

UNIVERSITY OF LEICESTER GRANTS FROM EXTERNAL SOURCES

PRESS COVERAGE OF RESEARCH GRANTS

The *Bulletin* is sent to the media as well as other external contacts. As a result, details of grants appearing in this section may stimulate press interest. The Press Office may also actively seek media coverage of particular grants detailed in this section. It is therefore the grantholder's responsibility to request that any grant of a sensitive/confidential nature be excluded from the *Bulletin*.

This can be done by contacting the Research Office, which has responsibility for compiling this Research section (2495).

ANAESTHESIA

Dr D G Lambert

PhD Studentship - Distribution and Functional Coupling of the Nociceptin Receptor in the Central Nervous System
£49,443 Pfizer Ltd

Prof G Smith

Supplement: The Effect of Early Oral Nutrition and Mobilisation on Post-Operative Recovery after Major Bowel Surgery
£2,149 (supp) NHS Trent

ARCHAEOLOGY

Dr E Sauer

Supp. - Alchester Roman Fort
£3,000(supp) Royal Archaeological Society
£1,750(supp) Society of Antiquaries

BIOCHEMISTRY

Dr J Emsley, Dr P C E Moody (Sponsor)

Structural Studies of Signal Transducing Receptor/Ligand Complexes - Research Career Development Fellowship - Dr Jonas Emsley

The body's tissues are not just made up of cells. A substantial part of their volume is extracellular space which is largely filled with a binding substance known as a matrix. This extracellular matrix is composed of an intricate network of macromolecules including versatile proteins such as collagen which are enmeshed with other proteins and polysaccharides. The extracellular matrix provides a physical support in which cells can move around and interact with one another.

The points of contact between cells and the extracellular matrix are of special interest as they relay vital information concerning cellular growth, death and everyday function. When this information flow breaks down a number of disease conditions arise including tumour formation, thrombosis, asthma and rheumatoid arthritis. The aim of this research project is to study these points of contact (receptor/ligand complexes) in order to gain a greater understanding of human physiology and disease.

Value Reported in October *Bulletin*

Dr C A Pritchard

Supp. - Use of Gene Targeting to Define the Roles of Raf Kinases in Signal Transduction and Oncogenic Transformation - Year 3
£53,846(supp) Cancer Research Campaign

Prof N S Scrutton, Dr P Moody

Elucidating the Mechanism of Explosive Degradation by PETN Reductase
£155,056 BBSRC

Dr A E Willis

Supplement - Regulation of c-myc mRNA Translation by Internal Ribosome Entry
£962(supp) Cancer Research Campaign

BIOCHEMISTRY (CMHT)

Prof G C K Roberts

Supplement - P450 Consortium - Structural Models of Human Cytochrome P450
£75,000 Merck & Co. via University of Dundee

BIOLOGY

Dr D M Harper

Trinity Broads Restoration Project
£19,698 Environment Agency

Dr R P Jarvis

Supplement - Year 1 Expenses Royal Society Rosenheim Research Fellowship
£11,000(supp) Royal Society

Dr E Rosato

Cryptochrome and the Drosophila Clock

The molecular analysis of circadian rhythms is currently one of the fastest moving areas of biology. Its popularity is partly due to the fact that everyone can relate to their own circadian sleep-wake cycle, and so this subject has an instant 'street credibility', and partly because the outcome of these studies will help in alleviating sleep and stress disorders born from the modern "24 h society". A number of model organisms are being utilised, but the fruit fly *Drosophila melanogaster* holds centre stage. Our study will investigate the role of the blue-light photoreceptor cryptochrome in the *Drosophila* time-keeping machinery. There is a remarkable conservation of clock molecules between the fruit fly and mammals so any progress in understanding the fly clock is directly applicable to the human circadian system.

£166,168 BBSRC

Dr M Sheehy

Supplement - Analysis of Stock Age Structure and Population Parameters in Edible Crab, Cancer Pagurus using Lipofuscin Age Pigment: Data for Resource Management
£11,154(supp) Ministry of Agriculture, Fisheries and Food

Prof D Twell, Dr E Lalanne

Functional Analysis of Transposon Tagged-Gametophytic Fertility Genes in Arabidopsis

Molecules mediating the major events of plant reproduction are still largely unknown and their identification represents a major challenge for crop and seed production. We have designed a genetic strategy to identify genes required for the development and fertility of male (pollen) and

female (ovule) structures in the model plant species *Arabidopsis thaliana* (thale cress). We have identified over 20 essential genes important for pollen and/or ovule development.

The aim of this grant is to uncover the biological roles of the products of three of these genes. PGP1 encodes a plasma membrane-associated protein, which may play a structural role during pollen tube growth. PGP2 encodes an enzyme involved in the modification of surface-associated polysaccharides. PGP3 belongs to large family of transducer molecules that may function as an adapter protein to bring together enzymatic components of signalling pathways.

The results will improve our understanding of the mechanisms underlying pollination and fertilisation. Furthermore, this information may be used to improve plant breeding strategies and to limit the spread of transgenic pollen, currently an important issue concerning bio-safety.

£221,064 BBSRC

CARDIOLOGY (MEDICINE & THERAPEUTICS)

Dr A Gershlick

TNF- α Antibody and Tyrphostin AG1295 Eluting Stents to Reduce Instant Restenosis
£9,590 Glenfield Hospital

CELL PHYSIOLOGY AND PHARMACOLOGY

Dr R J Challiss, Prof S R Nahorski

A Molecular Basis for Tissue-Specific Effects of Muscarinic Acetylcholine Receptor Antagonists

Muscarinic acetylcholine (mACh) receptor antagonists have been developed which demonstrate pharmacologically useful selectivity between the five mACh receptor subtypes expressed in many mammalian species including man. Subtype selectivity may allow such agents to be used therapeutically to treat specific disorders (e.g. urinary incontinence) whilst avoiding the side-effects associated with a generalised mACh receptor blockade.

