. However, it has been demonstrated in *Xenopus* that the "Spemann Organizer" and the dorsoanterior endoderm underlying the precardiac mesoderm, are both necessary and sufficient for the formation of beating heart tube (19).

Looping of heart tube and chamber formation

The muscular heart tube begins to beat about 48 hrs post-fertilisation (stage 33/34) in *Xenopus*, around E8 stage in mouse and about 3 weeks of gestation in man (20) but its remodelling persists whilst maintaining its physiological pumping function. Thus, the *Xenopus* heart undergoes a morphogenic process starting with "Right hand looping" that eventually leads to chamber formation, giving rise to both atrial and ventricular chambers of the heart (see reference (21) for a comprehensive review). This anticlockwise spiral looping along the anterior to posterior axis of the heart tube of *Xenopus* results in formation of non-linear heart by stage 35 (21). By stage 39/40, there is a significant compression of the heart along the AP axis (21). The spiral and atrioventricular valves become distinguishable by stage 45/46 and finally atrial septation concludes the final steps in *Xenopus* heart development.

However, despite comprehensive 3D modelling techniques that have documented the steps described above (21), the exact molecular mechanisms regulating the looping of the heart leading to chamber formation remain largely undetermined. Heart morphogenesis is a multifaceted process whose complexity is reiterated by the surprisingly large number of genes in which mutations have produced a cardiovascular phenotype in mice, zebrafish and *Xenopus*.

Signalling Pathways involved in Cardiac Specification and Differentiation

The timing of specification of cardiac progenitor cells and the molecules involved in this process have

been under intense investigation. *Xenopus* has served as an ideal model to address these questions particularly using explants, where tissue can be cultured and induced to form heart *ex vivo*, as described below.

Use of the Animal-Cap explant model system to determine molecular mechanisms involved in heart development

The roof of the amphibian blastula, known as the animal cap (AC), differentiates into ectodermal derivatives during *Xenopus* development (Figure 2). These ACs can be micro-dissected and cultured "*ex vivo*" in a simple salt solution where they will ordinarily differentiate into atypical epidermis. However, their fate can be altered either by incubation of ACs in a soluble inducer or by injection of RNA encoding a suitable inducing factor (Figure 2). Thus, *Xenopus* embryo AC explants have been exploited for understanding the induction and differentiation of a variety of different tissues, including the heart. This *ex vivo* model has been widely utilised to investigate the role of various tissues, molecules and signalling pathways in cardiac development, much of which is described in this review.

Role of endoderm tissue

The cardiac mesodermal precursor cells are in continuous contact with the presumptive anterior endoderm throughout their migration into the lateral plate (16). During this time, they become committed to become cardiomyocytes in response to signals from the surrounding tissue (22, 23). Early landmark grafting studies in *Xenopus* demonstrated that the heart-inducing properties of dorsoanterior endoderm, a region underlining the precardiac mesoderm, is necessary for cardiac specification (24, 25). In chick embryos, when blood precursor cells of the posterior primitive streak were cultured with the anterior (but not posterior) endoderm, these cells were induced to differentiate into cardiomyocytes (22). These data supported the notion that signals from the anterior endoderm influence the fate of the adjacent mesodermal layer to induce heart differentiation. The role of anterior endoderm on cardiac specification has been confirmed in both *Xenopus* (19) and in chick (23) embryos. However, it has thus far proven very difficult to retain this activity in explants of anterior endoderm.

Mohun's group took advantage of the AC explant model system to demonstrate that members of the

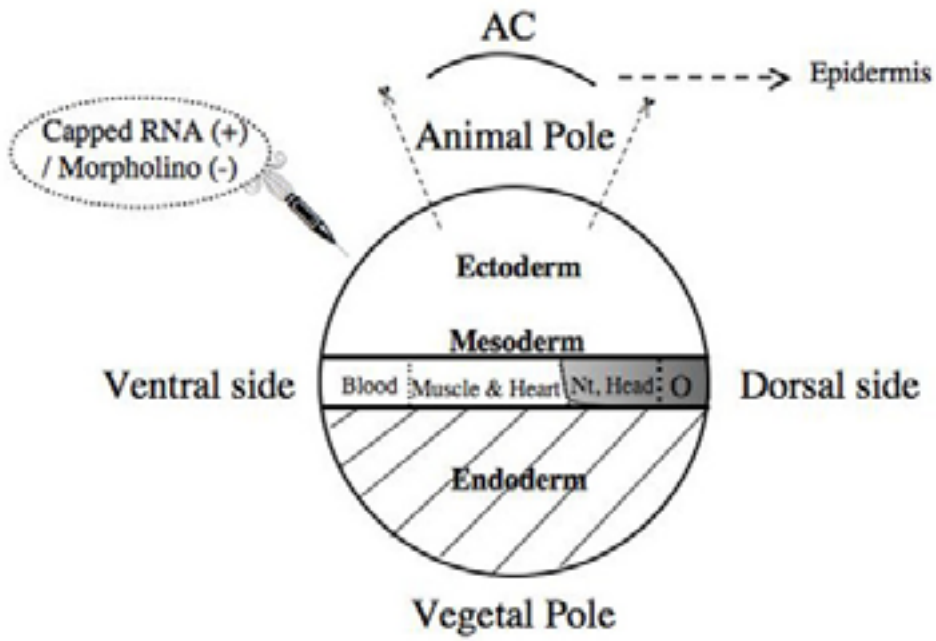

Figure 2: Schematic representation of Xenopus embryo

O: The Spemann Organizer
Nt: Notochord
AC: Animal Cap

GATA family of transcriptional factors can induce cardiogenesis and expression of late markers of cardiogenic markers in AC explants (as discussed in further detail in the "The GATA family" section) (26). Interestingly, authors reported that ectopic expression of GATA4 also induced the expression of endodermal marker, Sox17; however inhibiting formation of endoderm by co-injection of a potent repressor of endodermal formation, Sox17βEng, surprisingly resulted in further induction of cardiogenic markers. Thus, authors concluded that cardiogenic tissue might be formed at the expense of cardiogenesis in this AC model and differentiation of endoderm and cardiogenic tissue are "mutually antagonistic". However, they acknowledged that endodermal tissue might have still formed via a Sox17-independent pathway and could not dismiss the possibility that GATA4 may act downstream of endodermal signalling, and induction of cardiac tissue might be a secondary consequence of endodermal differentiation (26).

Alternative studies using chick embryo as a model of heart development have provided evidence that the signalling from the Bone Morphogenic Proteins (BMPs) from endoderm could induce cardiac fate in the adjacent mesodermal tissue (22, 27).

BMP signalling

BMPs are members of the TGF-β superfamily and it has been shown that the expression of members of BMPs are essential for cardiac differentiation in chick embryos (28). BMP2 signalling induces expression of markers of cardiomyocyte terminal differentiation, Nkx2.5 and GATA4, in the anterior (but not posterior) mesoderm in chick embryos (27).

Further studies in pluripotent P19 cells suggest that BMP4 signalling is also necessary and sufficient for the regulation of Nkx2.5, which in turn regulates transcription of cardiac specific genes during cardiogenesis (29). On the other hand, inhibition of BMP signalling in *Xenopus* embryos failed to affect early cardiac specification, but only induced cardiac differentiation and morphogenesis that occur later (30). Moreover, in the GATA4 AC explant model, co-injection of BMP4 or a soluble BMP-signalling antagonists, Chordin or Cerberus, alongside GATA4 failed to affect cardiac differentiation in these ACs, suggesting that cardiac induction in this model is unlikely to occur via BMP signalling (26).

Furthermore, the expression of BMP in chick embryos (31) and its expression (32) and activity in *Xenopus* embryos (33) are much more wide-ranging than the specified region of cardiac mesoderm, and BMP transcripts have not been detected in regions which are shown to play an important role in cardiac specification, i.e. the dorsoanterior endoderm and the Spemann Organizer in chick embryos (31). Taken together, this evidence suggests that additional signalling molecules must be required for cardiac specification.

