

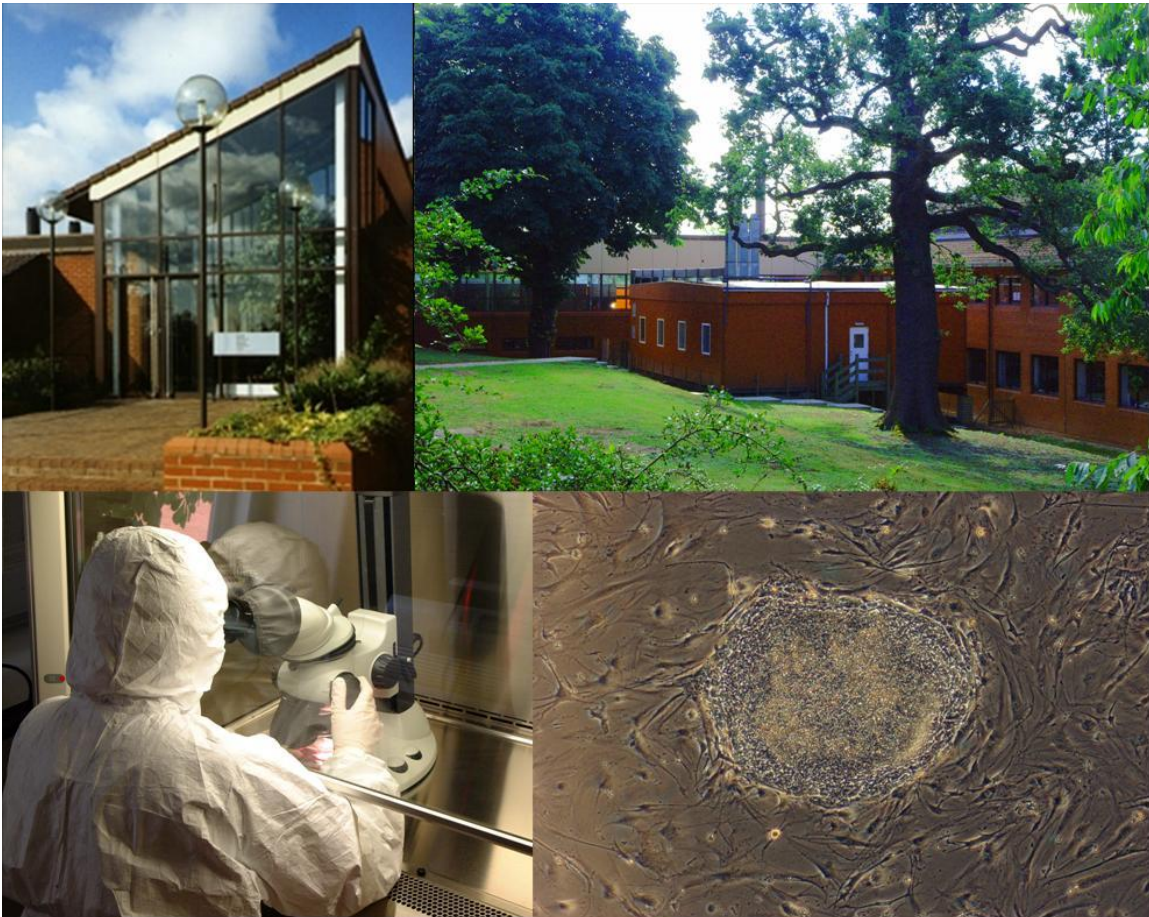
Third Report from The UK Stem Cell Bank

Glyn Stacey Ph.D., Director for the UK Stem Cell Bank

Division of Cell Biology and Imaging

National Institute for Biological Standards and Control

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1 Introduction

1.1 Summary by the Director for the UKSCB

This report covers the period from October 2005 to March 2006. This allows us to bring the Annual Report in line with the cycle of financial reporting and cover the period through to the end of the Bank's initial grant provided by the MRC and BBSRC. The period covered by this report continued to present fresh challenges but was also a very productive period for all involved in the UK Stem Cell Bank and there are a number of significant developments worthy of report.

