The Bulletin
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Welcome to the April issue of The Bulletin. This issue features a review article written by Dr Andrea Warner from Leicester University, discussing the role of vascular endothelial growth factor in angiogenesis. The Lab Profile, by Dr Barbara McDermott, highlights the research currently being undertaken in the Cardiovascular Cell Laboratory at The Queen's University of Belfast. The article provides a taste for the exciting research in progress at the University and for the City of Belfast. With this as an appetizing prelude, we look forward to the BSCR Autumn meeting which will be held at Queen's University. For most members, this will be their first 'overseas' meeting of the Society!

Rana Sayeed reports back from the AHA Scientific Conference held in Salt Lake City, for our Travel Report. The book review of 'Delayed Preconditioning and Adaptive Cytoprotection' has been written by Ravi Mohan. As is customary, we end with the traditional listings of the awarded BHF and Wellcome grants.

We continue to look forward to receiving your contributions to The Bulletin. If you would like to write a review, lab profile or career profile, please don't hesitate to contact us at the above address. We are especially interested in hearing from anyone wishing to contribute, or suggest, a new feature for inclusion in The Bulletin.

James Mockridge and Nicola Smart
Vascular Endothelial Growth Factor - an angiogenic stimulator

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Introduction

VEGF (vascular endothelial growth factor) was originally identified as a protein able to permeabilise microvessels to plasma and plasma proteins and named vascular permeability factor (VPF; Senger et al., 1983). VEGF was independently isolated because of its mitogenic effect on vascular endothelial cells (Connolly et al., 1989; Ferrara and Henzel, 1989; Gospodarowicz et al., 1989; Leung et al., 1989). Subsequent experiments demonstrated that VPF and VEGF were, in fact, the same molecule, referred to here as VEGF. VEGF has a critical role in vessel development; mice with only one functional copy of the VEGF-A gene demonstrated embryonic lethality, due to abnormal blood vessel development (Carmeliet et al., 1996; Ferrara et al., 1996). Vascular development is a requirement of embryogenesis and is also fundamental to wound healing and the female reproductive cycle (Folkman, 1995). Inappropriate blood vessel growth is involved in the pathology of, for example, proliferative retinopathy, tumour growth, rheumatoid arthritis and psoriasis (Folkman, 1995; Gamer, 1994). This article seeks to give an introduction to VEGF and to the molecular mechanisms by which VEGF causes angiogenesis and touch on the effects of angiogenesis in relation to cardiovascular disease. Given the vast wealth of VEGF literature, it will only be possible to discuss a subset here.

VEGF

VEGF, commonly referred to as VEGF, is a homodimeric glycoprotein of 45 kDa (Ferrara and Henzel, 1989). The VEGF family possesses a common central core region that contains eight invariant cysteine residues involved in inter- and intramolecular disulphide bonding. VEGF binds to its receptors with regions within this core domain (Keyt et al., 1996a and b).

The first identified VEGF protein is encoded for by the VEGF-A gene. Eight exons are alternatively spliced to give the mature VEGF forms VEGF_{121}, VEGF_{145}, VEGF_{165}, VEGF_{189} and VEGF_{206}; the subscript refers to their length in amino acids (Houck et al., 1991; Tischer et al., 1991). Most cells express different VEGF isoforms simultaneously. VEGF_{121} and VEGF_{165} are the predominant forms, with VEGF_{189} commonly detected whilst VEGF_{145} expression appears to be restricted to cells from the female reproductive system (Poltorak et al., 1997). VEGF_{165} and VEGF_{145} bind weakly to heparin whereas VEGF_{189} and VEGF_{206} display a higher affinity for heparin and are sequestered onto the surface of producing cells and in the extracellular matrix (Park et al., 1993). They can be released from the matrix by proteases, such as plasmin, cleaving at the C terminus to generate the active VEGF_{121} (Houck et al., 1992). VEGF_{110} and VEGF_{121} have a reduced mitogenicity for endothelial cells compared to the longer isoforms. It is hypothesized that a gradient will be established in vivo with the longer, more mitogenic, signals localised closer to the site of production than the shorter, more diffusible and less mitogenic VEGF isoforms.

VEGF gene expression

Hypoxia, acting through the transcription factor hypoxia-inducible factor-1 (Liu et al., 1995), induces the expression of VEGF mRNA. Growth factors and cytokines also up-regulate VEGF expression (Fink-Enzeller et al., 1993; Garrido et al., 1993; Pertovaara et al., 1994; Frank et al., 1995). Thus, VEGF may act as the paracrine mediator for other factors with angiogenic properties, such as transforming growth factor (TGF)-β. Increased ras activity leads to induction of VEGF mRNA, by potentiating the hypoxia effect (Mazure et al., 1996). The von Hippel-Lindau (VHL) tumour-suppressor gene appears to negatively regulate
VEGF expression (Gnarra et al., 1996).

VEGF Family

In addition to VEGF, five other dimeric growth factors have been identified which have a VEGF homology domain containing eight cysteine disulphide bridges. The second to be identified was placenta growth factor (PIGF), so-called because it is highly expressed in the placenta; PIGF is 53% identical to VEGF (Maglione et al., 1991). PIGF and VEGF naturally form heterodimers which appear to have similar migratory properties to VEGF homodimers but are 20-50 fold less mitogenic (Cao et al., 1996).

VEGF-B (Grimmond et al., 1996) is approximately 43% identical to VEGF and can form heterodimers with VEGF. It is not known whether this occurs naturally although VEGF-B co-localizes with VEGF in many tissues, most notably in the heart (Olofsson et al., 1996a,b).

VEGF-C and VEGF-D possess N and C-terminal extensions to the VEGF homology domain which are proteolytically cleaved following dimer formation (Joukov et al., 1996; Orlandini et al., 1996). The pattern of VEGF-C expression in the developing embryo suggests that VEGF-C functions in the formation of the venous and lymphatic vascular systems (Kukk et al., 1996). Over-expression of VEGF-C leads to hyperplasia of the superficial lymphatic network but has no effect on the vascular endothelium (Jeltsch et al., 1997). Therefore, VEGF-C is thought to induce a lymphangiogenic response (Oh et al., 1997). Constitutive expression of VEGF-C in adult tissues is consistent with a maintenance role of VEGF-C in differentiated lymphatic endothelium (Kaipainen et al., 1993, 1995; Kukk et al., 1996). It is possible that VEGF-D is functionally similar to VEGF-C, regulating growth and/or differentiation of lymphatic endothelium. VEGF-E is encoded for by the Orf virus; it binds and functions through VEGFR2 but not VEGFR1 (Ogawa et al., 1998). Its physiological role is not yet clear.

VEGF receptors

The VEGF receptor family consists of three receptor tyrosine kinases (see figure), VEGFR1 (Flt-1), VEGFR2 (KDR/Flk-1) and VEGFR3 (Flt-4; Shibuya et al., 1990; Ullrich and Schlessinger, 1990). VEGFR1 and VEGFR2 are 33% identical in their extracellular domains and 80% in their kinase domains. The extracellular domains of these two receptors contain seven immunoglobulin-like folds. The intracellular kinase domain is interrupted by an insert region characteristic of this family. VEGF binds VEGFR1 with the highest affinity (10-20pM; De Vries et al., 1992) whereas VEGF binds VEGFR2 with an approximately ten-fold lower affinity (75-125pM; Terman et al., 1992).

VEGFR1 has been identified in an alternatively spliced form in human umbilical vein endothelial cells (HUVECs; Kendall et al., 1996). This splice variant lacks the final immunoglobulin-fold, the transmembrane domain and the cytoplasmic portion of VEGFR1 and is therefore soluble (sVEGFR1). It can still bind VEGF with high affinity and may, therefore, be a naturally occurring negative regulator of VEGF signalling (Kendall et al., 1996). The extracellular domains of VEGFR1, sVEGFR1 and VEGFR2 all contain a heparin-binding site (Dougher et al., 1997; Cohen et al., 1995) so the soluble VEGFR1 may be retained by the extracellular matrix.

