

## **Biomedical and Pharmaceutical Research Theme**

### **(i) General Introduction**

Biomedical and pharmaceutical research encompasses a substantial component of health-related research at the University of Reading, and with the establishment of the new School of Pharmacy, critical mass in this area is increasing rapidly. While the research interests within this group, which are summarised below are wide, several areas of particular focus and international standing have developed over recent years. An important challenge for future years will be to nurture and develop these areas of expertise such that they become, or are maintained as, strengths for which this University is recognised. Several areas of research strength cut across the existing school structures (AMS, FBS, Pharmacy, Chemistry, Psychology), and with the current reorganisation of schools within the University, the establishment of a new building to house biomedical and pharmaceutical research, and the availability of new state-of-the-art facilities for biological studies on campus in the BioCentre, this is an ideal time to establish and develop this new research theme across the campus.

Biomedical and pharmaceutical research currently brings a substantial proportion of research income to the University from a range of sources including research councils (e.g. MRC, BBSRC), charities (e.g. CRUK, Diabetes UK, Wellcome Trust and BHF) and collaborations with industry e.g. GSK, Pfizer, AstraZeneca etc. This is a very strong area of research on campus, with income in the region of £12M over the last five years, and an enviable number of research publications in high impact journals (see attached appendices for details). The theme will incorporate a number of researchers who are active in service to the funding agencies in shaping and directing the national research agenda.

Given that research in this area is currently buoyant, it is reasonable to ask what this theme will bring that does not currently exist? The aim of this research theme will be to develop further our current strengths in this area and to consolidate research on this topic in different Schools. This will be achieved by focussing on common areas of interest, encouraging collaborations (at academic, postdoctoral and postgraduate levels), sharing of ideas and technologies, future new appointments and the establishment of sufficient critical mass within areas of focus that enable large collaborative projects to be undertaken. This theme will also encourage the expansion of collaborative projects to include clinical colleagues at the Royal Berkshire Hospital and teaching hospitals such as the John Radcliffe Hospital in Oxford. This will be further facilitated through established teaching by these centres within existing undergraduate programmes. The establishment of a research theme in Biomedical and Pharmaceutical Research will provide a platform to enable the strategic management of this important area of biological research at Reading. It will provide a high level of training for postgraduate and postdoctoral scientists, and will provide a centre that will enable the recruitment of high calibre academic staff, research staff and independent fellows.

The theme does not require substantial financial input for initial benefit, although in the longer term substantial investment will be required in order to support its development.

It is proposed that this research theme will play a major role in driving the development of facilities and infrastructure within the proposed new building that will house biomedical and pharmaceutical research, such that facilities will fully support the present and future requirements of researchers working within this area. This exciting development will enable co-localisation of research labs with shared facilities that will foster greater cross-fertilisation, collaboration and collective identity.

Research in this proposed theme draws on expertise in a number of current departments, and some areas of research will come close to topics covered within other research themes (for example Food Chain and Health, Integrated Systems Biology, From Gene Discovery to Protein Structure and Application). While direct duplication would not be productive, overlap between some aspects of research themes should be considered a strength that will allow the integration of different approaches to research.

#### **(ii) Introduction to the main areas of research focus**

Research is currently underway in a range of fields that will be incorporated in to this theme. At its inception, this theme should reflect areas in which several groups currently participate, whether this is currently collaborative or non-collaborative within the University. Specific areas of focus may change with time to account for new developments, new funding initiatives and new recruitment of academic staff. The remit of this theme will still, however, be relatively broad ranging from understanding the regulation of normal and diseased physiology, cell biology, and psychology; microbiology, virology and infection; the basis of the actions of drugs to treat diseased states at the molecular, cellular and whole animal levels; and the development of drug molecules and drug delivery systems.

Areas of focus are complex and highly specialised, and therefore the theme will be managed through subdivision into the following sub-themes, that will be explained in more detail below: cell signalling, cardiovascular biology, molecular endocrinology, medical microbiology, effects of nutrients and drugs on normal and disordered psychological processes, pharmaceutical research (medicinal chemistry and drug delivery systems).