Following submission of a full business case and feasibility study for a permanent building; £9.4M was secured from the MRC and BBSC to sustain the development of the Bank up to 2011. A comprehensive options evaluation for the Bank's future has now provided us with a forward plan for the Bank's development and NIBSC has started the programme to build a new permanent expanded laboratory facility.

During the year our staff have put a great deal of effort into the lengthy process of banking research-grade hES cell lines approved by the Steering Committee. They have also, through banking of a standard human cell line used for vaccine production, carried out a 'dry run' to prepare for banking of clinical grade lines, expected within the next 18 months. In addition to these core activities UKSCB staff have continued to provide central support for the completion of the International Stem Cell Initiative (ISCI) project. This project, intended to characterise over 60 hES cells from around the world, is now near completion.

In conclusion, the Bank has continued to make significant steps towards fulfilling its prime objective of producing high quality, well-characterised stocks of stem cells. It is on track to release its first "Research Grade" stem cell lines to researchers in late 2006 and develop further customer-focused activities to set it on the road to becoming highly regarded resource for the stem cell research community worldwide.

Dr Glyn Stacey

Director UK Stem Cell Bank

1.2 Commentary by the Chair of the UKSCB Management Committee

During the past year the bank has moved very much from the building and development phase to one focused on acquiring new stem cell lines and establishing the banking process. This has required considerable effort in a challenging field and I have been very pleased with the progress made. Though there is still much to do, and significant scientific uncertainties, we anticipate that the bank will soon begin to deliver on its primary objective to provide access to a range of well-characterised, quality assured cells in support of stem cell research nationally and internationally.

2 Background

2.1 Aims of the UKSCB

The principal aim of the UK Stem Cell Bank is to provide researchers with access to ethically sourced human stem cell lines of somatic and embryonic origin for ethically approved research into serious human disease. The Bank is also expected to provide appropriately qualified seed stocks of stem cell lines for clinical trials. Furthermore, the Bank operates at an international level responding to the technical needs of the stem cell research community.

The Bank aims to provide vital standardization of stem cell lines through careful quality control and characterisation of these cells and their culture conditions, to ensure that researchers have access to reliable and reproducible stocks of cells over time. In addition the Bank ensures that appropriate transfer agreements are in place to enable wide ranging use of the stem cell lines it holds for research purposes. It will be important to accompany the cells released by the Bank with accurate and user-friendly protocols and high quality technical backup. The Bank also supports training activities and in the longer term plans to develop further resources to support stem cell researchers.

2.2 Operational Principles

From its inception, a set of key operational principles has guided the Bank's development. These are:

- Transparent operation and accountability.

Day-to-day operation of the Bank is overseen by a Management Committee that includes stakeholder representation. In addition the Bank reports regularly to the Steering Committee for the UK Stem Cell Bank and for the Use of Stem Cell Lines, to its sponsors and to Clinical and User Liaison Committees.

The Bank aims to make its procedures and information on cell lines freely available for use by stem cell researchers and to disseminate information through its website and regular presentations at stem cell research conferences and meetings of other interested groups.

- Close interaction with its stakeholders.

The Bank seeks actively to establish close relationships with stem cell researchers nationally and internationally through laboratory visits, involvement in scientific conferences and training courses. Such interactions aid the development of highly trained staff with up to date knowledge relating to the culture and use of stem cell lines.

- Avoidance of conflicts of interest.

The Bank does not undertake research on fundamental stem cell biology and product development. Bank scientists do however work with those involved in development of therapeutics in academia and industry to address safety and to develop and improve methods for the culture, preservation and characterisation of stem cell lines.

- Future proofing of procedures, resources and facilities.

This is undertaken in order to maximise the relevance and value of the Bank to the stem cell research community. Given the dynamic nature of the stem cell field it is extremely difficult to future proof the work and resources of the Bank completely. However the Bank aims, through its close links with the research community, and its important interactions with its host Institution, the National Institute for Biological Standards and Control, and international regulatory authorities, including WHO, to ensure that its activities take account, as far as possible, of best practice, particularly with respect to the demands and requirements for clinical grade seed stocks of cells.

