

**Evaluation of BBSRC's Biochemistry and Cell Biology Committee
Responsive Mode Portfolio**

November 2006

*This document represents the conclusions of a Review Panel of experts in
biochemistry and cell biology.*

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EXECUTIVE SUMMARY AND KEY CONCLUSIONS

This document sets out the views of a specialist Review Panel convened to provide an independent evaluation of the research supported in responsive mode through BBSRC's Biochemistry and Cell Biology Committee (BCB) since the Committee's inception in September 1994. The objectives of the evaluation were to assess the quality of the research supported, to identify major outcomes arising from the research, to consider whether the BCB is currently funding the most appropriate areas of UK bioscience, and to identify ways to build on successes and address identified gaps and issues.

The Panel's analysis was based on the results of questionnaire surveys of a sample of 173 current and past grantholders, 19 current and past BCB members, and seven other UK funding organisations; and on the final reports that had been submitted for 145 sample completed grants.

The evaluation covered five subject areas: Research quality and research outputs; Balance and coverage of the portfolio; Interaction with industry; Public engagement; and Ultimate (longer-term) impacts. The Panel's main findings and conclusions are summarised below.

Research quality

The research supported through BCB over the past ten years has been mainly good. A significant proportion of BCB awards were of international standing, with some outstanding examples of outputs and achievements. This is considered to be a relatively good outcome, meeting expectations in light of the fact that the Committee had predominantly supported three-year, one-Research Assistant (RA) grants (i.e. relatively short, small grants). This model is a major constraint both on the quality of research and research outputs (and hence also to BBSRC's perceived role as a funder in this area) and on the development of research careers.

Key conclusion: The impact of research supported through BCB could be significantly improved by moving to a more balanced funding model aimed at encouraging the continuity and stability of research and research groups (i.e. supporting a greater proportion of longer and larger grants).

Research outputs

The research outputs were generally good: the majority of grants had produced papers in well respected journals; a large number of new contacts and collaborations had been developed; more than half of the sample PIs had received further funding to continue or develop the research supported by the grant; and a range of novel products, processes, tools and technologies had been developed. There are a number of issues of concern relating to research careers, and the impact of career instability on the maintenance of the UK research skills base.

Key conclusion: BBSRC and Research Councils UK (RCUK) should continue to identify ways in which they can contribute to improving job security, benefits and career prospects for research staff.

Balance and coverage of the portfolio

BCB's remit and the coverage of the portfolio has been and still is generally appropriate. There is an apparent gap in terms of support of research within BCB's remit that involves using and developing bioinformatics tools and resources, computational science, transgenic animals and cutting edge technologies such as imaging and 'omics technologies.

Key conclusion: BBSRC should investigate the apparent gaps in support for the development of bioinformatic tools for research at the cellular level, for cutting edge technologies (including imaging and 'omics technologies) within BCB's remit, and for transgenic animal research. Should these gaps be real, the Council should take steps to increase its support for research in these areas.

Priority Areas may play a useful role in enabling Committees to encourage applications in particular areas of science, but are poorly understood by the community, who are under the impression that PAs indicate preferential treatment with respect to funding.

Key conclusion: BBSRC should clarify the role and significance of Priority Areas to the community. The term priority should be changed, for example, to "highlight", to dispel the notion that applications in these areas are treated preferentially.

Interaction with industry

BCB-supported research contributes indirectly to industry through contribution to a 'bedrock' of knowledge on which future application is based, and the provision of a continued supply of trained scientists. Much of BCB's remit is potentially of interest to industry, and there is considerable scope for further, beneficial collaboration between researchers and industry.

Key conclusion: BBSRC should continue its efforts to promote this interaction, particularly through brokering contacts between industry and researchers.

Public engagement

Some PIs had made significant effort to engage with the public during their grant, but the majority had spent nothing like the required two days per year. Recent signs are more encouraging, and BBSRC is commended on its work to raise the importance of public engagement amongst the community.

Key conclusion: While the importance for public engagement is now widely accepted, BBSRC should continue to seek opportunities to encourage and facilitate bioscientists to engage with the public.

Ultimate impacts

The sample grants made a range of direct contributions to the public good (for example human health, animal welfare), with a number of notable highlights. However, as with other outputs, impacts in this area are lower than could be expected from longer and larger grants.

1. BACKGROUND

Introduction

1. The Biotechnology and Biological Sciences Research Council is one of eight Research Councils sponsored through the UK government's Office of Science and Innovation (OSI). Its principal aim is to foster a world-class biological science community in the UK. BBSRC's mission is to fund internationally competitive research, to provide training in the biosciences, to encourage opportunities for knowledge transfer and innovation, and to engage the public and other stakeholders in dialogue on issues of scientific interest.
2. BBSRC supports research in a number of ways, including research grants, studentships, fellowships, and Core Strategic Grants to Research Institutes. In financial year 2005/06, 38% of BBSRC's research funding was spent via the organisation's 'responsive mode' scheme, whereby research grants are awarded to unsolicited high quality research proposals from eligible applicants in any area relevant to the Council's mission.
3. For organisational purposes, BBSRC's remit is divided into seven key areas, each covered by a Research Committee: Agri-Food; Animal Sciences; Biochemistry and Cell Biology; Biomolecular Sciences; Engineering and Biological Systems; Genes and Developmental Biology; and Plant and Microbial Sciences.
4. This document sets out the views of the specialist independent Panel convened to provide an independent scientific evaluation of the Biochemistry and Cell Biology Committee (BCB) responsive mode portfolio.