Wnt signalling

It was demonstrated in both *Xenopus* (34) and chick (35, 36) embryos, that β-Catenin/Wnt-mediated signalling from the notochord and neural tube *suppresses* cardiomyocyte specification at those regions. In addition, the ectopic expression of either Wnt-3A or Wnt-8 in precardiac mesoderm have been shown to block cardiogenesis (34, 35). Conversely, administration of antagonistic soluble Wnt-binding proteins, Crescent or Dickkopf-1 (Dkk-1), to the posterior lateral plate of chick embryos induced cardiogenesis and repressed the default erythropoiesis fate suggesting that inhibition of Wnt activity induces cardiomyocyte specification (35). In addition, injection of another inhibitory component of β-Catenin/Wnt signalling cascade, GSK3β, also resulted in ectopic cardiac differentiation in the ventral marginal zone (equatorial, see Figure 2) of *Xenopus* embryos that would otherwise be destined to form blood cells (34). Hence, these data strongly suggest that the inhibition of β-Catenin/Wnt-signalling is a pre-requisite for cardiomyocyte specification.

The Spemann Organizer, located at the most dorsal mesodermal region of gastrula stage embryos (Figure 2 and 3B), is an important signalling centre for induction of cardiac fate as demonstrated by classical dissection studies in *Xenopus* embryos (12, 19). This role is fulfilled at least in part via production of the soluble Wnt-antagonistics, DKK-1 and Crescent, which diffuse to the adjacent mesodermal and endodermal tissue, inducing the specification of cardiomyocytes by suppressing Wnt-3A and Wnt-8 activity in an area of high BMP signal (Figure 3) (34). Hence, these results are consistent with the hypothesis that the heart field is restricted to the anterior lateral plate of mesoderm due to *high BMP* signalling from the nascent lateral endoderm in this area in conjunction with *low* β-*Catenin/Wnt*-activity, as a result of secretion of Wnt antagonists from the anterior endoderm to suppress Wnt signalling.

Furthermore, it is important to add that not all

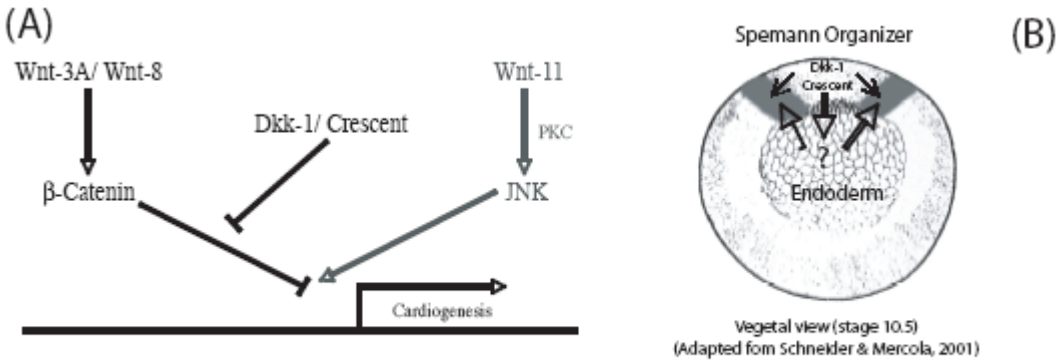

Figure 3: A) Proposed role of Wnt signalling pathway in cardiogenesis
B) Model of induction of cardiogenesis by Wnt-antagonists

Wnt signalling has an inhibitory effect on cardiogenesis. Overexpression of Wnt-11 in ventral explants of gastrula stage *Xenopus* embryos leads to cardiogenesis and, indeed, formation of beating heart tissue (Figure 3A) (37). Conversely, diminishing the expression of Wnt-11 via introduction of a specific anti-sense morpholino oligonucleotide was shown to significantly reduce the expression of late markers of cardiogenic differentiation (37). It should be noted that Wnt-11 signalling has been shown to induce cardigenesis via Protein kinase C and JUN amino-terminal kinase, independent of the β-Catenin pathway that mediates the inhibitory signalling of Wnt-3A and Wnt-8 (Figure 3A).

FGF and notch signalling

Both Fibroblast Growth Factor (FGF) and the FGF receptor are highly expressed during cardiogenesis in chick embryos, while their expression profile declines developmentally as the cardiomyocytes differentiate and loose their mitotic ability (38). Although FGF family members have been shown to have heart-inducing activity alongside BMP-2, they are not expressed in heart inducing tissues in *Xenopus* and thus their role is thought to be minimal. Consistent with these reports, no late marker of cardiac differentiation was detected in *Xenopus* AC explants incubated with basic-FGF, whereas Activin treatment induced MHC-α expression in such explants (39) (the role of Activin is described in the next section).

The most informative study thus far on the role of Notch signalling in cardiogenesis, has been carried out using *Xenopus* embryos (40). This suggests that activation of Notch signalling results in the inhibition of cardiac differentiation, and conversely that inactivation of the Notch pathway results in expansion of the heart and ectopic expression of markers of cardiac differentiation (40). However, endogenous Notch signalling was demonstrated to play a role in the cell fate decision between the myocardial and pericardial roof cells, and not at the earlier step of cardiomyocyte specification (40).

Activin and Suramin signalling

Finally, it should be noted that the *Xenopus* AC model has helped to identify the potent mesodermal inducing factor, Activin, which can induce ACs to differentiate into all types of mesodermal and endodermal tissue (41). Activin is a growth factor of the TGF-β protein superfamily and at high concentrations has been implicated in a complex regulatory circuit functioning in the induction process that is likely to include BMP, Wnt and FGF signalling (42). Incubation of amphibian ACs with high concentration of Activin induces differentiation into cardiogenic tissue including observable cardiac specific microstructures, such as Z-band and beating tissue (43). It has also been reported that incubation of isolated *Xenopus* dorsal blastopore lip explants (containing the Spemann Organizer) with a synthetic chemical, Suramin, also resulted in the expression of heart specific markers (44, 45).

Furthermore, it has been demonstrated that transplantation of either the Activin (46) or Suramin (45) -treated ACs into *Xenopus* embryos results in formation of a secondary ectopic heart that is both functional and has integrated into the host's cardiovascular circuit. These models not only offer attractive platforms for potential heart organ engineering (as discussed in further detail below), but also emphasise the role of these

substances in activating the signalling cascades that play an essential role for normal *Xenopus* heart development.

Transcription Factors Involved in Cardiac Differentiation and Heart Development

It has emerged that a surprisingly large number of transcription factors are involved in embryonic heart development, orchestrating this multifaceted process. However, it is important to bear in mind that for a particular transcription factor to be considered as *directly* involved in cardiac morphogenesis, it must be both expressed in the developing cardiac tissue and also exert transcriptional regulation which influences heart development. Thus, although numerous transcription factors have been suggested to play a role in the transcriptional regulation of cardiac gene expression, evidence for a direct role in heart development is often lacking and merits further investigation. For this reason, we have only focused on the transcription factors that have been established to play a clear role in cardiogenesis, as described below.

The NK Family

This family of homeobox transcription factors are at present the sole link between cardiac specification that occurs during gastrulation and cardiac differentiation that takes place later in tailbud stages of *Xenopus* embryo development (47). As discussed earlier, Nkx family members are some of the earliest transcription factors expressed in cardiac progenitor cells, first detected during gastrulation soon after they have been specified (18, 21). While in vertebrates there are several Nkx family members, in *Xenopus* Nkx2.5 is the most abundantly expressed in heart region(s). In *Xenopus*, the timing and area of expression of Nkx2.5 is restricted to the lateral plate mesoderm within the heart field, which almost (but *not* exactly) coincides with the area of heart specification. This suggests a potential role as an intermediate early inductive signals (18). In addition, it has been shown that BMP2 signalling regulates Nkx2.5 activity during cardiogenesis (29).

Overexpression of a dominant negative form of Nkx2.5 or a dominant negative Nkx2.3 in *Xenopus* embryos resulted in complete inhibition of cardiogenesis (48, 49). Conversely, ectopic expression of either Nkx2.5 or Nkx2.3 in *Xenopus* embryos have been reported to result in enlarged tadpole hearts (50).

Although these results strongly suggest that members of the Nkx family play an important part in heart development, it was unclear whether they play a role in cardiac specification or differentiation. It was reported that, although mouse mutants, homozygous for a null mutation of Nkx2.5, demonstrated severe disruption in heart tube morphogenesis, the heart tube was still formed (51), suggesting Nkx family members only play a critical role in the late steps of heart differentiation in this species. Hence, these results argued against the potential role of Nkx2.5 in cardiac specification in vertebrates and also raised the possibility of functional redundancy amongst the Nkx family members. However, double Nkx mouse mutant embryos were shown to have only a slightly more severe phenotype (52). Taken together, most available data argue *against* the role of Nkx family members in cardiac specification. Other studies have revealed that Nkx2.5 actually plays a specific role in the formation of the left ventricular chamber (53).

