UK Stem Cell Initiative

Report & Recommendations

November 2005

“It may be that, some ages hence . . . the restoration of grey hairs to juvenility and the renewing of the exhausted marrow may at length be elicited without a miracle.”

Joseph Glanvill,
Founder Member of the Royal Society,
1661AD

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Lastly, we acknowledge the enthusiasm and commitment with which researchers, academics and representatives from the commercial sector shared their thoughts and ideas on the future of UK stem cell research.

Executive Summary

Innovation forms the backbone of the knowledge-based economy and stem cell research represents a substantial opportunity for future innovation in the life sciences. The UK currently enjoys a position of strength in this area, largely because of a supportive regulatory environment. To ensure that the UK remains one of the global leaders in stem cell research, the UK Stem Cell Initiative (UKSCI) was established by the Chancellor, Rt. Hon. Gordon Brown, in his March 2005 Budget [***See Annex 1***]. UKSCI was charged with developing a ten-year vision and costed strategy for UK stem cell research, for implementation between 2006-2015 [***See Annex 2***]. Over the last 6 months, UKSCI has consulted widely with academia and the private sector [***See Annex 3***]. Strengths and weaknesses in UK stem cell research have become apparent and, in this report, we present our recommendations for preserving the former while remedying the latter.

The UKSCI vision is for the UK to consolidate its current position of strength in stem cell research and mature, over the next decade, into one of the global leaders in stem cell therapy and technology.

The development of new stem cell therapies to treat conditions such as Parkinson's disease, diabetes and heart disease is one of the most exciting and captivating aspects of stem cell research. This is a vital and worthy aspiration for UK stem cell research and it remains important for the public and research community to be inspired, energised and driven by this long-term goal. Although it is reasonable to anticipate that some new stem cell therapies will be developed within the next decade, we must also accept that it is probable that this area will take several decades of small incremental advances in science and medicine to come to fruition. In this context, it is worth remembering that conventional pharmaceuticals take between 12-15 years of research and development to bring a product to market.

In order to deliver direct benefit to patients and to the UK economy in the short to medium term, UKSCI foresee that at least some of the UK's investment in stem cell research could also be strategically directed to more conventional areas of medicine. Our vision encompasses the UK being in the vanguard of this area by developing novel stem cell therapies, but also by exploiting stem cell research and technology to develop safer and more effective pharmaceuticals, by illuminating the processes leading to cancer and by continuing to deepen our understanding of basic stem cell biology.

UKSCI has identified five major themes for development, to maintain and increase the momentum of UK stem cell research over the next decade:

- **A Public-Private Consortium in the UK for the Advancement of Stem Cell Technology:** The establishment of consortium of pharmaceutical, healthcare and biotechnology companies with the UK Government to develop stem cells as a resource for discovery in medicine.

- **Extension of the Capacity of UK Stem Cell Research**: Fortification of infrastructure needed to develop stem cell therapy via support for Centres of Excellence, the UK Stem Cell Bank and Cell Therapy Production Units.

- **Consolidation of Research Funding for UK Stem Cell Research**: The development of the UK as a centre for translational and clinical stem cell research, with the help of a public-private partnership between the Government and the *UK Stem Cell Foundation*, along with continuing strategic investment in basic stem cell research via the Research Councils and private funding bodies.

- **Judicious Regulatory Measures to Enable UK Stem Cell Research**: The favourable regulatory climate in the UK for stem cell research should be extended to include clinical applications.

- **Enhanced Coordination & Communication of UK Stem Cell Research**: More coordinated activities between Government bodies, research councils and stem cell researchers and increased dialogue with the public over the next decade on stem cell research.

To build upon these themes, UKSCI have made 11 recommendations to act as a strategic guide for public and charity sector investment in UK stem cell research over the next decade [***See Box 1***]. Whilst these recommendations have been designed as a cohesive and comprehensive package of measures, UKSCI believes that the implementation of each one should, by itself, enhance UK stem cell research and, therefore, merits consideration.

Box 1
The 11 Recommendations of the UK Stem Cell Initiative

Recommendation 1: The UK Government should establish a public-private partnership to develop predictive toxicology tools from stem cell lines.

Recommendation 2: *The UK Stem Cell Bank* should be consolidated in new permanent facilities adjacent to its current site and its operational and development costs should be secured for the next decade.

Recommendation 3: The Research Councils should monitor the emergence of Centres of Excellence in stem cell research, designate them as such and strengthen them with core funding.

Recommendation 4: Research Councils and private sector funding bodies should support the development of stem cell therapy production units at UK Centres of Excellence in stem cell research.