Evaluation context

5. Evaluation is of growing importance to BBSRC and, with its emphasis on evidence-based decision making, to the UK government. Evaluation plays a central role in:
 - Justifying BBSRC's funding allocation and contributing to the Evidence Base that all Councils are required to submit to OSI for Spending Review negotiations;
 - Informing internal funding decisions, providing evidence of progress and achievement, and facilitating the development of a strategic overview for future funding decisions;
 - Enabling BBSRC to account to government, the general public, the scientific community and other stakeholders for the funds it allocates; and
 - Helping BBSRC to improve its policy and practice, through informing policy decisions and the design of new schemes, programmes and processes; and through identifying good practice, lessons learned, and ways to improve processes.
6. Formal evaluation of research is currently conducted at a number of levels in BBSRC:

Grant	<ul style="list-style-type: none">• Evaluation of final reports from individual grants
Scheme	<ul style="list-style-type: none">• Evaluation of the responsive mode scheme, evaluating the portfolio of each Research Committee in turn• Evaluation of Research Initiatives (time-limited research funding in strategically significant areas), 2-3 years after the grants have ended
Institution	<ul style="list-style-type: none">• Institute Assessment Exercise, conducted every four or five years at BBSRC-sponsored Research Institutes

7. BBSRC recently published its Evaluation Strategy, outlining the Council's approach to evaluation and methodology used. BBSRC's responsive mode portfolio is evaluated by

Research Committee area on a rolling basis whereby two Committee portfolios are evaluated every year. Following a pilot evaluation of the Biomolecular Sciences Committee, BCB is the second Committee to be evaluated, following an evaluation of the Animal Sciences Committee responsive mode portfolio in 2005.

8. The evaluation covered research supported in responsive mode through the BCB Committee since its inception in 1994. The objectives of the evaluation were to:
 - Assess the quality and international standing of research funded through BCB;
 - Identify the major outputs and, where possible, outcomes of BCB's responsive mode portfolio over the past 10 years;
 - Identify strengths, weaknesses and gaps in the scheme, the way it is structured, the influence of initiatives and priority areas on the way that the scheme has developed, and the way in which it is administered;
 - In consultation with the research community and other relevant funding bodies (government and non-government), assess whether BCB is currently funding the most appropriate areas of UK bioscience; and
 - Identify ways to build on successes, and ways to address identified gaps and issues.

9. BBSRC's evaluations are evidence-based, and conducted by an independent Review Panel comprising scientists not closely involved with BBSRC, but who between them have expertise across BCB's remit, who are asked to provide an independent scientific evaluation of the evidence presented. This was:
 - **145** sample final reports (representing **50%** of all BCB responsive mode grants that had been completed and graded at the time);
 - Questionnaires returned by **103** PIs of completed grants (representing **35%** of all completed and graded BCB responsive mode grants) and **70** current PIs (**24%** of all current BCB responsive mode grants that had at the time been underway for more than a year);
 - Questionnaires returned by **19** current and former BCB Committee members; and
 - Questionnaires returned by **seven** other government and non-government funding bodies relevant to BCB's remit.

The sample final reports and PIs were chosen randomly from the point of view of the science, but in a structured way to be representatives of the years and final report grades.

10. Further information on responsive mode funding in BBSRC, the evaluation objectives and methodology, and the BCB Committee is included at Appendix 2.

2. RESEARCH QUALITY AND RESEARCH OUTPUTS

Research Quality

11. The Panel reviewed 145 sample final reports, with updated output information from the questionnaires received from 103 of the PIs. The 145 represented 50% of all BCB grants starting from September 1994 that had been completed and graded. The analysis of the research quality and outputs was limited by the information provided in the final reports, which were of variable quality in terms of how well they had been written and the detail provided.
12. The research supported through BCB over the past ten years has been mainly good. A significant proportion of BCB awards were of international standing, with some outstanding examples of outputs and achievements. This is considered to be a relatively good outcome, meeting expectations in light of the fact that the Committee had predominantly supported three-year, one-Research Assistant (RA) grants (i.e. relatively short, small grants), a model which constrained the system (and the quality of the outputs) in a number of ways. The overall impact of the research supported through BCB could be significantly improved by moving to a more balanced funding model aimed at supporting the continuity and stability of research and research groups (i.e. incorporating a greater proportion of longer and larger grants). This issue is discussed in more detail in Chapter 7.
13. The fact that the outputs were successful in light of the constraints in the system is reflected in two other overview measures of quality:
 - **70%** of the final reports of BCB responsive mode grants since September 1994 had been graded A or B¹ by Committee members at the time (final reports are submitted three months after the end of the grant, and peer reviewed and graded on a scale of A to D by Committee members); and
 - In their questionnaire responses, **87%** of the sample PIs felt that their grant had been (or was likely to be) successful.
14. A small number of the sample grants had been less successful than might be expected, and the Panel identified (from the sample final reports and the questionnaire responses) three main reasons for lower performance in these grants:
 - The progress of the research had been affected by problems with the recruitment or retention of staff (discussed later in this Chapter);
 - The length and/or budget of the grant had been significantly cut from that which had been applied for; and
 - The research idea appeared to be flawed and should perhaps not have been supported in the first place (the Panel acknowledged, however, that this judgement could not be made definitively in the absence of the original application forms).

Highlights

15. **18** grants in the sample were judged to have produced outstanding research outputs, and/or had had particular impact at the time. These are described below, organised by BCB's three themes. Other notable grants are included at Appendix 5.

¹ A: Very high class work that has produced results of considerable scientific importance in a cost effective way, and met all or almost all of the agreed or related key objectives

B: Work that has added significantly to knowledge in the field and met the majority of its agreed or related key objectives

C: Work that has fallen short of the contribution to knowledge or cost effectiveness expected from the original proposal even though it may have met some or all of its agreed or related key objectives

D: Work that has not added significantly to knowledge in the field and/or has failed to address the agreed or related objectives.

Fundamentals of Cell Biology and Biochemistry

Elucidation of the mechanism of myosin ATPase through directed probes. This study exploited the crystal structure of myosin II motor domain to examine the mechanism of myosin ATPase. They were able to resolve conformational changes associated with nucleotide binding and converter domain rotation and distinguish them from the chemical hydrolysis step. The group used physical techniques to take forward findings from structural biology and relate them to biological function (ie myosin II ATPase activity). This cross-disciplinary approach covered a number of areas within the BCB remit, and is a good example of how structural studies can be related to biochemistry. The work resulted in several good quality publications.