Like other receptor tyrosine kinases, VEGFR1 and 2 are thought to dimerise and transphosphorylate to produce active kinases. A number of tyrosine residues have been shown to be phosphorylated upon VEGF binding to VEGFR1 and 2 (Ito et al., 1998; Dougher-Vermazen et al., 1994). These phosphorylated tyrosines act as docking sites for signalling proteins. Despite the higher affinity of VEGF for VEGFR1 compared with VEGFR2, VEGFR1 does not appear to mediate mitogenicity or chemotaxis in endothelial cells. This lack of effect correlates with the very low or undetectable levels of VEGFR1 autophosphorylation observed in porcine aortic endothelial cells (PAECs) expressing VEGFR1 (Waltenberger et al., 1994; Landgren et al., 1998). However, VEGF causes migration of monocytes and smooth muscle cells, and, at least in the monocytes this occurs through activation of VEGFR1 (Barleon et al., 1996; Grosskreutz et al., 1999). Thus, VEGFR1 may not transduce a functional response in endothelial cells but in other VEGF-sensitive cells. A number of adaptors and enzymes have been reported to interact with both VEGFRs in either the yeast two-hybrid assay or in vitro assays (Waltenberger et al., 1994; Ito et al., 1998). The functional relevance of these observations remains confusing as much of the published data is conflicting. VEGFR3 is approximately 35% identical to VEGFR1 and 2 in the extracellular domain and about 80% in the tyrosine kinase domain (Pajusola et al., 1992). The immature VEGFR3 is proteolytically cleaved to produce a disulphide linked two-chain form (Pajusola et al., 1994; see figure). Both VEGF-C and -D bind to
Figure. Summary of interactions between VEGF family members and receptors. VEGF\textsubscript{165} and PlGF-2 bind to neuropilin-1. Only VEGF\textsubscript{165} has been demonstrated to bind to neuropilin-2.

VEGF3 and cause it to autophosphorylate (Joukov et al., 1996; Achen et al., 1998).

Neuropilin-1, originally identified as a receptor for the collapsin/semaphorin family of neural adhesion molecules, is a low-affinity co-receptor for VEGF and PlGF-2 (Soker et al., 1996). Neuropilin-1 acts to enhance VEGF binding to VEGFR2 and leads to a more efficacious migratory response (Soker et al., 1998). The neuropilins have short intracellular domains and are unlikely to transmit a functional response through their cytoplasmic domains. However, neuropilin-1 deficient mice die because their cardiovascular system fails to develop properly, demonstrating the importance of neuropilin-1 in VEGFR signalling (Kitsukawa et al., 1997).

**VEGF receptor expression**

Embryonic mRNA for VEGFR1 and VEGFR2 is generally expressed in an endothelial-cell specific manner (Peters et al., 1993; Kaipainen et al., 1993) with VEGFR2 being the first expressed during embryonic development (Shalaby et al., 1995; Fong et al., 1995). The differential regulation of the two VEGFRs suggest they have distinct functions (Millauer et al., 1993). Null mice for each receptor die in utero. The vessel walls of VEGFR1 null mice are disorganized and endothelial-derived cells are found within blood vessels (Fong et al., 1995). This suggests VEGFR1 functions to control endothelial cell organisation possibly through contact inhibition of endothelial cell growth or modulation of expression of adhesion molecules. VEGFR2 null mice do not possess differentiated endothelial cells implying VEGFR2 involvement in endothelial cell development and cell proliferation (Shalaby et al., 1995).

VEGFR3 mRNA is expressed in vascular and lymphatic endothelium in mouse embryos but is gradually lost from developing arteries (Kaipainen et al., 1995). Mice lacking a functional VEGFR3 gene die in utero. The phenotype of these embryos suggests that VEGFR3 promotes the formation of major blood vessels during early development as VEGFR3 is still expressed in most endothelial cells at this stage. The continued expression of VEGFR3 in lymphatic endothelial cells is consistent with the hypothesis that it plays a role in the development of the lymphatic system (Kukk et al., 1996).

**VEGF function**

The de novo formation of blood vessels from haemangioblasts is termed vasculogenesis. VEGF is thought to be involved in the differentiation of angioblasts into endothelial cells (Flamme and Risau, 1992). In addition, VEGF participates in the formation of the primary vascular network and its development into a more complex vascular plexus (Carmeliet et al.,
VEGF also stimulates angiogenesis, the sprouting of new blood vessels from existing ones, in both in vitro and in vivo models (Pepper et al., 1992; Tolentino et al., 1996). Angiogenesis is a complex process including digestion of the surrounding basement membrane and the extracellular matrix, loosening of inter-endothelial cell contacts and those with the pericytes and smooth muscle cells. This is followed by the formation of a new provisional matrix, cell division, cell extension and migration towards the angiogenic stimulus. To become mature, vessels may fuse with other vessels then go on to attract pericytes and smooth muscle cells to form the supporting muscle wall. Changes in lumen diameter, vessel wall thickness, hyperpermeability and elasticity may result (Carmeliet and Collen, 1997).

VEGF is a very strong permeabilising factor (Dvorak et al., 1992; Senger et al., 1993). Vascular permeability is the first response detected following VEGF application, occurring within seconds. This is thought to be mediated by Nitric oxide (NO) as VEGF stimulates NO production in cultured endothelial cells and vascular endothelium (Murohara et al., 1998). NO synthase (NOS) production is increased during VEGF-induced endothelial cell mitogenesis and angiogenesis, suggesting VEGF increases vascular permeability via NO production (Ziche et al., 1997). VEGF stimulates NO production via a phospholipase C (PLC) γ-stimulated increase in intracellular calcium ion concentration leading to NOS activation (He et al., 1999). Both VEGFR1 and 2 have been shown to bind to PLCγ in the yeast two hybrid assay and phosphorylate this enzyme in endothelial cells (Seetharam et al., 1995; Takahashi and Shibuya 1997; Landgren et al., 1998; Guo et al., 1995). VEGF is also thought to cause either opening in endothelial cells or widening of inter-endothelial junctions via phosphorylation of tight junction proteins to allow larger molecules to pass into the extravascular space (Dvorak et al., 1996; Antonetti et al., 1999).

Degradation of the basement membrane is necessary for endothelial cells to migrate into the surrounding tissues. VEGF increases protein levels of the transcription factor ETS-1 which induces the expression of urokinase-type plasminogen activator (uPA; Iwasaka et al., 1996). VEGF also increases expression of interstitial collagenase in HUVECs (Unemori et al., 1992). To further aid migration through collagen-rich extracellular matrices VEGF stimulates endothelial cells to express the collagen receptors α,β1 and α,β integrins (Senger et al., 1997) and the fibronectin, fibrinogen and osteopontin receptors α,β1 and α,β integrins (Friedlander et al., 1995; Warner et al., 1995). VEGF binding to endothelial cells results in their up-regulation of VCAM-1 and ICAM-1 expression. These adhesion molecules attract leukocytes, which release more angiogenic growth factors (Weihrauch et al., 1995). The ability of VEGF (and PI GF) to attract macrophages may also function to increase the concentration and range of angiogenic factors in the local environment (Barleon et al., 1996; Clauss et al., 1996).

Endothelial cells are able to migrate directionally towards VEGF (Waltenberger et al., 1994). VEGF leads to increased phosphorylation of Paxillin and focal

1996; Ferrara et al., 1996).
adhesion kinase, and their recruitment to new focal adhesions, which may facilitate VEGF-stimulated migration (Abedi and Zachary, 1997). In addition, VEGF stimulates the phosphorylation of the endothelial adherens junction components, consistent with a loosely confluent and migratory endothelial cell state (Esser et al., 1998), a pre-requisite for migration and perhaps hyperpermeability too. The receptors and intermediary signalling molecules necessary for these responses are not clear. Migratory responses can be transduced through PI3K and PLCγ. Furthermore, NO is implicated in VEGF-induced migration since a NOS inhibitor prevented VEGF-stimulated HUVEC migration (Goligorsky et al., 1999). Both VEGFR1 and 2 also interact with the adaptor protein Nck (Guo et al., 1995; Kroll and Waltenberger 1997; Ito et al., 1998). The downstream binding partners of Nck suggest it functions to couple receptor tyrosine kinases to Rho family members, thereby mediating cytoskeletal changes (Buday, 1999).