Recommendation 5: The Government and Research Councils should strengthen the levels of funding for basic stem cell research over the next decade.

Recommendation 6: The Government should provide funding for clinical and translational stem cell research over the next decade at a level matching that raised by the UK Stem Cell Foundation (UKSCF), up to a maximum of £10M per annum, and administer it via a UKSCF/ Medical Research Council collaboration.

Recommendation 7: The Department of Health must ensure that the promised increase in R&D resources is forthcoming and furthermore, that the full NHS costs of stem cell clinical research trials within the NHS are supported with extra funding from each Spending Review over the next decade to match the increase in research grants and activity.

Recommendation 8: The Government should continue to ensure that regulation of stem cell research is risk-based and proportionate and does not stifle the development of the full range of safe and effective new cell therapies for the benefit of patients. In particular, (i) the Department of Health should establish a specialised research ethics committee for stem cell clinical research; (ii) the Government should clarify the regulatory requirements for the use of animals and animal cells in human stem cell research; & (iii) for the *in vitro* use of embryonic stem cell lines, researchers should be registered with, and submit an annual research summary report to, the UK Stem Cell Bank.

Recommendation 9: The *UK Clinical Research Collaboration* should help to (i) coordinate organisations supporting stem cell research, including all of the relevant Research Councils and the UK Stem Cell Foundation and (ii) ensure that the *National Health Service* is optimally engaged in this area.

Recommendation 10: The Government should allocate additional funding to establish *The UK Stem Cell Cooperative*, to maximise the cross-fertilisation between those involved in the sub-disciplines of UK stem cell research.

Recommendation 11: The Research Councils, charitable funding bodies, and Government Departments should develop a sustained and coordinated programme of public dialogue on stem cell research over the next decade.

We have estimated that our total programme of recommendations over the next ten years has a projected cost range of some £41M to £104M per annum [*See Section 5.5*]. We have calculated that pre-existing public and private sector funding bodies' investment to support ongoing research efforts in this area is likely to account for approximately £30M per annum over the next decade [*See Box 11*]. It is vital for the UK to maintain this level of investment in stem cell research and we propose that additional investment is made, ranging from approximately £11M to £74M per annum over the next decade, specifically to supplement funding for the new endeavours recommended in this report.

Although, we recognise that stem cell research is one of many demands on the public purse, our view is that the ultimate health and wealth gains that the UK will enjoy are directly proportional to the proposed additional investment. For example, our strategic approach to support for UK stem cell research is likely to attract further home-grown and overseas researchers and investment from the private sector to the UK. The pharmaceutical and healthcare industries are likely to focus their stem cell research activities in close proximity to the international centres of excellence in stem cell and clinical research, such as those we envisage evolving in the UK over the next decade. In addition, any development of stem cell therapies within NHS structures will considerably strengthen the future capacity of our Health Service to deliver regenerative medicine to the future population of the UK.

We commend the foresight and long-term commitment to stem cell research demonstrated by the UK Government in the establishment of this Initiative. As well as prospective wealth creation within the UK economy, our investment is likely to deliver health benefits to patient populations, both in the UK and globally, long into the future.

Section 1: The Biology of Stem Cells

1.1 The Properties of Stem Cells

Stem cells have two biological properties that make their clinical exploitation both feasible and attractive. Firstly, they are capable of *self-renewal*[1]. When a stem cell divides, it invariably gives rise to a carbon copy of itself. Secondly, stem cells can also *differentiate* into more specialised cells.

In the human brain, for instance, there are some rare neural stem cells. These can turn into more neural stem cells or, under the appropriate conditions, differentiate into specialised types of cells to replace old or damaged tissue in the brain [***See Box 2***].

1.2 Sources of Stem Cells

Stem cells, with varying capacities for self-renewal and differentiation, can be isolated from a number of sources [***See Box 3***]. To date, the most versatile stem cells are obtained from the early embryo. Embryonic stem cells are *pluripotent*, i.e. they can become almost any specialised type of cell in the human body. Stem cells also occur in significant numbers in some tissues of the developing foetus, and in some adult tissues, notably bone marrow. In addition, stem cells can be isolated from the umbilical cord or placenta at birth. Unlike stem cells from the embryo, stem cells from adult and foetal tissue do not seem to be pluripotent but they can turn into a limited range of specialised cell types which are likely to be clinically relevant.

There are advantages and disadvantages to using stem cells from a particular source and it is still unknown which type will provide the most suitable material for a particular stem cell therapy. For this reason, researchers are continuing to explore the use of the full spectrum of stem cells in the hope of developing new clinical treatments and this broad approach offers the greatest promise for medical advances.