Interestingly, it has been revealed that Nkx2.5 is not a very potent transcriptional activator by itself; however, binding to additional regulatory proteins ensures the efficient transcription from target promoters (54). Nkx2.5 has been shown to regulate the expressions of gap junction protein, connexin 43 (55) and Myocardin (56). It has also been verified that Nkx2.5 physically interacts with transcription factors such as Tbx and GATA4, and synergistically activates the transcription of cardiac specific genes (57).

The GATA family

Nkx family members do not fulfil the role of master regulators of cardiac differentiation, as do MyoD family members in myogenesis, and indeed thus far no equivalent master cardiomyogenic regulator has been identified. Instead cardiac differentiation is thought to occur in response to a number of transcription factors that *together* regulate cardiac transcription. These include members of the GATA family and MADS box genes such as Serum Response Factor (SRF), Myocardin and Mef2.

The GATA family of zinc-finger transcription factors play a critical role in the progressive differentiation of precardiac cells. In the majority of vertebrates, Nkx2.5 expression coincides with simultaneous expression of GATA4, 5 and 6 in the precardiac mesoderm and the developing heart. Homozygous GATA-deficient mouse models have been used to investigate the role of these transcription factors in cardiogenesis. Although the GATA5 deficient mice have no cardiac phenotype (58) GATA6 knockout

results in early embryonic lethality (59) and GATA4$^{-/-}$ embryos carry early endodermal defects and a general disruption of the ventral body pattern (60-62). In the GATA4$^{-/-}$ mouse, there was a uniform lack of the linear heart tube due to failure of migration of precardiac mesoderm to ventral midline, and instead two aberrant cardiac structures were formed in the anterior and dorsal lateral embryo (60, 61). Furthermore, it was demonstrated that the expression of GATA4 in the endoderm, rather than cardiogenic mesoderm, is necessary for the morphogenesis of the ventral side of embryo (63). Altogether, results from mouse models suggest that GATA4 does *not* play a role in cardiac specification, but instead it plays a critical role in regulating the lateral to ventral folding of the embryo that is required for embryo and cardiac morphogenesis (60, 61, 63). However, as GATA4 is required for general embryonic morphogenesis, these mouse models have not been so useful for investigating the direct role of this family of transcription factors in cardiac differentiation. Instead, the *Xenopus* model has proved an attractive alternative that has provided intriguing insight.

Overexpression of GATA6 in *Xenopus* embryos has been shown to inhibit cardiomyogenic differentiation in heart precursor cells, thus suggesting high GATA6 levels in cardiac precursors may act to keep them in an undifferentiated state, whereas the developmental reduction of GATA6 expression might contribute towards cardiac differentiation (64). Animal cap (AC) explants from *Xenopus* embryos have an ectodermal fate and, when cultured, differentiate into epidermis (Figure 2) (42). However, it has been demonstrated that AC explants from GATA4 or GATA5 injected embryos actually go on to express the markers of cardiac differentiation, Troponin Ic and Myosin light chain (26), frequently resulting in spontaneously beating tissue (http://dev.biologists.org/cgi/content/full/130/16/3865/DC1). Furthermore, GATA4, GATA5 (26) and GATA6 (65) have all been shown to induce expression of markers of endoderm, emphasising their additional role as regulators of endodermal differentiation. However, it was reported that inhibiting endodermal formation by co-injection of Sox17βEng, resulted in further induction of cardiac differentiation in ACs (26). Thus, an intriguing model was proposed, suggesting that GATA4 induces differentiation of ectodermal tissue into both endodermal and cardiomyocytes, with the endodermal tissue being formed at the expense of cardiac tissue. However, as discussed earlier, it remains ambigious whether induction of cardiac tissue in GATA4 injected *Xenopus* AC model is due to the direct effect of GATA4 on specification of cardiac progenitors or is secondary to the induction of endodermal differentiation (26). Nevertheless, GATA4 or 5 expression is sufficient to induce cardiac differentiation in *Xenopus* embryos, and GATA4-injected ACs provide a powerful model to study molecules and signalling pathways involved in cardiac differentiation *ex vivo*.

Importantly, GATA4 has been shown to work in synergy with other cardiogenic transcription factors to induce differentiation of cardiac specific genes. Functionally important GATA4 binding sites have been found to be located upstream of the Nkx2.5 gene, and GATA4 directly interacts with Nkx2.5 to synergistically activate transcription of cardiac target genes (57). It has also been demonstrated that GATA4 can modulate the transcriptional activity of another very important cardiogenic transcription factor, myocardin, thus providing a mechanism for gene specific regulation of Serum Response Factor target genes, as described below (66).

Myocardin

Serum Response Factor (SRF), belongs to the MADS (MCM1, Agamous, Deficiens, SRF) box family of transcription factors, and many cardiac genes such as Atrial Natriuretic Factor (ANF) (67) and Cardiac α-Actin (68) contain binding site for this ubiquitous transcription factor, SRF. Myocardin is a potent SRF co-activator, which is expressed specifically in cardiac and also smooth muscle cells (69). Cardiac specific genes are activated following formation of a ternary structure upon binding of myocardin and SRF to the promoters of these genes. However, unlike Nkx2.5 and GATA4 that are expressed much earlier in *Xenopus* embryo development, the timing of myocardin expression in cardiomyocytes (~stage 24) suggests that it acts as an intermediate in the pathway of myocardial differentiation, since its expression *just* precedes the expression of markers of cardiac differentiation (54). *Xenopus* embryos injected with a dominant negative form of myocardin showed that myocardin is necessary for early stages of cardiac differentiation, including expression of high levels of Nkx2.5 (69). On the other hand, overexpression of myocardin in the *Xenopus* embryo resulted in early expression of the cardiac specific differentiation markers, MHC-α, cardiac Troponin I and cardiac α-actin. Interestingly, however, myocardin could not induce the expression of all cardiac differentiation markers since myosin light chain 2

(MLC2) expression was never observed (54). AC explants excised from myocardin-injected *Xenopus* embryos also expressed markers of cardiac differentiation. However, unlike GATA4 injected ACs, they did not form beating tissue. Thus, myocardin is another important transcription factor required for cardiogenesis whose expression is shown to be regulated by Nkx2.5 (56).

The T-Box proteins

The T-box family of transcription factors play an important role in organogenesis including the vertebrate heart development. Tbx5 and Tbx20 are amongst the earliest genes expressed in the cardiac lineage (70), the timing and expression profile of which coincides with that of Nkx2.5 and GATA4 (18, 71). It has been reported that, in mouse, Tbx20 synergistically activates the cardiac gene expression by physical interaction with other cardiac transcription factors, namely Nkx2-5, GATA4 and GATA5 (57). Furthermore, ectopic expression of Tbx20a isoform in *Xenopus* embryos specifically induced cell migration and the expression of mesodermal and endodermal lineage markers (57). More recent studies demonstrate that Tbx5 and Tbx20 have non-redundant functions and can heterodimerize and synergistically regulate cardiac gene expression (70). *Xenopus* embryos injected with specific Tbx5 and Tbx20 morpholino antisense oligonucleotides, develop heart tubes but fail to undergo looping and chamber formation (70). Subsequent investigations using murine models have confirmed the role of Tbx20 in cardiac looping and in cardiac chamber formation, since mice carrying a targeted mutation of the Tbx20 gene also developed a linear heart tube that fails to undergo looping and subsequent chamber formation.

The Amphibian Embryo as a Model for Heart Organ Engineering

It is perhaps fitting to finish by discussing reports on the use of amphibian embryos as a model for heart organ engineering, in which the *Xenopus* AC model has been exploited to develop an *ex vivo* heart induction system.

In the fascinating work done by Asashima's group, they reported that treatment of *Xenopus* ACs with Activin resulted in the induction of all the important cardiac transcription factors such as Nkx2.5, GATA4 and Tbx5. Moreover, these aggregates would go on to form beating tissue that express all markers of cardiac differentiation (46). Intriguing results were obtained following the transplantation of such aggregates *in vivo*, either to replace the cardiac "rudiment" tissue or as ectopic transplantation in the abdomen of neurula stage *Xenopus* embryos. Results alongside supplementary videos (http://www.ijdb.ehu.es/abstract.0306/esm1.htm) demonstrated that embryos, which received a replacement transplant, developed as normal with the substitute heart beating normally. Moreover, ectopic transplantation of AC aggregates in the abdomen led to development of a *second* ectopic heart in the recipient's abdomen with normal physiological function and anatomy that had integrated with the host's vascular system, even after embryos had metamorphesised into adult frogs (46).