Analysis of the redox components, role and biosynthesis of the periplasmic nitrate reductase system of *Paracoccus denitrificans*. The periplasmic nitrate reductase (NAP) is now recognised to be widely distributed amongst Eubacteria and contributes to nitrogen flux in multiple environments. This study contributed to understanding the coupling of NAP to respiratory electron transport pathway and how electrons are transferred between member entrapped quinols and periplasmic oxido-reductases in different systems. An outcome of this work is that nitrate reductases have been employed in optical biosensors. The work represents an elegant coupling of biochemistry with genetics. The work was continued with further funding from the BBSRC as well as a number of collaborative grants.

The mechanism of action of acidic transcriptional activators. The aim of this work was to understand the function of the N-terminus of the transcription factor TFIIB, which is a highly conserved region of TFIIB, in transcription. The data provide novel insight into transcriptional activation by activators, demonstrating that they contact TFIIB within a transcriptional complex and modulate the ability of TFIIB to engage in DNA contact. The work led to a paper in *Genes and Development*, and contributed to a paper in *Molecular Cell Biology*. This represented a high quality study in a competitive area. The work is being continued with funding from the Wellcome Trust.

Regulation and activity of the mitotic polo-like kinases (plks) of *Xenopus* and *Drosophila*. This research resulted in a number of high impact papers. The group established that a polo kinase is required for activation of the centrosome and plays a role in cytokinesis, processes critical for cell division. Moreover, they identified on 2D gels about 20 new proteins whose expression or modification (electrophoretic mobility) was altered in *polo* mutants. This research offers tremendous opportunities to further delineate the process of mitosis and in particular the specific role of polo kinase.

Functional characterisation of BiP subdomains to unravel its function in protein synthesis, folding and quality control by the Endoplasmic reticulum (ER). This project exceeded expectations. Highlights were showing that: (i) vacuolar transport of immunoglobulin binding protein (BiP) does occur and relies on signal-mediated transport; (ii) BiP overproduction depends not on the increased use of pesticides but on the natural defence mechanisms of plants, a finding that may have consumer benefits. The work also generated BiP- and calreticulin- overproducing plants and calreticulin-silenced plants for community use. A patent was filed on pathway engineering and a spin-out company negotiated.

Using protein ligands and site-directed mutants to study porin channel dynamics. By showing that colicin binding triggers gating of porin channels, this work suggested using the system as a biosensor to detect soluble proteins electronically. For the first time, they (i) fixed membrane proteins directly to the gold electrode and (ii) established the conditions in which the protein is stabilised and protected from denaturation, allowing binding events to be measured easily. A patent application was filed concerning gold electrode-immobilised membrane proteins as biological transducers, this and other BCB-supported work forming the basis of a spin-out company. The PI also gave presentations in schools about biotechnology.

Internal molybdenum metabolism and molybdate-dependent gene regulation in bacteria.

This group studied the *E. coli* ModE protein that is an important molybdate-dependent transcriptional regulator involved in the uptake and utilization of the essential element, molybdenum. Structural and mutational analysis were used to explore the molecular mechanisms of transcriptional regulator function in detail. In addition, a system was developed in *E. coli* for assessing molybdate binding proteins from a variety of sources (bacterial and plant). A number of excellent publications were produced.

Ribozyme-mediated cell-specific downregulation of gene expression in the adult central nervous system using adenovirus vectors. This project developed hammerhead ribozymes that cleaved mRNA specific for neuronal genes and thus downregulated expression of specific genes. These were delivered by adenovirus vectors *in vivo*. This work has future applications for the treatment of neuronal disease. Aside from good publications, the researchers were successful in establishing a number of links with industry, filed one patent application and communicated their work to the public.

Dissection of the enzyme activities involved in transcription and replication of the dsRNA genome of bluetongue virus. This important work defined the enzymatic activity of a number of bluetongue virus proteins with respect to virus replication and transcription of genes. Bluetongue virus is an animal pathogen and the group's findings have implications for the understanding of virus replication and novel interventions. A number of important publications arose from the grant, and the work was communicated to the public.

Identification of novel Ran binding proteins. Previous work had established a clear role for the small GTPase Ran in nuclear import/export. This grant supported work demonstrating novel functions of Ran, independent of its role in nuclear transport. The most important of these demonstrated that Ran is essential for the reformation of the nuclear envelope after mitosis. Specifically, the authors showed that a Ran mutant protein mimicking the GTP-bound form, when coupled to small beads, was sufficient to induce the assembly of a nuclear envelope around the bead in the absence of DNA, thus demonstrating a central role for Ran in 'making a nucleus'. This grant helped to fund work that led to three high profile papers (Science, Current Biology, Journal of Cell Science).

Specialised Cell Function

Genetically engineered control of the primary photosynthetic reactions of photosystem II. This research demonstrated that it is genetically possible to change the quantum yield of photosystem II, potentially resulting in increased photosynthetic efficiency/stress tolerance of plants. In an age of climate change, such a demonstration is significant. Presentations on this topic were made to the public via World Science/New Scientist and Radio 4.

Dynamic aspects of the structure and function of the light-harvesting complexes of photosystem II in plants. A second study on the light harvesting complex in plants examined the role of pigments and protonation in regulating the reversible switch from light harvesting to energy dissipation as heat. This work is notable for its prolific output (14 papers were published in high-quality journals).

Expression of tubulin and mutant tubulin in transgenic maize calli. This work led to increased understanding of both the nature of the microtubule network in plants and its sensitivity to certain herbicides, and was published in Nature and Nature Biotechnology. A herbicide-resistant goosegrass (a major crop weed) was found to be resistant to the dinitroaniline herbicides developed by the agrochemical industry. An analysis of the tubulin gene of the weed showed specific base changes which, when genetically 'swapped' into maize cells, conferred herbicide resistance to maize plants. The PI was interviewed on BBC News 24 and Radio 5 Live. The work was an extremely successful collaboration with an agro-chemical company.