3 Scientific Progress

3.1 Stem Cell Line Accession and Cell Banking Activities

During the year, the work of the bank was largely focused on acquiring and banking the first batch of stem cell lines approved for accession by the Steering Committee. The current status of cell lines approved by the Committee to end March 2006 is shown in the Table 1 below:

The term accession is defined as the receipt into the Bank of the stock of cells supplied by the Depositor and the assigning to this deposit of a unique Accession number. The banking process involves the preparation of three levels of bank: pre-master, master and distribution. This is time consuming, but is vital to provide both archive stocks of cells for future decades as well as reproducible stocks cells for immediate use by researchers. It has become evident that each line may require a different level of attention and grow differently to others. This means that the banking process is not always predictable and may take anywhere from 8 to 23 weeks to complete depending on the cell line. Certain lines have proved particularly difficult to recover from frozen stock, particularly from very early passage material. Consequently, the Bank has changed its accession policy to ensure that, so far as is possible, only cells consistent with the characteristics of the cell line, but which are known to be capable of resuscitation from the frozen state, are accessioned into the Bank.

For growth in culture, hES cells require a feeder cell layer. Initially the cell lines are maintained on feeder cells obtained from the depositor. However, in the longer term, logistically it will not be possible to maintain cell lines on their original

mouse feeder strains. The Bank is therefore testing a range of potential feeder cells including human diploid fibroblast cell lines and primary mouse embryonic fibroblasts from the different mouse strains used by depositors for their capacity to support the growth of a range of hES cell lines. Thus, when necessary, hES cells once established in culture, will be transferred from their original feeder cells to an appropriate UKSCB stock feeder cell line for the establishment of the hES master and distribution cell banks.

Earlier in the year, as part of its process validation and qualification, the Bank working with staff from NIBSC, produced its first cGMP bank; a mouse fibroblast feeder cell bank for use in the production of cultured human keratinocytes. In conjunction with staff from the Division of Cell Biology and Imaging, a further cGMP bank of human fibroblasts (MRC-5) cells was prepared during November and December of 2005. This bank of cells, with its history of successful use as a cell substrate in the pharmaceutical industry, will be used both for this application as well as in human keratinocyte culture for patients undergoing treatment for severe burns. It may also have potential as a cGMP-compliant human feeder layer for future use in the production of "Clinical Grade" hES cell banks.

Table 1: Status of Stem Cell Lines Approved by the Steering Committee for Banking at the UKSCB**Table 1A. Cell lines currently undergoing cell banking**

Stem Cell Lines Banked							
Cell Line	UKSCB Accession Number	Cell Type	Grade	Depositor / Principle Investigator	Depositing Centre	Country of Origin	Probable Release Date
Shef 1	R-05-007	Human Embryonic	Research	Prof. H. Moore	Axordia Ltd., Sheffield	UK	September 2006
Shef 2	R-05-028	Human Embryonic	Research	Prof. H. Moore	Axordia Ltd., Sheffield	UK	September 2006
Shef 3	R-05-008	Human Embryonic	Research	Prof. H. Moore	University of Sheffield	UK	September 2006
hes-NCL 1	R-05-015	Human Embryonic	Research	Prof. A. Murdoch	Newcastle Fertility Centre at LIFE	UK	September 2006
HuES 7	R-05-035	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	December 2006
HuES 9	R-05-037	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	December 2006
HuES 1	R-05-033	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	March 2007
HuES 3	R-05-034	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	March 2007

Table 1B. Cell lines accessioned into the UKSCB

Stem Cell Lines Accessioned by the UKSCB (as of Q1, 2006)							
Cell Line	UKSCB Accession Number	Cell Type	Grade	Depositor / Principle Investigator	Depositing Centre	Country of Origin	Accessioned
Shef 4	R-05-029	Human Embryonic	Research	Prof. H. Moore	Axordia Ltd., Sheffield	UK	Q3, 2005
Shef 5	R-05-030	Human Embryonic	Research	Prof. H. Moore	Axordia Ltd., Sheffield	UK	Q3, 2005
Shef 6	R-05-031	Human Embryonic	Research	Prof. H. Moore	University of Sheffield	UK	Q3, 2005
KCL-001 (formerly WT3)	R-05-019	Human Embryonic	Research	Dr. S. Minger / Dr P. Broude	King College, London	UK	Q2, 2005

