BCM BITES

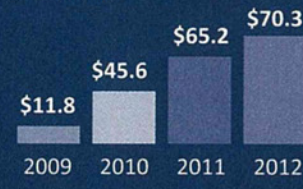
Fiscal stability is a necessary prerequisite to fullfilling the mission of Baylor College of Medicine to set the standards for excellence in training of health care providers and scientists, innovative scientific achievement and provision of patient-centered care in service to our community and our world.

As the country, and in particular, healthcare institutions, in the U.S. have struggled over the last few years, BCM has also had its share of challenges.

With a new leadership team in place since mid-2010 and an institution-wide focus on fiscal discipline and strategic growth, BCM is building a strong financial foundation for future growth.

OPERATIONS

Cash Flow from Operations
in millions



Total grant applications submitted to all funding sources grew by

18.5%

from FY 2011 to FY 2012.

RESEARCH FUNDING

Total Research Funding
in millions

In FY 2011, BCM submitted **635 applications** to the National Institutes of Health. Of these, 136 were funded for a success rate of **21.8%**.

The national average success rate for 2011 was 18% according to the NIH. Comparable numbers for FY 2012 are not available yet.

CLINICAL CARE REVENUE

Medical services revenue grew by **12.7%** from FY 2011 to FY 2012

Affliliiliate hospital contract revenue grew by **14.7%** from FY 2011 to FY 2012

PHILANTHROPY

Total commitment to the Best Minds Best Medicine campaign in FY 2012 reached

$160 million

NHS
National Institute for Health Research

NIHR Cambridge Biomedical Research Centre

28 January 201

NIHR
Cambridge Biomedical Research Centre

NIHR
Cambridge Biomedical Research Centre

Aims of the Presentation

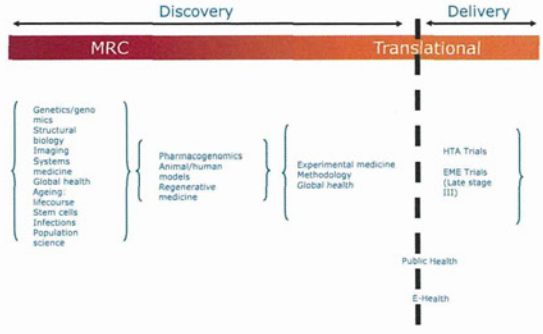
Overview of the NIHR Cambridge Biomedical Research Centre

NIHR
Cambridge Biomedical Research Centre

Key organisations and partnerships

- Cambridge University Hospitals NHS Foundation Trust
- University of Cambridge School of Clinical Medicine
- NIHR
  - Cambridge Biomedical Research Centre
  - West Anglia Comprehensive Local Research Network
- Wellcome Trust Clinical Research Facilities
- CRUK Cambridge Research institute
  - 22 Research Groups
  - Additional core facilities
- MRC Centres and Units
  - MRC Biostatistics Unit

NIHR
Cambridge Biomedical Research Centre



NIHR
Cambridge Biomedical Research Centre

- Economic **growth**
- **Life Science industries** as an engine of growth
- **Health research** as a driver of growth - international competitiveness
- Crucial role of **translational research** in harnessing basic/discovery science
- Partnership between **Universities, NHS and Industry** in driving economic benefits - through open collaboration and health improvement - through research and education
- Partnership between **research funders**
- Crucial role of **NHS** in supporting research, adoption and uptake of innovation

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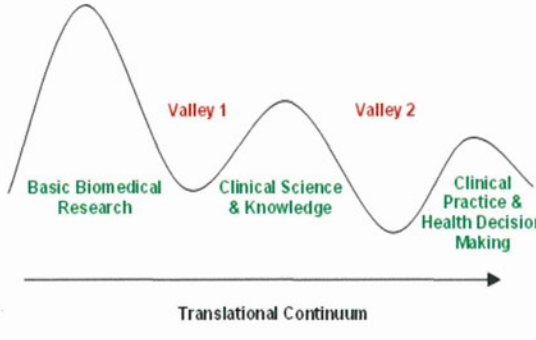

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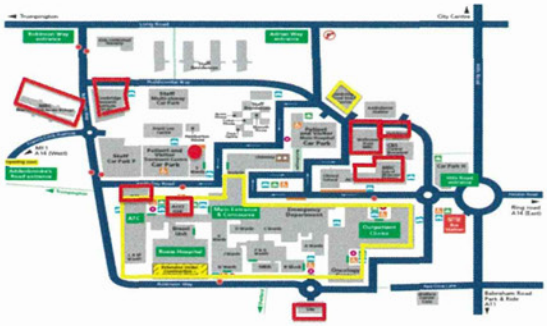