1 Technical terms are highlighted in italics as they first appear in the text of this report. See Annex 4, for a full *Glossary of Terms*.

Box 2
Neural Stem Cells in Animal Models

The study of stem cells in the nervous system has a short history. Even ten years ago, it was widely believed that neurons in the human brain and spinal cord could not regenerate. For this reason, clinical research into diseases of the nervous system did not envisage replacing lost neurons but was focused on limiting the potentially damaging consequences of lesions.

It is only in the last decade that basic research has revealed that new neurons are generated in the adult brain by specific groups of stem cells. After this landmark discovery was initially made in mice [Reynolds, B. A. and S. Weiss. *Science* 255: 1707 (1992)], it could then be rapidly confirmed in primates and humans [Eriksson, P. S. *et al. Nat Med* 4: 1313 (1998); Kornack, D. R. and P. Rakic. *Proc Natl Acad Sci U S A* 96: 5768 (1999)]. Stem cells produce new neurons in only two small regions of the adult brain, the olfactory bulb and the hippocampus. These adult stem cells normally generate only one or two types of specialised neurons, and are therefore very different from their counterparts in the embryo, which typically generate a wide diversity of neurons and glial cells [Temple, S. and A. Alvarez-Buylla. *Curr Opin Neurobiol* 9: 135 (1999)]. From the perspective of future stem cell therapies, it is fortunate that the small neuronal repertoire of adult stem cells is not an intrinsic hard-wired property. In the presence of appropriate environmental signals provided by transplantation into the embryonic nervous system or cultivation in a Petri dish, adult neural stem cells can be induced to generate a wide diversity of neurons and glia [Alvarez-Buylla, A. *et al. Prog Brain Res* 127: 1 (2000)].

Researchers envisage two main strategies for using stem cells to repair the nervous system of patients affected by spinal cord injuries, strokes and many neurodegenerative diseases such as Parkinson's and Alzheimer's. The first approach is to grow large numbers of stem cells in the laboratory and then to add appropriate factors causing them to differentiate into the particular type of neuron needed for transplantation into the patient [Bjorklund, A. and O. Lindvall. *Nat Neurosci* 3: 537 (2000)]. The alternative approach is to stimulate the patient's own stem cells into expanding their neuronal repertoire, thus allowing lost neurons to be replaced without introducing any foreign tissue [Kruger, G. M. and S. J. Morrison. Cell 110: 399 (2002)]. In order to develop either approach as a viable patient treatment, we must first learn how to stimulate stem cells to produce the right numbers of the right neurons needed to repair any given type of neural lesion. This necessitates identifying those molecules that regulate cell proliferation, survival and differentiation into specific subtypes of neurons. Although most of these molecules have yet to be discovered, many of those that are already known to be important, such as Notch and Hedgehog, were initially identified from studies of nervous system development in embryos of the fruit fly [Kornberg, T. B. and M. A. Krasnow. Science 287: 2218 (2000)]. This remarkable evolutionary conservation of basic genetic mechanisms strongly suggests that animal models such as the fruit fly and mouse will continue to provide efficient tools for expediting the discovery of new molecules with important stem cell applications.

Courtesy of Drs Francois Guillemot and Alex Gould,
National Institute of Medical Research

Box 3
The Origins of Stem Cells

There are many different types of stem cells, with different characteristics based on (1) the tissue from which they are derived, (2) their ability to proliferate in culture, (3) their ability to differentiate into specialised cell types, & (4) their therapeutic use.

(1) Derivation
Based on tissue of origin, there are two principle kinds of stem cell: Embryonic stem cells (ESCs) and Adult Stem Cells (ASCs). ESCs are derived from embryos which are either (i) surplus to IVF requirements, (ii) created by IVF specifically for research purposes or (iii) created by therapeutic cloning. ESCs are isolated from a four to six day old embryo, known as a blastocyst, which consists of a ball of about 100 cells, before the embryo would implant in the uterus. Because the ESCs are generated from the *Inner Cell Mass* of the blastocyst, their derivation necessarily involves the destruction of the blastocyst, leading to ethical controversy and debate. By contrast, the ethics surrounding the use of ASCs are more straightforward. ASCs can be further subdivided into a variety of different types according to their tissue of origin, including Haematopoietic Stem Cells (HSCs), Mesenchymel Stem Cells (MSCs) and Neural Stem Cells. HSCs and MSCs are found in bone marrow. The use of the term "Adult" for ASCs is actually misleading. As well as adult tissues, ASCs can be found in umbilical cord blood taken at birth. This is why ASCs are sometimes instead referred to as 'post-embryonic' or 'somatic' stem cells.