Many tyrosine kinases stimulate a proliferative response by activating mitogen-activated kinases (MAP kinases). VEGFR1 and 2 have been demonstrated to activate the MAP kinases ERK1 and ERK2 (Kroll and Waltenberger, 1997; Landgren et al., 1998; Seetharam et al., 1995; Takahashi and Shibuya, 1997). The pathways involved have not been fully elucidated. However, the phosphorylation of She, the formation of a She/Grb2 complex, the binding of the Nck adaptor protein, rasGAP and also the association of the protein tyrosine phosphatases SHP-1 and SHP-2 to VEGFR2 were all observed following VEGFR2 stimulation and may result in ERK activation (Waltenberger et al., 1994; Kroll and Waltenberger, 1997). Both PI3K and JNK have been shown to contribute to the effect of VEGF on ERKs (Thakker et al., 1999; Pedram et al., 1998). In addition, VEGF has been reported to activate p38 (Rousseau et al., 1997).

Remodelling of the vascular network occurs in growth and development necessitating regression of blood vessels, possibly through apoptosis of endothelial cells. Reduced levels of VEGF are associated with endothelial cell apoptosis. For example, using an inducible VEGF expression system, it has been documented that decreased VEGF expression led to apoptosis and detachment of endothelial cells from the walls of preformed vessels in tumours (Benjamin and Keshet, 1997). VEGF stimulates cell survival through the PI3K/Akt pathway (Gerber et al., 1998). A reduction in VEGF-induced endothelial cell survival during development was noted in mice deficient in a functional VE-cadherin adhesion molecule (Carmeliet et al., 1999). The authors proposed a model whereby a complex is formed of VE-cadherin, β-catenin, PI3K and VEGFR2. VE-cadherin and β-catenin appear necessary for VEGF to activate Akt and increase Bcl2 levels, both anti-apoptotic messengers.

VEGF appears to be involved in many facets of angiogenesis, although the mechanisms remain to be defined. A clear and cohesive view of the pathways stimulated by VEGF and their temporal relationships are required. Knowledge of the intermediary signalling molecules involved is of primary importance to our understanding of the angiogenic response.

**Therapeutic potential**

The pivotal role of VEGF in angiogenesis and the dependence of a number of pathological states on angiogenesis make inhibiting VEGFR function an attractive therapeutic target. Human sVEGFR1 has been shown to suppress abnormal angiogenesis in vivo in an experimental solid-tumour system and in hypoxia-induced retinopathy in mice (Aiello et al., 1995; Kendall and Thomas, 1993). A similar truncated dominant negative VEGFR2 led to inhibition of tumour growth in rats (Millauer et al., 1996). VEGF linked to diphtheria toxin, immunoneutralisation and anti-sense gene transfer have been used to inhibit neovascularisation during cancer and diabetic retinopathy (Ferrara and Davis-Smyth 1997; Kim et al., 1993; Klagsbrun and D’Amore, 1996; Yuan et al., 1996).

**Role of VEGF in cardiovascular disease**

VEGF is up-regulated in atherosclerotic plaques compared to normal coronary arteries (Inoue et al., 1998). VEGF-stimulated neovascularisation is an essential response to arterial injury. Remodelling of the vascular network to alleviate the symptoms of coronary ischaemia by collateral growth to bypass a blocked vessel is crucial. Intra-arterial administration of recombinant human VEGF markedly increased collateral development and blood flow in a rabbit model with chronic hindlimb ischaemia (Takeshita et al., 1994). Fortuitously, neovascularisation predominantly occurs in the ischaemic tissue, possibly due to the hypoxia-induced up-regulation of the VEGFRs (Li et al., 1996; Tuder et al., 1995). In a limited number of phase I clinical trials direct myocardial injection of naked plasmid DNA encoding for VEGF led to a reduction in anginal symptoms and a reduction in...
ischaemia (Losordo et al., 1998).

VEGF gene therapy has also been successful in the re-endothelialisation of a freshly injured arterial surface (Ashara et al., 1996). Ross (1993) proposed that dysfunctional endothelium and subsequent exposure of the intima to circulating monocytes and lymphocytes is a primary event in atherogenesis. VEGF therapy reduced intimal thickening and mural thrombus formation in balloon injury endothelial denudation by promoting re-endothelialisation (Ashara et al., 1995, 1996). In human patients this led to reduced restenosis compared to historical controls (Vale et al., 1998).

More recently neovascularisation in atherosclerotic plaques has taken on a more ominous tone. Vascularisation of plaques facilitates greater fat deposition and monocyte attraction leading to increased plaque size. VEGF can cause intimal hyperplasia and intima haemorrhage leading to plaque rupture (Yonemitsu et al., 1996; Lazarous et al., 1996). Indeed, angiogenesis inhibitors have been shown to reduce plaque area, suggesting neovascularisation is a necessary condition for plaque growth, much like the role of angiogenesis in solid tumour growth (Moulton et al., 1999). However, trials using VEGF to promote re-endothelialisation have shown no evidence of accelerated atherosclerosis (Isner et al., 1999). Nonetheless, questions about the overall therapeutic benefit of VEGF administration to the cardiovascular system have now arisen and are currently being addressed.

The future

VEGF, and in particular VEGF, is the best studied growth factor of the VEGF family, but data is emerging on the functions of other VEGF-A gene splice variants and PIGF, VEGF-B, -C, -D, -E and VEGFR3. Although much interest has focussed on this area a number of key questions remain unanswered. These include: the role of each member of the VEGF family; the functional subtleties of the VEGF splice variants; the functional similarities and differences between the receptors; whether growth factors or receptors heterodimerise; the role of particular intracellular signalling pathways which mediate the VEGF response, and their role in angiogenesis.

As more detailed studies are being performed it is now apparent that varying the VEGF levels is not the ultimate key to modulating the angiogenic process. Many other growth factors modify the VEGF response, these include FGF2, TGF-B1, PDGF and angiopoietins. The current working hypothesis suggests that it is the balance of positive and negative factors that regulates angiogenesis and more players in this field, particularly angiogenic inhibitors, are only now being discovered (O'Reilly et al., 1999; Hanahan and Folkman, 1996). Thus the most efficacious form of therapy may be a combination of stimulators of one side of the equation and inhibitors of the other to tip the physiological balance towards the desired outcome, either stimulation or inhibition of angiogenesis.

As more compounds are progressing through clinical trials and more players in the angiogenic game are being identified I foresee even more exciting times ahead for VEGF and family.

References

Dougher, A.M., Wasserstrom, H., Torley, L., Shridaran, L., Westdock,
Cardiovascular Related Meetings

British Cardiac Society. Glasgow, UK, 14-18 May. For further information, see the BCS website: http:\www.cardiac.org.uk. The BCS/ BSCR Joint Symposium - Nitric Oxide and Cardiac Function: From the Laboratory to Clinical Practice - will be held during the meeting. Please see page 16 of this issue of The Bulletin for further details.