Unexpectedly, some subtype-selective mACh receptor antagonists (e.g. darifenacin, a M3-mACh receptor-selective antagonist) appear to demonstrate tissue-selective effects even where the physiological action being antagonized is mediated by the same mACh receptor subtype.

In the present study, we will examine this phenomenon and attempt to establish the molecular basis of such tissue-specific, rather than receptor subtype-specific, discriminatory activities of certain mACh receptor antagonists.

£149,016 Pfizer Limited

Dr R J Evans, Dr I D Forsythe

The Role of P2 Receptors in the Brainstem and Spinal Chord



The aim of this project is to address the functional role of P2 receptors in sensory and motor regions of the brainstem and spinal cord, with particular reference to, receptor-subtype expression and nerve synaptic function. P2 receptors have been implicated in a variety of disease processes and may provide novel drug targets for the development of new medicines e.g. P2X1 receptors in the control of fertility and P2Y1 receptor antagonists as anti-thrombotics. In addition to gaining important new information regarding the role of defined P2 receptors in the spinal cord and brainstem, this study will contribute to general knowledge of P2 receptor function and their suitability as drug targets and/or predicting possible side effects.

£229,422 Medical Research Council

**Dr I D Forsythe, Prof S R Nahorski, Prof P R Stanfield, Dr R J Evans,
Dr G B Willars, Dr B D Grubb**

Integration and Modulation of Synaptic Transmission

The aim of this co-operative is to explore communication between brain cells.

The nervous system is made up of billions of nerve cells (neurones) which integrate incoming information and distribute the result via electrical signals travelling along nerves. Each of these cells has the potential to receive inputs from thousands of other neurones via specialised connections called 'synapses'. This co-operative will bring together several laboratories, each of which is concerned with mechanisms regulating information flow at these synapses.

Since each cell is physically isolated from its neighbours, information must be transmitted by a chemical messenger ('neurotransmitter') which is packaged and released at the synapses. This process is called synaptic transmission. Over 100 different neurotransmitters bind to specific sensing proteins ('a receptor') within the receiving cell's surface membrane.

Our ability to respond to our environment, to sense and to move and particularly to learn and to remember are wholly dependent upon the ability to regulate the strength of these synaptic pathways. In addition the cellular basis of several common brain disorders (e.g. epilepsy, stroke, schizophrenia, Parkinson's and depression) result from destruction or dysfunction of specific transmitter systems.

£179,815 Medical Research Council

Dr B D Grubb, Prof P R Stanfield The Role of Potassium Channels in Regulating Neuronal Excitability in Primary Afferent Nociceptors

Potassium channels expressed in nerve cells regulate membrane potential, cell excitability and firing rate. Anatomical studies have revealed that many potassium channel subtypes are selectively expressed in different regions of the nervous system suggesting that they may subserve special functions. This project will examine the role of two classes of potassium channels, inward rectifiers and calcium-activated potassium channels, in the regulation of excitability of primary afferent neurones that detect painful stimuli. We are particularly interested in the mechanisms by which the opening of these potassium channels can be modulated by inflammatory mediators since this might provide a molecular basis for touch and heat hypersensitivity. The long term aim of this



research is to identify putative targets for the development of novel analgesic drugs.

£236,062 Medical Research Council

Prof P R Stanfield

Characterisation of Normal and Dysfunctional Cardiac Potassium Channels Associated with an Inherited Arrhythmia - Travelling Research Fellowship - Dr John Mitcheson

£48,008 Wellcome Trust

CHEMISTRY

Dr A P Abbott

Solvent Effects on Reaction Dynamics in Supercritical HFC Fluids

£56,455 ICI Klea

Dr D Davies

New Environmentally Friendly Solvents - CASE Studentship (Miss S Kandola)

£20,100 Glaxo Wellcome

Dr G Solan

Case Studentship - New Catalysts for Olefin Polymerisation Based Upon Multidentate Monanionic Ligands and Trivalent Transition Metals

£14,598 Exxon Chemical Group Inc.

Dr A M Stuart

Fluorous-Derivatised Phase Transfer Catalysts

Phase transfer catalysis is a powerful tool for organic chemists for promoting the reaction between reagents which are mutually immiscible and has been applied to a wide range of organic syntheses in industry. The phase transfer catalysts normally increase the rates of reaction, increase product selectivity and lower energy requirements but a fundamental problem in their application to industrial processes is the difficulty associated with the recovery and removal of the catalyst from the product. This research seeks to synthesise new phase transfer catalysts derivatised with perfluoroalkyl groups in order to offer a straightforward separation of the product from the reagent/catalyst either by liquid-liquid extraction or by solid-phase extraction. This approach is generic technology which could be applied to a wide variety of phase transfer catalytic reactions but, in

the first instance, work will focus on two important industrial applications, catalytic oxidations and aromatic nucleophilic substitutions.

Value Reported in October Bulletin

Dr M J Sutcliffe

Supplement - Research Studentship - Rajesh Sangar

£1,500 AstraZeneca R & D Charnwood

CHEMISTRY, PHYSICS & ASTRONOMY

Dr P S Monks, Prof A Wells, Prof D T Llewellyn-Jones

Development of the GeoSCIA Mission Concept

The Geostationary Scanning Imaging Absorption Spectrometer (GeoSCIA) will detect the spectral signature of a range of atmospheric parameters, such as trace gas concentrations and cloud optical depths, at high spatial and high temporal resolution. The GeoSCIA mission would be the first time that atmospheric constituent measurements are made from a satellite in geostationary orbit. The initial focus of the GeoSCIA mission is to accurately assess the changing atmosphere and the relative influence of anthropogenic activity and natural phenomena originating in Europe, Africa and the surrounding oceans and seas. The mission will address key and critical scientific and policy based questions about the changing chemistry, physics and meteorology of the Earth's atmosphere in this region. The grant awarded to the team at the University of Leicester will allow the development of new technologies to address critical scientific and technical questions in respect to the GeoSCIA mission concept.

