



Second 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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Summary by the Director for the UKSCB

The first annual report from the UK Stem Cell Bank (September 2004) showed how the essential elements required for the Bank's operation were being established. This second annual report demonstrates how the bank is developing its fully operational capability. With the increasing number of stem cell lines approved for deposition in the Bank, the staff have become engaged in the demanding task of preparing large scale stocks of frozen cells ready for release. This is a major challenge and the staff, who have shown tremendous commitment to the Bank's work, have designed and implemented a system that should ensure the Bank's ability to provide reproducible and reliable seed stocks for researchers into future decades. The quality of our work has remained a high priority and, increasingly, we have been asked to share our experiences with others involved in building clinical grade stem cell facilities. We have also supported developments in standardisation for research grade cells and have become increasingly engaged within the research community as a member of the UK stem cell community. In 2006, the first stem cell lines will be available for researchers and we look forward to developing a new set of positive relationships with the customers of a fully functioning UK Stem Cell Bank.

Dr Glyn Stacey
Director UK Stem Cell Bank

Commentary by the Chair of the UKSCB Management Committee

It is a great pleasure to introduce the [second] Annual Report from the UK Stem Cell Bank. It has been a crucial year in the Bank's development, during which it has moved from a construction to an operational phase. Having established an excellent, well equipped facility, a strong scientific team, and a very comprehensive set of procedures for handling stem cells, the emphasis is now very firmly on accession of cell lines and the generation of well characterised materials to support stem cell research.

The future success of the Bank will depend completely on the value that it provides to the stem cell community and so I am very pleased to note the co-operative spirit that has been engendered between the Bank's staff and research groups around the country and abroad. We are still only just at the starting post and there is a great deal still to do, but I am confident that we have built a strong platform for the future, and that the Bank is poised to play a very important supporting role in the development of stem cell therapy in the UK and abroad.

Dr Stephen Inglis
Director NIBSC

1. Ethos of the UK Stem Cell Bank

1.1. Aims

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 will ensure 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.

1.2. Operational Principles

From its inception, a set of key operational principles have 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 stem cell companies 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 to maximise relevance and value 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.

2. Progress

2.1. Laboratory Facilities

The completion of laboratory facilities for research grade and clinical grade cell lines and the successful accreditation of the cGMP facility by the MHRA under the DH Code of Practice for Tissue Banks (2001) were reported in the Annual Report to September 2004. Since then the Bank has instituted a planned preventative maintenance programme with biannual shut down of the facility for maintenance, cleandown and recertification to EU cGMP. This process, utilising a number of contractors, is controlled through a Service Level Agreement with the NIBSC Maintenance and Estates Department who also carry out routine maintenance and repairs. This allows the Bank to maximise throughput of stem cell lines as all servicing of equipment is carried out during these shut down periods.

2.2. Recruitment

The post of Quality Manager was filled in November 2004. The successful candidate was previously a senior manager in a pharmaceutical and medical devices manufacturer and has Qualified Person (QP) status under the permanent provisions of EU Directive 2001/83/EC. The appointment provides the Bank with a high level of expertise in the area of quality systems and training and crucial experience for the release of cell banks for clinical use.

Three further appointments were made. Two scientists were recruited to provide additional support for cell banking. Their previous experience in the areas of developmental biology and virology provides an additional resource for the Bank. In addition a cell biologist, with direct experience of cell therapeutic production in a commercial setting, was appointed to support Bank's activity on the International Stem Cell Initiative with additional funding from the Medical Research Council (see 2.3.2.1 below).

2.3. Scientific and Technical Development

2.3.1. Scientific Liaison

From September 2004 to August 2005 the UKSCB received numerous visitors including representatives of national government (e.g. Foreign and Commonwealth Office, Department of Trade and Industry), delegations from foreign governments (e.g. China, Japan, Germany, Canada and USA) and industry representatives (e.g. BioIndustry Association).

Together with NIBSC staff we organized and contributed to a number of workshops for stem cell workers including:

- UKSCB workshop on Deriving Embryonic Stem Cell Lines within a GMP Environment, NIBSC, October 2004.
- Symposium on human tissue banks, ECCO XXIII Conference, NIBSC November 2004.
- UKSCB Technical Forum on human embryonic stem cell derivation, May 2005.

Our involvement in training programmes increased during the year. Bank staff contributed to the practical training course on hES cell culture at the University of Sheffield once again and also to a practical stem cell culture course at the Jackson Laboratories in Maine, USA in August 2005. The Bank has also been invited to contribute to other training courses in the USA and elsewhere in 2006.