Elucidation of the bacterial c-type cytochrome biogenesis pathway; redox protein assembly in the periplasm. This research made important progress in the understanding of the biogenesis of c-type cytochromes in bacteria using a combination of genetics and biochemistry. A number of excellent papers were published.

Identification and characterisation of signals for self-renewal and differentiation in haemopoietic stem cells. This grant sought to identify the factors that regulate the two potential outcomes when stem cells divide: self renewal or differentiation. The resulting publication (in Blood) was a contribution to the field at the time. However, the explosion of interest since that time has radically altered the field.

Cell-Cell Interactions

The role of CD31/PECAM-1 in T cell adhesion, migration and survival. This research helped to explain how the T cell surface protein CD31 can play different signalling roles in different contexts, influenced by the state of phosphorylation of Ser/Thr residues in the cytoplasmic domain. Identification of a role for the small GTPase Rap-1 suggested a mechanism by which signals mediated by cell contact could be integrated with soluble cytokine signals. This work has been highly influential in the field, having garnered a total of about 350 citations for the three publications that arose from it.

A functional approach to the study of ligand-gated ion channels. This research addressed the question of how resistance arises to insecticides targetted to ligand-gated ion channels. In principle, resistance can arise directly through changes in the target, or through mechanisms that detoxify the insecticide. The majority of mutations, in fact, led to the upregulation of a particular type of cytochrome P450, which degrades the common insecticides. A population genetics study on resistant strains of *Drosophila* (published in Science) showed that all field isolates shared the same mutation, implying that this mechanism of resistance has spread around the world. This work, which may help to predict how resistance to future insecticides will arise in the field, has led to an industrial collaboration with an agro-chemical company.

Selective agonist definition of G-protein signalling. This work focused on the ability of seven transmembrane spanning G-protein coupled, receptors to activate multiple G-proteins in an agonist selective manner. These receptors are of major importance, not only in the regulation of many major biological processes but also as they are the target of numerous commonly prescribed drugs. The molecular mechanisms of receptor and G-protein interactions are of fundamental importance to the study of cellular recognition; by being able to activate more than one type of G-protein (so-called agonist channelling or trafficking) a receptor may be able to differentially regulate cellular activity under the control of a single agonist. The group employed and developed techniques to monitor these interactions, including measurement of GTPase activity in GPCR-G-protein fusion constructs. The project was unable to provide evidence for agonist specific channelling to different G proteins, at least for the GPCR sub-family studied, but it guided the development of novel techniques and thinking in the area, which have been extremely influential to both the wider community and the pharmaceutical industry.

Research Outputs

16. The Panel considered a number of types of research output:

- Publications
- Trained people, new skills
- New collaborations, further funding
- New products, processes, tools and technologies
- Intellectual property, spin-out companies
- Contribution to the reduction, refinement and replacement of animals in research

Longer-term outcomes arising from the research supported through BCB are discussed in Chapter 6.

Publications

17. The publications reported by sample PIs as having arisen from the research supported by the grant were mostly good, again with some particular highlights. Amongst the sample completed grants, there was a median of **four** peer-reviewed publications per grant for sample completed grants². The majority of the reported publications were in highly respected journals in the field (e.g. *Journal of Biological Chemistry*, *Journal of Cell Biology*, *Journal of Virology*, *Molecular Pharmacology*). The Panel was pleased to note that a relatively high proportion of the reported publications (**15%**) had been in journals with an Impact Factor greater than 10, including a number in high profile general journals (e.g. *Nature*, *Science*, *Proceedings of the National Academy of Sciences*).
18. The Panel added the caveat, however, that the publications data in final reports should be interpreted with caution as there was wide variation in the way in which PIs had reported publications in their final reports and questionnaires. In particular, it is likely that many of the cited publications resulted from work funded at least in part by other grants.

New collaborations, further funding

19. As would be expected, a high proportion of the sample PIs reported new or improved academic contacts and collaborations as a result of the research supported by the grant (**60%** of PIs reported new or improved contacts both in the UK and overseas; **41%** reported new academic collaborations in the UK, and **31%** new collaborations overseas). These new and improved linkages often lead to new research ideas, directions and approaches, and are therefore a major outcome of BBSRC's support for research. Some PIs also reported new industrial contacts and collaborations, which are discussed further in Chapter 4.
20. Another encouraging output was that **62%** of the PIs of sample completed grants had received further funding to continue or develop the research supported by the grant. Half of these had secured their further funding through BCB.

² The median is used because the distribution of papers per grant is left-skewed (the majority of grants lead to the publication of 0-6 papers, but a small proportion resulted in larger numbers of papers, with a maximum of 16). The average per grant was 4.4.

Trained people, new skills

21. The Panel was concerned to note that, of the RAs for whom the first destination was given, only **2%** had secured a permanent post in an academic institution following the grant. Lack of information in the final reports made it impossible to investigate this statistic in any greater depth, and this itself was further cause for concern. Furthermore, **38%** of the sample PIs reported difficulties with recruiting and retaining research staff. These figures appear to reflect the continuing lack of job security and career prospects in research in academic establishments. The situation is exacerbated by BCB's three-year grant model, which forces RAs to look for new posts every few years (this is discussed further in Chapter 7).
22. While not entirely BBSRC's responsibility, the Council might consider ways in which institutions could be encouraged to think more strategically and longer-term about their staffing needs, and to see people development as an important responsibility and a major output from research grants. The panel also felt strongly that BBSRC had a part to play in ensuring that RAs employed on grants were identified, and sufficient information gathered about their circumstances to ensure that career structures could be properly monitored. A fairly 'quick win' could be achieved from requiring PIs to supply BBSRC with the name and CV of the RA once recruited. This would send the signal that RAs are an important part of the grant, and enable BBSRC to monitor their career progress more effectively. Another potentially good model is EPSRC's Platform Grants, where funds are invested in world leading groups to provide stability and flexibility to permit the retention of key research staff and to facilitate longer-term and more strategic research.
23. Similarly, Research Committees should be encouraged to take account of whether proposed research represents an investment in the sustainability of the skills base in that area. The proposal relating to longer, larger grants (see Chapter 7) should also go some way towards improving the stability of research careers, and reducing the difficulties in recruitment and retention of research staff on grants.
24. BBSRC is commended for its work to encourage those at an early stage in their careers, in particular the New Investigator scheme, which assists high quality researchers at an early stage in their careers to secure their first research grant. However, BBSRC could do more in this field, including considering ways in which it might further contribute to career opportunities for high quality researchers, for example Career Development Fellowships (supporting first independent positions), and allowing postdoctoral researchers to write their own grant applications (with a more senior colleague as Co-Investigator or sponsor).
25. A further issue of concern is the increasing need for highly skilled staff to work with the newly emerging technologies (e.g. genomics, proteomics). These staff are expensive and often difficult to maintain on short-term grants.