#### **(iii) Significant research questions to be addressed:**

- a. What are the structures and functions of systems that detect hormones, neurotransmitters and other chemical messengers? How do these systems go wrong in disease? What are the effects of drugs on these systems?
- b. What mechanisms determine the normal and abnormal function of the cardiovascular system? How may cardiovascular diseases be treated?
- c. How does the secretion and action of hormones control fertility?
- d. What are the endocrine actions of pituitary hormones?
- e. How may infection and immunity be controlled?
- f. How is drug structure related to function?
- g. What factors determine the delivery of drugs?

h. How do drugs affect appetite, memory and perception?

i.

**(iv) Names of theme leaders:**

Profs Philip Strange and Jon Gibbins

With the establishment of key sub-themes, individuals from these groups will be selected for the coordination of these.

**(v) Names of key people and current Schools who would be involved in this theme:**

AMS	FBS	Pharmacy	Chemistry	Psychology
W Barclay	J Lovegrove	G Brooks	R Cramer	P Beaman
A Bicknell	C Williams	C Krasel	L Harwood	L Butler
K Bicknell	P Yaqoub	H Osborn	W Hayes	J Ellis
P Darbre	R Frazier	P Strange	J McKendrick	J Freeman
M Fry		E Williamson	C J Cardin	J Harris
J Gibbins		A Williams		A Ho
I Goodfellow		R Green		R Mitchell
I Jones		A Cobb		T Riddell
P Knight				C Williams
D Leake				
S Macintyre				
K Watson				

**(vi) Research subthemes: current areas of focus**

**Cell signalling**

Almost every process in humans and other organisms involves the reception of a signal and the transmission of a response. This overall mechanism is referred to as Cell Signalling. The majority of prescribed drugs have their effects by altering activity in these processes of cell signalling. The area of Cell Signalling is, therefore, of great importance to normal physiology and to therapeutic intervention and interfaces strongly with the Pharmaceutical Industry. Cell Signalling also underpins most of the sub-themes to follow

Cell Signalling has been a growth area at the University of Reading and indeed for more than five years there has been a Cell Signalling Discussion Group based around several of the active groups in the biomedical/pharmaceutical area. Research on this topic at Reading is strong and expanding and includes the following strands, (i) understanding the signalling processes in normal and pathological platelets, (ii) investigation of the molecules (G protein coupled receptors) in cells that respond to stimuli such as neurotransmitters and hormones, (iii) investigation of the downstream

processes following receptor activation and their role in disease states, (iv) studying protein-protein interactions in cell signaling systems in living cells using fluorescence techniques, (v) examining the structure and function of proteins involved in calcium signalling and glucose uptake and insulin release in pancreatic cells, (vi) investigation of steroid hormone and steroid hormone-like molecules in breast cancer, (vii) investigation of the mechanisms that control physiological and pathophysiological cardiovascular cell growth, (viii) investigation of the influence of dietary factors on metabolic syndrome and coronary heart disease, (ix) investigation of the effects of dietary fatty acids on immune function and inflammation.

Current cell signalling research involves several productive collaborative projects between groups currently located in AMS, FBS, The Biocentre and Chemistry. This is supported by joint grants and studentships. There is continuing interaction with Pharmaceutical companies in collaborative projects and studentships. The Cell Signalling group currently incorporates research in the laboratories of Prof Philip Strange, Prof. Gavin Brooks, Prof. Jon Gibbins, Dr Phillipa Darbre, Dr Cornelius Krasel, Dr Gary Stephens, Dr Katrina Bicknell, Dr Mike Fry, Dr Julie Lovegrove, Dr Parveen Yaqoob, Prof. Laurence Harwood and Dr Kim Watson, and this includes a number of key international and UK collaborations.

Much of the research in Cell Signalling could also be labelled as Pharmacology, one of the cognate disciplines of the new School of Pharmacy, although Cell Signalling extends beyond the confines of Pharmacology.