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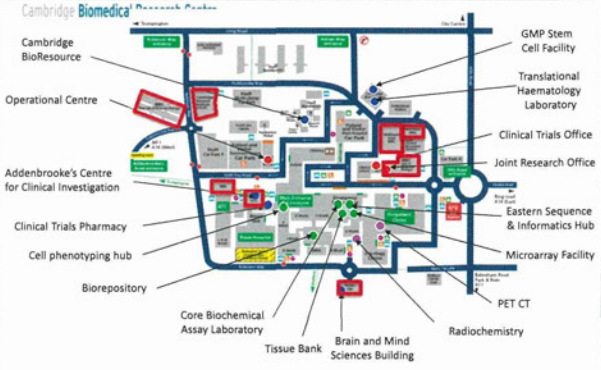

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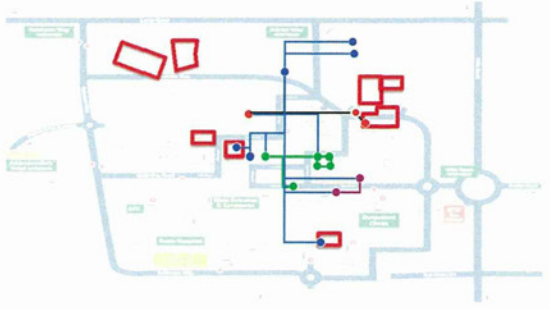

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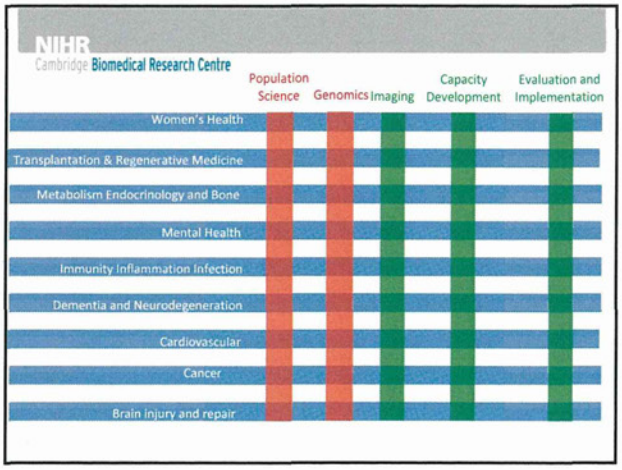

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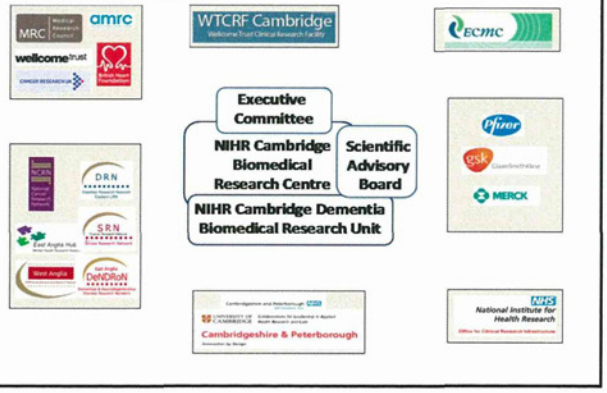

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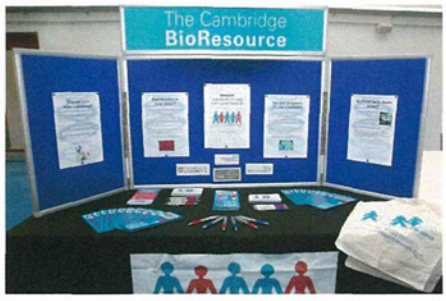

Cambridge BioResource

School of Clinical Medicine

Research Directory 2009–2011

UNIVERSITY OF CAMBRIDGE

Introduction

It is my pleasure to introduce the *Research Directory for the School of Clinical Medicine* at Cambridge University for 2009–2011.

This Research Directory provides a brief description, department by department of the main areas of our research and lists a small number of our key publications. As a document of record, it is presented on a departmental basis, although of course this belies the reality of how modern medical research takes place: multi-disciplinary teams, thematically, and across departments. Readers interested in a fuller description of our research may wish to consult, in addition to this Directory, our Bi-ennial Review and the research pages on our website www.medschl.cam.ac.uk

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PJ Voshol
GS Yeo

NHS Consultants (Dept of Clinical Biochemistry and Immunology)

J Calvin
D Halsall
DS Kumararatne
A Park
A Sarker

Research synopsis

Research in the Department is focused on two areas: a) the aetiology and pathogenesis of obesity, diabetes and related metabolic disorders, and b) the molecular cell biology of membrane traffic. Investigators working in metabolic disorders are largely based in the Institute of Metabolic Science (IMS). The Cell Biology group is located entirely in The Cambridge Institute for Medical Research (CIMR). The Department has played a leading role in several recent major initiatives, including the opening of the IMS, the creation of the MRC Centre for Obesity and Related Metabolic Disease (MRC CORD) and the Cambridge Phenomics Centre. Professor Stephen O'Rahilly is Scientific Director of the NIHR Cambridge Biomedical Research Centre, and leads the Metabolic, Endocrine and Bone Theme.