International Symposium on The Developing Heart to be held at the Congress Centre of the hotel Diplomat, Prague, Czech Republic, 18-20 May, 2000. Further details can be obtained from the symposium secretariat at: Congress Centre, Czech Medical Association J.E. Purkyne, PO Box 88, Sokolska 31, 120 26 Prague 2, Czech Republic. E-mail: senderova@els.cz Internet: www.biomed.cas.cz/fgu/cardiol/dh2000.htm Fax: 420-2-294 610

"Molecular Signalling in Cardiovascular Biology" First Annual Research Day of the Guy's, King's and St Thomas' Schools of Medicine, Biomedical Sciences & Dentistry to be held at Lecture Theatre 1, New Hunts House, Guy's Hospital Campus on Wednesday, 31st May, 2000. Further details can be obtained from Carole Meads, telephone: 020 7848 3177 or e-mail: carole.meads@kcl.ac.uk


Heart Failure 2000 - European Society of Cardiology Working Group on Heart Failure, will be held in Venice, Italy, 29th June-1st July, 2000. For further information and registration details, please contact the ECOR Registration Department at Tel:+33 (0)4 92 94 76 12/ 92 94 76 14; Fax: +33 (0)4 92 94 76 10 or visit the society's web site at: www.esc.be

XXII Congress of the European Society of Cardiology to be held at the RAI Congress Centre, Amsterdam, Netherlands, 26-30 August 2000. Further details can be obtained from ECOR -The European Heart House, 2035 Route des Colles, Les Tempiers, BP179, 06903 Sophia Antipolis, France. E-mail: webmsater@escardio.org; Tel: +33 4 92 94 76 00; Fax: +33-4 92 94 76 01.

Travel Reports for The Bulletin

The Bulletin regularly publishes travel reports written by members. These are up to 3 pages in length including photographs, and can be on any conference, course or laboratory visit of interest to other members. If you are planning on travelling to a cardiovascular-related meeting and would like to write a report for the Bulletin, please contact the editors. A bursary of £100 is available towards the cost of your visit, and this will be provided on receipt of the report. Bon voyage!
Laboratory Profile:
Cardiovascular Cell Laboratory,
Centre for Cardiovascular
Research, The Queen’s University
of Belfast (QUB)

The Cardiovascular Cell Laboratory is a small part of what is the largest of the research partnerships in the School of Medicine at QUB, namely, the Centre for Cardiovascular Research, which brings together over 100 individuals in total. These include staff engaged in different disciplines, from epidemiology to molecular genetics, all actively involved in investigating cardiovascular risk and disease. The Centre is a relatively new research structure and certainly provides quite a different environment from that which existed when the Cardiovascular Cell Laboratory was set up in the Department of Therapeutics and Pharmacology in 1988, just about pre-dating the multidisciplinary era. Since the research interest in the Department was concentrated then largely on the clinical pharmacology of cardiovascular drugs, it was decided to underpin this with a complementary basic science programme. At the time, there was an emerging awareness of the important role of newly discovered (neuro)peptides acting either as co-transmitters (neuropeptide Y, 1982; calcitonin gene-related peptide, 1984) or as paracrine agents (endothelins, 1988) in regulation of the heart and also the vascular system. It seemed probable that drugs acting at peptide receptors would have increasing significance in treatment of diseases of the cardiovascular system. For these reasons, a programme of work was initiated to study peptide receptor mechanisms in the heart.

In order to investigate direct effects on myocardium and for ease of investigation of signal transduction mechanisms, the preparation of isolated adult rat cardiomyocytes was chosen as a model system. In the early development of this methodology, we were indebted to Michael Piper of der-Justus-Liebig Universität in Giessen, who was then in Dusseldorf, where he accommodated one of our postgraduate students on a number of occasions to carry out video microscopy of contractile function and assays of cyclic nucleotides. Stuart Jacobson at Carleton University in Ottawa was also a wonderful host in his laboratory and at home. He introduced us to the vagaries of isolating and working with human cardiomyocytes, particularly patch clamping and calcium ion imaging. This could all, of course, have been organised through collaborations in the U.K., but it always seemed easier to obtain funding for foreign laboratory exchange programmes and sabbatical arrangements. It was more stimulating too, being particularly appealing to students, who were happy to leave the province for their first extended period abroad.

Subsequently, cell models of disease states in vitro and ex vivo were developed. Firstly, David Bell after completing a Ph.D. in 1993 in the Cardiovascular Cell Laboratory got his initial taste for the international research scene during a 2-year postdoctoral position to investigate peptide growth factors in hypertrophy, when he spent time in laboratories in Germany, Japan and the United States. Along with the Dusseldorf group, he examined peptide-stimulated ventricular cell hypertrophy in short-term (rapid attachment model) and long-term (redifferentiated model) cultures. With Hiroshi Ito in Tokyo, he investigated the altered pattern of gene expression that occurs when synthesis of proteins, which are abundant in the foetal state of development, is induced in cardiomyocytes in culture. In the laboratory of Ralph Kelly at Harvard University, he investigated altered gene expression at the protein level, particularly of β-myosin heavy chain. From these and subsequent studies in Belfast, carried out when he was appointed to a newly-established academic position in the Laboratory, we were able to establish the hypertrophic effects of a number of peptide growth factors (endothelin-1, angiotensin II, neuropeptide Y, calcitonin gene-related peptide and the structurally related peptide, amylin, and insulin-like growth factor-1) and their receptor and signal transduction mechanisms. For example, the effects of endothelin-1 are due to de novo synthesis of protein and are mediated by both the ET\(_1\) and ET\(_2\) receptor subtypes through, at least partly, the activation of protein kinase C. Also, the angiotensin II-mediated increase in de novo protein synthesis involves both the AT\(_1\) and AT\(_2\) receptor subtypes and...
increased activity of protein kinase C; activation of S6 kinase in response to \(AT_3\) receptor stimulation is associated with a foetal shift in gene expression, shown by enhanced expression of the BB isoform of creatine kinase. In contrast, neuropeptide Y’s action to increase protein content in cardiomyocytes results not only from de novo synthesis but also from an attenuation of protein degradation; these processes are linked to different receptor subpopulations, most likely the \(Y_2\) and \(Y_3\) receptor subtypes, respectively; neuropeptide Y does not appear to affect the re-expression of a number of foetal isoform genes, but alters expression of the constitutively expressed gene, myosin light chain-2. It has been, and still is, a major aim to identify differences between the various receptor populations for each peptide with regard to their involvement in altered protein turnover and in the induction of the foetal programme of gene expression, also addressing the associated down-stream mechanisms.

Another major area of research in the Cardiovascular Cell Laboratory has been centred on an ex vivo cell model of ‘heart failure’, in which cardiac myocytes are isolated from the hearts of epirubicin-treated rabbits, functional effects determined by image analysis of electrically-stimulated contraction, and voltage and patch clamping performed to examine electrophysiological parameters. This programme has been driven by Elizabeth Kelso, a postdoctoral fellow in the Laboratory, who also did her Ph.D. there, in 1982. In characterising this model, both structural and mechanical alterations observed in ventricular cardiomyocytes are compatible with a mild cardiomyopathy. Heart-failed cells are more heterogeneous with respect to cell dimensions. Also, action potential duration is prolonged and an increased basal amplitude of contraction indicates more efficient coupling of electrical stimulation. Depressed inotropic responsiveness to isoprenaline and endothelin reflects either desensitisation of the \(\beta\)-adrenoceptor and endothelin receptor populations or post-receptor alterations in calcium homeostasis. Re-expression of foetal isoform genes (skeletal-a actin, myosin heavy chain and atrial natriuretic factor) is apparent, although there is no evidence of altered expression of endothelin-1 or its receptor subtypes, \(ET_A\) and \(ET_B\), in mild cardiomyopathy. Also using the epirubicin-treated rabbit model, we have identified alterations in end-stage heart failure, which is confirmed using echocardiographic techniques. Expression of the atrial endothelin-1 gene is up-regulated in dilated cardiomyopathy. Increased
expression of transforming growth factor-β, collagen, matrix metalloproteinase-9 and tissue inhibitor of matrix metalloproteinase-1 mRNAs reflects significant remodelling of the ventricular myocardium, observed in both non-dilated and dilated cardiomyopathy.