### **Cardiovascular biology**

Cardiovascular disease is a major cause of morbidity and mortality, causing about 25% of the deaths in the UK each year. Indeed this dramatically exceeds the mortality rate from cancer. Substantial advances have been made in the last two decades towards lessening the burden of cardiovascular disease, but there is clearly still a substantial unmet clinical demand. Underpinning future advances is research on cardiovascular biology in health and disease, and a broad spectrum of research in this area is contributed by a number of research groups at the University of Reading. This incorporates: (i) understanding the regulation mechanisms of platelets in normal haemostasis, and in thrombosis which leads to heart attacks and strokes; (ii) investigation of the processes that lead to the development of atherosclerosis, an inflammatory condition of arteries that is characterised by fatty deposits in the vessel wall that frequently form a trigger for thrombosis; (iii) understanding cell cycle mechanisms that control physiological and pathophysiological cardiovascular cell growth; (iv) targeting cell cycle molecules using virus- and non-virus-mediated gene therapy in cardiovascular cells; (v) investigating the effects and mechanisms of dietary components that modulate platelet cell signalling and function; and (vi) nutritional studies of the relationship between dietary fat and phytochemicals on coronary heart disease risk factors in different population groups

Current cardiovascular research involves several productive collaborative projects between groups currently located in AMS, FBS and Chemistry. This is supported by joint grants and studentships. Business development activity is underway in several cardiovascular research groups towards the exploitation of discoveries at Reading in the treatment or prevention of cardiovascular disease. The Cardiovascular Biology

group currently incorporates research in the laboratories of Prof. Gavin Brooks, Prof. Jon Gibbins, Dr David Leake, Dr Katrina Bicknell, Dr Julie Lovegrove, Dr Parveen Yaqoob, Prof. Christine Williams and Dr John McKendrick, and this includes a number of key international and UK collaborations.

### **Molecular endocrinology**

The University of Reading is recognised for its expertise in Molecular Endocrinology, and its application to aspects of human and animal health. This, therefore, naturally forms an individual sub-theme. The current areas of interest include: (i) understanding the regulation of physiological responses to stress, including characterization of the role of peptides derived from the adrenocorticotropin precursor, pro-opiomelanocortin in the regulation of adrenal growth, steroidogenesis and lipolysis; (ii) the molecular and cellular actions of oestrogens and oestrogen-mimicking chemicals in human breast cancer cells, and the mechanisms by which breast cancer cells escape from oestrogen/antioestrogen control of cell growth and thus the molecular basis of loss of response to endocrine therapy; (iii) understanding the mechanisms that regulate ovarian follicular development, ovulation and early embryo development. As well as being of fundamental scientific interest, it is anticipated that the research will underpin the development of improved methods for manipulating reproduction and for diagnosing and treating infertility. Current research in molecular endocrinology currently involves a high level of collaboration between members of the group. The Molecular Endocrinology group currently incorporates the laboratories of Prof. Phil Knight, Dr Philippa Darbre, Dr Andrew Bicknell, Dr Kim Watson and Dr Gail Hutchinson. In the future, this group holds the potential for greater interaction with laboratories of the Cell Signalling and Cardiovascular Research groups in the future.

### **Medical microbiology**

Whilst Reading is recognised for research in several areas of microbiology, a particular strength that should be incorporated into this theme is Medical Microbiology. This incorporates the study of bacteria and viruses of medical importance. The current areas of interest include (i) analysis of bacterial surface structures and secreted toxins and enzymes that are key factors in bacterial virulence and are often targets for prevention of bacterial disease. This research is aimed at optimization of vaccine design, leading to more effective means to protect against infection.

This sub-theme might also include Ian Jones, Wendy Barclay and Ian Goodfellow.

### **Effects of nutrients and drugs on normal and disordered psychological processes**

*Effects of Cannabinoids on Appetite and Cognitive Functioning:* Cannabis sativa has been cultivated for at least 10,000 years, in part to obtain fibres for the manufacture of textiles and rope, but to an important extent because of the wide variety of pharmacological actions that follow ingestion or inhalation of the leaves or resin extracts. These pharmacological actions include ataxia, hypothermia, analgesia, short-term memory deficits, a sense of time dilation, enhanced sensation, euphoria, stimulation of appetite and higher-order cognitive impairments. Research in the School of Psychology has examined the effects of THC (the main psychoactive ingredient of cannabis) and the endogenous cannabinoids on appetite and spatial memory in rats. While more recently we completed a human study looking at the

effects of THC on stimulation of appetite and various measures of human cognitive function such as short-term verbal memory, visuospatial recognition memory and so-called “working” memory. The Cannabinoid Research group currently incorporates the laboratories of Dr Claire Williams, Dr Elizabeth Gaffan, Dr Phil Beaman, Dr Judi Ellis, Dr Rachel Mitchell, Dr John Harris, Dr Laurie Butler, Dr Jayne Freeman and Dr Patricia Riddell. The foundation of the School of Pharmacy and the appointment of Professor Liz Williamson will complement our existing strengths in this area, while allowing the development of complimentary lines of research (e.g., ERP, neuroimaging).