It is also noteworthy to highlight the report by Horst Grunz in which the author reported that incubation of dorsal blastopore lip explants of *Xenopus* embryos with a synthetic chemical, Suramin, led to change of fate of the explants from notochord and somites to beating heart precursor tissue expressing both Troponin I and Nkx2.5 (45). Subsequent ectopic transplantation of these explants in the posterior trunk of early stage embryos, led to the formation of secondary functional heart. Furthermore, replacement transplantation of heart primordium with Suramin treated ACs also rescued the heart anlage (45) (for supplementary video material go to: http://www.uni-essen.de/zoophysiologie/).

The successful development of a functional ectopic heart following *in vivo* transplantation, suggests that the *Xenopus* models described above provide an attractive platform for future heart organ engineering experimentation.

Summary

Despite obvious anatomical differences between the mammalian and *Xenopus* heart, it has been documented that the majority of the pathways involved in vertebrate heart development are conserved. Translucent *Xenopus* embryos are abundant in number, can be fertilised externally, thus all stages of heart development are accessible for investigation. Moreover, ablation of genes affecting early heart development are amenable as developing embryos do not rely on a functional heart for oxygen delivery until later stages of development. Furthermore, embryos are robust enough to survive microinjection to modulate the expression of specific genes. Explant tissue obtained from microsurgery have been used to address the role of various molecules and signalling pathways in cardiac specification and differentiation and, significantly, have

been utilized successfully in heart organ engineering. Thus, the use of *Xenopus* has provided a simple and versatile model for investigating the role of specific molecules and signalling pathways in vertebrate heart development.

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Secretary's Column

Just after I last wrote in April, the BSCR met at the University of Leicester. The scientific meeting on the subject of 'Emerging concepts in atherothrombosis', reported here by Professors Nilesh Samani and Alison Goodall, was particularly successful, benefiting from a relaxed atmosphere in the very pleasant surroundings of the residential campus. Abstracts of free communications given at BSCR meetings are now published in *Heart Online* as true electronic pages which are easily searchable and citable, and the Leiceister abstracts are the first for the BSCR to be published in this format. Another first at this meeting was the award of the 'Clinical Science' Young Investigator Prize and we are grateful to Erica Callandar and James Mockridge for their initiative and backing of the BSCR in setting up this award, which will be offered at each main meeting. Along with the existing BSCR prize, it is expected that our twice-yearly meetings will be increasingly attractive for young investigators. Not only is student membership free, but there is now a reduced joint BSCR/ISHR student membership fee negotiated recently by clued-in BSCR Treasurer, Mike Curtis, which will be available from next January for just £12 per annum.

The May event on the BSCR calendar was the joint symposium 'Oxidative stress and cardiovascular disease', which took place during the British Cardiac Society annual scientific meeting in Manchester. A good audience of over 100 was generated no doubt by the subject matter which had broad appeal to both BSCR and BAS members. Also, I might add, the timing was favorable, the session coming just after lunch rather than in the breakfast slot assigned to the BSCR symposium in recent years.

The end of this year will see a number of significant changes on the BSCR Committee. Firstly, I am delighted to announce that Professor David Eisner has been elected unanimously by the present Committee to succeed Professor Michael Marber as Chairman. Subject to approval by the membership at the next AGM to be held in London on 16 September, he will take up the position in January 2006. David is a long standing member of the Society, dating from prior to 1987 when it was known as the Cardiac Muscle Group. Over this time, he has been involved in running very successful BSCR meetings and recently has contributed as an active member of the Committee. As such, he has much experience of BSCR activities and, coupled with his strong links to other relevant organisations, it puts him in an ideal position to provide leadership in developing the Society as a key scientific forum. In addition to the vacancy left by David, there will be three further vacancies at the end of 2005, when Professor Keith Channon, Professor Nilesh Samani and Dr Peter Weinberg will retire from the Committee. Five nominations have been received for the four vacancies and biographies of the individuals are given in this issue of the Bulletin. It is necessary now to hold a postal ballot and a voting paper for the purpose has also been included. I would encourage you all to make your choice known, using only the official stamped form and by no later than 9 September. The result will be announced and approval sought from the membership present at the AGM.

As referred to earlier, the Autumn meeting will be held in London, at St Thomas' Hospital on 15-16 September. Professors Marber and Avkiran have put together an exciting collection of symposia with a focus on 'Stress signals in the cardiovascular system', and the final programme is published here. Notice of the AGM to be held during this meeting is included with this issue. The BSCR is returning to Cambridge next spring. Dr Andrew Grace and colleagues have put forward the programme for a meeting on "Cardiovascular Genomics" which will be held on 27-28 March 2006 at the Hinxton Hall Conference Centre. And next September, we will be back in London.

Barbara McDermott

Nominations for Membership of the BSCR Executive Committee

Barbara Casadei

Year of first joining the Society: 1995

I graduated in Medicine from the University of Pavia and started my specialist training in Cardiology in Italy. In 1989 I came to Oxford with a 6-month training fellowship and I have been in the UK ever since. I became the Joan and Richard Doll Research Fellow at Green College and obtained a DPhil in 1995 under the supervision of Professor Peter Sleight. I have been honorary consultant physician since 1995. In 2001 I was awarded a Senior Research Fellowship from the British Heart Foundation and in 2002 I became Reader in Cardiovascular Medicine in Oxford. I was elected to the Basic Science Council of the European Society of Cardiology in 2004.

I started my research career as a clinical investigator and I progressively drifted into mice, cells, molecules and back to humans. This development has been made possible thanks to the help and friendship of many colleagues from whom I learned (and still learn) a great deal. By the time I completed my DPhil, I had become addicted to the collegiality of the academic environment and the excitement that comes from being part of it. If elected to the Society, I hope I will be able to transmit my enthusiasm for a career in research and academic medicine to younger colleagues and will do my best to increase the visibility (and ideally the funding) of integrative and translational research in the UK by promoting interdisciplinary communication and wider exchange between research groups with similar interests and complementary expertise.

Proposed by: **Michael Marber** Seconded by: **Metin Avkiran**

Andrew Grace

Year of first joining the Society: 1990

I am a Senior Research Fellow in the Department of Biochemistry, University of Cambridge and Consultant Cardiologist at Papworth Hospital, Cambridge. I have specialist interests in the investigation and management of arrhythmias with a large clinical practice. In addition, over the last several years my research group in Cambridge has gained a focus on a detailed characterization of the properties of the heart that provide the so-called 'substrate' for arrhythmias. The central, simple hypothesis that drives the work is that the determinants for the clinical risk of arrhythmias and sudden cardiac death (SCD) reside within the heart itself and much of this has a genetic basis. The core of the programme is to link the genetic alterations determining SCD to the observed arrhythmogenic phenotypes and relies on genetically modified mouse models. I have a track record of publishing high quality research in both specialist and non-specialist journals; I attract funding from research organizations including the MRC, Wellcome Trust and the BHF. My work is known and respected internationally and I am regularly invited to participate in international research initiatives and conferences and contribute to the scientific literature. The BSCR provides an important voice arguing for the translation of ideas between basic science and clinical practice and I would welcome the opportunity to contribute.

Proposed by: **Keith Channon** Seconded by: **Michael Curtis**

Chris Newman

Year of first joining the Society: 2005

I trained at Cambridge and Westminster Medical School, qualifying in 1983. After junior medical training in London and Oxford I became registrar in Cardiology and Clinical Pharmacology at the Royal Postgraduate Medical School, Hammersmith Hospital. I then became an MRC Clinician Scientist and undertook PhD training at the National Institute for Medical Research with Tony Magee studying posttranslational lipid modifications of small GTP-binding proteins. Thereafter I spent 3 years in Peter Weissberg's group in Cambridge before being appointed Senior Lecturer in Cardiology in Sheffield. My major interest is non-viral gene delivery using ultrasound, with an increasing involvement in the vascular biology of pulmonary hypertension and some aspects of diabetes.