These two programmes of work have laid the basis of our current main schedule of research, in which the themes of ventricular hypertrophy and heart failure are consolidated using an appropriate single experimental model, namely the ageing spontaneously hypertensive rat (SHR). The SHR, a model of chronic pressure overload displaying many similarities to human essential hypertension, is being used to investigate alterations that occur at cellular level in cardiomyocytes during the evolution from hypertension to hypertrophy to heart failure. This programme supports a number of Ph.D. projects, in which altered receptors and function have been identified. For example, blunting of contractile responses to stimulation of neuropeptide Y Y receptors in myocytes occurs in 16 week-old SHRs, when ventricular hypertrophy is established; this may indicate a compensatory mechanism to offset the greater negative inotropic effects of expected increases in neuronal release of the peptide. Also, since the affinity of ET β receptors for ET-3 is enhanced and there is an increased responsiveness in sarafotoxin 6c-stimulated de novo protein synthesis, it is possible that the ET β receptor subtype is involved in the pathogenesis of hypertrophy in response to pressure overload. With a view to development of this project on endothelin receptor mechanisms in hypertrophy, we have recently welcomed a new postdoctoral research assistant to the Laboratory, Cymone Argent, who comes from the London Area. So now we are not completely self-sustaining and in fact, have just exported two recently completed postgraduates to a laboratory in Rochester, NY. The remaining complement in the Laboratory includes two Ph.D. students, Adrian Allen and Graham Lee, and our technical support staff, Kevin Given and Aine Mallon. Soon we are to embark on the next phase of the programme, in which proof is sought in intervention studies that peptide substances, particularly in relation to the angiotensin II – endothelin-1 interaction, are causal agents in the development and progression of ventricular hypertrophy and the transition to heart failure.

In addition to addressing the research agenda, as part of the QUB Medical School, we have also a major commitment to the undergraduate teaching programme, which is implicit in our Vice-Chancellor’s mantra of ‘balanced excellence’. A change for the good with the recent implementation of an integrated curriculum and emphasis on small group teaching has been the greater opportunities for research-led teaching. Our research laboratories have become, therefore, a useful resource for teaching and learning. In a special study module in ‘Hypertension’, second year students have the opportunity to evaluate the appropriateness of the various experimental animal models of hypertension, gain practical experience in the
measurement of blood pressure in the SHR model and are asked to review experimental data obtained by members of the research group. In the third year ‘Drug Development’ module, the story of losartan, the AT₁ receptor-selective antagonist, is used to illustrate the various processes in the development of a drug ‘from molecule to man’. The fundamental principles and methods underlying the characterisation of receptor (sub)populations in cells and tissues, and determination of antagonist potency are taught through ‘hands on’ exercises or demonstrations by research personnel using research materials and equipment. Projects are also carried out in the Laboratory as part of intercalated degree programmes, such as that of our current student, Ruth Little, who is investigating the protection by the anaesthetic agent, propofol, of oxidant-mediated injury in cardiomyocytes. A number of recent honours and master degree projects have been centred on the question of direct versus indirect protective effects in ischaemia-reperfusion injury, the latter being investigated using a co-culture model bringing together cardiomyocytes and microvascular endothelial cells.

To conclude, in the Cardiovascular Cell Laboratory, indeed as is typical in Northern Ireland, there is abundant space, excellent facilities and not many people. It is hoped that the relative political stability in the province will result in greater traffic in this direction, both to the Laboratory and the neighbouring attractions. If you imagine that this report is a promotional exercise for the forthcoming meeting of the Society to be held in Belfast on 4/5th September on the theme of ‘Mediators and mechanisms in myocardial disease’, then you would be mostly correct.

Dr. Barbara McDermott is a Senior Lecturer in Pharmacology, Head of the Cardiovascular Cell Laboratory and Director of the Centre for Cardiovascular Research at The Queen’s University of Belfast

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**BSCR/British Cardiac Society Joint Symposium**

**Nitric Oxide and Cardiac Function:**

**From the Laboratory to Clinical Practice**

Wednesday, 17th May, 2000, 11:00-12:30
The Loch Suite, SECC, Glasgow

**Speakers:**

**Dr Thomas Hintze** (New York Medical College)

**Professor Jean-Luc Balligand** (Brussels)

**Professor Ajay Shah** (London)

**Professor Patrick Vallance** (London)
Meeting Report:
AHA Scientific Conference on Molecular, Cellular and Integrated Physiological Approaches to the Failing Heart
18-22 August, Salt Lake City, Utah
by Rana Sayeed, MRC Clinical Training Fellow, Section of Cardiovascular Biology, Department of Biochemistry, University of Cambridge

This was the third conference on heart failure sponsored by the Council on Basic Cardiovascular Sciences of the American Heart Association, prompted by the advent of transgenic and gene-targeting techniques and recent progress in murine cardiac physiology and imaging. The setting was the Snowbird Conference Centre, nestling at almost 8 000' in the spectacular Wasatch Mountains, 29 miles east of Salt Lake City, and the combination of an interesting programme and this impressive venue attracted almost 400 delegates from North America, Europe, Australia and the Far East. The conference included lectures, workshops, and poster presentations, and also hosted the Final of the 1999 Council on Circulation Cardiovascular Research Prize competition. The objectives of the conference were to provide an update on the molecular genetics and signal transduction pathways of cardiomyopathy and cardiac development and to review the advances in transgenic and gene-targetted models of cardiac disease. These aims achieved over the course of 4 days during an interesting and stimulating meeting.

Over 60 invited lecturers presented papers at the conference; lectures were grouped into 23 sessions on topics including G protein and adrenergic signalling, protein kinases and signal transduction, arrhythmias and sudden cardiac death, and the transcriptional regulation of cardiogenesis and cardiac hypertrophy. The speakers, predominantly based in the United States and acknowledged leaders in their particular fields, presented a mixture of published and unpresented results to illustrate their lectures. Transgenic and gene-targetted mice featured prominently in many of these talks. These techniques have enabled progress towards the molecular dissection of the signal transduction and transcriptional regulatory pathways involved in cardiac development, cardiac hypertrophy, and heart failure. Most lectures were well-attended and followed by interesting discussions. A number of lectures were of particular interest and these are referenced, where work has been published, below.

Walter Koch (Duke University) described his group's work studying β-adrenergic receptor (BAR) signalling in the myocardium. Dysfunctional BAR signalling in heart failure arises from receptor down-regulation and desensitisation of the remaining receptors, possibly through the action of a β-adrenergic receptor kinase (βARK1). βARK1 knock-out mice exhibit hyper-contractile function, similar to the effects of β2-AR over-expression. Over-expression of repressors of βARK1 leads to the functional 'rescue' of several murine models of cardiomyopathy; the challenge is the development of a βARK1 inhibitor as a novel therapeutic agent to enhance contractile performance in the failing heart.

Mark Keating (Howard Hughes Medical Institute, University of Utah) gave an elegant description of the molecular and cellular mechanism of cardiac arrhythmias, with particular reference to the long QT syndromes. These are a group of inherited diseases characterised by syncope, sudden cardiac death, and prolongation of the QT interval of the surface ECG. A number of ion channel mutations have been identified in long QT pedigrees; there may be defects in SCN5A, which carries the fast sodium current, HERG or MIRP1, which together form the rapid delayed rectifier potassium channel, or KvLQT1 or minK, together forming the slow delayed rectifier. Altered ion channel function leads to prolongation of the cardiac action potential and the risk of arrhythmias.

In a related session, Raimond Winslow (Johns Hopkins University School of Medicine) described the results of computer modelling of arrhythmias in heart failure. Alterations in repolarising potassium currents and in the activity of calcium-regulatory proteins are found in several animal models of heart failure. Incorporation of these changes into a computational model of a canine ventricular myocyte closely reproduces the action potential morphology of in vivo canine cardiomyopathy. Whole heart computational
models now allow the simulation of polymorphic VT to elucidate further the mechanisms of arrhythmogenesis in human heart failure.