Furthermore, a number of possible collaborative projects involving the effects of cannabis have been discussed with Liz Williamson. It is known that some of the natural components of cannabis herb or resin can override the inhibitory effects on neurotransmitters exhibited by the major psychoactive cannabinoid tetrahydrocannabinol (THC): this work has implications for the health of cannabis users, whether illicitly or medicinally. This particular study would encompass the investigation of different aspects of the phytochemistry of the cannabis plant (since it is the total content of the herb which is taken illicitly and will be used medicinally, rather than isolated THC) and comparing in vitro pharmacological activities with in vivo psychological effects including memory, cognition and other parameters (as deemed appropriate by the psychologists). Another area of interest is examining the effects of long-term administration of cannabis and cannabinoids on epileptiform activity, and in bone metabolism, a project which has been started in collaboration with colleagues outside Reading. At present this has been only carried out using in vitro tests, but which could usefully be extended to include chronic effects of cannabis in vivo, both psychological and physiological or incorporated into a larger project within the remit of the theme.

*Impact of Plant-derived Flavonoids on Mood and Cognition:* Many age-related cognitive conditions, including common neurodegenerative diseases such as Parkinson’s disease and Alzheimer’s disease have been linked to free radical mediated damage and oxidative stress in brain tissue. Consequently, recent attention has focused on the neuroprotective effects of a major group of dietary plant derived compounds called flavonoids, which are widely distributed in a variety of fruits, vegetables and beverages. An ongoing collaboration with SFB is investigating the effects of these flavonoids on cognition and mood in healthy and impaired older adults (Alzheimer’s disease and people with Mild Cognitive Impairment). Currently we have been awarded a Life Sciences RETF studentship (commencing October 2005) to look at the effects of these compounds on K adults. While an ERASMUS student will be working over this summer to investigate the effects of these compounds in a rat model of cognitive decline. In addition, we will be broadening these current studies to utilise our expertise in ERP and fMRI facilities at the School of Psychology. This research incorporates the laboratories of Drs Miniham and Spencer from SFB, with Drs Ellis, Mitchell, Butler, Freeman & Williams from Psychology.

*Effects of Dopaminergic Drugs on Perception and Cognition:* three members of the School of Psychology (Drs Harris, Ho & Mitchell) have active interests in the functional role of dopaminergic systems in the brain. They all have current funded collaborative projects on Parkinson’s disease (PD) with Professor RP Gregory

(Neurology, RBBH), looking at visuo-spatial impairments and their effects on gait (Harris) and abnormalities of emotional processing (Ho, Mitchell). Mitchell is also developing a collaborative study of language processing in schizophrenia with Professor TJ Crow (Oxford), her co-author of a recent review, while Ho is planning joint work with colleagues in Clinical Linguistics on the nature of stammering (in which dopamine has been implicated), and has an interest in the effects of medication used to treat PD on speech motor control. It is a natural extension of all these projects to examine in normal healthy individuals the effects of drugs which affect brain dopamine systems on variations of the relevant tasks. Such studies will help to confirm that changes in PD or schizophrenia are produced by the illness not the medication used to treat it, that they are mediated by dopamine rather than another neurotransmitter, and which of the various receptor sub-types is likely to be involved. The development of the School of Pharmacy and collaborative links with the RBBH provide an ideal opportunity to set up a range of studies in this area. In addition to expertise in the School of Psychology in measuring behavioural effects, the availability of an MRI scanner means that drug-induced changes in activity throughout the brain can be monitored during tasks. This 3-pronged (drugs, behaviour, fMRI) attack on an important but poorly understood brain system seems to suit the multi-disciplinary approach increasingly favoured by research councils.

### **Pharmaceutical Research**

With the inception of the School of Pharmacy there has been the opportunity to consolidate existing strengths in Medicinal Chemistry and to bring in new areas of research in Drug Delivery. Together these research areas constitute strong work in Pharmaceutical Science that complement existing strengths in Cell Signalling/Pharmacology. The work involves collaborations between Pharmacy, Chemistry, AMS and FBS and has direct application to the Pharmaceutical Industry and as such is supported by collaborative grants and studentships.