- Following the workshop on GMP cell banking organized by NIBSC in November 2004, the Bank has provided ongoing support to the IVF clinics and stem cell laboratories engaged in establishing facilities for the derivation of hES cell lines for clinical use. In addition to hosting visits from the Sheffield, Edinburgh and Serono (Bourne Hall) groups to discuss aspects of quality assurance and cGMP, as it applies to their facilities, the Bank was invited onto the newly formed human Embryonic Stem Cell Co-ordinators Network (hESCCO). This group, representing those assisted conception units and their closely associated stem cell derivation centres, with members from the NBS and the HFEA was set up in June 2005 to harmonise donor information, testing and consent procedures between centres. We have also contributed to and helped arrange the joint BBTS/NIBSC Stem Cell Forum workshops on

standards for haematopoietic stem cells held at NIBSC in November 2004 and June 2005.

The technical forum organised by the Bank in May 2005 has been particularly successful, bringing together those technical and scientific staff in UK stem cell laboratories that are deriving hES cells “at the bench”. This informal meeting was well attended and participants have requested further meetings and a password protected bulletin board to be set up on the UKSCB website. UKSCB staff were also invited to join the UK hES Cell Scientific Forum which meets twice annually to provide a scientific communication forum for current work on hES cell research.

Approximately 30 presentations and key note lectures were made at scientific conferences during the year. We also contributed to initiatives for development of regenerative medicine in the UK organized by the Biotechnology and Biological Sciences Research Council and the BioIndustry Association.

The Economic and Social Research Council now has a strong programme evaluating stem cell research and during 2005 the Bank hosted Dr Neil Stephens (CESAGen University of Wales, Cardiff) who is undertaking a social science research project entitled “Curating and Husbandry in the UK Stem Cell Bank”.

UKSCB contacts have also been widened to include key scientific groups and regulatory bodies in India, Korea and China.

2.3.2. Research Collaborations

2.3.2.1. International Stem Cell Initiative

The International Stem Cell Initiative project aims to carry out a basic set of characterisation studies including flow cytometric analysis of the expression of 17 surface antigens and quantitative RT-PCR of transcription levels of ~ 100 genes characteristic of pluripotent stem cells and markers of differentiation. This will be carried out on a large number of stem cell lines grown under defined culture conditions. In addition each cell line will be subjected to DNA fingerprinting, karyotyping and microbiological screening that will include a screen for endogenous retroviruses. The project was initiated at the International Stem Cell Forum (ICSF) where a number of national funding bodies from around the world meet to discuss stem cell funding on an international basis. Seventeen Laboratories in 11 Forum member countries have agreed to take part contributing a total of 75 hES cell lines to the study. Such a large scale comparison may provide the first firm data on the variability of embryonic stem cell lines and inform the choice of representative stem cell markers for future research. It will also establish a formal mechanism for future large scale international collaborations in this area.

The role of the UK Stem Cell Bank has been to act as the technical hub for the project. In addition to standardising the protocols to be used in the study, the Bank has prepared antibody preparations for use in the flow cytometric and cytochemical marker studies. This has involved the preparation of cell banks of 18 hybridomas and a control cell line, together with the preparation of antibody-containing supernatant and the distribution of antibody panels and other analytical materials to the participating laboratories. The Bank has also co-ordinated collection of all materials from the participants, undertaken DNA/RNA extraction and distributed the resulting analytes to expert laboratories for analysis.

In addition to this the Bank, together with the Division of Cell Biology and Imaging, has undertaken investigations for retroviral contamination and mycoplasma testing and some limited ultrastructural studies by transmission electron microscope. The ISCF, through the MRC has provided additional funding (for materials and staff) for the activities undertaken at the Bank. The aims of the project were published in Nature Biotechnology in June 2005 (Andrews et al., 2005). Initial data available from the project was reviewed at an ISCI partners meeting in August 2005 and the final data set will be published in 2006.

2.4. Patent Depository Status

Patent depository status was notified to NIBSC by the World Intellectual Property Organisation on 16 December 2004, meeting the timeline required by one of the depositing centres. This facility at the Bank now enables any cells deposited with UKSCB to be automatically converted to patent depository status as required to support stem cell patent under the Budapest Treaty 1977. The Bank's first hES cell patent accession was deposited in January 2005.

2.5. Safe Depository at NIBSC

Following a number of requests from the members of the stem cell community, NIBSC with the help of the Bank is engaged in developing a service whereby derivation centres can deposit newly developed stem cell lines at NIBSC. These can act as a contingency reserve for disaster recovery should the need arise. The service would be completely separate from the formal process, overseen by the Steering Committee, of depositing stem cell lines in the Bank. To avoid any conflict of interest, the process of safe deposit would be handled by the Division of Cell Biology at NIBSC rather than by the UK Stem Cell Bank.

2.6. Stem Cell Line Accession and Cell Banking Activities

Cell line accession involves a number of critical steps including gathering detailed information on the cell line from the depositor, negotiating a Materials Deposit

Agreement with the "owner" of the line, carrying out the cell banking process and undertaking quality control and safety testing on the resulting cell banks.