(2) Proliferation
ESCs are capable of a considerable number of rounds of replication in culture. This makes them potentially useful sources of unlimited supplies of cell material. But it also raises the concern that their prolonged growth in culture could induce genetic instability and select for deleterious types of cells. The capability for expansion of ASCs depends on their tissue of origin. For example, epidermal (skin) stem cells can be expanded more readily than HSCs.

(3) Differentiation
ESCs show the greatest flexibility to differentiate into specialised cells. The human body is made up of three fundamental classes of tissue: mesoderm, endoderm and ectoderm. ESCs can be converted into cell types from all three classes of tissue. ESCs have been differentiated into cells of the nervous system, heart, skeletal muscle, blood, pancreas and liver. This level of plasticity is known as pluripotency. ASCs are not pluripotent, but do show vigorous ability to differentiate into the types of specialised cell in their tissue of origin. HSCs differentiate into cells which make up the blood and immune systems. In some cases, ASCs show wider differentiation potential following laboratory culture.

(4) Therapeutic use
The utility of bone marrow transplantation, the Edmonton protocol (where pancreatic islet cells are transplanted into diabetic patients from cadavers) and epidermal cell transplantation in skin grafting all lie in the successful clinical manipulation of ASCs. Although offering great promise for therapeutic application, ESCs have yet to be used for the treatment of disease.

Section 2: Exploitation of Stem Cells

2.1 Stem Cell Therapy

Most high-profile publicity for stem cell research currently focuses on the prospect of *regenerative medicine.* Here, the idea is that stem cells are grown to very large numbers in culture before *differentiation* into the desired therapeutic cell type. The cells would then be transplanted into patients in order to restore the function(s) lost due to accident or disease. It is anticipated that regenerative medicine will one day be used to treat conditions such as Parkinson's disease, diabetes, coronary artery disease and spinal cord injury. In combination with other technologies, such as *tissue engineering*, it may even be possible to direct these cells to grow in the laboratory into highly organised tissues, or even organs for implantation into patients. Further embellishments include the use of *therapeutic cloning*, or *somatic cell nuclear replacement*, which may one day make it possible to generate cells which are genetic matches with the tissues of the patient, obviating concerns over immune system rejection of the stem cell transplant. If successful, stem cell therapy via therapeutic cloning would greatly contribute to personalised medicine.

However, it is important to recognise that stem cell research does not just encompass regenerative medicine. Furthermore, it is a misconception that stem cell research is new, or that we await the "proof-of-principle" that stem cells will one day find therapeutic use. Indeed, the biological properties of stem cells have been exploited over the past several decades to develop a number of highly successful treatments.

For example, when bone marrow is transplanted into patients affected by certain types of cancer or chemotherapy, a special set of stem cells within the marrow can replenish the cells of the blood and immune systems [***See Box 4***]. This approach has proved remarkably successful. In 2002, there were more than 45,000 bone marrow (and related)

transplantations worldwide [***See Box 5***]. Stem cells from umbilical cord blood are an effective alternative to stem cells from the bone marrow when transplanted into adults and children with cancer and immune system conditions. There have now been over 2,000 unrelated and related donor cord blood transplants performed worldwide[2]. These have demonstrated the efficacy of cord blood transplantation, even in cases where there is incomplete tissue matching between donor and recipient.

The cornea forms part of the front ocular surface of the eye and provides our window to the world. The role of the outermost corneal epithelium is to absorb nutrients and oxygen while protecting the eye from infection and injury. Stem cells transplanted from the limbic region of the cornea have been used to re-establish vision in patients whose eyes have been damaged by a variety of agents [***See Box 6***].

For burns victims, skin grafting is routinely used to replace damaged tissue. Key to skin grafting is the ability to grow large amounts skin in the laboratory. Production of often large amounts of replacement skin is only feasible because stem cells are present in the epidermis [***See Box 7***].