I am currently honorary secretary of the British Atherosclerosis Society and Chairman of the Basic Science Panel of Heart Research UK. I would very much like to see closer links between the BAS and BSCR with the aim of increasing the profile of cardiovascular research generally in the UK. I feel that being on both committees would facilitate this, and would provide continuity of links between the two societies upon the retirement of the new BAS Chairman, Keith Channon, from the BSCR Committee.

Proposed by: **Michael Marber**

Seconded by: **Metin Avkiran**

Nicola King

Year of first joining the Society: 1998

Following the completion of my PhD studies in 1995, I joined the late Prof. Chapman's team investigating the role of amino acids in heart under normal and pathological conditions. This topic has been central to my research ever since, during which time I have completely profiled the expression and activity of acidic amino acid transporters in the normal and hypertrophic heart, and have begun to dissect the complex relationship that exists between amino acids and antioxidant defences in cardiomyocytes. The work is at the interface between clinical and non-clinical cardiac research. I am currently based at the Bristol Heart Institute working alongside Prof. Suleiman.

I have three reasons for wanting to join the BSCR Executive Committee. The first of these is my desire to raise awareness both within the scientific and clinical communities as well as to the general public of the excellence and scope of cardiovascular research in this country. Secondly, I would like to facilitate communication and collaboration between cardiac cellular physiologists (who I represent), vascular biologists, and clinicians. Finally I would like to seek out new opportunities in order to encourage and support young cardiovascular researchers in their careers.

Proposed by: **Saadeh Suleiman**

Seconded by: **Gianni Angelini**

Cathy Holt **Year of first joining the Society: 1992**

In 1989, I was awarded a PhD from the University of Sheffield on the involvement of the vasculature in the pathogenesis of autoimmune diseases. This sparked my interest in all things vascular and I subsequently went on to a British Heart Foundation funded post doctoral position with Professor Gianni Angelini, working on organ culture of human and porcine vessels. In 1992, I was appointed Lecturer in Cardiac Sciences at the University of Sheffield and in 2001 moved to the University of Manchester as Senior Lecturer in Cardiovascular Biology. My research interests include the biology of the vessel wall and what happens following injury such as occurs following bypass graft surgery, angioplasty and stenting. In particular, I am interested in the role of transcription factors in the response of the vessel wall to injury and novel modes of inhibition including antisense and dominant negative genes. I am a strong advocate of the BSCR and have spoken at various meetings held by the Society. I see the BSCR as the main forum for Cardiovascular Researchers within the UK, encompassing both vascular and myocardial biology. I was co-organiser of the Spring BSCR meeting, entitled: "Frontiers in Cardiovascular Signaling" hosted in Manchester, 2003. This meeting comprised presentations from a combination of vascular and myocardial scientists. BSCR meetings are also an ideal forum for graduate students to present their data and meet scientific colleagues. If elected to the BSCR committee I will be committed to encouraging younger members of the cardiovascular scientific community to attend and present at BSCR meetings. In addition, having spent my entire career to date in Clinical Departments, I would like to enhance the link between cardiovascular clinicians and basic scientists and see future meetings as an opportunity for this to occur.

Proposed by: **David Eisner** Seconded by: **Barbara McDermott**

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BSCR Spring Meeting Report
21st-22nd April 2005

"Emerging Concepts in Atherothrombosis"

Organised by
Professor Nilesh Samani and Professor Alison Goodall
University of Leicester

The events that lead from the early development of an atherosclerotic plaque to the thrombotic consequences of plaque rupture or erosion are important therapeutic targets for the prevention and treatment of cardiovascular disease. Rapid advances over recent years mean that our understanding of the role of the various cells of the vessel wall and blood is constantly evolving. A meeting focussed on specific aspects of these processes was therefore felt to be timely.

The meeting began with a session on **Plaque and Vessel Wall,** a session that allowed the audience to consider the way in which plaque development is regulated through endothelial cell dysfunction, plaque growth leading to the formation of a vulnerable plaque and the risk of an atherothrombotic event. Professor Raffaele De Caterina (Chieti, Italy) gave an overview of the role of endothelial cells in the development of atherosclerosis, in particular the regulation of expression of the key adhesion molecules V-CAM-1 and CD40L, and the regulation of endothelial cell function by oxidative stress. This was followed by a presentation by Professor Andrew Newby (Bristol) who gave an overview of the current thinking into the role of metalloproteinases in regulating plaque stability, again with a focus on CD40L and oxidative stress as regulators of MMP gene expression. The session ended with a presentation from Dr Trevor Littlewood from the University of Cambridge exploring the role of apoptosis of macrophages and smooth muscle cells within the atherosclerotic plaque in which he described conditional knockout mouse models in which monocytes and smooth muscle cells could be switched to undergo apoptosis. After tea, Professor Lina Badimon (Barcelona) presented a Keynote Lecture, giving a wide-ranging overview of experimental data on plaque thrombogenicity describing work carried out in her laboratory from her days in the Cleveland Clinic to her current investigation of gene expression profiling within the plaque. This presentation developed the hypothesis that thrombus can build up slowly over time. Elegant studies employing the Badimon chamber were used to illustrate the effect of different plaque substrates on the thrombotic response and a double knock out mouse model demonstrated the importance of tissue factor in plaque thrombogenicity.

This was followed by a session of free communications in which fourteen posters were presented by Young Investigators and Research Students, over a wine reception. This was followed by the conference dinner, held at the

National Space Centre in Leicester. As well as an excellent meal, delegates were able to explore the many informative and interactive exhibits ranging from the history of astronomy to current ideas in astrophysics and space exploration and examples of space vehicles and rockets.

The second day began with a session entitled **Current Insights in Platelet Biology** with three presentations by leading experts in the field. Professor Steve Watson (Birmingham) gave a comprehensive overview of many of the intracellular signalling pathways in platelets with a particular focus on the GPVI collagen receptor signalling pathway, using knockout mice to explore the roles of specific signalling molecules such as Vav1-3 and Rac-1 and their effect on platelet adhesion under static and flow conditions, and *in vivo*, studied by intra-vital microscopy. He described recent proteomic and genomic approaches in his laboratory to identify novel platelet signalling receptors. This was followed by a presentation from Professor Richard Evans (Leicester) on the role of the P2X1 receptor in smooth muscle cells and platelets and the differential regulation of depolarisation and calcium signalling within these cells. Finally, Professor Johan Heemskerk (Maastrict) reviewed current ideas of the way in which platelets regulate the pro-coagulant response by providing a surface on which the coagulation cascade can assemble and contribute to thrombin generation of the site of thrombus formation.

After coffee there were five oral presentations selected from the submitted abstracts. Dr Karanam presented a talk entitled "*Thrombin inhibition with melagatran prevents plaque rupture in apolipoprotein E knockout mice*" on behalf of her colleagues in Bristol and at AstraZeneca. Dr Piqueras gave a talk entitled "*Expression of Peroxisome Proliferators-Activator Receptor-δ and Retinoid X receptors in endothelial cells*" on behalf of her colleagues at the William Harvey Research Institute, London. This was followed by a presentation by Professor Trevor Barrowcliffe entitled *"Effects of apoptosis and lipid peroxidation on leucocyte procoagulant activity"* on behalf of colleagues at the National Institute for Biological Standards & Control & the University of Leicester. Dr Robin Poston then presented a talk entitled *"CD14 dependent adhesion of monocytes to oxidised LDL and HSP60 via lipid rafts"* on behalf of his colleagues at Guy's Hospital, London and finally Dr Scott Brouillette gave a presentation entitled *"A prospective analysis of the association of mean leucocyte telomere length with risk of coronary heart disease, and interaction with statin treatment"* on behalf of colleagues at Leicester and the *WOSCOPS* Investigators.

All abstracts from this meeting can be viewed online at the following link:

http://heart.bmjjournals.com/cgi/content/full/91/7/e52.

The session after lunch focussed on **Current Clinical Perspectives in Atherothrombosis.** Professor Peter Grant (Leeds) explored the factors affecting fibrin clot formation in particular genetic variations associated with fibrinogen and factor XIII. This was followed by a presentation from Professor Alison Goodall (Leicester) who discussed the inherent variability in platelet reactivity again with a genetic focus. Finally, Dr Rob Storey (Sheffield) explored current and future perspectives for anti-platelet and anti-thrombotic therapy presenting the exciting prospect of some novel anti-platelet agents to target inhibition of the ADP P2Y12 receptor.