£200,707.92 NERC

CHILD HEALTH

Dr M Wailoo

Further Statistical Analyses and Draft Papers for Publication Relating to Projects 217 and 178/17

£3,600 The Foundation for the Study of Infant Deaths



ECONOMICS (MANAGEMENT CENTRE)

Prof A Bendell, Dr L Boulter

UTC Globalisation Benchmarking and Assessment - Extension to RS10QAK
£317,139 *Rolls-Royce plc*

EDUCATION

Mrs J Harrison, Mr N Kitson, Dr M Morrison

Evaluation of Northamptonshire Healthy Schools Award Scheme
£8,000 *Northamptonshire Health Authority*

ENGINEERING

Dr D Bates

Performance Robustness Analysis for Aerospace Applications using the Structured Singular Value

This project builds on recent collaborative research between the Universities of Leicester and Limerick in the area of robustness analysis of aerospace systems. The main aim of the project is to develop and apply the structured singular value analysis tool to realistic aerospace applications. New technologies developed in this research will be exploited as part of the GARTEUR (Group for Aeronautical Research and Technology in EUROpe) Action Group on new techniques for the clearance of flight control laws.

£14,559 *EPSRC*

Prof C Pollock

Supplement - SRM Motor Development
£16,900(supp) *Black and Decker*

ENGLISH

Prof G Walker

Leverhulme Major Research Fellowship - Writing under Tyranny : Politics and Literature in the Reigns of Richard II and Henry VIII

This project proposes an ambitious comparative study of literary and political culture in England in two distinct but closely related periods. The two reigns chosen witnessed not only the production of highly significant bodies of literature, but also profound political and religious crisis, initiated and shaped chiefly by the sovereign himself. How closely were these phenomena related? How did political change, which called into question long held assumptions about culture and society effect literary production? More specifically, how, in a culture dominated by notions of obedience and loyalty, did writers react to a growing apprehension that power was being abused, and that the monarch was the source of that abuse?

Did the writers of the later reign consciously respond to the experiences of their forebears? Can we talk of continuing literary communities over such extended periods? If so, how did they constitute themselves and for what purpose(s)? And, crucially, how did political change affect their functions and identity? In addition to examining the work of specific writers and readers in two highly significant periods, this study will also address questions of more general significance. The result will be a broad cultural biography of writing (and reading) communities at two moments of major political rupture.

£77,734 *Leverhulme Trust*

EPIDEMIOLOGY & PUBLIC HEALTH

Dr K R Abrams

Research Associate in Health Services Research
£92,270 *Leicester General Hospital*

Dr M D Tobin, Supervisors: Prof P Burton/Prof N Samani

The Genetic Regulation of Arterial Pressure of Humans in the Community (GRAPHIC Study) MRC/Trent Special Training Fellowship in Health Services Research and Health of the Public
£95,836 *Medical Research Council*

EPIDEMIOLOGY & PUBLIC HEALTH (UKCCSG)

Dr S Ablett

UKCCSG Tumour Bank

Great advance has been made in the treatment of children with cancer over the last 30 to 40 years. Much of that progress has been due to the successful use of chemotherapy. Scientists and clinicians now believe that the next major advances will be gained by better understanding of the biology of the disease. Tumour material for biological studies of childhood cancer represents a particularly scarce resource. The UKCCSG has now introduced a system for national tumour tissue registration as part of a national tumour bank. This is designed to ensure that the best possible use is made of rare tumour material and the UKCCSG has recognised the need for an adopted custodial role which is designed to encourage and facilitate high quality biological studies of childhood cancer.

£101,268 *Cancer Research Campaign*

Supplement - UKCCSG Support

£2,606.10(supp) *Lisa Thaxter Trust*

GENERAL PRACTICE

Prof R Baker/Dr F Cheater

Supplement - Pilot Project for Community Mothers

£1,000 *Leicestershire Health*

Prof R Baker, Dr K Khunti, Dr A Hay, Ms S Adams

Outreach Visits to General Practice to Improve Prescribing Antibiotics and Analgesics
£13,787 *Leicestershire Health*

Dr T Coleman

National Evaluation of the New Smoking Cessation Services: Targeting Disadvantaged Smokers
£4,630(supp) *NHS Trent*

Dr J F Middleton

Outcomes of Consultation Skills Training
£12,000 *NHS Executive Trent*

GENETICS

Dr R H Borts

Controlling Elements of Yeast Meiotic Recombination: Their Role in the Fidelity of Chromosome Transmission - Senior Research Fellowship in Basic Biomedical Science

The proper distribution of chromosomes during the production of eggs and sperm is a highly regulated, precise process and is essential because unbalanced chromosome complements lead to genetic disorders or death. It is dependent on the normal shuffling of genetic traits between parental chromosomes called "recombination". This project is designed to characterise the genes and mechanisms by which genetic exchange is controlled using a model organism, *Saccharomyces cerevisiae*. Our work has demonstrated that genes normally involved in the prevention of cancers, mismatch repair genes, have an important role in regulating recombination. We have demonstrated that certain of these genes can block recombination before it even begins when the chromosomes are not sufficiently alike. Some of these same genes exert entirely different effects at later stages of the recombination process. These results have important consequences for understanding of the process of speciation as well as the mechanics of recombination.