Diabetes, Obesity and Metabolism Group

Research themes include the following: molecular mechanisms in human obesity insulin resistance and type 2 diabetes (Barroso, Farooqi, O'Rahilly, Savage, Semple, in collaboration with Prof NJ Wareham and colleagues from the MRC Epidemiology Unit) neurobiology of hunger and satiety (Farooqi, with Prof P Fletcher, Dept of Psychiatry); animal models of obesity and insulin resistance (Coll, Sethi, O'Rahilly, Voshol, Vidal-Puig, Yeo); adipocyte biology (Rochford, Sethi, Vidal-Puig) and how this relates to 'lipotoxicity' resulting from inappropriate storage of excess lipids (Vidal-Puig); developmental programming of late-onset metabolic disease (Ozanne); signaling by insulin and insulin-like growth factors (Semple, Siddle); endoplasmic reticulum stress (Ron, Harding, Volmer), entero-endocrine physiology (Gribble, Reimann), non-transcriptional control of circadian rhythms (O'Neill) and improving health outcomes in diabetes. (Murphy)

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Intracellular Membrane Trafficking Group

Investigators working on the molecular cell biology of intracellular membrane traffic are based in the Cambridge Institute for Medical Research (CIMR). These investigators are: Paul Luzio, working on endocytic pathways and lysosome biogenesis; Margaret Robinson, studying adaptor complexes in coated vesicles; David Owen, studying the structures of proteins involved in membrane traffic; Folma Buss, studying molecular motors and their role in organelle/vesicle movement; Matthew Seaman, studying retrograde traffic between lysosomes/vacuoles and the Golgi complex; Andrew Peden, working on proteins involved in membrane fusion; and Symeon Siniossoglou, studying how lipids regulate the structure and function of membranes and organelles.

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NHS Department of Clinical Biochemistry and Immunology

Members of the NHS department run the genomics (Dr Ian McFarlane) and Biochemical Assay (Keith Burling) Core Laboratories of the NIHR Cambridge Biomedical Research Centre. Drs Kumararanatne and Doffinger investigate the molecular basis of the immune deficiencies. Dr Halsall runs specialist endocrine services with important links to genetic research.

Clinical Neuroscience

Head of Department and Professor of Neurology

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JW Fawcett, Professor of Experimental Neurology, Chairman of the Brain Repair Centre
K Martin, Professor of Ophthalmology
JD Pickard, Professor of Neurosurgery, Chairman of Wolfson Brain Imaging Centre and NHS Divisional Director for the Clinical Neurosciences
M-G Spillantini, Professor of Molecular Neurology
P St George Hyslop, Professor of Experimental Neuroscience and Wellcome Trust Principal Research Fellow

Readers

A Carpenter, Reader in Imaging Sciences
M Czosnyka, Reader in Brain Physics
P Hutchinson, Reader in Neurotrauma
JB Rowe, Reader in Cognitive Neurology
S J Sawcer, Reader in Neurogenetics

University Lecturers

AJ Coles
P Nestor
S Pluchino
C Watts

Senior Research Staff

FI Aigbirhio
K Carpenter
Z Czosnyka
T Fryer
Y Hong
S Price
A Reddy
H Richards
R Roberts
P Smielewski
G Williams
D Williamson

NHS Consultants/Associate Lecturers

C Allen
R Laing
R MacFarlane
M Manford
P Kirkpatrick
E Warburton

Main research themes

Traumatic brain injury and stroke

The Wolfson Brain Imaging Centre (WBIC) uses positron emission tomography (PET) and magnetic resonance (MR) data to investigate disease mechanisms in traumatic brain injury and neurodegeneration. Adrian Carpenter is establishing the technology for combined PET/MR imaging and elastography. Franklin Aigbirhio is developing novel radiopharmaceutical probes for molecular imaging using PET. Tim Fryer directs an imaging programme that has introduced experimental microPET and the computing support for experimental and clinical aspects of PET and Cyclotron physics. Guy Williams directs the computing and imaging MR science group with the development of real-time MR for brain-computer interface studies of patients with low awareness.

Marek Czosnyka leads the neurosurgical physics group whose research focuses on cerebral autoregulation following head injury and subarachnoid haemorrhage, and the importance of cerebrovascular and CSF dynamics for hydrocephalus and idiopathic intracranial hypertension. Peter Smielewski has developed software (www.neurosurg.cam.ac.uk/icmplus) required to capture and analyse real-time signals derived from bedside monitoring now introduced into several neuroscience intensive care units worldwide.

John Pickard leads a research group that explores the pathophysiology of traumatic brain injury from initial ictus through intensive care to final outcome using PET, MR and multimodality bedside monitoring. Recent advances include the definition of how early insults after head injury lead to late changes in the brain and cognitive outcome, the effects of cognitive stimulation on brain activation in altered states of consciousness (with David Menon, Department of Medicine), and new insights into parts of the brain affected by hydrocephalus and idiopathic intracranial hypertension including the development of venous stenting (with Nicholas Higgins, Neuroradiology).