The role of calcineurin in the hypertrophic signalling pathway generated most discussion and controversy at the conference. Beverley Lorell (Beth Israel Deaconess Medical Centre) presented data showing that the calcineurin inhibitor, cyclosporin A, failed to prevent pressure-overload cardiac hypertrophy in aortic-banded mice. Moreover, cardiac calcineurin activity was reduced at 4 weeks after aortic banding despite the development of hypertrophy. In contrast, Jeffrey Molkentin (Children's Hospital of Cincinnati) presented the results of an elegant series of experiments showing that calcineurin was not only sufficient but necessary for the induction of hypertrophy of neonatal rat ventricular myocytes in culture. Furthermore, cardiac calcineurin activity was elevated in a rat model of pressure-overload hypertrophy, in which cyclosporin did have an inhibitory effect on the development of hypertrophy, and increased calcineurin activity is found in both hypertrophied and failing human cardiac tissue. The disparity between these results appear to relate to differences in model species, developmental stage, nature and degree of haemodynamic stress and relative dose of cyclosporin. However, it is likely that the calcineurin story will continue to enliven heart failure meetings over the next few years.

Aside from the excellent lecture series, there were two evening workshops on murine physiology and imaging and cardiac cell culture. The imaging workshop was the more memorable; there were extraordinarily detailed echo cardiographic images of transgenic mice in utero studies to assess fetal cardiac phenotype and a false-coloured 3D reconstruction generated by MRI allowing a ‘fly-through’ of the developing murine vascular tree. Lastly, there were over 200 posters presented over 3 afternoons on the whole spectrum of heart failure research: from basic molecular biology to clinical cardiology and cardiac surgery.

Overall, this was an enjoyable, if exhausting, meeting that fulfilled its objectives giving delegates an up-to-date overview of current progress in heart failure research. The next conference on this theme will be held in two years time and I recommend that researchers with an interest in any aspect of this broad field should attend.

**SELECTED REFERENCES**

**β-adrenergic receptor function in heart failure**


**Cardiac ion channels and the long QT syndromes**


Sanguinetti MC, Curran ME, Zou A, Shen J, Spector PS, Atkinson DL, Keating MT. Coassembly of K(V)1.2/LQT1 and minK (K(S)) proteins to form cardiac I(Ks) potassium channel. *Nature.* 1996;384:80-3.


**Modelling of cardiac arrhythmias in heart failure**


**Calcineurin and cardiac hypertrophy**


BSCR Bulletin Book Review:
Delayed Preconditioning and Adaptive Cardioprotection
By Baxter and Yellon

In 1993, laboratories in London, U.K. and Osaka, Japan independently recognised a delayed form of myocardial adaptation (preconditioning), referred to as the “second window of protection”, occurring 12-24 hours after the initial ischaemic insult. Their findings prompted a surge of literature describing the ability of delayed preconditioning and its adaptations to protect the ischaemic and reperfused heart against a variety of pathologies.

This multi-authored book addresses the recent advances in delayed preconditioning research, from its molecular basis to potential clinical significance. The editors stated purpose is to provide an “authoritative, comprehensive and thoroughly up-to-date overview for scientists and clinicians” engaged in this particular area of ischaemic preconditioning research. As the book is organised as a collection of reviews written by leading researchers who have made direct experimental contributions to their area, the editors are able to successfully meet their stated objectives. Those who stand to gain the most from this book are graduate students, post-doctoral fellows and research scientists who are actively engaged in this area of cardiovascular research.

The first 4 chapters focus on the cardioprotection against lethal ischaemic injury, myocardial stunning, endothelial dysfunction and ventricular arrhythmia conferred by delayed preconditioning. Each of these chapters discusses the potential mechanisms of protection, using work conducted in the authors’ respective laboratories as a focal point. A very good tabular review of delayed preconditioning against myocardial infarction is presented in Chapter 1 by Baxter and Yellon. Similarly, they succinctly describe their theoretical paradigm of delayed preconditioning which includes: (1) Upstream Triggers of Adaptation (eg. Adenosine, Free radicals, Nitric oxide); (2) Kinase Signalling (eg. Protein kinase C, MAP kinase); (3) Distal Mediators and Effectors (eg. Heat shock proteins, Inducible nitric oxide synthase, Manganese superoxide dismutase).

Chapters 5-8 emphasise the cellular and molecular aspects of delayed preconditioning. Chapter 5 describes the molecular signalling pathways associated with preconditioning. This chapter is well written, however, the content may be too detailed for researchers not specifically investigating kinase signalling. Chapters 6-7 are more general in nature and include reviews of (1: tabular) Genes up-regulated in models of cardiac ischaemic-reperfusion and (2) Classification and localisation of heat shock proteins. Chapter 8 is an excellent chapter summarising the role of anti-oxidant defences, specifically, manganese superoxide dismutase, in myocardial adaptation.

In the final 3 chapters, the functional and in some cases clinical significance of Monophosphoryl Lipid A (Ch.9), Adenosine (Ch.10) and Angina (Ch.11) and cardioprotection are discussed. Similar to earlier chapters, Chapters 9 and 10 discuss the mechanisms through which adaptation occurs. Chapter 11 is of particular interest as it focuses on clinical research conducted on humans.

Considering the volume of information published since 1993, this up-to-date review of literature is timely. The editors have provided extensive coverage of a variety of fields with a common focus on delayed preconditioning. While mechanistic factors, such as nitric oxide, heat shock proteins, adenosine and ATP-sensitive potassium channels have been implicated in delayed preconditioning, a complete understanding of their cellular and molecular interactions is still required. In a field that is rapidly advancing, the editors have done a commendable job of assembling well known experts in cardiovascular research to compile this essential review of delayed preconditioning research.

Ravi Mohan is a DPhil student at the University Laboratory of Physiology, Oxford University OX1 3PT
BRITISH HEART FOUNDATION GRANTS

Project Grants Committee, November 1999

DEFERRED APPLICATIONS AWARDED

Prof J MacDermot, Hammersmith Hospital, London. “Antibodies to ART1 from a phage display library” (2 years) £90,866

Professor R K Patient, University of Nottingham. “The role and control of the transcription factor GATA6 in cardiogenesis” (3 years) £230,898

Dr J Colyer, University of Leeds. “Selective degradation of phospholamban” (1 year) £42,749

Dr N A Flores et al., St Mary’s Hospital, London. “The role of the renin-angiotensin system in the changes to myocardial conduction induced by left ventricular hypertrophy and its regression” (2 years) £99,712

NEW APPLICATIONS AWARDED

Dr P R Shepherd, University College London. “Leptin action in macrophages: its role in foam cell formation and links with the increased incidence of atherosclerosis in diabetics” (3 years) £119,383

Dr K M Fox et al., Royal Brompton Hospital, London. “The diagnositics and prognostic significance of inflammation and the possession of certain vascular and inflammatory polymorphisms in coronary in-stent restenosis” (2 years) £131,592

Dr P D Langton, University of Bristol. “The mechanism of endothelial derived hyperpolarising factor (EDHF) in rat mesenteric arteries: Its dependence on potassium-induced relaxation and the role of the endothelium” (3 years) £135,722

Dr R T Smolenski et al., Harefield Hospital, Middlesex. “Investigation into novel genetic marker of progression of heart failure and its relation to the effects of adenosine” (2 years) £125,569

Prof A J Camm, St George’s Hospital Med Sch, London. “Investigation of the pathomechanism of heart rate turbulence and its applicability in stratifying cardiac patients at high risk of ventricular tachyarrhythmias” (1 year) £43,807

Prof J T Powell & Dr M J Dunn, Charing Cross Hospital, London. “Saphenous vein smooth muscle protein expression in response to haemodynamic stress” (2 years) £120,054

Drs L H Clapp & A Tinker, University College London. “An investigation into the molecular identity of smooth muscle ATP-sensitive K+ channels from human pulmonary and mesenteric artery” (3 years) £145,901

Prof R M Wadsworth, University of Strathclyde, Glasgow. “L-arginine supplementation: a technique to boost NO formation by endothelial NOS” (2 years) £79,676

Dr T H Thomas et al., University of Newcastle upon Tyne. “The role of tropomyosin in the cell membrane abnormalities of essential hypertension” (2 years) £67,784

Prof D S Latehman et al., Institute of Child Health, London. “Urocortin: Cardioprotective effect and mechanism of action” (2 years) £98,339