£276,000 *Wellcome Trust*





Prof Sir A Jeffreys

Variant Repeat Analysis at the Insulin Minisatellite: Investigation of Lineage Diversity and Association with Type 2 Diabetes and PCOS

The unstable regions of minisatellite DNA within human chromosomes, which form the basis of genetic fingerprinting, are generally thought not to have any effects on an individual, for example on disease risk. There are however exceptions. One of the best characterised is a minisatellite near the insulin gene for which strong evidence exists that variation at this minisatellite can influence the risk of type 1 diabetes mellitus (T1DM). We have recently developed a powerful new method for studying variation at the insulin minisatellite and have shown that the apparent associations between the minisatellite and T1DM are due to very ancient chromosomal lineages in Caucasian populations and that disease association is likely to be much more complex, involving not only the minisatellite but also as-yet unknown DNA variations lying near this unstable DNA. The present grant is aimed at exploring the origin and diversification of variants at the insulin minisatellite, in particular by surveying genetic diversity in African populations which are known to be the most genetically diverse of all human populations. In addition, disease association studies will be extended to the other main form of diabetes (type 2 diabetes mellitus, T2DM) and to the disease polycystic ovary syndrome; there is evidence for both of these diseases that variation at the insulin minisatellite may also influence disease risk.

Value Reported in October *Bulletin*

Supplement - Isolation of Polymorphic DNA Marker Probes from the Pig Genome - Wolfson Research Professorship - Year 10 Support Costs
£61,752(supp) Royal Society

Prof E Louis

The Structure, Function and Dynamics of Telomere Regions in Yeast : Evolutions of Telomere Associated Repeat Sequences

£203,000 Wellcome Trust

GENETICS, CARDIOLOGY, BIOCHEMISTRY

Prof Sir A J Jeffreys, Prof R Trembath, Dr N Royle, Prof N Samani, Dr I C Eperon

Supplement - Variability, Instability and Pathology of the Human Genome - Co-operative Group Grant

£32,304 MRC

GENETICS WITH UNIVERSITY OF CAMBRIDGE

Prof R C Trembath

The Molecular Pathology of Primary Pulmonary Hypertension

Primary pulmonary hypertension (PPH) is a rare but devastating disease. We recently identified a defective gene (BMPR-II) by screening families with this disease. This finding provides for the first time an opportunity to develop a structured programme of research to understand the events leading to the development of PPH. We now need to determine the full range of alterations in the BMPR-II gene and determine its role in susceptibility to other forms of pulmonary hypertension. In addition, we aim to determine the localisation of the gene product in the normal and diseased lung and show how alterations within the gene lead to the clinical manifestations of the disease. Understanding the function of this gene will enable us to predict patients at risk of pulmonary hypertension and design new treatments for this condition. This major programme award will provide an important opportunity to develop Leicester as a leading centre for the molecular understanding of this condition.

£723,937 Total Grant

£486,950 Leicester's share
British Heart Foundation

GEOLOGY, CAMBRIDGE, ROYAL HOLLOWAY

Prof P K H Maguire, Prof R S White, Dr C J Ebinger

The Acquisition of Seismic Recording Systems to Study 'Rifting Processes: Inception Transition and Spreading' - Joint Infrastructure Fund Award

The Geophysics Group in the Geology Department at Leicester University, lead players in a consortium (SEIS-UK (Seismic Equipment Infrastructure for the UK)) that includes Cambridge, Leeds and Royal Holloway, London Universities, have been awarded £2 million from the Joint Infrastructure Fund for the purchase of 175 seismic data acquisition systems to study how continents and oceans rift apart. Seismic recorders are to be deployed in Greenland and Northwest Europe to study the deep structure of the Iceland mantle plume, rising beneath the North Atlantic mid-ocean rift. The equipment is to be used in a study of the very early stages of rifting induced by subduction of the Pacific oceanic plate beneath North Island New Zealand. A further application is in the pipeline for the study of the East African Rift System transition from continental to oceanic style rifting in Ethiopia. The equipment base at Leicester will be a focus for UK seismic research for some time to come.

£2,027,518 NERC

HISTORY

Dr J E Story

Writing History: "Minor" Annals in Anglo-Saxon England and Francia

£1,450 British Academy

MATHEMATICS & COMPUTER SCIENCE

Dr B J Leimkuhler

Switched and Multiple Time-Scale Geometric Integrators for the N-Body Problem

N-body problems are ubiquitous in chemical and physical modelling, representing for example the motion of the atoms in a biopolymer or the evolution of stars in a globular cluster. In this project, new types of adaptive numerical methods are to be developed and applied to selected problems in N-body simulation.

While simulation has taken great leaps forward in recent years with the advent of powerful supercomputers and improved modelling techniques, there is still a long way to go. To illustrate, biologically interesting motions in proteins typically occur on timescales of the order of milliseconds, while the best modern simulations barely reach the nanosecond scale, as the "timestep" used in computing successive snapshots of the motion is severely limited by the need to resolve high frequency oscillations in the interatomic dynamics.

This project seeks to improve the state of the art in N-body timestepping through the application of adaptive schemes and multiscale simulation methods which decouple the fast and slow degrees of freedom. Using what are known as

"geometric integration" techniques, key qualitative and physically-related invariants and symmetries of the solutions are retained, leading to improved long-term simulation properties, and, ultimately, improved fidelity of the approximations. This work will be performed under the auspices of Leicester's newly formed and highly interdisciplinary Mathematical Modelling Centre, and in partial collaboration





with researchers in the Leicester-based UK Astrophysical Fluids Facility.