Table 1C. Cell lines approved by the Steering Committee

Stem Cell Lines Approved by the Steering Committee but not yet Accessioned by the UKSCB (as of Q1, 2006)							
Cell Line	SCSC Number	Cell Type	Grade	Depositor / Principle Investigator	Depositing Centre	Country of Origin	Approved
HuES 2	SCSC04-30-(2)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 4	SCSC04-30-(4)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 5	SCSC04-30-(5)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 6	SCSC04-30-(6)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 8	SCSC04-30-(8)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004

Stem Cell Lines Approved by the Steering Committee but not yet Accessioned by the UKSCB (as of Q1, 2006)							
Cell Line	SCSC Number	Cell Type	Grade	Depositor / Principle Investigator	Depositing Centre	Country of Origin	Approved
HuES 10	SCSC04-30-(10)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 11	SCSC04-30-(11)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 12	SCSC04-30-(12)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 13	SCSC04-30-(13)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 14	SCSC04-30-(14)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 15	SCSC04-30-(15)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 16	SCSC04-30-(16)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
HuES 17	SCSC04-30-(17)	Human Embryonic	Research	Dr. D. Melton	Harvard University, HHMI	USA	Q4, 2004
Edi 1	SCSC04-34	Human Embryonic	Research	Prof. A. Smith	Universities of Edinburgh & Oxford	UK	Q4, 2004
MEL 1	SCSC04-35 [Formerly E78-12-04]	Human Embryonic	Research	Dr C O'Brien / Dr M Pera	Stem Cell Sciences Ltd, Australia (SCS) & Australian Stem Cell Centre (ASCC)	Australia	Q4, 2004
Nott 1	SCSC06-02	Human Embryonic	Research	Prof. L. Young	University of Nottingham	UK	Q1, 2006

3.2 Scientific and Technical Development

3.2.1 *Scientific Liaison*

Following the successful launch of the UKSCB Technical Forum in May 2005, a second forum was held at NIBSC in November 2005, attracting scientific and technical staff from many of the UK's leading stem cell centres and also contributors from outside the UK. At the request of those attending the forum, further meetings have been planned and a discussion board will be hosted on the Bank's website to facilitate dialogue between those undertaking the day-to-day culture of stem cells.

The Bank has continued to actively support the IVF clinics and derivation centres through its involvement with the human embryonic stem cell coordinators organisation (hESCCO) – the new stem cell co-ordinators forum. The Bank continues to host visits from these centres and a quality forum to assist the IVF and derivation laboratories in their programme of improvements to meet the requirements of EU legislation has been proposed.

Staff from the Bank have continued to contribute to a significant number of stem cell scientific meetings (Stem Cell Conference Brussels, 15th/16th December 2005) and also assist in workshops on developing UK and international stem cell research activities and initiatives (e.g. BBSRC Cell Supply Chain Workshop, 17th/18th November; International Stem Cell Forum Paris, 13th January 2006; Transnational Cooperation in Stem Cell Research Steering Committee Cambridge, 22nd February 2006). The Bank also maintained and developed its US contacts including meetings with the Californian Institute for Regenerative Medicine (CIRM) and WiCell.

The Bank has also hosted a large number of international visitors, receiving Government ministry delegations from numerous countries (e.g. Singapore, China, Japan, and Korea). These visits have allowed the Bank to showcase its mechanisms of governance and its banking and testing procedures, as well as highlight safety issues to a wider audience. Commercial organisations too have continued to show interest in interaction with the bank and we have hosted visits from Cellartis (Sweden) and the BioIndustry Association.

The Bank has welcomed closer interactions with charitable organisations interested in stem cells and since the last report has received a visit from Mary Baker, the president of the European Parkinson's Disease Association. This has led to an invitation for the Bank to attend an open public debate on stem cell therapy at the European Commission to be held in November 2006.