Drs M J Shattuck & G Brooks, St Thomas’ Hospital, London. “Role of T-type calcium channels in vascular smooth muscle cell proliferation and cardiac hypertrophy” (3 years) £104,567

Dr J N Townsend et al., Queen Elizabeth Hospital, Birmingham. “Characterisation of HDL-Response elements within the proximal promoter of E-selectin and Cox-2” (3 years) £144,005

Prof A M Gurney & Dr O N Osipenko, University of Strathclyde. “Role of ADMA and DDAH in the regulation of NOS activity” (2 years) £76,251

Prof S Haworth et al., Institute of Child Health, London. “Role of nuclear factor kappa B in human vascular smooth muscle cells” (3 years) £144,005

Dr J Colyer, University of Leeds. “SR Ca-channel and pump phosphorylation in cardiac muscle” (2 years) £84,118

Dr G W Cockerill & Prof N E Miller, St Bartholomew’s Hospital, London. “Characterisation of HDL-Response elements within the proximal promoter of E-selectin and Cox-2” (3 years) £147,842

Dr G B Newby & Prof A C Newby, Bristol Royal Infirmary. “Molecular studies of cytosolic 5’-nucleotidases in ATP homeostasis and adenosine formation of the heart” (3 years) £81,886

Prof A M Gurney, University of Strathclyde. “Membrane potential and pulmonary vascular tone” (1 year) £32,498

Prof P L Weissberg et al., Addenbrooke’s Hospital, Cambridge. “Imaging of macrophage activity in human and experimental atherosclerosis in vivo by positron emission tomography” (2 years) £39,296
Dr C D McCaig et al., University of Aberdeen. “Directing Angiogenesis” (3 years) £104,190
Dr G A Gray et al., University of Edinburgh. “Role of the oestrogen receptor beta in regulation of coronary perfusion and the response to myocardial infarction” (3 years) £109,566
Prof F Muntoni & Dr S Brown, Hammersmith Hospital, London. “Genetic analysis of the lamin A/C gene in limb girdle muscular dystrophy and in dilated cardiomyopathy” (1 year) £35,790
Mr S R Large et al., Papworth Hospital NHS Trust, Cambridge. “Right ventricular function in heart transplantation” (2 years) £135,927
Dr D R Greaves, Sir William Dunn Sch of Pathology, Oxford. “Macrophage expression of plasminogen activator inhibitor-1” (3 years) £106,206
Prof H C Watkins & Dr E M Blair, John Radcliffe Hospital, Oxford. “An investigation into the role of sarcomeric protein gene mutations in beta-blocker responsive cardiac hypertrophy” (2 years) £119,561
Dr MJ Holness & Prof M C Sugden, Queen Mary and Westfield College, London. “Evaluation of the role of uncoupling protein-3 in the regulation of cardiac fatty acid utilisation” (2 years) £79,074
Dr M H Hall et al., Aberdeen Maternity Hospital. “Long term association of folate status and coronary mortality and morbidity in a cohort of women of child-bearing age” (2 years) £83,895
Prof A R Green & Dr B Gottgens, University of Cambridge. “Transcriptional regulation of endothelial cells” (3 years), £261,126
Dr A M Buckle, UMIST, Manchester. “Notch regulation of monocye and granulocyte production” (3 years) £134,106
Dr M S Suleiman et al., Bristol Royal Infirmary. “Metabolic changes in paediatric hearts during open heart surgery: a comparison between cold crystalloid and cold blood with (hot shot) cardioplectic solutions” (2 years) £114,508
Mr R Bonser et al., Queen Elizabeth Medical Centre, Birmingham. “Hormonal substrate support in coronary artery surgery: instability without increased oxygen consumption” (2 years) £135,327
Prof L C Archard et al., Imperial College, London. “Analysis of sequence mutations controlling cardioirulence and virus persistence in coxsackie B3-induced heart muscle disease” (2 years) £75,594
Drs J S Kooner & J C Chambers, Hammersmith Hospital, London. “A study to examine the relationship between reduced, oxidised, and protein bound plasma homocysteine species and vascular endothelial function, in healthy human subjects” (1 year) £45,571
PDRs J S Skinner & P C Adams, Royal Victoria Infirmary, Newcastle upon Tyne. “Late (ten year) outcome after coronary artery graft bypass surgery: the impact of risk factors and graft disease on later clinical events” (6 months) £13,284
Prof C N Hales et al., Addenbrooke’s Hospital, Cambridge. “Catecholamine sensitivity in the metabolic syndrome” (2 years) £88,122
Dr B Keuvney et al., John Radcliffe Hospital, Oxford. “Cladistic/measured haplotype analysis of three candidate genes for blood pressure regulation in a quantitative genetic study of 295 extended pedigrees selected for hypertension” (2 years) £59,841
Dr P Collins, National Heart & Lung Institute, London. “Does chronic testosterone in men with coronary heart disease beneficially affect myocardial ischaemia, vascular reactivity and quality of life?” (2 years) £92,647

Project Grants Committee, January 2000

DEFERRED APPLICATIONS AWARDED

Dr M D Brown University of Birmingham. “The effect of acute and chronic low frequency stimulation on calf muscle vasodilator capacity and endothelial function in patients with chronic heart failure” (3 years) £110,602
Dr P D Wheeler-Jones & T Carter Royal Veterinary College, London. “Thrombin regulation of cyclooxygenase expression in human endothelium: implications for vascular function and proliferation” (2 years) £104,359
Drs J Frampton & S P Watson John Radcliffe Hospital, Oxford. “Megalakaryocyte specific ablation of the alpha2 integrin gene as a means to study the role of alpha2beta1 (GPIIa-GPIIa) integrin in platelet activation by collagen” (3 years) £141,931

NEW APPLICATIONS AWARDED

Dr P D Weinberg University of Reading. “Do NO-mediated transport properties of the arterial wall play a critical role in coronary atherogenesis” (2 years) £77,525
Dr J R Petrie et al Western Infirmary, Glasgow. “Regulation of vascular endothelial nitric oxide production by insulin” (3 years) £125,595
Drs T Santalucia & N J Brand National Heart & Lung Institute, London. “Sp1 mediates the up-regulation of the glucose transporter GLUT-1 in cardiac myocytes in response to hypertrophic agonists” (2 years) £103,594
Drs P J Kemp & C Peers University of Leeds. “Oxygen sensing in airway chemoreceptors: coupling of NAPH oxidase to a novel K+ channel” (2 years) £96,526
Prof M S Marber et al St Thomas’ Hospital, London. “The use of protein kinase C deficient mice to investigate late preconditioning” (3 years) £156,610
Dr M Crompton University College London. “On the involvement of mitochondria in ischaemia-induced apoptosis in the heart” (3 years) £149,041
Drs R C Saumarez & A Grace Papworth Hospital, Cambridge. “Mapping and characterisation of fractionated electrograms in the isolated small mammalian heart” (2 years) £117,087
Ms J Bruce et al University of Aberdeen. “The Grampian study of pain after cardiac surgery” (1 year) £11,980
Profs J H Coote & N G Bowery University of Birmingham. “Specific GABA inhibitory mechanisms with a functional role in regulating cardiac vagal neurones” (3 years) £100,617

Prof M R Wilkins & Dr N Morrell Hammersmith Hospital, London. “Role of PPARs in the vascular remodelling of pulmonary hypertension” (2 years) £104,305

Dr D N F Harris et al Hammersmith Hospital, London. “Regional abnormalities of cerebral metabolism using 18FDG-PET during hypothermic and normothermic cardiopulmonary bypass” (1 year) £44,983

Fellowship Grants Committee, January 2000

Intermediate Research Fellowships

Dr T Kamishima and Dr J M Quayle, University of Leicester, “Regulation of calcium-activated chloride channels in rat arterial smooth muscle cells by mitochondria and sarcoplasmic reticulum” (3 years) £132,617