£129,881 EPSRC

Prof W A Light

Strategic Equipment Initiative - Multi-Scale Modelling and Simulation

£380,000 EPSRC

MEDICINE & THERAPEUTICS

Dr L L Ng

Na⁺/H⁺ Exchanger Isoform Activity, Protein Endocytosis and Cytokine Secretion from Renal Proximal Tubular Cells in Hypertension - Junior Research Fellowship - Dr R J Westacott

This British Heart Foundation Fellowship to Dr R Westacott, supervised by Dr Leong Ng, will investigate the role of Na⁺/H⁺ exchangers in the process of albumin or protein absorption in renal tubule cells. Protein leads to stimulation of the production of inflammatory mediators from these cells, resulting in inflammation and scarring of the kidney with loss of function. Furthermore, there is evidence that such processes are hyperactive in hypertensive individuals, and thus may contribute to progression of renal damage when tubule cells are exposed to high concentrations of protein in the urine. The work would reveal a role for certain forms of the Na⁺/H⁺ exchanger in these processes, and may lead to new therapies to limit renal damage due to protein in the urine.

£85,086 British Heart Foundation

MEDICINE & THERAPEUTICS - NEPHROLOGY

Dr K P G Harris, Dr I Z A Pawluczyk

Macrophage Mediated Glomerulosclerosis

The aetiology of progressive renal scarring is complex but both haemodynamic (systemic and glomerular hypertension) and non-haemodynamic factors (prosclerotic cytokines and growth factors) play a role. We have previously reported that macrophage derived products (MPCM) are able to promote prosclerotic responses in cultured rat mesangial cells emphasising the importance of infiltrating macrophages in the initiation of glomerulosclerosis.

The beneficial effects of antihypertensive treatment in renal disease is beyond doubt, but the mechanisms underlying this are difficult to define since contributions from modulation of renal haemodynamics can never be discounted.

The proposed studies will use a cell culture system to investigate mechanisms independent of the influence of any haemodynamic effects. Such observations should provide a scientific basis for the rational choice of antihypertensive medication in progressive renal diseases by delineating the mechanism of action underlying the renoprotective, or more specifically, the anti-fibrotic effects of commonly used classes of antihypertensive drugs.

£13,000 Leicester General Hospital

MEDICINE & THERAPEUTICS - NEPHROLOGY WITH DUNDEE UNIVERSITY

Dr J Barratt, Prof J Feehally, Dr A Allen



Molecular Characterisation of the Human Mesangial Cell Fc Alpha Receptor Cell

£20,000 National Kidney Research Fund

MEDICINE & THERAPEUTICS - NEPHROLOGY WITH UNIVERSITY OF BRISTOL

Dr A Allen, Prof J Feehally

IgA Nephropathy: Lymphocyte Homing Mechanisms and the Role of Vd3 T Cells

IgA nephropathy (IgAN) is a common kidney disease caused by a type of antibody called IgA, which accumulates inside the kidney and damages it. IgA antibodies are normally made by cells in the gut. These cells travel around the body in the blood before homing to the gut to make IgA. In IgAN, the cells go to the bone marrow instead, and the IgA made here eventually reaches the kidney. We have discovered that a cell type called Vd3 is missing from the gut and the bone marrow in IgAN. We believe that Vd3 cells may normally ensure that IgA is made in the gut but not the bone marrow. In this project, we will investigate why IgA-producing cells go to the bone marrow in IgAN. We will also study Vd3 cells to find out whether their absence in IgAN is the reason that IgA is made in the wrong place.

£74,564 National Kidney Research Fund

MICROBIOLOGY & IMMUNOLOGY

Prof W D Grant

Supplement - Environmental Gene Screening to Obtain DNA Libraries

£65,000 Genencor International

Dr W Schwaebel

Prize Studentship - Dr Saeed-ul-Hassan Khan - Composition of the Lectin Pathway of Complement Activation in Gallus : is this Central Route of Innate Immunity Relevant to the Serious Problems that Microbial Infections Pose to the Poultry Industry?

One of the most striking developments in current immunological research is the reappraisal of innate immunity. Very recently, a novel pathway of complement activation, initiated by the interaction of lectin-like recognition molecules for microbial carbohydrate structures, termed the lectin pathway, has been described. So far, three

serum lectins were shown to serve as carbohydrate recognition molecules of the lectin pathway activation complex, i.e. Mannan Binding Lectin (MBL) and two members of the ficolin family (M-Ficolin and L-Ficolin). Like MBL, ficolins were shown to form multimolecular complexes capable of activating complement after binding to microbial carbohydrate structures using the same serine proteases that were first described as constituents of the MBL complex. Our research laboratory has pioneered the understanding of the molecular processes involved in the activation of this novel and phylogenetically conserved route of innate immune defence by the isolation and characterisation of two novel components of the lectin pathway activation complex, the serine protease MASP-2, and a MASP-2 related plasma protein of 19 kDa, termed MAP19. Activation of the multimolecular MBL pathway complex (composed of up to 18 MBL monomers, the MBL-associated serine proteases MASP-1 and MASP-2, and MAP19) is initiated by the interaction of the C-terminal C-type lectin domains of MBL with carbohydrate structures present on yeasts, bacteria and viruses. This interaction is translated into activation of the complement cascade by the conversion of the MASP-2 proenzyme (it is not yet clear if and how MASP-1 participates in this process) into its enzymatically active form. The proposed PhD project aims to characterise the lectin pathway components of the chicken by cDNA and genomic cloning, identify the degree of conservation within the phylogeny by DNA sequencing, localise the source of biosynthesis of lectin pathway components by Northern blotting and by in situ hybridisation techniques, and create specific tools by recombinant expression to measure the composition and the functional activity of the lectin pathway in normal chicken populations and such with frequent microbial infections. Supporting the innate immune response within the life stock might lead the way to reduce the usage of antibiotics presently required to control infectious diseases.