"The BBSRC New Investigator funding has helped me to establish my own group, develop international collaborations and to attract further funding in the research area." Grantholder

There are a number of issues of concern relating to research careers, and the impact of career instability on the maintenance of the UK research skills base. BBSRC and Research Councils UK (RCUK) should continue to identify ways in which they can contribute to improving job security, benefits and career prospects for research staff.

New products, processes, tools and technologies

26. A healthy **47%** of PIs reported new products, processes, tools or technologies that had or could result from the work supported by the grant. Given the fundamental nature of the research supported through BCB, many of these were tools and resources that will be primarily useful to other researchers, for example reagents and cell lines.

Intellectual property, spin-out companies

27. **11%** of the sample PIs reported having secured intellectual property (all in the form of patents) as a result of the work supported by the grant. A further **3%** of current PIs reported that they were likely to apply in the near future. Three spin-out companies (**2%** of sample PIs) had been established from the research supported by the grant, two of which were currently trading. Another company was in the process of being set up. These numbers are lower than might be hoped, and are discussed further in Chapter 4.

Contribution to the reduction, refinement and replacement of the use of animals in experiments

28. While few of the sample PIs reported their work as contributing directly to the reduction, refinement and replacement of animals used in experiments (the '3Rs'), the Panel agrees with the majority of the surveyed Committee members that the research supported through BCB does contribute broadly to the '3Rs'. Given the basic nature of the research supported through BCB, this contribution is often not obvious, but is nonetheless important. Examples of BBSRC's contribution to the 3Rs in BCB's remit include:
- Support for systems approaches, particularly fostered through recent BBSRC initiatives and support for the use of genomic and proteomic technology leads to a reduction in the number of animals used in experiments;
 - The same is true for BBSRC's support for stem cell research; and
 - The group working on BiP in plants (Functional characterisation of BiP subdomains to unravel its function in protein synthesis, folding and quality control by the ER), worked on techniques to produce antibodies in plants, which may offer a cheap, safe and efficient alternative to producing antibodies in animals, animal cells or microbes.

3. BALANCE AND COVERAGE OF THE PORTFOLIO

Overview

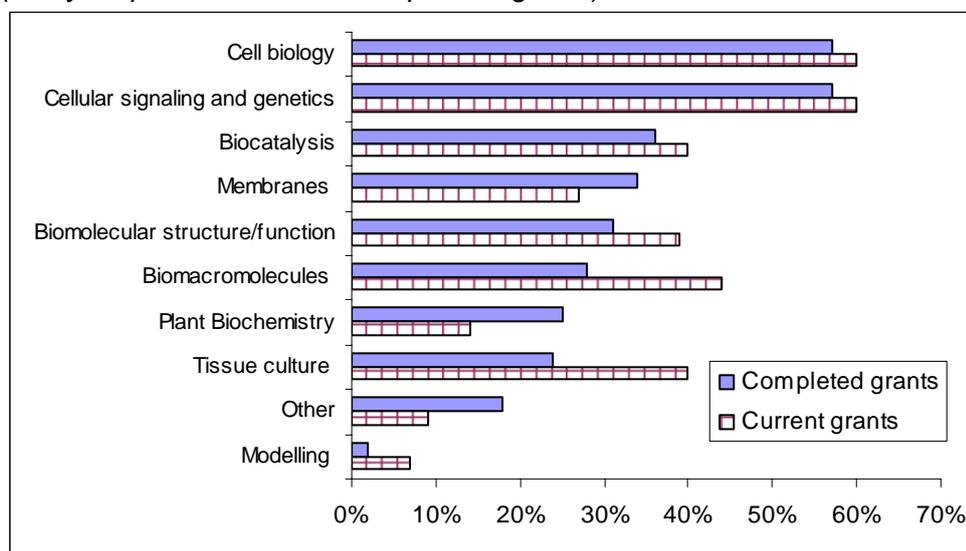
29. Review of the sample final reports and of the responses submitted by other funding organisations indicates that BCB's remit has been and still is generally appropriate. This is supported by the fact that **96%** of the sample PIs reported that they had not significantly changed the direction of their research to fit into BCB's remit.

Coverage of the portfolio

30. The coverage of BCB's portfolio is also broadly appropriate to its remit. The figure below provides a rough illustration of the coverage of the portfolio, as indicated by the areas of expertise selected by sample PIs in their questionnaires.

Areas of expertise indicated by sample PIs

(many respondents ticked multiple categories)



31. However, the Panel noted that the sample contained less research using and developing a number of technologies, tools and resources than could be expected. The Panel then reviewed brief information on BBSRC's current support in these areas across all seven Research Committees (title, Committee area and size both of grants and projects at Research Institutes), and concluded that there remains an apparent lack of support for research in BCB's remit (i.e. at the cellular level) using and developing bioinformatics, computational science, and (more generally) cutting edge technologies, including imaging and 'omics technologies. It was, however, difficult to draw conclusions without more detailed data on the research supported by BBSRC in these areas. BBSRC should therefore investigate across all funding committees both of these apparent gaps in more detail and, if they are real, take steps to encourage and support more research in this area.
32. Research using and developing transgenic animals is also an apparent gap that should be investigated. This is likely to be linked to the prevalence of the three-year grant model in BCB, as transgenic animal research often takes longer than three years and is expensive (discussed further in Chapter 7). While much of this research is on animal models for human disease and therefore does not fall within BBSRC's remit, transgenic animals are a key tool in bioscience research, and should the gap be real, BBSRC should take steps to encourage research applications relevant to its remit in this area.