Once approved for deposit by the Steering Committee, information on cell culture conditions and handling of the cell line is gathered through detailed discussions with scientific and technical staff in the depositor's laboratory. This usually involves several visits before the Cell Line Master File can be generated by the Bank and a small stock of early passage cells can be identified for accessioning into the Bank from which the pre-master cell bank (PMB) is generated.

Cell banking requires the generation of three banks - a pre-master, a master and a distribution cell bank - each of which is subject to appropriate quality control testing and cell characterisation. The pre-master cell bank serves to provide the material for initial sterility, mycoplasma and viability testing and to establish base line cell characterisation. It also functions as an archive of the depositor's material for future reference. A proportion of the vials or straws will be expanded in culture to provide the master cell bank. The master cell bank itself will form the permanent stock of material at the Bank. It undergoes extensive testing and small proportion of it (usually one to two straws/vials) is expanded to form the distribution cell bank. This stock of cells is the material which will be provided to the user community for research. Once this stock is exhausted, further material from the master cell bank is resuscitated in order to provide another Distribution bank. This process is time consuming especially with slowly growing embryonic stem cell lines.

The first cell lines approved by the Steering Committee (those from the Newcastle Centre for Life and King's College, London - NCL1 and WT3 respectively) were accessioned by the Bank between November 2004 and April 2005) following lengthy discussions with the depositor. A further 22 cell lines were approved by the Steering Committee for accession in December 2004, and in January 2005 the depositors were contacted and Bank staff began the process of visiting the derivation centres to begin the process of accession.

During the period of this report, 8 of the 24 lines approved by the SC were accessioned into the Bank and pre-master cell banks established. These cell lines were Shef 1, 2 and 3 from the University of Sheffield and Axordia Ltd and the first (and most popular) of the huES lines (huES 1, 3, 7, 8 and 9) from Professor Doug Melton at Harvard University.

Over the period of this report, the Bank began the process of expansion of these cell lines to provide the required master and distribution cell banks. While considerable difficulties were encountered at the outset in establishing master cell banks from very early passage material, the Bank has established both master cell banks and distribution cell banks for Shef 1 and 2 during 2005 and the Bank's process of identifying stocks of cells suitable for deposit has been informed by these experiences.

During 2005 interactions with stem cell research groups have developed significantly on an international basis and numerous groups are considering depositing their stem cell lines in the UK Bank which will hopefully ensure a busy cell banking programme of new cell lines leading into 2007.

3. Quality Assurance

3.1. Site Validation Master Plan

Since November 2004, a Site Validation Master Plan was developed which brought together the many elements of validation into a single comprehensive high level document. This completed the outstanding actions raised by the MHRA in their April 2004 inspection and provides a solid platform for its next inspection.

3.2. Off-Site Storage

As part of the Bank's risk reduction programme, an off-site low temperature storage facility was sought in order to mitigate the risk of catastrophic system failure of the liquid nitrogen storage refrigerators at NIBSC with consequential loss of stem cell material. A detailed specification for storage requirements was prepared and a suitable commercially-operated facility was identified. This facility, used by other health-care groups for critical off-site storage of materials for therapeutic and research use, will house strategic stocks of stem cell lines and other materials. The next phase will be to develop a set of robust operational quality procedures with the service provider before transfer of any critical materials.

3.3. Safety Testing of Clinical Grade Cell Lines

The Bank continued to develop its testing strategy for "Clinical Grade" stem cell lines ahead of the expected deposit of a suitably qualified stem cell line in 2007/8. The strategy, together with a proposed validation model, was endorsed by the Management Committee and piloted using a 'test' human cell line. The strategy involves outsourcing the tests required for release of the cell line to an accredited laboratory. Discussions have taken place with a prospective testing laboratory and a detailed specification and a Service Level Agreement is being drafted.

A proposal for generic testing and characterisation of human cell lines for therapeutic use, based on the strategy developed by the Bank, was submitted by NIBSC to the Biological Sub-committee of the Committee for the Safety of Medicines in December 2004. The proposal was endorsed by the Sub-committee, subject to certain qualifications. NIBSC has been encouraged to

publish the proposed strategy in a peer-reviewed journal and a manuscript is in preparation.

Consideration of appropriate hES cell characterisation test to be undertaken by the Bank will be informed by the outcome of the International Stem Cell Initiative (see 2.3.2.1 above).

4. Management of the Bank

The Bank's operational procedures continue to develop through discussion by the Management Committee and a number of specific working groups. Procedures relating to charging policy, communications, validation, risk management and quality assurance were reviewed at the Management Committee meetings in November 2004 and May 2005. The Bank's charging procedures still require to be finalised with the Bank's sponsors and the Steering Committee.