The pivotal role of the Bank and the need for continued support was endorsed in the report to the Treasury on stem cells prepared by Sir John Pattison (UK Stem Cell Initiative: Report and Recommendations, November 2005). The increasing international activity of the Bank was recognised when NIBSC was awarded a

World Technology Award for innovation in the establishment of the UK Stem Cell Bank and its achievements in promoting stem cell research. Whilst this award was presented to NIBSC, it recognises the contribution made by national research groups, individual scientists and the Bank's sponsors to the successful establishment of the UK Stem Cell Bank.

3.2.2 *The ISCI Project*

Following a successful meeting at Bar Harbour in August 2005 of the participants of the International Stem Cell Initiative project, including the Bank, work has continued on the analysis of the data produced on the 60 plus embryonic stem cell lines included in the study. This has been a challenging project for all laboratories concerned.

Members of staff from both the UKSCB and NIBSC not only acted as the technical hub (preparing and encoding samples for subsequent dispatch to specialist analytical laboratories) but also undertook microbiological investigations: detection of adventitious agents by cell line inoculation, transmission electron microscopy and mycoplasma and sterility testing.

During the period of this report, data from the various analytical laboratories has been collated by the ISCI steering group, led by Professor Peter Andrews (University of Sheffield) and information posted on the ISCI webpage on the International Stem Cell Forum website (<http://www.stemcellforum.org>). An article outlining the main aims of the project has been published in Nature Biotechnology (see publications section) and a final publication will be prepared for publication in 2006/07.

3.2.3 *Internal R&D*

During the latter half of 2005, the Bank began to develop its own programme of research and development work within the guidelines laid down by the Steering Committee and detailed in both the UKSCB Code of Practice and the Code of Practice for the Use of Human Stem Cell Lines.

A project to investigate the ability of a range of mouse and human diploid fibroblasts to support human embryonic stem cell proliferation has been initiated. In conjunction with this, the Bank is undertaking preliminary collaborative studies with the Proteomics group at NIBSC to investigate the potential for proteomic techniques to be used in identifying and quality controlling, feeder cells for their ability to support hES cell growth.

In 2005, the UKSCB was awarded an MRC Doctoral Training Award. This will be applied to a project currently under development with the University of York's Medical Cryobiology Unit to develop and optimised protocol for cryopreservation of embryonic stem cells suitable for application to "Clinical grade" stem cell lines.

3.3 Quality Assurance

3.3.1 Inspection and Accreditation

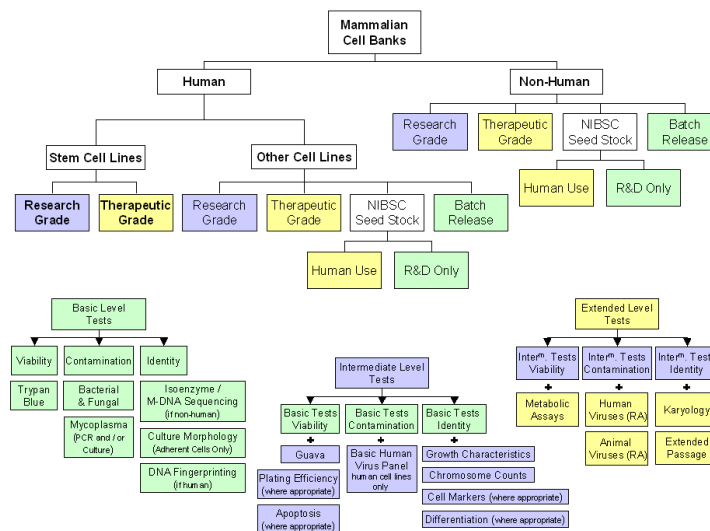
In September/October 2005, the bank completed the outstanding equipment validation remaining from the first MHRA inspection. The licence granted by the MHRA under the DH Code of Practice for Tissue Banks, ran for two years from June 2004. This Code of Practice will be replaced by the Human Tissues Act (2004) and the EU Directive 2004/23/EC on Tissues and Cells. In March 2006, the Bank submitted its licence application to the Human Tissues Authority for the storage of human cells for clinical use. This involved the completion of the HTA's detailed self-assessment questionnaire. Submission of this document secures a "deemed licence, which will lead to a full licence or inspection in due course. The institution of this process ahead of the expiry of the MHRA licence will ensure continuity of cover for the Bank under the appropriate guidelines.