Junior Research Fellowships

Dr R K M Wong and Dr L L Ng, Leicester Royal Infirmary. “Advanced glycation end products and the release of reactive oxygen species by NADPH oxidase of monocytic and lymphoblastoid cells from normal and hypertensive humans” (2 years) £92,253

Miss L K K Teoh and Prof D M Yellon, University College Hospital, London. “An investigation into lethal reperfusion injury and the potential cardioprotective properties of growth factors in human myocardium” (2 years) £85,178

Dr L D Greig and Dr S Maxwell, Western General Hospital, Edinburgh. “The role of lipoprotein oxidation in endothelial dysfunction” (2 years) £72,722

Dr F Osman and Dr M D Gammage, Queen Elizabeth Hospital, Birmingham. “Studies of the cause of vascular mortality in thyrotoxicosis” (2 years) £72,843

PhD Studentships

Ms C M Elton and Dr R W Farndale, University of Cambridge. “Role of cell-surface calreticulin in the modulation of human platelet activation” (3 years) £65,640

Dr G Sperber and Dr J S Owen, Royal Free Hospital, London. “Gain-of-function chimeraplasty: preclinical studies of hepatic gene targeting in situ to generate atheroprotective ApoAlMilano and LCAT Ser216Ala Phenotypes” (3 years) £65,675

Mr S Capey and Dr C W van den Berg, University of Wales College of Medicine, Cardiff. “Interaction of complement and matrix metalloproteinases in atherosclerosis” (3 years) £64,582

Dr J P Winter and Prof P J Grant, Leeds General Infirmary. “The role of DNA damage in the development of atheroma and myocardial infarction” (2 years) £83,109

Mr B I Hudson and Prof P J Grant, Leeds General Infirmary. “Functional analysis of polymorphisms in the RAGE gene and their relation to myocardial infarction” (2 years) £51,979

Dr Osman and Dr M D Gammage, Queen Elizabeth Hospital, Birmingham. “Studies of the cause of vascular mortality in thyrotoxicosis” (2 years) £72,843

Dr M S Hamid and Prof W McKenna, St George’s Hospital Medical School, London. “The identification of abnormal structural protein genes of the cardiac cell junction in autosomal dominant arrhythmogenic right ventricular cardiomyopathy” (2 years) £84,680

PhD Studentships (Clinical)

Ms R Yadav and Dr S Nourshargh, Hammersmith Hospital, London. “An investigation into the anti-inflammatory effects of the anti-thrombotic drug, ABCIXIMAB (REOPRO)” (3 years) £145,920

Why Not Organise a BSCR Meeting or Workshop?

The most recent meetings of the BSCR were Molecular Genetics of Cardiovascular Disease at Glasgow University, March 1999 and Myocardial responses to sublethal ischaemia at University College London, September 1999. The format for BSCR events can range from a small gathering with a few speakers to a full meeting, as above. Please discuss your ideas with the BSCR Secretary Dr. Gary Baxter in the first instance.

Tel.: 020 7380 9888/9881

Grants of £1,000 are available for organising a Workshop, and £8,000 for a Meeting.
Cardiovascular Related Wellcome Trust Grants
November 1999 to January 2000

Project Grants

Dr L Leach, Dept of Human Morphology, Queen’s Medical Centre, University of Nottingham, Nottingham. The endothelial junctional complexes of the diabetic human placenta. 12 months £5,800

Prof Janet T Powell, Dept of Biochemistry & Surgery, Charing Cross & Westminster Medical School, Imperial College School of Medicine, London. Role of Chlamydia pneumoniae in experimental aortic dilatation. 3 months £8,211

Prof J MacDermot, Division of Medicine, Imperial College School of Medicine, Hammersmith Hospital, London. The functional link between neutrophil chemotaxis and ADP-ribosyltransferase activity. 24 months £65,970

Prof D B Dunger, Dept of Paediatrics, Addenbrookes Hospital, University of Cambridge, Cambridge. Investigation into the effects of fetal growth restraint and fetal genotype on adiposity and insulin sensitivity at 7 years. 18 months £177,228

Dr Margaret R Maclean, Division of Neuroscience & Biomedical Systems, Institute Biomedical & Life Science, University of Glasgow, Glasgow, Scotland. Pharmacological synergy: role in pulmonary hypertension. 36 months £120,597

Dr L-P Berg, Dept of Histopathology, Imperial College School of Medicine, St Mary’s Campus, London. Modulation of endothelial cell activation by chronic shear stress. 12 months £17,430

Dr P Clark, Biomedical Sciences, University of London, Imperial College School of Medicine, South Kensington, London. The role of inter-endothelial cell adhesion in human blood vessel permeability and angiogenesis. 36 months £152,690

Dr J F X Jones, Dept of Human Anatomy & Physiology, University College Dublin, Dublin 2, Ireland. Classification of cardiac vagal preganglionic neurones. 36 months £101,565

WHAT WERE YOU DOING BETWEEN 1973 AND 1998?

The British Society for Cardiovascular Research was founded in 1973, originally as the Cardiac Muscle Research Group.

Last year was the 25th anniversary of the Society’s foundation and we didn’t celebrate the event. We would like to rectify this omission by publishing a special article in 2000 to commemorate our first 25 years but we need your help.

We are particularly keen to acquire documentary material such as photographs. But we would also like to record the memories and anecdotes of older members, founding members, former Committee members and officers, and meetings organisers. Younger members may also have anecdotes of the society and its personalities that they can contribute.

Everything will be considered
(if it is fit to print and within the law).

Please contact either Dr Angela Drake-Holland (e-mail: a.drake-holland@ic.ac.uk) or the Secretary, Dr Gary Baxter (e-mail: g.baxter@ucl.ac.uk; telephone: 020 7380 9888).
BSCR Autumn Meeting 2000

MEDIATORS AND MECHANISMS IN MYOCARDIAL DISEASE

Dates: Monday 4th and Tuesday 5th September 2000
Venue: The Queen's University of Belfast, Peter Froggatt Centre
Organisers: Barbara McDermott and David Bell

Speakers will include: Ralph Kelly (Boston), Ajay Shah (London), Barbara McDermott (Belfast), Paul Nicholls (Belfast), Håvard Attramadal (Oslo), Sian Harding (London), Jos Lamers (Rotterdam), Michael Böhm (Cologne), Derek Nunez (London), Alun Evans (Belfast), Ken McDonald (Dublin), John McMurray (Glasgow).

Major Symposia: Neurohormonal / autocrine-paracrine activation; Altered receptors and signalling; Genetics, epidemiology and therapeutic aspects.

Communications: Part of this meeting will be devoted to the presentation of free communications. Abstracts, on any topic, are welcomed and several abstracts related to the main theme of the meeting will be selected for oral presentation. Accepted abstracts will be printed in the Quarterly Bulletin of the British Society for Cardiovascular Research. Abstract deadline 7 July 2000.

Travel: The Peter Froggatt Centre is behind the Lanyon Building on the main University campus, which is easily accessible from Belfast International Airport (45 min), City Airport (20 min) and Central Station (10 min).

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

Accommodation: Rooms are available at the Queen's Elms Halls of Residence and there are a limited number at the QUB Senior Common Room (most with en suite facilities). A block reservation has also been made in the nearby Wellington Park Hotel.

Registration: Free to members, £40 to non-members. The Society’s Dinner will be held in Cultra Manor at the Ulster Folk Museum at a cost of £20 per head. Registration and abstract forms are included with this issue of the Quarterly Bulletin of the British Society for Cardiovascular Research and can also be obtained from the Conference Secretary:
Ms. Francis Price, Department of Therapeutics and Pharmacology, The Queen’s University of Belfast, Whittla Medical Building, 97 Lisburn Road, Belfast BT9 7 BL. Tel: (0)2890-335770; Fax: (0)2890-438346; e-mail: f.price@qub.ac.uk

Applications for membership and student bursaries are available from Dr Gary Baxter, Secretary of the BSCR, The Hatter Institute for Cardiovascular Studies, University College Hospital, Grafton Way, London WC1E 6DB