£93,323 Wellcome Trust

MUSEUM STUDIES

Prof E Hooper-Greenhill, Jocelyn Dodd

Evaluating the CMAL/DCMS Education Challenge Fund

An Education Challenge Fund of £500,000 has been made available over two years to the seven Area



Museums Councils (ACMs) in England, by Resource: the Council for Museums, Archives and Libraries (CMAL) on behalf of the Department for Culture, Media and Sport (DCMS). This fund supports museum and gallery education projects instigated by the ACMs which are designed to build capacity in museum education; a range of educational projects are now in progress which will benefit over 400 museums in the seven regions. The Research Centre for Museums and Galleries (RCMG) in the Department of Museum Studies has been commissioned by CMAL to evaluate the outcome of the Education Challenge Fund and to assess how far it has enabled ACMs to build the capacity within museums and galleries in their areas to provide educational projects for life-long learning.

Value Reported in October *Bulletin*

ONCOLOGY

Dr G D D Jones

PhD Studentship - Gabriela Martinho de Almeida

£6,740 (Year 1) Portuguese Ministry for Science and Technology

Dr K J O'Byrne

A Phase II, Open-Label, Multicentre Trial to Assess the Activity and Tolerability of ZD0473 in Patients with Malignant Mesothelioma Who Have Failed One Prior Chemotherapy Regimen

Pleural Mesothelioma is a disease which results for the most part from exposure to asbestos. The incidence of the disease is increasing dramatically. Already the mortality from Malignant Mesothelioma is higher than that seen for cervical cancer. It is estimated that 1 in 100 men will die from the disease. Recent studies have indicated that cytotoxic chemotherapy may have a role to play in controlling the symptoms of the disease, in particular, malaise, dyspnoea and pain. Cisplatin based combination regimens shrink the tumour by more than 50% in 20-40% of patients. Furthermore, symptoms are improved in between 60-80% of patients. In a proportion of cases retreatment at the time of relapse can result in a further tumour response and improvement in symptoms. ZD0473 is a novel platinum analogue which has activity in tumour's resistant to cisplatin. The role of this agent in relapsed Mesothelioma, both in terms of objective tumour response rate and symptom control, is being evaluated in this Phase II Open-Label Multicentre Study. This agent may add to the armamentarium of agents used to treat what is a disease with a very poor prognosis under normal circumstances.

Value Reported in October *Bulletin*

Herceptin and Taxotere in Metastatic Breast Cancer Patients - Study M77001

Recent studies indicate that Herceptin, a monoclonal antibody, 2-erbB-2 may induce tumour shrinkage in patients with relapsed Metastatic Breast Cancer (MBC). A combination of Herceptin with cytotoxic chemotherapy has also been shown to improve survival in the first line treatment of MBC. The purpose of this open access programme is to evaluate the response rate to Herceptin with or without Taxotere in the second and third line treatments of patients with MBC. Herceptin is likely to be introduced into routine practice in the near future and the experience gained in this study in handling the agent and dealing with the side effects of treatment will be of paramount importance.

Value Reported in October *Bulletin*

Prof W P Stewart

Phase II Study of BBR3464 as First Line Treatment in Patients with Gastric or Gastro-Oesophageal Adenocarcinoma (PH2/042)

£44,831.70 Novuspharma S.p.A. via Cancer Research Campaign

BCH-4556-212 Phase II Study of Toxactabine (BCH-4556) as Treatment for Patients with Cancer of the Pancreas

£4,566.55 BioChem Pharma Inc. via Ilex Services Ltd

Dr M Williams

Chemopreventive Activity of 13C

£9,855 Royal Society

PATHOLOGY (HAEMATOLOGY)

Prof J Pasi

MCMDM-1VVD - Molecular and Clinical Markers for Diagnosis and Management of Type 1 Von Willebrands Disease

£22,245 CEC via University of Sheffield

PATHOLOGY WITH UNIVERSITY OF BIRMINGHAM

Prof J Lunec, Dr M Evans

Preliminary Gene Microarray Investigation of the Genetic Basis for Early and Increased Incidence of Ischaemic Heart Disease in Rheumatoid Arthritis

Disability and pain because of damage to joints is the major cause of morbidity in patients with rheumatoid arthritis (RA); however, patients are unlikely to die from these joint problems. About half of all RA patients die because of problems with their heart, brought on by the disease. Many of the risk factors for heart disease, such as high fat diet and smoking are no greater in RA patients compared to the general population. Consequently, as yet unknown reasons related to RA itself, are the probable cause for the greater risk of heart disease in RA. Our research, using cutting edge technology to look at genes in blood cells, aims to explore possible reasons why RA patients are at more risk of heart disease compared to healthy people. Ultimately the information from our project could lead to better tests and improve patient treatment.

£74,190 Arthritis Research Campaign

PHYSICS & ASTRONOMY

Dr C Binns, Prof C Norris

Magnetic Properties of Embedded Nanoscale Clusters

A new process developed in the Physics department to manufacture thin metal films made out of pre-assembled clusters of atoms rather than single atoms offers enormous potential in the creation of new materials whose properties can be flexibly adjusted. Control of the behaviour of the material is achieved by changing the size of the deposited clusters and their landing energy on the substrate. Such 'cluster assembled materials' offer the possibility of very high performance in a number of applications. This grant, which is jointly funded by the EPSRC and Seagate Technology, Northern Ireland, is to explore the possibility of achieving a record magnetisation density by using the cluster assembly process to make

nanostructured granular Fe-Co films. If successful, the development will herald a new generation of ultra-high density magnetic storage devices.