Peter Hutchinson has developed care pathways from acute emergency treatment through to neuro-rehabilitation and leads the MRC RESCUEicp (evaluation of Decompressive Craniectomy for raised intracranial pressure following trauma: www.RESCUEicp.com). With Keri Carpenter, he uses intracerebral microdialysis to study changes in metabolic pathways and energy substrates used by the brain to conserve function after traumatic injury; the role of acute inflammation after head injury; and the penetration of neuroprotective agents across the blood brain barrier.

Peter Kirkpatrick leads translational research into neuroprotection, carotid atheroma imaging, and the pathophysiology of cerebrovascular disease. He uses non-invasive assessments of cerebral haemodynamics to improve outcome from cerebrovascular neurosurgical procedures; and leads the STASH (STatins in Aneurysmal Subarachnoid Haemorrhage) trial.

Liz Warburton is studying mechanisms of deterioration and recovery of speech and motor function after stroke. Perfusion and metabolic consequences of acute stroke and the nature of tissue injury are being characterised; and carotid artery plaque imaged and correlated with microembolism and watershed ischaemia. Plasticity for motor, visual and language functions is being studied in relation to clinical outcome using MRI and PET.

Dementia and neurodegeneration

Peter St George Hyslop studies the genetics of Alzheimer's and related disorders and is using structural biology to develop novel molecules for inhibiting the formation of intracellular protein aggregates that destroy nerve cells.

Peter Nestor works in the Herchel Smith Building for Brain and Mind Sciences on the early features of Alzheimer's disease, frontotemporal dementia, and related disorders – combining cognitive neuropsychology with structural, metabolic and amyloid brain imaging, and quantitative neuropathology. Recent work has focused on defining the nature of early neuronal vulnerability in incipient Alzheimer's disease and the development of structural image analyses as surrogates for the regional molecular pathology.

Maria-Grazia Spillantini has provided molecular classifications for disorders characterised by intracellular aggregates of microtubule-associated proteins (tau and alpha-synuclein) and studies mechanisms of intracellular protein aggregation in human brain tissue and transgenic mice. The focus is on accumulation of alpha-synuclein in the substantia nigra and studies on the microtubule associated protein tau which binds the motor protein dynactin and is abnormally distributed in the brain of patients with MAPT mutations and relevant transgenic mice.

James Rowe provides a bridge between the Department of Clinical Neurosciences, the Herchel Smith Building for Brain and Mind Sciences and the MRC Cognition and Brain Sciences Unit. He investigates behavioural disorders associated with neurodegenerative disease and focal brain injury using structural and functional magnetic resonance imaging and magnetoencephalography. The focus is on restoring function in the brain networks that enable the cognitive control of actions in neurodegeneration, especially Parkinson's disease, frontotemporal dementia and progressive supranuclear palsy.

Roger Barker conducts clinical work that improves prediction across the spectrum of clinical deficits in Parkinson's and Huntington's disease using biomarkers for the natural history and heterogeneity of these disorders in epidemiological studies of cohorts studied for clinical and imaging phenotypes, and genomics. He studies abnormalities in adult neural stem cell turnover and differentiation in transgenic models of neurodegeneration, work that has implications for the translation of novel therapies including the use of cell-based therapies for Parkinson's and Huntington's disease.

Plasticity and brain repair

James Fawcett works on recovery of function through adaptation, plasticity and repair of the injured brain and spinal cord. In axon regeneration the focus is on removing inhibitory chondroitin sulphate proteoglycans produced in scar tissue after damage, and using integrin engineering to enhance the ability of axons to regenerate. In plasticity, the enzyme chondroitinase is being used to degrade the inhibitory proteoglycan structures that normally prevent plasticity in the adult nervous system. The work is seeing applications not only in experimental studies of injury but also in neurodegeneration including Alzheimer's disease.

Keith Martin studies the mechanisms of visual loss in glaucoma, and is currently investigating the integration of stem cells into the retina in experimental glaucoma, and studying the role of axonal transport dysfunction associated with glaucomatous retinal ganglion cell death.

Stefano Pluchino works in regenerative neuroscience and studies the physiology of neural stem cells and their application in cell therapies for repair of the central nervous system. He also aims at modeling their role in modulating the fate of inflammatory and degenerative lesions – work that relates to the clinical problems of multiple sclerosis, stroke, spinal cord injury, Parkinson's disease and glioma.

Multiple sclerosis

Stephen Sawcer and Alastair Compston use whole genome screening to study the genetics of multiple sclerosis and Parkinson's disease as part of national and international consortia. They have recently identified 57 susceptibility genes, including 34 not previously considered, that demonstrate a genetic basis for the primary role of cell-mediated immune mechanisms in the pathogenesis of multiple sclerosis.