BBSRC should investigate the apparent gaps in support for the development of bioinformatic tools for research at the cellular level, for cutting edge technologies (including imaging and 'omics technologies) within BCB's remit, and for transgenic animal research. Should these gaps be real, the Council should take steps to increase its support for research in these areas.

Priority Areas

33. As identified by the sample BCB Committee members, Priority Areas (PAs) have been helpful in enabling the Committee to encourage researchers to submit applications in particular areas of science. The minor role played by PAs in the assessment process³ is appropriate, as they should not be promoted to the detriment of support for the best science through responsive mode (especially because Research Initiatives are used successfully by BBSRC as a mechanism for providing targeted support where it is clearly needed).
34. However, the fact that almost all of the comments made by sample PIs about PAs were negative indicates that there is a perception in the community that PAs afford a genuine advantage during assessment. BBSRC should urgently address this perception, providing more detailed information to the community on the rationale behind PAs and the way in which they are used in the grant assessment process. The panel felt that the word 'priority' implies a greater level of significance than is actually the case. One option would be to consider an alternative name, for example "highlight".

Priority Areas play a useful role in enabling Committees to encourage applications in particular areas of science. BBSRC should clarify the role and significance of Priority Areas to the community.

Interdisciplinary research

35. Interdisciplinary research is widely recognised as having great potential to solve problems in the biosciences. A small number of the sample grants had involved interdisciplinary approaches:
- The group working on the Dictyostelium Myosin II motor domain (Elucidation of the mechanism of myosin ATPase through directed probes) coupled crystallography to transitional states of proteins to cellular/protein function in 1999, when combining crystallography analysis with cellular function was less common;
 - Another group (Investigation of the influence of perturbations of the cAMP relay dynamics on multicellular Dictyostelium morphogenesis) used mathematical modelling to study movement in Dictyostelium;
 - Molecular biologists in Glasgow and structural biochemists in Edinburgh combined their expertise to elucidate the roles of specific enzymes in protein folding and formation of the normal exoskeleton in nematodes.
36. Although much of BCB's remit is very basic research that does not necessarily lend itself to interdisciplinary research, the level of interdisciplinarity (as indicated in the final reports and from recent BBSRC analysis), nonetheless appeared to be lower than might be expected. Again, this is likely to be partly due to the lack of longer larger grants –

³ PAs are intended to encourage PIs to submit applications in certain specific areas within the Committees' remits (for example to address important gaps in the portfolio or to promote new/developing areas of science), rather than to have a major influence on the peer review. Scientific excellence remains the most important criterion in the appraisal of applications. The other criteria of strategic relevance (which includes fit to PAs), prosperity & quality of life, timeliness and promise, and cost effectiveness can contribute to the final prioritisation; in practice this is mainly used where grants of comparable scientific excellence are being prioritised.

interdisciplinary research often requires a longer timescale, as scientists from different fields need to adapt to new 'language' and approaches (discussed further in Chapter 7).

Overlap with other funders

37. A number of other UK funding bodies support research in areas that overlap with BCB's remit. These include: the Wellcome Trust, the Medical Research Council, the Engineering and Physical Sciences Research Council, Cancer Research UK and the British Heart Foundation. As noted by these organisations in their questionnaire responses, and the surveyed Committee members, this overlap is beneficial as it gives researchers a number of options, and ensures that there are no gaps in support for research in this area.

38. Conversely, the plant sciences aspects of BCB's portfolio are otherwise poorly supported in the UK. This is a concern, as it leaves plant scientists with few options for funding other than BBSRC (some support is available through the Gatsby Foundation and the EU), and hence highly dependent on (and constrained by) three-year, one-RA grants.

4. INTERACTION WITH INDUSTRY

39. The level of interaction with industry in the sample grants appears to be fairly low. This is partly to be expected, given the basic nature of much of the research supported through BCB. Furthermore, it is important to note that knowledge transfer and interaction with industry occur at a number of other levels (for example specialist networks, direct funding of research by industry), which were not included in this study on research grants.
40. Perhaps the most important contributions that BCB-supported research makes to industry are longer-term, and more difficult to measure and attribute:
- The basic research supported through BCB contributes to the 'bedrock' of knowledge from which industry can conduct more applied research; and
 - BCB's support for UK research in this area provides industry with a continued supply of scientists trained in biochemistry and cell biology research methods, as illustrated by the fact that the private sector was the first destination for **11%** of the RAs employed on the sample grants.
41. There were a few good examples of interaction with industry amongst the sample grants:
- An outcome of the work on periplasmic nitrate reduction (Analysis of the redox components, role and biosynthesis of the periplasmic nitrate reductase system of *Paracoccus denitrificans*) was the use of nitrate reductase in optical biosensors;
 - BASF were exploring their BiP over-producing tobacco lines for increased resistance to fungal pathogens, and following one BCB grant were interested in on-going collaboration with the possibility of developing a license agreement.
42. The level of initial investment by industry in the sample grants was low: only **4%** of sample PIs reported having had co-funding or in-kind support from industry at the start of the grant. However, the level of interaction, and the potential for collaboration, appears to be slightly higher once the research has been conducted:
- **13%** of sample PIs reported new or improved contacts with UK industry as a result of the research supported by the grant, and **8%** with overseas industry; and
 - **3%** of sample PIs reported new collaborations with UK industry, **5%** with overseas industry.
43. Much of BCB's remit has the potential to be of interest to UK industry, and the success and general popularity of CASE studentships illustrates that interaction between industry and academia can be very beneficial. Research on validation tools, transgenics, targets, bioinformatics, small molecules, biomarker development, and modelling for example, is of direct relevance to the pharmaceutical industry. BBSRC's efforts to promote interaction between grantholders and industry are commended and, given the potential for interaction in BCB's area, the Council is encouraged to continue and expand its 'light touch' activities such as grantholder workshops.