In the area of Drug Delivery we have research on (i) developing delivery vectors for both conventional small organic and macromolecular therapeutic agents including biologically-triggered drug release for targeting to diseased sites, (ii) topical and transdermal delivery of various pharmaceutical agents, including active herbal principles and in the formulation and stability of proteins and peptides for therapeutic use, (iii) development of novel enzyme mediated prodrug strategies for the selective delivery of anti-cancer agents to melanomas, (iv) application of dendritic polymers as biomaterial substrates to enhance biocompatibility through highly controllable surface chemistry.

In the area of Medicinal Chemistry the University has a strong presence within chemistry at the biological interface and this has naturally evolved to allow the design and synthesis of new molecules of biomedical use. Areas of particular interest have included:- i) The synthesis of carbohydrate based therapeutics, namely a) glycosidase inhibitors, of interest as anti-cancer and anti-viral agents, b) anti-infective agents, of potential use for inhibiting bacterial infections, c) 2-deoxy glycosides that have proved of use as selective inhibitors of cell proliferation; ii) The synthesis and bioanalysis of prodrugs for the treatment of melanoma; iii) The synthesis of polymer libraries as enzyme mimics, of potential application to non-viral gene therapy; iv) the synthesis of symmetrical ligands for binding to symmetrical proteins implicated in

amyloidosis; v) The synthesis of new hyperbranched polymers that are suited to use in drug delivery.

Research Groups included in this topic include those of Prof Adrian Williams, Prof Gavin Brooks, Dr Helen Osborn, Dr Rebecca Green, Dr Andre Cobb, Dr Richard Frazier and Dr Wayne Hayes. Research on this topic has included collaborations with Dr Parveen Yaqoob, Dr Bob Rastall and Dr Wendy Barclay and that the development of the School of Pharmacy is likely to increase collaborations in this area.

**(vii) Research strengths to date in the area of the Theme**

Researchers in this theme currently generate a substantial level of research income (~£12 million over the last 5 years) and this is mirrored by a very good level of output in terms of research papers and other indicators of esteem. The attached appendices contain a summary of research income and published papers by many members of the proposed theme.

**(viii) Funding sources for future bids**

The research to be funded in this theme will be supported (as it is now) by grants and awards from a number of sources. This includes research councils such as the MRC and BBSRC, and charities such as the Wellcome Trust, British Heart Foundation. This will be at the level of PhD studentships, project grants, equipment grants and programme grants. Increasing the critical mass will have a more-than-additive effect of research income and will enable application for large collaborative projects that may interface with bids from the Systems Biology theme. A number of laboratories to be included are engaged in industrial collaborations, and the exploitation of intellectual property generated in existing programmes. Continued and expanded engagement with enterprise activities will be encouraged.

**(ix) Added value and competitive advantage**

By forming a research theme in this way it should be possible to focus research in this area on the Reading Campus to foster the strong areas of research and to increase collaborations. This will act as an important prelude to the construction of the new building in Biomedical and Pharmaceutical Sciences and will strengthen health-related science on the campus in general.

The theme could take advantage of the following current appropriate research initiatives:

BBSRC/EPSRC Stem Cell Science & Engineering initiative

BBSRC industrial CASE studentships

Highlight notices from MRC to encourage application for research into: antibiotic resistance, health of the public, cognitive foresight project

Wellcome Trust Stem cells, cognitive foresight

**(x) Proposed use of pump priming funding**

A sum of £10K is requested to support activities for establishment of a theme in biomedical and pharmaceutical research. This funding will be used to (i) organise a Biomedical and Pharmaceutical Research Symposium (one day meeting) - at which the vision for the research theme is presented, and research in each of the sub-themes is showcased. The target audience would be members of the theme (who for the next two years will be dispersed around campus) and any other members of the University who may be interested; (ii) the establish regular Biomedical and Pharmaceutical research seminars; (iii) provide secretarial support for administration of joint biomedical and pharmaceutical research bids across campus and to ensure, with RES, that the auxiliary data required by many electronic applications are in place; (iv) establish a small fund, which will be increased in the future, to support pilot projects and to support training for members of the theme in techniques and experimental approaches (e.g. in the BioCentre or at other institutions) that will be of value to other members of the theme; and (v) a small contribution to a social event to launch the theme.

**(xi) The next steps for development of the theme**

This depends on the response from the centre