Two Young Investigators Prizes were

awarded at the meeting, one sponsored by the Society and one by the journal Clinical Science. Professor Barbara McDermott presented the BSCR Prize to Dr Veryan Codd (Leicester) for a poster presentation entitled "*Circadian clock genes cause activation of the human PAI-1 gene promoter with 4G/5G allelic preference*" and the Clinical Science Young Investigators Prize was presented to Dr Scott Brouilette (Leicester) for his oral presentation. The meeting concluded with a second Keynote lecture by Professor Gordon Lowe (Glasgow) who gave an informative and provocative discourse that challenged the evidence for the role of some novel risk factors such as C-reactive protein and infection in atherothrombosis.

The excellent scientific content of the meeting was enhanced by beautiful spring weather. The meeting was assisted by generous sponsorship in the form of educational grants from AstraZeneca and from Sanofi-Aventis-Bristol Myers Squibb and the organisers were indebted to the help of Fiona Legate of Millbrook Conferences Ltd for handling the organisation of this meeting.

Alison Goodall and Nilesh Samani

THE *Clinical Science* PRIZE

Clinical Science (Portland Press) have generously offered to sponsor a Young Investigator prize, to be awarded for the best oral presentation at each of the Spring and Autmun BSCR Meetings.

Two prizes will, therefore, be awarded at each main meeting:

The *Clinical Science* Prize - awarded for the best Oral Presentation (selected from submitted abstracts) - £250 and a personal online subscription to *Clinical Science*

The BSCR Prize - awarded for the best Poster Presentation - £250

All abstracts accepted for presentation at BSCR meetings are published in *Heart Online*

PRIZES AWARDED AT THE SPRING 2005 MEETING

The *Clinical Science* Prize was awarded to Dr Scott Brouilette for his Oral Presentation: 'A prospective analysis of the association of mean leucocyte telomere length with risk of coronary heart disease, and interaction with statin treatment' S Brouilette, J Moore, JR Thompson, A McMahon, C Packard, AH Goodall, NJ Samani, on behalf of the WOSCOPS Investigators.

The BSCR Prize was awarded to Dr Veryan Codd for her Poster Presentation: 'Circadian clock genes cause activation of the human PAI-1 gene promoter with 4G/5G allelic preference' V Codd, VD Chan, NJ Samani, MW Chong.

http://heart.bmjjournals.com/cgi/content/full/91/7/e52

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BSCR 2005 AUTUMN MEETING

Thursday 15th - Friday 16th September 2005

Governors' Hall, St Thomas' Hospital, London

Stress Signals in the Cardiovascular System

Organisers: Professors Michael Marber and Metin Avkiran

Programme

Thursday, 15th September

12.30-14.00 Registration and Lunch

14.00-14.05 Welcome

Session 1: Stem cells and response to injury

Chair: Michael Marber (London) and Sian Harding (London)

14.05-14.45 *Cell origins in atherosclerosis*

Qingbo Xu (London)

14.45-15.25 *Cardiac tissue replacement: native cells versus engineered tissue*

Thomas Eschenhagen (Hamburg, Germany)

15.25-15.45 Coffee break

15.45-16.45 **The National Heart Research Fund Lecture**

Circulating progenitor cells in infarct repair

Stefanie Dimmeler (Frankfurt, Germany)

16.45-18.00 Cheese, wine and posters

19.30- Meeting Dinner

Friday, 16th September

Session 2: Stress-activated signalling

Chair: Angela Clerk (London) and Thomas Wieland (Mannheim, Germany)

09.00-09.40 *Signal transduction of mechanical stress in vasculature*

Stephanie Lehoux (Paris, France)

09.40-10.20 *Signal transduction of mechanical stress in myocardium*

Mathias Gautel (London)

10.20-10.40 Coffee

10.40-11.20 *Oxidant signals in response to stress*

Ajay Shah (London)

11.20-12.00 *Anti-inflammatory strategies based on inhibition of p38-MAPK*

Andrew Protter (Fremont, USA)

12.00-12.30 AGM

12.30-13.30 Lunch

Session 3: Free communications

Chair: Barbara McDermott (Belfast) and Michael Curtis (London)

13.30-14.30 Oral presentation of 4 selected abstracts (10 min presentation plus 5 min discussion)

Session 4: Novel mediators in stress signalling

Chair: Metin Avkiran (London) and Peter Sugden (London)

14.30-15.10 *Mono/p63RhoGEF in myocyte signalling*

Thomas Wieland (Mannheim, Germany)

15.10-15.30 Tea

15.30-16.30 **The British Cardiac Society Lecture**

Redox-mediated atheroprotective signals stimulated by laminar flow.

Bradford Berk (Rochester, USA)

16.30-16.45 Presentation of **Clinical Science Young Investigator Award**

Presentation of **BSCR Young Investigator Award**

Meeting close

Cardiovascular Related Meetings

European Society of Cardiology Congress 2005. 3rd-7th September, 2005. Stockholm, Sweden. E-mail: congress@cardio.org.

3rd European Meeting on Vascular Biology and Medicine 2005. 28-30 September, 2005. Hamburg, Germany. For further information: Address: M:con, Rosengartenplatz 2, 68161 Mannheim, Germany; Tel: +49 621 4106-137; Fax: +49 621 4106 207; E-mail: daniela.ruckiegel@mcon-mannheim.de; http://www.embvm.org

Scientific Sessions of the American Heart Association. 13-16 November, 2005. Dallas, Texas. Enquiries: www.americanheart.org.

Euroecho 9 - The Ninth Annual Meeting of the European Association of Echocardiography (EAE) - will take place in Florence, Italy, 7th-10th December, 2005. For further information, please e-mail: euroecho@escardio.org

Keystone Symposia: Hypoxia and Development, Physiology and Disease Breckenridge, Colorado 16th-21st January, 2006. **Cardiac Arrhythmias: Linking Structural Biology to Gene Defects** Tahoe City, California 29th January - 3rd February, 2006. **Molecular Mechanisms of Cardiac Disease and Regeneration** Santa Fe, New Mexico, 19th-26th February, 2006. **Atherothrombosis** Keystone, Colorado 2nd-6th April 2006. **Molecular Biology of the Vasculature** Keystone, Colorado 2nd-6th April 2006. Further details can be obtained by contacting Keystone Symposia**,** 221 Summit Place #272, Drawer 1630 Silverthorne, CO 80498; www.keystonesymposia.org

XXVI European Section Meeting, International Society for Heart Research. 14-17 June, 2006. Manchester, UK. Enquiries: Mrs R Poulton, The University of Manchester, Room 1.302, Stopford Building, Oxford Road, Manchester M13 9PI. Tel: +44 161 2751628. Website: www.meeting.co.uk/confercare/ishr2006

World Congress of Cardiology 2006: Joint Congress of the European Society of Cardiology and the World Heart Federation. 2nd - 6th September 2006. Barcelona, Spain. Further information can be obtained from: EUROECHO Secretariat: ESC, 2035 route des Colles, Les Templiers - BP 179, 06903 Sophia Antipolis Cedex, France. Tel: +33 (0) 4 92 94 76 00; Fax: +33 (0) 4 92 94 76 01; E-mail:webmaster@escardio.org; Website: www.escardio.org

Just returned from the ISHR meeting in Tromso?

We are keen to publish a report on the 25th European Section meeting of the International Society for Heart Research meeting held recently at the University of Tromso, Norway. If you attended this meeting , you may like to share the experience with other Bulletin readers by writing a report of the proceedings. If you would like to write about this or any other Cardiovascular conference, course or laboratory visit, please contact the editors. The BSCR will pay £100 towards the cost of your visit, which will be provided on receipt of the report.