Much of BCB's remit is potentially of interest to industry, and there is considerable scope for further, beneficial collaboration between researchers and industry. BBSRC should continue its efforts to promote this interaction, particularly through 'light touch' activities such as grantholder workshops.

5. PUBLIC ENGAGEMENT

44. PIs (or a member of their group) are required to spend one to two days per year on public engagement activities as a condition of their grant, and report their progress in their final report. The most common reported activities amongst the sample grants were in schools or with schoolchildren, in the context of university events (e.g. open days, fundraising), and participation in externally organised events (e.g. science weeks, festivals). There was some evidence of work with the media, including television, radio and the internet, but less than could be expected.
45. There were some notable achievements in this area amongst the sample grants:
- The group working on lignin biosynthesis (Manipulation of lignin biosynthesis by down regulation of multiple enzymes) contributed to a public exhibition, 'Weekend of Wood' at Dundee Botanic Gardens, hosted work experience placements for school children, and the PI gave a presentation to local school teachers;
 - The research on photosystem II (Genetically engineered control of the primary photosynthetic reactions of photosystem II) was reported to the public in New Scientist, the World Science news website, and on Radio 4;
 - The PI of the group investigating the microtubule network in plants (Expression of tubulin and mutant tubulin in transgenic maize calli) was interviewed on BBC News 24 and Radio 5 Live; and
 - The group working on amino acid transport (Regulation of System A amino acid transport by insulin, cell stress and microtubular dysfunction) gave annual research presentations to a forum of Sixth Formers, and to a number of local lay groups.
46. It was, however, disappointing to note from the final reports that, apart from a few exceptions, the sample PIs appeared to have spent much less than the requested time on public engagement activities. This was reflected by the fact that in the majority of final reports, the summary section for the 'informed but non-expert' reader was poorly written, being often difficult to understand even for an expert, and with little explanation of the wider context of the research.
47. Encouragingly, a recent study by BBSRC's External Relations Unit found that 75% of the BCB final reports returned between June and September 2005 reported having carried out at least some public engagement activities, suggesting a genuine level of activity in this area. This was consistent with the BBSRC average across all Committees (76%).
48. BBSRC is therefore commended for the work that it has done to raise awareness of the importance of public engagement amongst the community. However, there remain a number of issues and barriers.
49. Firstly, it was apparent from the information given in final reports that PIs did not have a clear understanding of what BBSRC means by 'public engagement activities', and what the Council expects of them as grantholders (although this could partly be explained by the fact that BBSRC's expectations and definition of public engagement changed during the evaluation period, with the emphasis moving from public understanding to public engagement, and with increasing expectation on grantholders to engage with the public).
50. Secondly, as recognised by BBSRC, PIs do not always have the expertise and support needed to undertake these activities. It can be difficult, for example, to attract media interest, and it is often not easy to make this area of science accessible to the public. Even then, some PIs are concerned that the media will misrepresent the science, a particular concern for those working with animals. Finally, there is a lack of incentive for

PIs in this area: unlike writing papers or grant applications, there is no obvious reward for putting time into (or penalty for not doing) public engagement activities.

While the importance for public engagement is now widely accepted, BBSRC should continue to seek opportunities to encourage and facilitate bioscientists to engage with the public.

51. Suggestions include:

- Engage with the institutions and departments funded by BBSRC, encouraging them to provide more support to scientists in relation to public engagement. For example, some universities have employed communications and media experts to work with researchers to present the science to the public;
- Require PIs to ensure that the 'summary for the informed but non-expert reader' section of their grant application and final report is intelligible to non-experts. This may involve sending the application back to the PI until the section is appropriate;
- Be more proactive in providing PIs with support to help them 'translate' their research findings for public consumption. For example, to promote the science it funds, the Royal Society funded Sheffield Hallam University to interview volunteers from the Society's University Research Fellows. Some of the material was then used to create interactive activities or 'games' designed to encourage school children to engage with science;
- Encourage and support RAs on grants to conduct public engagement activities – they often have more time than PIs, and may be enthusiastic about engaging with the public;
- Encourage PIs to develop 'layperson' webpages on their websites, which would be a first step towards presenting their science to the public;
- Consider ways to offer PIs incentives for conducting these activities, for example establishing a BBSRC Public Engagement Award; and
- Provide additional funding to applicants whose grant applications include a good public engagement plan.

6. ULTIMATE IMPACTS

Introduction

52. Ultimate impacts are those that relate to BBSRC's overall objectives as an organisation, and would generally be expected to arise in the longer-term. The logic chart used to guide the evaluation identifies the following 'ultimate' impacts (relating to the objectives expressed in BBSRC's 10-year vision) that should arise from BBSRC's support for BCB research through responsive mode funding (Appendix 2):
- Research findings are used for the 'public good', e.g. medical research, biotechnology, government policy;
 - Income to research community and 'UK plc', e.g. from new technologies, intellectual property;
 - The UK maintains its international standing in biochemistry and cell biology research;
 - BBSRC maintains its role as a key funder of biochemistry and cell biology research in the UK; and
 - Public confidence in UK biochemistry and cell biology research is maintained.
53. These impacts are clearly difficult to measure, and even more difficult to attribute. However, it is particularly important that they are evaluated because they relate to the organisation's overall objectives: they help to answer the question 'how effectively is BBSRC doing its job?'
54. Income to the research community and UK plc, and the UK's international standing in biochemistry and cell biology research (as measured by the quality of UK research in this area) are discussed in Chapters 4 and 2 respectively.