£218,414 EPSRC

Prof A R King

Support for UKAFF Fellowship Scheme Value Reported in October *Bulletin*

Prof D Llewellyn-Jones

Supplement - AATSR Principal Investigator

£32,332 DETR

Dr J P Pye

Supplement : Contract for Experimental Spectroscopist

£18,526(supp) UKAEA

Dr J Reeves

X-Rays from Super-Massive Black Holes - Special Research Fellowship

This fellowship concerns the study of the energetic emissions from the central engines of distant quasars, the most luminous known astronomical objects in the Universe - their power is equivalent to the output of 100,000 billion Suns. The source of this enormous power is thought to be generated in the centre's of distant galaxies, at a time when the Universe was only a fraction of its current age. The most accepted paradigm is that quasars are powered by a super-massive black hole, one billion times more massive than the Sun, which releases prodigious amounts of energy when surrounding material falls inwards. My research will explore the energetic signatures of this matter, released in the form of X-rays, which are emitted before the material falls through the event horizon and into the black hole. The work will take advantage of data from ESA's new space-based X-ray astronomy telescope, XMM-Newton, which has been partly developed by scientists at the University of Leicester. This will enable us to enhance our understanding of the quasar phenomenon, exactly how the energy output is produced and how quasars evolve with time in the Universe.

£24,628 Leverhulme Trust

Prof A Wells

Supplement - Catsat Project - Amendments 3 and 4

CATSAT is an education satellite project being developed jointly by the University of New Hampshire and the University of Leicester. The satellite and its instruments are in advanced stages of development and preparation for the satellite launch in December 2001. The satellite and its instruments draw heavily on laboratory projects and development programmes performed by undergraduate and postgraduate students, working under academic supervision. All exchanges of design and test data between the USA and UK have been managed using internet and e-mail links between students of the two countries. The scientific objectives are to make new measurements of the properties of gamma-ray bursts and the Leicester instrument will use x-ray spectroscopy to study the local environment in which the gamma-ray burst occurs, i.e. whether the burst occurs within a host galaxy or as a result of merging of a pair of neutron stars in extragalactic space. The contract extension is to support completion of the satellite construction and test and preparation for mission operations,



which will be conducted through a Satellite Control Centre now being installed by the University at the National Space Science Centre.

£117,175(supp) University of New Hampshire

PHYSICS AND ASTRONOMY, CHEMISTRY

Prof A Wells, Dr P Monks

Geostationary Earth Observation

£13,250 Astrium Ltd

PHYSICS & ASTRONOMY WITH UNIVERSITY OF CAMBRIDGE

Prof A R King

UK Astrophysical Fluids Facility - Support
for Running Costs

£121,542.16 PPARC

PSYCHOLOGY

Prof C Hollin

Supplement - Evaluation of the Crime
Reduction Programme (Offenders)
Pathfinders Projects

£9,400(supp) Home Office

RESPIRATORY MEDICINE

Prof A Wardlaw

Effects of Stretching on Bronchial Epithelial
Cells - Entry Level Training Fellowship for
Medical, Dental and Veterinary Graduates -
Dr R Macdonald

This grant which funds a clinical fellow aims to test the hypothesis that stretching of resident cells in the lung particularly the cells that line the bronchi results in marked changes in their behaviour. The normal breathing cycle involves regular stretching of the cells in vivo yet most studies have investigated their behaviour in a static system. In addition lung diseases are often associated with hyperventilation which results in increased stretching and even the normal respiratory cycle involves the occasional deep breath which is crucial to normal regulation of breathing. In collaboration with Professor Bryan Williams who has studied this question in the

context of stretching of the vascular endothelium we aim to see whether the different patterns of stretching of bronchial epithelial cells causes them to release more or different mediators which might affect both their behaviour and that of the underlying smooth muscle; as an important mechanism for regulating our breathing in both health and disease.

£49,025 Wellcome Trust

Genetics of COPD

£4,427 Glenfield Hospital NHS Trust

SCARMAN CENTRE

Mr A Beck

The Development of Crime Reduction Schemes for At-Risk Groups: Context-Specific Approaches for Transitional Societies Funded by the Department for International Development, and working with colleagues in Omsk, Smolensk and Volgograd, this three year project aims to critically evaluate how the police in these three Russian cities currently respond to the problem of domestic burglary. Using the wealth of experience in the UK on preventing and detecting burglary, the project will then implement a series of burglary reduction schemes deemed to be most appropriate within the context of Russia. In addition, the project also intends to develop a new course on crime prevention, to be taught in the first instance, at the training institutes in each of the chosen cities, and then more broadly across the Russian Federation. Finally, the project will attempt to develop a better theoretical understanding of how crime impacts upon states in transition and whether there are lessons to be learnt from this project for other central and east European countries.

£254,163 Department for International
Development

Dr M Gill

Supp. - Evaluation of 21 Burglary Strategic
Development Projects in the Yorkshire and
the Humber, East Midlands and East
Regions

£25,842 Home Office via University of Keele

Dr T Skinner

Domestic Violence and Mental Health

£4,094 Leicestershire Health

Dr L Vassie

Development of a Continuous Improvement
Process for Health and Safety Management

A key element in achieving continuous improvement in health and safety management is the involvement and participation of employees at all levels of the organisation in health and safety related activities, including health and safety improvement programmes.

The aims of the project are to:

- develop an approach to achieving continuous improvement in health and safety performance through employee involvement in a process which promotes and measures safe working practice; and
- facilitate the implementation of the improvement process.

The proposed approach to achieving continuous improvement in health and safety performance comprises four stages:

- (i) assessment of the organisation's current health and safety management performance;
- (ii) development of a framework, goals and targets for the proposed improvement process;
- (iii) training in supporting techniques; and
- (iv) formalisation of the process management system.