BRITISH HEART FOUNDATION GRANTS

Chairs and Programme Grants Committee February 2005

Programme Grants

Dr C M Shanahan Addenbrooke's Hospital, Cambridge. "The role of vascular smooth muscle cells in the development and progression of vascular disease" 5 years (renewal) £986,195

Prof P J T Vallance et al University College London. "ADMA and DDAH signaling in vascular disease" 5 years (renewal) £1,302,907

Dr D E Newby et al Royal Infirmary, Edinburgh. "Atherothrombotic effects of air pollution" 5 years £1,178,407

Project Grants Committee March 2005

DEFERRED APPLICATIONS AWARDED

Professor P G Camici et al Hammersmith Hospital, London. "Development and implementation of ultra-short TE-MRI for the assessment of myocardial fibrosis in mice and patients with myocardial infarction" 2 years £129,981

Dr T Palmer & Dr S Yarwood, University of Glasgow. "Suppressor of cytokine signalling-3 (SOCS3) induction: a new physiological role for the cyclic AMP sensor "EPAC" in limiting endothelial dysfunction" 3 years £162,924

NEW APPLICATIONS AWARDED

Dr D Proudfoot, Addenbrooke's Hospital, Cambridge. "Regulation of vascular calcification by matrix Gla protein (MGP)" 3 years £135,971

Dr N P J Brindle, University of Leicester. "Regulation of endothelial function by Tie1 RIP signalling" 3 years £134,336

Dr S Stedman & Dr L Leong, Birmingham Heartlands Hospital, "Magnesium sulphate for the prevention of superventricular dysrhythmias following non-cardiac thoracic surgery" 2 years £35,506

Dr N King et al Bristol Royal Infirmary. "An investigation into the expression and activity of cysteine transporters in heart: relationship to glutathione synthesis and cardioprotection" 2 years £142,251

Professor G L Smith, University of Glasgow. "Electrophysiology of ventricular myofibroblasts within myocardial infarction scars of rabbit hearts" 1 year £43,044

Professor C H Orchard et al, University of Bristol. "Effect of acidosis on the cardiac atrio-ventricular node" 3 years £204,326

Professor PG Camici et al, Hammersmith Hospital, London. "Myocardial insulin resistance: molecular mechanisms and their contribution to heart failure" 2 years £120,278

Dr J Saxton & Dr A Pockley, Sheffield Hallam University. "Effect of upper- and lower- limb exercise training on biomarkers of atherosclerosis and cardiovascular risk in intermittent claudication" 6 weeks £15,819

Dr C Shoulders et al, Hammersmith Hospital, London. "Cloning of the genes within the chromosome 11p14.1-q12.1 interval conferring susceptibility to the lipid abnormalities of familial combined hyperlipidaemia" 3 years £231,358

Dr P S Gill et al, University of Birmingham. "Heart failure amongst the ethnic minority communities in Birmingham: E-ECHOES (Ethnic - Echocardiographic Heart Of England Screening) study" 3 years £324,438

Professor D P Taggart et al, John Radcliffe Hospital, Oxford. "A randomised trial of on pump beating heart surgery and blood cardioplegia in patients with impaired left ventricular function using cardiac magnetic resonance imaging and biochemical markers" 2 years £143,125

Dr I A Greenwood , St George's Hospital Medical School, London. "Regulation of calcium-activated chloride currents in vascular smooth muscle cells by dephosphorylatory mechanisms" (3 years) £182,225

Dr S S Ye, Southampton General Hospital. "Molecular genetic and functional analysis of TLR4 gene variants" (3 years) £138,263

Professor K Channon et al, John Radcliffe Hospital, Oxford. "Pre-operative, non-invasive ultrasound assessment of radial artery endothelial function to predict early graft failure and outcome from coronary bypass surgery" (3 years) £136,704

Dr D J Henderson, University of Newcastle upon Tyne. "Regulation of outflow tract remodelling by non-canonical Wnt signalling" (3 years) £206,994

Dr I M Fearon, University of Manchester. "Hypoxic regulation of cardiac sodium channels" (2 years) £129,357

Dr R Haworth et al, St Thomas' Hospital, London. "A novel regulatory role for protein kinase D in myofibrillogenesis?" (3 years) £197,475

Dr P A Kalra et al, Manchester Royal Infirmary. "The effect of renal revascularization upon cardiac structure and function in atherosclerotic renovascular disease (ARVD)" (3 years) £64,014

Professor D F Goldspink et al, John Moore's University, Liverpool. "Gender differences and exercise thresholds in improving aerobic capacity, cardiovascular risk factors, peripheral and cardiac adaptations in endurance trained older people" (3 years) £137,742

Dr C H D Fall, Southampton General Hospital. "Relationship of growth in infancy and childhood to adult endothelial function and body composition; the New Delhi birth cohort" (3 years) £184,538

Dr M Sandhu et al, University of Cambridge. "Insulin-like growth factors and risk of coronary heart disease: genetic and molecular epidemiology" (3 years) £168,645

Fellowships Committee April 2005

DEFERRED APPLICATIONS AWARDED

Junior Research Fellowship

Dr I J Gudmundsdottir, University of Edinburgh. "The role of proteinase activated receptors in the human vasculature" 2 years £95,504

Clinical PhD Studentship

Dr H B Fallouh, St Thomas' Hospital, London. "Protection of the ischaemic myocardium: calcium desensitization and polarization as alternatives to hyperkalaemia" 3 years £162,787

PhD Studentship

Miss S Schievano Institute of Child Health (UCL). "Computational structural analysis as a tool to develop valved stent applications and technology" 3 years £78,961

NEW APPLICATIONS AWARDED

Basic Science Lectureships

Dr D J Henderson, University of Newcastle upon Tyne. "Neural crest cell interactions in outflow tract development and congenital heart defects" 5 years (Renewal) £286,455

Dr C Emanueli, Bristol Heart Institute. "Pathways and therapeutic potential of neurotrophins in neovascularisation and healing of the ischaemic and diabetic heart" 5 years £296,459

Dr A Zhou, University of Cambridge. "Structural mechanisms in the control of fibrinolysis" 5 years £271,750

Intermediate Research Fellowships

Dr J Selvanayagam, John Radcliffe Hospital. Oxford. "Imaging of myocardial oxygenation with blood-level dependent magnetic resonance imaging". 3 years, £232,423

Dr M I Wilson, University of Cambridge. "Turning NADPH oxidase and atherosclerosis off: structural studies of the P-Rex1, Rac GTPase and Gβγ" 3 years £129,115

Dr R Stevens, Churchill Hospital, Oxford. "An integrated cardiovascular risk calculator for use in individuals with or without diabetes and with or without prior treatment for risk of cardiovascular disease" 18 months £73,564

Dr M T Ghorbel, Bristol Royal Infirmary. "The identification of the molecular processes underlying reoxygenation injury in children undergoing repair of cyanotic congenital heart disease" 3 years £157,417

Junior Research Fellowships

Dr J L Guy, University of Leeds. "Regulation and function of angiotensin-converting enzyme-2 (ACE2) expression in human cardiac fibroblasts" 2 years £72,748

Dr J S Webb, University of Nottingham. "The relationship between germline and somatic mutations in congenital heart disease" 2 years £113,482

Dr T L Mwambingu, University of Leeds. "Fibrin structure/function in pre-menopausal women with polycystic ovary syndrome: the effect of insulin resistance independent of glycaemia, and the role of post translational modifications to fibrinogen" 2 years £91,032

Dr T W R Doulton, St George's Hospital Medical School, London. "Does sodium affect endothelial function in individuals with chronic kidney disease?" 16 months £68,206

Mr D M Espino University of Birmingham. "Computational modelling of the mitral heart valve for improved surgical repair of the chordae tendineae" 2 years £69,004

Dr N Hadjiloizou St Mary's Hospital, London. "The effect of regional ventricular dysfunction on coronary artery haemodynamics" 2 years £92,539

Dr S P Page, The Heart Hospital, London. "Prevalence and significance of disease in relation to age in patients with hypertrophic cardiomyopathy caused by MyBPC3 mutations" 2 years £87,395

Dr J P Kaski, Great Ormond Street Hospital, London. "Idiopathic hypertrophic cardiomyopathy in pre-adolescent children: development of a paediatric cardiac symptom evaluation and suddent death risk stratification algorithm" 2 years £84,563

Clinical PhD Studentships

Miss A Burdess, University of Edinburgh. "Role of inflammation and platelet activation in the adverse cardiovascular outcomes of patients with critical limb ischaemia: a double-blind randomised controlled trial of clopidogrel" 3 years £143,039

PhD Studentships

Unnamed and Dr D S Leake, University of Reading. "The mechanisms of low density lipoprotein oxidation by iron at acidic pH" 3 years £75,793

Unnamed and Dr G F Baxter, The Royal Veterinary College. "Roles and mechanisms of action of the L-cysteine/cystathionine-γ-lyase/hydrogen sulphide pathway in the heart" 3 years £78,850.