Alasdair Coles and Alastair Compston lead international trials of lemtrada (formerly Campath-1H and alemtuzumab) in early active relapsing-remitting multiple sclerosis; results from the two Phase III trials will be available in 2011 with proposed application for a drug licence in 2012. Their laboratory work focuses on the mechanisms of autoimmunity after alemtuzumab; strategies to avoid the development of anti-idiotypic auto-antibodies; and interactions between inflammatory and neurobiological processes that underlie the sustained recovery of function seen in most patients. A Phase II study in secondary progressive multiple sclerosis using autologous bone marrow-derived mesenchymal stem cells showing preliminary evidence for structural, functional and physiological improvement consistent with neuroprotection has recently been completed.

Other topics

Colin Watts has a programme of research in neuro-oncology that combines Phase I/II clinical trials with biomarker-based stratification of participants; development and evaluation of a Brain Tumour Symptom Algorithm for Primary Care (BraTSA: collaboration with the Cambridge University Primary Care Research Unit); and improved treatment for cerebral metastatic disease. Stephen Price is developing a research programme using MR and PET imaging to understand heterogeneity in brain tumours; the main focus is in studying the invasiveness of glioblastomas and understanding the biology of glioma invasion in individual patients (the MALTING Study).

Akhilesh Reddy works in the Institute of Metabolic Science on circadian rhythms in eukaryotic cells and microorganisms. Rhys Roberts works in the Cambridge Institute for Medical Research on membrane traffic and recirculating endosomes in the context of genetic disorders of peripheral nerve.

Clinical Neuroscience

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WH Ouwehand, Professor of Experimental Haematology
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K Ottersbach
P Smethurst
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PJ Campbell
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C Crawley
Dr G Follows
D Foukaneli
M Gattens
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M Scott
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M Van't Veer
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Voluntary Research Agreement

J-P Allain

Clinical Lecturers

N Bolli
CC Wong

Research synopsis

Research in the department falls into three main areas with major relevance for human disease. The Haematopoiesis and Leukaemia Group are based in the Cambridge Institute for Medical Research (Professor Green, Professor Göttgens, Dr Huntly, Dr Ottersbach) and the MRC Laboratory of Molecular Biology (Professor Warren). The Structural Medicine and Thrombosis Group (Professor Read, Professor Huntington) are based in the CIMR, and the Transfusion Medicine Group (Professor Allain, Dr Lee, Professor Ouwehand, Dr Ghevaert) are based in the NHS Blood and Transplant Building. Recent research initiatives include the establishment of a $6.0m Specialist Centre for Research, funded by the US Leukemia and Lymphoma Society, the only one in Europe. The department has also played a leading role in establishing a £5.8m European Bloodomics programme.

Haematopoiesis and leukaemia

Haematopoiesis represent the best characterised adult stem cell system and continues to provide important paradigms for understanding other stem cells as well as cancer biology. The focus of this group continues to be the transcriptional regulation of blood stem cells, and the mechanisms whereby such stem cells are subverted to form leukaemias.
Current research programmes include:

1. Myeloproliferative neoplasms, JAK/STAT signalling and stem cell subversion (Professor Green).
2. Transcriptional networks regulating blood stem cells (Professor Göttgens).
3. The pathogenesis of bone marrow failure syndromes and leukaemia (Professor Warren).
4. The biology of leukaemia stem cells (Dr Huntly).
5. The developmental origin of haematopoietic stem cells (Dr Ottersbach).

Structural medicine and thrombosis

Structural biology gives an unparalleled insight into the molecular details of biological mechanisms, an insight that has the potential to lead to rationally-designed therapies. This is illustrated by some recent studies. Professor Huntington is studying the details of the delicate control of coagulation by members of the serpin family of serine protease inhibitors; over the past year, new insights have been gained into the control by serpins of factor IXa and thrombin. Dr Zhou is studying members of the serpin family adapted for non-inhibitory roles, with a series of structures of angiotensinogen and its complex with renin revealing a new mechanism by which oxidative stress modulates the control of blood pressure. The determination of such structures is heavily driven by computer methods, an area to which Professor Read's group is making significant contributions.

Transfusion medicine

The focus of transfusion medicine research is in blood borne viruses, diagnostics and transfusion in resource poor areas, biology and genomics of megakaryocytes and platelets. Particular highlights include:

1. Global studies of the molecular epidemiology of Hepatitis B virus in collaboration with major blood centres around the world. The genomes of HBsAg- and HBsAg+ strains have been sequenced and analysed. (Professor J-P Allain).
2. A Genome-Wide Association Study meta-analysis which identified 15 genetic loci that regulate the volume and count of platelets and the discovery of novel genetic loci that regulate platelet function (Professor H Ouwehand).
3. A rapid low cost diagnostic test for Chlamydia trachomatis has been developed and is now widely available. A test for HBsAg is being submitted for licensing (Dr H Lee).

Haematology

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Research synopsis

The Division combines research, teaching and diagnostic histopathology. The research focuses on analysing the molecular and cell biology of disease and applying advances in this area to clinical histopathology, and where relevant, therapy.