£55,860 Unilever

Dr L Vassie, Dr C Fuller

Health and Safety Survey

£8,670 Magnox Electric plc

SOCIOLOGY WITH ROEHAMPTON INSTITUTE

Prof S Westwood

Globalisation and Regional Developments =
The Case of Bangladesh

£42,614 ESRC

SURGERY

Prof P R F Bell

Supplement - Non Heart Beating Donor
Programme - Research Fellow

£222,254(supp - Leicester General Hospital includes
£158,760 previously unreported)

Mr M Galinanes

The Role of Adrenoreceptors in
Ischaemia/Reperfusion Injury

£2,950 Mason Medical Research Foundation

Dr R James, Dr S Swift, Prof P R F Bell

Maintenance of the Human Islet Facility at
the University of Leicester and supply of
Human Islets for BDA and other Diabetes
Research Grant Funded Projects

£87,012 Diabetes UK

Mr M M Thompson, Prof P R F Bell

The Pathophysiological Consequences of
Endovascular Repair of Ruptured Abdominal
Aortic Aneurysms

£16,000 Sir Jules Thorn Charitable Trust





DEPARTMENT OF CELL PHYSIOLOGY AND PHARMACOLOGY AWARDED £3 MILLION OF NEW RESEARCH GRANTS

Over the last 6 months research teams in the Department of Cell Physiology and Pharmacology have been awarded 12 new external research grants amounting to almost £3 million. These include the establishment of a Medical Research Council Co-operative Group with two component grants and a Wellcome Trust 5 year Programme Grant.

A major project grant from BBSRC (£245,000) to investigate the role of the stress-activated protein kinases in mitotic cell cycle arrest has been awarded to Dr Jonathan Blank in collaboration with Drs Martin Dickens and Raj Patel (Biochemistry).

A Wellcome Trust equipment grant of £170,000 to purchase a confocal imaging system will enhance projects lead by Dr Gary Willars, Dr Caroline Dart, Professor Steve Nahorski. Professor Nick Standen and Dr Andrew Tobin. The Trust also awarded project grants of £74,000 to Dr Caroline Dart to study PDZ-domain proteins in regulating the distribution and function of inwardly rectifying K⁺ channels and Dr J D Cavieres £179,000 to investigate the binding sites for ATP on the enzyme Na,K-ATPase.

Professor Nick Standen and Dr Noel Davies have received £134,000 from the British Heart Foundation to investigate K⁺ ATP channels and Ca²⁺ signalling in cardiac myocytes.

Finally, a series of industrially funded grants: Pfizer £149,000, Novartis £61,000 to Dr John Challiss and Professor Steve Nahorski who will examine different aspects of acetylcholine muscarinic receptor signalling and the potential for the development of new drugs. Furthermore, Glaxo-Wellcome have awarded Dr Blair Grubb £135,000 to examine the expression of G-protein coupled receptors in sensory neurones. These grants will predominantly fund investigation of the mechanisms that regulate the communication between individual cells in the cardiovascular and central nervous systems. It is generally agreed that dysfunction of such communication underlies diverse diseases such as hypertension, strokes and perhaps depression, schizophrenia and senile dementia. Certainly new drug treatments increase target cell-cell communication.

"The competition for external research funding is at its fiercest in this run up to RAE 2001 and these substantial grants reflect the overall international standing of research within the Department of Cell Physiology and Pharmacology here in Leicester" said Professor Nahorski.

MAJOR NEUROSCIENCE INVESTMENTS IN CELL PHYSIOLOGY AND PHARMACOLOGY

Recent investments within the Department of Cell Physiology and Pharmacology emphasise the development of neuroscience research in the University.

The Department has been awarded only the second MRC Co-operative Group grant to the University. Such grants were initiated about three years ago with the aim of encouraging focussed and collaborative research and each Cooperative consists of a 5 year group grant to which any number of 3 year component grants can be added. This grant is for £613,000 and consists of a Co-operative Group Grant and two component project grants. The Co-operative is entitled '*Integration and Modulation of Synaptic Transmission*' whereas the two component grants are lead by Dr Richard Evans (*The role of P2 receptors in the brainstem and spinal cord*) and Dr Blair Grubb (*The role of potassium channels in regulating neuronal excitability in primary afferent nociceptors*). The Co-op also includes a Wellcome Trust Programme grant awarded to Professor Ian Forsythe who is the Co-op Convenor. The establishment of such a research Co-op is crucial to the development of MRC

funding of neuroscience in Leicester in that it now provides the basis for further component grant applications over the next 5 years.

In addition, a new 5 year Programme Grant, totalling £959,000 from the Wellcome Trust entitled 'Regulation of Ca²⁺ mobilising G-protein coupled receptors in neurones' has been awarded to Professor Steve Nahorski and Dr John Challiss. This grant will predominantly examine the role of certain members of the large family of G-protein coupled neurotransmitter receptors in the central nervous system and in particular to use recently developed methods to image sub-cellular signalling events in living single nerve cells.

Both these research initiatives in neuroscience are linked through a common theme of signalling with the aim of exploring mechanisms of communication between nerve cells within the brain. All neurones pass information to their neighbours by releasing chemical messengers in response to electrical signals in a process known as synaptic transmission. Understanding this process is crucial to i.e. our abilities to sense our environment, to think, to move, to learn and remember. Many psychiatric and neurological disorders arise from dysfunction of synaptic signalling; i.e.

epilepsy/schizophrenia, depression, Alzheimer's and Parkinson's disease. The significance of these awards in neuroscience are emphasised by the recent announcements that this year's Nobel Prize for Physiology and Medicine was awarded jointly to Arvid Carlsson, Paul Greengard and Eric Kandel for their discoveries concerning signal transduction in the nervous system.

Further developments are anticipated with the appointment of a new University funded Readership/Chair in neuroscience and the recent appointment of Professor Pierluigi Nicotera as director of the MRC Centre for Mechanisms in Human Toxicity (CMHT) is of particular significance since his research interests include neurodegeneration and mechanisms of neuronal apoptosis. Professor Nicotera holds a Honorary Chair of Neuroscience in the Department of Cell Physiology and Pharmacology and Ian Forsythe has also recently been promoted to a Personal Chair of Neuroscience in the same Department.

"We anticipate that these developments will give critical mass to establish neuroscience as a major new interdepartmental discipline at the University of Leicester, CMHT and hopefully in a clinical context within the Leicester/Warwick Medical School" commented Professor Nahorski.