Research findings used for the public good

55. Some of the sample PIs identified direct contributions to the public good that the research supported by the grant had made (or could potentially make). Examples included:
- The group working on herbicide resistance (Expression of tubulin and mutant tubulin in transgenic maize calli) made significant progress in understanding plant sensitivities to pesticides;
 - Research on the function of BiP subdomains in protein synthesis, folding and quality control, could pave the way for examining the use of BiP to protect crops without over use of pesticides;
 - Work on nematode structural protein folding catalysts led to results which could inform future design of ligands of potential value as anti-nematode agents.
- The contributions to the 3Rs discussed in Chapter 2 are also relevant here, helping the UK research community to move towards using fewer animals in research, in line with government policy.
56. However, as with other outputs, impacts in this area are lower than could be expected from longer and larger grants (discussed further in Chapter 7).

BBSRC's role as a key funder of BCB research

57. BBSRC is clearly one of the key funders for BCB research in the UK, and is particularly important in areas where there are few other funders, for example plant sciences. However, as discussed in Chapter 7, a move to improve the continuity of research funding (through funding significantly more longer and larger grants) would significantly increase BBSRC's impact as a funder of BCB research. The large and increasing

number of applications received by BCB is evidence of the health of this research community in the UK.

Public confidence in UK BCB research

58. The public can draw confidence from the fact that BCB-supported research is peer reviewed and funded only when judged to be of sufficiently high quality. There are no particular issues with BCB's remit or portfolio in this respect but BBSRC should continue to encourage public engagement with science (as discussed in Chapter 5).

7. GENERIC ISSUES

59. A number of general issues relating to BBSRC's grant administration processes and support for the UK biosciences arose in the surveys and during the Panel meetings. These findings are reported in detail separately, and will be considered by the appropriate BBSRC body in combination with the results of other current responsive mode portfolio evaluations. The main points are summarised here.
60. The Panel was pleased to note that all of the surveyed Committee members said that the Committee works very well as a team, and that there is robust discussion of difficult cases. As with all funding bodies relying on peer review, the Committee's effectiveness is limited by difficulties in obtaining sufficient and useful input from referees. BBSRC's current responsive mode success rate of around **25%** is appropriate, and compares well with other funders in the area.
61. When asked about BBSRC's grant application and administration processes, PIs and Committee members mainly commented that the processes are good or satisfactory, and that it is very valuable to be able to respond to referees comments before the Committee meeting. The most common negative comments were that the process is too slow, and that better feedback should be given for unsuccessful applications.
62. The Panel's main concern is that there has been a significant decline in the proportion of grants awarded for longer than three years, and no real increase in the number of large grants awarded, despite BBSRC's encouragement of longer and larger grants. In 2005, for example, 93% of the responsive mode grants awarded by BBSRC were for three years. There appear to be two main factors: firstly, with such high competition, the Committee is apparently reluctant to fund longer and larger grants; secondly, there is a strong feeling in the community that longer and larger grants have a lower chance of success, and PIs are therefore not submitting these types of application.
63. The low proportion of longer larger grants in BCB's portfolio (and in BBSRC more widely) is a major constraint – on the quality of research and research outputs (and hence on BBSRC's corporate image), and on the careers of researchers. This is of particular concern in the plant sciences aspects of BCB's remit, where there are no other major UK funders, and where PIs are likely to be relying almost entirely on these shorter grants from BBSRC.
64. Shorter (3 years or less with one RA) grants are of value and have their place, in supporting smaller groups, new investigators, allowing the piloting of new approaches or ideas, and providing a stopgap between larger grants. But a balance is required - longer (e.g. 5 years) and larger (e.g. more than one RA) grants have many advantages. A longer grant (or a larger one with more than one RA) enables the researcher to investigate more complex problems and to take more risks (for example exploring interdisciplinary approaches). As noted in Chapter 3, this is reflected in the apparent lack of support for the research using and developing transgenic animals and interdisciplinary approaches – both areas where longer term approaches are generally required. Similarly, the relatively low level of outcomes such as industrial interactions, and contributions to the public good is likely to be due, in part, to the lack of longer and larger grants in the portfolio.
65. Longer and larger grants also foster the stability of research groups, enabling the recruitment, retention and career development of high quality research staff. Conversely, the progress of research on short grants is significantly more likely to be affected by staff issues:
 - Almost all of the sample grants supported only one RA, and were therefore heavily dependent on the quality of the RA;

- This is exacerbated by the fact that longer grants are generally more popular (given the added career security), and hence it is more difficult to recruit high quality staff to short grants;
- The lack of job security afforded to the RA causes some to leave the profession; and
- The RA's need to secure a subsequent position can, especially towards the end of the grant, detract from the progress of the research work.

66. BBSRC is commended on the recent launch of its Longer Larger Grants Scheme⁴, but is strongly encouraged to take more proactive and structural steps towards facilitating continuity and stability in research groups - encouraging longer and larger grants where they are appropriate, and addressing the apparent discrepancy between BBSRC policy and Committee practice in relation to longer and larger grants. Indeed, to change the perception and practice both of the community and Committees, a separate funding stream or mechanism may be required (at least in the short term).

The predominance of the three-year, one-RA grant model in BCB (and BBSRC as a whole) is a major constraint both on the quality of research and research outputs (and hence also to BBSRC's perceived role as a funder in this area) and the development of research careers. The impact of research supported through BCB could be significantly improved by moving to a more balanced funding model aimed at encouraging the continuity and stability of research and research groups (i.e. supporting a greater proportion of longer and larger grants).

67. In addition to its general points on staff and career development in Chapter 2, and the role of Priority Areas in Chapter 3, the Panel also noted that:

- Grants that had had significant budget cuts were rarely productive;
- Studentships linked to grants can be very beneficial; and
- There was significant variation in how well the final reports had been written, and in how outputs (particularly publications) had been reported, leading to difficulties and potentially unfairness in the evaluation of the reports.

⁴ www.bbsrc.ac.uk/science/areas/crosscommittee/multidisciplinary_programmes.html.