The Division takes part in the teaching and examining of Pathological Sciences in Pt. Ib and Pt. II tripos as well as being responsible for the clinical pathology course at Addenbrooke's and the Final MB Part I Examination. The Division has a number of major projects, studying in particular neoplastic disease. These include the study of human tumours of the central nervous system, tumours of the lower intestinal tract, lymphomas, breast and ovarian tumours. Many of the projects are in collaboration with other research groups within Addenbrooke's or the University of Cambridge. The Division has an established tissue bank, and through this can provide researchers with well-characterised human tissue, subject to project approval by NHS R&D and NRES.

The Cambridge Brain Bank, a division of the Tissue Bank is also located in the Division and underpins a number of major projects on aging and degenerative neurological disease.

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Research synopsis

The Department's research examines mechanisms responsible for important single gene and polygenic disorders. The major areas under study include: type 1 diabetes; neurological diseases such as Huntington's disease; hereditary spastic paraplegias; renal disorders such as renal tubular acidosis and polycystic kidney disease; X-linked intellectual disability disorders; prenatal brain growth and genetics disorders of pain sensing.

The Department currently has particular strengths in three major areas:

1 Large scale gene mapping, expression, functional, statistical and bioinformatic technologies, being applied to developing strategies for the primary prevention of type 1 diabetes in the Juvenile Diabetes Research Foundation/Wellcome Trust Diabetes and Inflammation Laboratory; and to X-linked intellectual disabilities.

2 Experimental analysis of the molecular cell biology of genetic disease, with novel disease mechanisms identified over the last two years for a number of different kidney, renal and neurological disorders.

3 Development of therapeutic strategies for brain and muscle diseases associated with intracellular aggregate formation and autophagy.

The expectation is that this research into genetic cause and mechanism will lead, in the long term, to treatments for genetic diseases.

Medical Genetics is also a major participant and contributor to the National Institute for Health Research Cambridge Biomedical Research Centre, which focuses on translational experimental medicine studies in neurodegeneration, clinical genetics, renal disease and type 1 diabetes. The Department is actively involved in two cross-cutting activities, the Eastern Sequence and Informatics Hub and the Cambridge BioResource, providing key resources for the Biomedical Research Centre.

Whilst most research is carried out in the Cambridge Institute for Medical Research the Academic Laboratory of Medical Genetics is located alongside the Clinical Department on level 6 of the Addenbrooke's Treatment Centre. The medically qualified members of the Department also have clinical duties, and there is close interaction and joint projects between the University and NHS departments.

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Research synopsis

The Department of Medicine is one of the largest in the Clinical School comprising 11 Divisions and over 400 members of staff, including 22 professors, and holding current grants in excess of £38m. The Department has an active research programme whose broad aim is to understand disease processes at the molecular level and apply this knowledge to clinical management. The thematic focus of the Department of Medicine is in the broad area of immunity, inflammation and infection, and a number of new posts are currently being appointed to increase the Department's strength in these areas. The Department is also home to the NIHR Biomedical Research Centre Cell Phenotyping Hub, which provides state of the art flow cytometry facilities for unscreened human samples.

Medicine

Anaesthesia

The research in the Division has three main strands: The first involves physiological imaging in traumatic brain injury (TBI), at all stages, from ictus to late outcome. Positron emission tomography (PET) and magnetic resonance imaging (MRI) in the acute phase currently addresses novel mechanisms of energy failure, including diffusion hypoxia and mitochondrial dysfunction. Allied studies have addressed the mechanisms of action of novel interventions such as hyperoxia. Our late studies with 11C-flumazenil PET have shown selective neuronal loss and late diffusion weighted imaging has been used to map the extent and severity of white matter loss. Both of these subtle sequelae of TBI are missed by conventional MR imaging, and may account for the mismatch between structural lesions and cognitive outcomes. A second strand focuses on the neuro-anatomical basis of coma and consciousness, both in pathological states, and in the controlled situation of sedation induced by anaesthetic agents. Finally, the Division has a growing program in pain research that involves functional imaging, pain phenotyping and pain genetics.

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Cardiovascular Medicine

The Division has assembled a collaborative group of cardiovascular investigators who collectively provide expertise in basic, translational and clinical cardiovascular research and who employ genomics, epigenetics, high throughput sequencing, biomarker identification and validation, through to novel imaging, diagnostics and experimental medicine studies to improve patient outcomes. Atherosclerosis leading to myocardial infarction (MI) and stroke is the commonest cause of death in the UK. Inflammation, cell death (apoptosis), and cell senescence in atherosclerotic plaques are major contributors to plaque rupture and MI, and cardiomyocyte apoptosis underlies heart failure. Our research examines the causes and regulation of these processes in atherosclerosis, with a particular focus on DNA damage, and more recently the role of epigenetics in human heart failure. Professor Ziad Mallat has recently joined the Division, with a major interest in immune regulation of atherosclerosis and aneurysm formation, and Dr Helle Jørgensen as a University Lecturer interested in epigenetic regulation of stem cell differentiation, to support the MRC-funded Cambridge Cardiovascular Consortium, a network of researchers focused on cardiovascular stem cells and development.