Mr R D' Elia, University of Manchester. "The role of calmodulin in decoding the calcium signal in muscle excitation-contraction coupling" 3 years £73,668

Unnamed and Dr A J Baines, University of Kent, Canterbury. Mechanisms and specificity in targeting plasma membrane Ca^{2+} -ATPase 2 to intercalated discs" 3 years £74,418

Unnamed and Dr B Latinkic, Cardiff University. "Learning the rules of heart morphogenesis in the xenopus embryo model" 3 years £74,164

Ms P Matthews, St Thomas' Hospital, London. "Developmental programming of cardiovascular disease by maternal dietary fat; a mechanistic study using a murine model" 3 years £79,710

Mr D C Waithe, University College London. "Trafficking of cardiac and sympathetic neurone voltage-gated calcium channel subunits" 3 years £79,710

Unnamed and Dr I Hers, University of Bristol. "Identification and characterisation of protein kinase B substrates in human platelets" 3 years £74,737

Unnamed and Dr M G Tomlinson, University of Birmingham. "Regulation of platelet collagen receptor GPVI signalling by tetraspanin superfamily proteins" 3 years £74,898

Unnamed and Dr R N Khan, Derby City General Hospital. "Ion channel characterisation in the human fetoplacental unit" 3 years £71,426

Mr P Calcraft, University of St Andrews. "Differential activation of Ca^{2+}-sensitive ion channels in the plasma membrane of arterial smooth muscle: spatial co-ordination of Ca^{2+} signalling by IP_3 cADPR and NAADP" 3 years £74,758

Miss A Zagorska Hammersmith Hospital, London. "Would inhibitors of the asparaginyl hydroxylase FIH (factor inhibiting HIF) be useful in ischaemic disease?" 3 years £80,170

Unnamed and Prof M A Geeves, University of Kent, Canterbury. "The role of tropomyosin hetero-dimers in cardiac muscle regulation and cardiomyopathy" 3 years £71,418

Miss L C Diffley, University of Manchester. "Role and regulation of the sarcoplasmic reticulum in the ageing myocardium" 2.5 years £60,930

Mr D Thomas, Aston University. "Activation and pharmacology of CGRP and AM receptors; studies with chimeric receptors and other techniques" 3 years £74,658

Unnamed and Dr D Lodwick, Leicester Royal Infirmary. "Molecular characterisation of the unique properties of the vascular ATP-sensitive potassium channel" 3 years £74,418

Ms K Baeten, University of Aberdeen. "Thrombospondin as a modulator of thrombus lysis" 3 years £75,350

Unnamed and Dr R Maytum, Queen Mary, University of London. "Skeletal versus cardiac isoform effects on muscle regulation" 3 years, £79,710

Travelling Fellowships

Dr A Nicolaou, From: University of Bradford To: Harvard Medical School, Boston, USA. "Lipidomic analysis and profiling of novel omega-3 fatty acid-derived anti-inflammatory mediators and their aspirin-triggered epimers" 3 weeks £2,177

Chairs and Programme Grants Committee May 2005

Programme Grants

Prof S G Ball et al, The General Infirmary, Leeds. "Cardiac magnetic resonance imaging in coronary heart disease: from research to clinical practice" 5 years £1,290,448

Prof S Neubauer et al, John Radcliffe Hospital, Oxford. "Energy metabolism in heart failure - role of high-energy-phosphate storage and delivery via the creatine kinase/phosphocreatine system" 5 years £1,074,252

Prof A P A Steptoe, University College London, "The psychophysiology of coronary heart disease" 5 years £1,229,792

Special Project Grants

Prof J P Bourke et al, Freeman Hospital, Newcastle upon Tyne. "The Duchenne muscular dystrophy heart protection study - a randomised trial of ACE-inhibitor and beta-blocker therapy in preventing cardiomyopathy" 5 years £379,794

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*
18(4)	***October 2005***	*September 1st*
19 (1)	***January 2006***	*December 1st*
19 (2)	***April 2006***	*March 1st*
19 (3)	***July 2006***	*June 1st*

Cardiovascular Related Wellcome Trust Grants

March to April 2005

Programme Grant

Professor Peter J Ratcliffe, Wellcome Trust Centre for Human Genetics, Henry Wellcome Building of Genomic Medicine, University of Oxford. Biochemical and physiological analysis of the HIF Hydroxylases In signalling hypoxia. 60 Months £1,305,905

Senior Research Fellowship

Dr Hisao Kondo, Cambridge Institute for Medicine Research (CIMR), The Wellcome Trust/MRC Building, Addenbrooke's Hospital, Cambridge. p97-Mediated membrane fusion in Golgi and Er assembly. 60 Months £1,025,277

Research Career Development Fellowships

Dr Fabien Brette, Department of Physiology, School of Medical Sciences, University of Bristol. Sub-cellular modulation of calcium current in cardiac myocytes. 48 Months £457,890

Dr Aleksandar Ivetic, Cardiovascular Medicine Unit, Hammersmith Hospital, Imperial College School of Medicine, London. The role of Ezrin-Radixin-Moesin (Erm) Protein/L-Selectin interactions during leukocyte recruitment. 48 Months £501,988

Project Grants

Dr Asipu Sivaprasadarao, School of Biomedical Sciences, Medical School, University of Leeds. Molecular basis of Voltage Gating in Potassium Channels. 36 Months £304,237

Dr Katalin Torok, Department of Basic Medical Sciences, Section of Pharmacology and Clinical Pharmacology, St. George's Hospital Medical School, London. The role of nucleotide and protein substrates in the activation mechanism of Ca2+/Calmodulin-Dependent Protein Kinase II. 36 Months £196,618

Dr Stefan Bagby, Department of Biology and Biochemistry, University of Bath. Molecular Mechanism of an anti-thrombotic protein and potential vaccine targetmetal binding, structure and interactions of Staphylococcus Aureus Extracellular Fibrinogen Binding Protein. 36 Months £191,147

Professor Stefan Grimm, Department of Toxicology, Imperial College London, Hammersmith Campus. The Role of Creatine Kinase and Ant-1, two components of the Permeability Transition Pore, In Apoptosis. 36 Months £200,917

Dr James F X Jones, Conway Institute of Biomole and Biomedical, University College Dublin. Dublin 4 Ireland. The physiological role of paraganglia of the superior laryngeal nerve of the rat. 24 Months £19,352

BSCR Autumn Meeting 2005

Stress Signals in the Cardiovascular System

Dates: 15th and 16th September 2005

Venue: Governors' Hall, St Thomas' Hospital

Organisers: Professor Michael Marber and Professor Metin Avkiran

Overall Aim: The aim is to provide a series of state-of-the-art overviews of how the vasculature and myocardium respond to stress by adaptive signalling pathways and recruitment of progenitor cells.

Invited Speakers include: Bradford Berk (*USA*), Thomas Eschenhagen (*Hamburg*), Stefanie Dimmeler (*Frankfurt*), Mathias Gautel (*London*), Stephanie Lehoux (*Paris*), Andrew Protter (*USA*), Ajay Shah (*London*), Thomas Wieland (*Mannheim*), Qingbo Xu (*London*),

Travel & Accommodation: The conference will be held at St Thomas' Hospital (nearest tube is Westminster and BR is Waterloo), with student accommodation potentially available nearby at Great Dover Street Apartments.

Communications: Part of the meeting will be devoted to oral presentation of selected abstracts and posters. Prizes will be awarded for the best oral and best poster presentations given by young investigators.

Registration: Free to BSCR members, £40 for non-members.

Bursaries: The Society will consider awarding travel grants of up to £150 to *bona fide* students.

Deadline for submission of abstracts and application for student bursaries: Tuesday, 30th June 2005.

A full programme, the abstract pro-forma, meeting registration form and forms for application for BSCR membership or student bursaries can be downloaded from: http://www.bscr.org/autumn_2005_meeting.html

Any further enquiries to: Professors Michael Marber and Metin Avkiran, Cardiovascular Division, King's College London, The Rayne Institute, St Thomas' Hospital, London SE1 7EH; Tel: 020 7188 1008; Fax: 020 7188 0970; tony.cavalheiro@kcl.ac.uk

Or: Professor Barbara McDermott, BSCR Secretary, Therapeutics & Pharmacology, Queen's University Belfast, Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL; Tel 02890-972242; Fax 02890-438346; b.mcdermott@qub.ac.uk