4.1. Working Groups

Options for providing a suitable look-back mechanism from banked cells to donors were considered by the Working Group on Consent and Adverse Event Reporting. The proposals generated will be taken forward with the UK centres establishing clinical grade hES cells.

Key principles for safety of stem cell lines in the Bank were established by a working group on Adventitious Agents and Safety Testing. These principles will be explored further at a future meeting engaging a wider group of experts.

A Communications Working Group was established to develop a suitable strategy for public communication.

5. Communications

The 1st Annual Report to the Steering Committee was presented to and endorsed by the Management Committee and presented to the Steering Committee in December 2004. The Bank continued to provide bimonthly written reports to the Steering Committee throughout the year, and has presented updates to the Clinical and User Liaison Committee meetings in March and June 2005. Regular liaison meetings were also held with MRC staff and a visit to the Bank by BBSRC representatives was hosted in December 2004.

In addition to numerous presentations at conferences and organizing workshops (see 2.3.1 above) the Bank was also invited to attend the 1st European Stem Cell Network Meeting in Seville, Spain and to contribute to formal discussions at the

MRC and MHRA on formulation of plans for upgrading IVF clinics for GMP derivation of ES cell lines. Representation regarding regulation of stem cell lines for therapeutic applications was made via the DoH and EU to the committee dealing with the technical annexes to the EU Tissues and Cells Directive. Staff from the Bank also contribute to the National Blood Services' Standing Advisory Committee on Tissues and The Royal College of Obstetrics and Gynaecology Scientific Working Party on Cord Blood Banking. Staff from the UKSCB have also maintained active engagement with the UK stem cell research networks with an ongoing programme of laboratory visits by Bank staff. In 2004-05 Bank staff contributed presentations at formal meetings and conferences organized by the Eastern England Stem Cell Network and the new London Regenerative Medicine Network.

Consultation with lay-groups, MRC communications experts and the MRC-led Communications Coalition continued to consider opportunities for communicating the Bank's activities to non-scientific audiences while a set of publicity materials for scientific meetings, including a UKSCB information leaflet and exhibition stands, was prepared by Bank staff.

The UKSCB website underwent further development during the year. The website is not only the Bank's "shop window" but also provides an increasingly important access point for many people searching the web for information on stem cells. Further resource will be needed to enhance the site and to update it on a regular basis.

6. Risk Management

The risk register for the UKSCB and associated action plan was updated during the year, as part of an annual review process. Risk assessment and management is a key element of the Bank's operational strategy for its current and future development.

7. Financial Report 2004-2005

7.1. Spend and Forecast

The spend for 2004 and the budget forecast to the end of Phase 1 of the project in December 2005 has been reported to the Steering Committee. The project is forecast to remain within budget.

7.2. Development of a Charging Policy for the Bank

A charging policy developed by the Bank is under discussion with the Bank's sponsors and the Steering Committee and options for charging will be submitted

as part of the Full Business Case to be submitted in October 2005. The proposal for Phase II funding from 2006-2011 also includes the development of charges for testing and other services to offset the costs of the Bank.

7.3. NIBSC Proposal for Funding 2006-2011

In November 2004, an Expression of Interest was submitted by NIBSC to the MRC for funding from 2006. A forward plan, an options appraisal together with outline costings for Phase II (2006-2010) and a review of Phase I (2003 – 2005) was submitted to the MRC in March 2005. The response from the panel of fifteen reviewers to this proposal was overwhelmingly supportive and the panel recommended continued funding.

An MRC committee also endorsed the proposals put forward by the Bank in July 2005. However, the funds requested were higher than expected and the MRC and BBSRC requested that the Bank submit a full business case and building feasibility study by 3rd October 2005 for review by the MRC SCOPE committee in advance of a formal recommendation to MRC Council in December 2005.

8. Forward Plan

Over the next year, the Bank will focus on:

- Completion of process validation for clinical grade cells. This will be assisted by the preparation of a large bank of MRC-5 human diploid cells used in vaccine manufacture, and with potential applications in cell therapy as feeder cells for skin engraftment procedures.
- Continuation of the process of accession and cell banking of lines already approved by the bank.
- Standardisation of processes for cell culture with the development of qualified feeder cell banks.
- Validation of cell characterisation and other tests to be employed by the Bank.

As part of the Business case required by the MRC, the Bank will prepare a detailed programme of development for the new purpose built and permanent facility, an R&D programme for stem cell bank (in those areas of research permitted by the Bank's Code of Practice) and proposals for income generation to offset running costs which will include proposals for developing reference reagents of value to the stem cell community.

The Bank will continue to support and contribute to training activities and maintain a programme of visits to stem cell research groups both in the UK and elsewhere. As 2006 progresses cell banks will be released for distribution to researcher groups both in the UK and abroad.

9. Publications by UK Stem Cell Bank Staff

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