The Division's major clinical research interests include the diagnosis of heart failure, assessment of viability in dysfunctional myocardium, and the utility of transient ischaemia or novel therapeutics to protect the heart from further insults. We have developed metabolic cardioprotection during PCI (both primary emergency and elective intervention), examined the effect of new agents to treat diabetes on cardiac performance in type 2 diabetes, and determined the optimum use of cardiac resynchronisation therapy based on the underlying pathophysiology. As part of our unstable atherosclerosis and aneurysm programme, we have developed novel methods and ligands for imaging of unstable plaques, particularly using PET, CT and VH-IVUS, to utilise imaging for risk stratification and to monitor drug therapy. We are determining (a) whether inflammation, hypoxia and neovascularisation detected by PET/CT and MRI at baseline predict future aortic aneurysm expansion over a 3-year period: (b) the mechanism of increased cardiovascular death in patients with rheumatoid arthritis, using PET/CT to detect changes in arterial inflammation after anti-TNFalpha therapy: (c) whether a novel anti-atherosclerosis drug could reduce vascular inflammation. This was the world's first multi-centre PET/CT vascular imaging study, conducted in collaboration with GSK.

Selected references

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Clinical Pharmacology

This Division hosts the £5.5m Wellcome Trust/GSK interdisciplinary training programme in Translational Medicine and Therapeutics, which includes a full- or part-time MPhil in Translational Medicine, and annual competitions for posts as MBPhD,

ACF, PhD Fellowship, and Clinical Lectureships. The programme enables trainees in almost any branch of Medicine to acquire skills that bridge the bench-to-bedside divide. The division's internal research interests are:

1 Professor Morris Brown investigates genetic and non-genetic approaches to relating pathogenesis of hypertension to finding the best treatment or cure in individual patients. Clinically, he leads the BHF's multicentre programme of trials, PATHWAY, which will lead to the routine use of plasma renin analysis, and has validated use of 11C-metomidate for PET-CT scanning of Conn's adenomas of the adrenal. Laboratory discoveries include the finding of somatic mutation of a K+ channel in 50% of 50 Conn's adenomas, and the role of an orphan G-protein coupled receptor (GPCR), GPR61, in regulating aldosterone secretion.
2 Dr Anthony Davenport studies apelin and other novel G-protein couple receptors that are emerging as drug targets. He has identified apelin peptides as transmitters in the human cardiovascular system with potent inotropic and vascular actions. In collaboration with the Department of Chemistry selective agonists and the first apelin antagonists have been discovered.
3 Dr Ian Wilkinson studies large artery function and endothelial function. He holds a BHF Senior Clinical Fellowship, which centres on dissecting out the mechanisms responsible for arteriosclerosis or arterial stiffening, which underlies systolic hypertension. Thus far inflammation and calcification have been identified as important drivers of stiffness. He was recently awarded a £3m TSB grant to identify cardiovascular biomarkers in patients with COPD and test the effectiveness of two novel GSK compounds.
4 Dr Thomas Krieg investigates pathways of myocardial protection following ischaemic injury.

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Diabetes & Endocrinology

This Division has three main areas of research:

1 Dr Evans is interested in (1) how the brain detects changes in blood glucose and how this glucose-sensing interacts with peripheral metabolism, (2) how defences against hypoglycaemia may become abnormal in diabetes, (3) the effects of hypoglycaemia on the brain, and (4) improving the ability of patients with type 1 diabetes to manage their own diabetes through structured education and judicious use of new and innovative technology for monitoring and managing diabetes, including in collaboration with Dr Roman Hovorka (Department of Paediatrics) and colleagues, the closed loop insulin pump systems (the 'artificial pancreas').
2 Dr Gurnell's research interests include (i) the role of nuclear hormone receptors in human disease, and genetic disorders of the hypothalamic-pituitary-thyroid axis, (ii) functional imaging in endocrine neoplasia, (iii) novel approaches to sparing hypothalamic-pituitary function in patients with sellar/parasellar tumours, and (iv) the endocrine and neural basis of financial decision making.
3 Professor Chatterjee's research interests relate to disorders of nuclear hormone synthesis and action. He is studying several human cohorts: congenital hypothyroidism (CH) that is familial, syndromic or on a consanguineous background; Resistance to Thyroid Hormone (RTH); and lipodystrophic insulin resistance associated with PPARγ gene defects. Candidate gene and whole exome approaches are used to identify novel genetic aetiologies mediating thyroid dysgenesis or hormonogenesis and defective hormone action. These approaches are supported by human phenotypic studies, studies in multisystem selenoprotein deficiency disorders and translation through our national diagnostic laboratory service to develop biomarkers of hormone action and therapies applicable to commoner thyroid disorders.

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Gastoenterology and Hepatology

Research in this Division focuses on immunity and inflammation and its consequences, and the genetic underpinning of gastrointestinal diseases.