3.3.2 Off-Site Storage

A Service Level Agreement has been put in place with Cryonics UK for the off-site storage of both "Research Grade" and "Clinical Grade" material. Two liquid nitrogen refrigerators have been purchased for siting at Cryonics and the qualification documentation for these tanks is being prepared. The tanks will undergo validation during 2006 prior to the transfer of any material.

3.3.3 Safety Testing and Characterisation of Cell Lines

During the period of this report, considerable work was undertaken on the testing and characterisation strategy proposed by the Bank. This provides a set of core tests applicable to all human cell line banking and an extended set of tests suitable for "Clinical or Therapeutic Grade" cell lines. Studies to validate the testing protocols are underway. The strategy is shown in Figure 1 below:



4 Resources

4.1 Laboratory Facilities

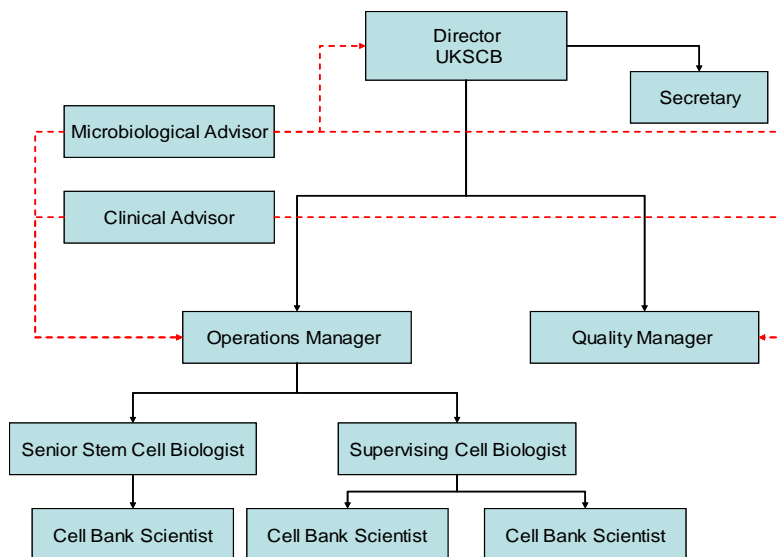
To date, the Bank has shared general laboratory facilities for internal R&D and quality control testing with colleagues throughout NIBSC. Over the last year, NIBSC has undergone a programme of extensive space re-allocation to meet scientific demands. This has resulted in the Bank being allocated temporary laboratory space on an *ad hoc* basis. It was recognised that this situation, if allowed to continue, would have an adverse effect on the ability of the Bank to meet its medium term targets.

Therefore, during the period of this report, work began on the provision of new laboratory facilities to be shared between the Bank and NIBSC Division of Cell Biology and Imaging. This will bring together, within one suite of laboratories, quality control testing currently undertaken throughout NIBSC and provide much need additional space for undertaking technical and assay development associated with characterisation and testing. These facilities will be operational in time for the testing necessary for the release of the first stem cell lines later in 2006.

The facilities have continued to undergo planned preventative maintenance and equipment servicing under the Service Level Agreement with the NIBSC maintenance department. Following a pharmaceutical cleandown the cleanrooms were re-certified to the appropriate ISO standard (ISO14644).

4.2 Recruitment

The current staff structure over the period of this report is shown below. It reflects the current emphasis on banking activities and the development of the safety testing and cell characterisation tests required for release of cell banks.



Only one additional post has been created since the last report, though overall, the staff complement remains the same. This is due to the movement of the staff member employed on the International Stem Cell Initiative project (ISCI) from this post to cell banking duties within the Bank. This has allowed the Bank to expand its stem cell banking activity as the work on the ISCI project nears completion. The Bank will continue to monitor its staffing requirements over 2006 as it moves into the distribution phase of its activity.