1. Professor Kaser's group has a research focus on inflammation at mucosal body surfaces and inflammatory bowel disease (IBD). Specifically his group investigates the role of the intestinal epithelium at the interface between the intestinal microbiota and the sterile host environment, with a particular interest in the epithelium's endoplasmic reticulum stress response.
2. Dr Parkes investigates the genetic basis of IBD through genome-wide association studies (GWAS) performed in collaboration with the Wellcome Trust Sanger Centre. He has also been leading the International IBD Genetics consortium's GWAS meta-analysis, which revealed almost 100 distinct genetic loci associated with IBD.
3. Dr Fitzgerald (based in the MRC Cancer Cell Unit) investigates the molecular pathogenesis and progression of Barrett's disease and oesophageal cancer to provide tools for early diagnosis, accurate prognostication and therapy which can be applied to clinical practice.
4. Further research topics covered in the Division are on chronic liver disease (Dr Alexander), liver transplantation (Dr Gimson), small bowel transplantation (Dr Middleton and Dr Woodward), non-alcoholic fatty liver disease (Dr Allison) and inherited liver disease (Dr Griffiths). In translational research, multi-centre trials of novel biological therapies for IBD, which target specific immune functions, are pursued within the Division.

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Immunology

Work in the Division of Immunology covers three mains areas:

1. The Fearon lab has shifted its interest from the memory CD8+ T cell to tumor immunology. The immune system should be able to control the growth of many tumors because cancer cells with genomic instability generate neoantigens, which serve to make them appear as 'foreign' to the immune system. However, this obviously does not occur. One problem appears to be that the tumor microenvironment is immune suppressive, so that the systemic T cell responses to tumor antigens that can be demonstrated are prevented from

attacking the cancer cells. Our lab has recently shown that one type of tumor stromal cell (ie. a cell in tumors other than the cancer cell), the FAP+ cell, mediates local immune suppression, and its elimination allows immune control of tumor growth. We have also found that the FAP+ cell resides in normal tissues where it has unexpected functions, such as the prevention of cachexia, the muscle wasting syndrome often associated with cancer. We wonder whether the biological role of the FAP+ cell is related to tissue maintenance and repair, accounting for its regrettable presence in tumors? We are trying to discover how to interrupt the immune suppressive function of the FAP+ stromal cell.

2 The Griffths lab studies cytotoxic T lymphocytes (CTL) and Natural Killer (NK) cells, which use polarised secretion to destroy virally infected and tumorigenic target cells. Specialised secretory lysosomes, containing the pore forming protein perforin and a series of serine proteases, termed granzymes deliver the lethal hit in a specialised domain of the immunological synapse. The research is focused on understanding the molecular basis of polarised secretion from CTLs and has used a series of rare genetic diseases including Hermansky-Pudlak and Haemophagocytic syndromes to identify the roles of proteins involved in secretion from CTL and NK cells.

3 The Lehner lab studies mechanisms used by viruses to evade immune recognition, with a particular interest in the role of ubiquitin in receptor regulation. While initially focusing on viral evasion of MHC class I molecules, they recently developed a quantitative proteomics technique termed 'plasma membrane profiling' which takes an unbiased approach to analyze how viruses alter expression of any cell surface receptor to enable their replication. This powerful approach has identified novel immune as well as metabolic receptors, such as transporters downregulated by latent human cytomegalovirus infection (collaboration with Prof John Sinclair), and is now being used to interrogate cell surface receptor regulation by several different intracellular pathogens.

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Infectious Diseases

Infectious diseases research encompasses basic studies on viruses, bacteria and host immune responses.

1 Professor John Sinclair's group studies how human cytomegalovirus (HCMV) persists in healthy individuals studying cellular factors which control virus latency and reactivation. In collaboration with Professor Sinclair, Professor Sissons and Dr Wills' group study the control of HCMV infection by the immune system. They have shown dendritic cells to be a major site of HCMV carriage. More recently the group has defined novel viral immune evasion molecules.

2 Professor Lever's group studies retroviruses, including structural and molecular studies of RNA and RNA:protein interactions involved in genome encapsidation and the development of gene vectors. He and Dr Desselberger are investigating rotavirus RNA structures involved in encapsidating the viral genome and which host cell proteins or organelles may interact with the virus and be involved in viral assembly.

3 Dr Nejentsev's group investigates the genetic basis of susceptibility to mycobacterial infection and tuberculosis (TB). Discovery of such genes will help to understand mechanisms of resistance to infection and may point to new targets for therapeutic intervention. The group is part of the TB-EUROGEN consortium. In collaboration with the Wellcome Trust Sanger Institute they are performing a genome-wide association study aiming to discover genomic regions associated with TB.

4 Professor Sharon Peacock's group aims to introduce high-throughput whole genome sequencing technologies into diagnostic and public health microbiology collaborating with the Wellcome Trust Sanger Institute and the Health Protection Agency. Proof of principle will be achieved by developing a system to track transmission of, methicillin resistant Staphylococcus aureus (MRSA) in real-time. This technology will subsequently be extended to other important human pathogens.

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