5 Governance

5.1 Planning and Reporting

The Bank, in conjunction with the Division of Cell Biology and Imaging at NIBSC, develops a detailed annual workplan which is the subject of regular reviews to ensure delivery of the key outputs identified in the plan.

Progress is reviewed quarterly by the operational group for the Bank consisting of UKSCB senior staff (director, operations manager, quality manager) and senior staff from NIBSC (director and heads of operations, quality and finance. This group reports via the Bank's senior staff to the Bank's Management Committee at its 6 monthly meetings.

The Bank has continued to provide bimonthly written reports to the Steering Committee throughout the period of this report, and has been available to present updates to both the Steering Committee and the Clinical and User Liaison Committee meetings.

5.2 Sponsor Liaison

Liaison with the sponsors is both formal and informal. During the period in question the Bank has met informally with representatives of the BBSRC, while a formal link through a UKSCB/MRC Liaison Group has been established and has met regularly.

It has produced a revised Materials Deposit Agreement (MTA) and a shortened version of the Application to Deposit, which will be undergo trials with depositors in 2006. Further work on application forms will be also be undertaken with a view to developing electronic submission of applications via the MRC and UKSCB websites.

The Bank has continued to present regular updates to the funder's forum.

5.3 Risk Management

A set of key risks to the Banks establishment and operation were presented to the Bank's Management Committee in 2003. This list was reviewed and developed in 2004. During the reporting period there have been no significant changes made to the risk register, and the risks will be re-reviewed in June 2006.

6 Communications

In October of 2005, the Bank met with MRC communications experts to review the communications strategy for the Bank that had been prepared with MRC support in 2004. Media coverage of the Bank continued to show a low-key but positive message that was considered appropriate given the bank's remit. More proactive mechanisms for publicising the work of the Bank were considered that could be taken forward under existing activities funded by the MRC. Further meetings with MRC Press Office staff on communications were held during the period of this report and a programme of engagement of the Bank in published literature and public awareness events was planned to start from the summer of 2006.

7 Financial Report 2005-2006

7.1 Spend and Forecast

The spend for 2005 has been reported to the Steering Committee. The project is forecast to remain within budget.

The 3-year, Phase I grant for the UKSCB ran from January 2003 to the end of December 2005. It was agreed with the funders that any underspend, accrued over the lifetime of the grant, could be used to bridge the funding gap between the end of the Phase I grant and the beginning of the Phase II grant due to start on 1st April 2006.

7.2 Proposal for Phase II Funding 2006-2011

A UKSCB Phase II proposal and 5-year plan to build and equip a permanent facility and operate it over the 5-year period was approved, by the MRC/BBSRC Review Panel on 1st July 2005. The Research Councils requested that a full business case and feasibility study be prepared for their consideration in awarding the full amount requested by the Bank. The full business case, prepared by NIBSC, and a feasibility study, prepared by the architects Shepard Robson, was presented to the MRC/BBSRC at the end of September 2005.

The business case and feasibility study were considered by the MRC SCOPE committee following a visit by members of this committee to the Bank. These were endorsed by SCOPE and presented to MRC Council in December 2005. The Medical Research Council approved the full funding of £9.4M requested by the UKSCB in the Phase II proposal, of which £1M will be provided by the BBSRC.

8 Permanent UK Stem Cell Bank

The options appraisal included in the documents presented to the Research Councils provided the starting point for the programme to build a new permanent expanded laboratory facility.

During the period covered by this report, the project team (which includes representation from the funders) has been formed and the Project Initiation Document (PID) has been completed. The Design Qualification (DQ) has been initiated. The project will be controlled under PRINCE 2 project management principles. Future developments on the new facility will in future be reported in the Facilities section of the Annual Report.

9 Publications by UK Stem Cell Bank Staff

Hunt CJ, Pegg DE, and Armitage SE. (2006). Optimising cryopreservation protocols for haematopoietic progenitor cells: a methodological approach for umbilical cord blood. *Cryo Letters* 27, 73-86.

Stacey GN, and Hunt CJ. (2006). The UK Stem Cell Bank: a UK government-funded, international resource centre for stem cell research. *Regen. Med.*, 1, 139-142.