2 http://www.blood.co.uk/hospitals/services/sc7.htm

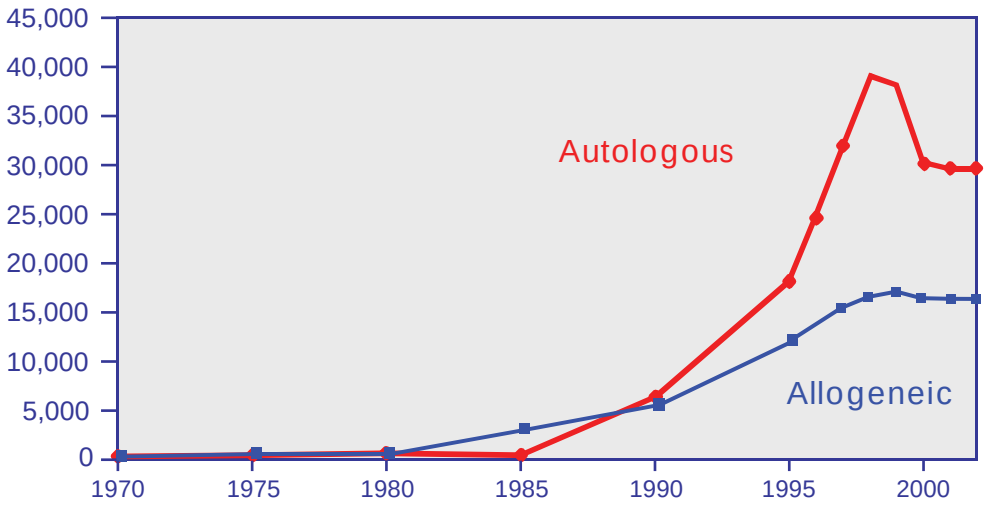
Box 4
The history of bone marrow transplantation.

A great deal of the research which lead to Bone Marrow Transplantation (BMT) was fuelled by concerns over the effects of radiation from World War II. In 1939, Osgood and others infused a few millilitres of marrow into patients with aplastic anaemia, but without success [E.E. Osgood *et al. Ann Intern Med* **13**: 357 (1939)]. In 1949, Jacobson's group discovered that shielding the spleen with lead protected mice from, what would otherwise have been lethal, total body irradiation [L.O. Jacobsen *et al. J Lab Clin Med* **12**:1538 (1949)]. The team of Lorenz showed that intravenous infusion of bone marrow from the same strain of mice could generate similar levels of protection. [E. Lorenz *et al. J Natl Cancer* Inst 12:197 (1951)]. Ford and colleagues demonstrated that donor cells were present in irradiated mice that had been protected by marrow infusion [C.E. Ford *et al. Nature* **177**: 452 (1956)]. In the same year, Main and Prehn showed that mice protected from irradiation by marrow infusion could accept a skin graft from the donor strain of mice [J.M. Main & R.T. Prehn. *J Natl Cancer Inst* 15:1023 (1955)].

In the late 1950's, several groups tried to exploit these concepts to cure cancer by transplanting human bone marrow after lethal doses of chemotherapy and radiation. In 1957, Donnall Thomas wrote: "*In an atomic age, with reactor accidents not to mention stupidities with bombs, somebody is going to get more radiation than is good for him. If infusion of marrow can induce recovery in a mouse or monkey after lethal radiation, one had best be prepared with this form of treatment in man.*" His group showed that dogs could be protected against lethal doses of irradiation by intravenous injection of bone marrow cells and, later, standardized the collection and infusion of human haematopoietic stem cells from the bone marrow [E.D. Thomas *et al. N Engl J Med* **257**:491 (1957)]. However, results in patients following BMT were initially poor. Mathé's group treated several radiation accident cases with marrow infusions without success. They did show survival of a marrow graft in an adult patient with acute leukaemia. [G. Mathé *et al. Brit Med J* **2**:1633 (1963)]. But the patient died from complications. A major problem lay in the fact that marrow cells could later produce an immunological reaction against host tissues, in a phenomenon now known as graft versus host disease.

A decade of disappointing results from BMT in patients followed. It was only as the principles of tissue-matching became better understood that doctors started to transplant bone marrow which was matched to the tissue type of the patient. This, along with the development of cytotoxic drugs, helped to reduce the risk of rejection and graft versus host disease. Slow but steady improvements continued as clinicians resorted to BMT earlier in illnesses and in less severely ill patients [E.D. Thomas & K.G. Blume. *Biol. Blood. Marrow. Transplant.*, **5**:341 (1999)]. It was not until the 1970's, with further refinements in infusion techniques, antibiotics and chemotherapy, when the real impact of BMT on patients started to occur. In 1991, Donnall Thomas won the Nobel Prize for developing BMT.

Box 5
Annual numbers of blood and marrow transplants worldwide (1970-2002)



Estimates of the annual numbers of blood and marrow transplants worldwide extrapolated from data compiled by the National Marrow Donor Program, the European Blood and Marrow Transplant Group, independent market surveys, U.S. hospital discharge data and data reported to the International Bone Marrow Transplant Registry. The past few years has seen a slowing in the growth of both autologous (red) and allogeneic (blue) transplants. The drop in autolgous transplants was due to a decrease in their use for breast cancer. The flattening in growth for allogeneic transplants results from a decreased in their use for chronic myelogenous leukemia. Use of allogeneic transplants for other indications continues to increase.

Courtesy of Dr Cristina Navarrete, National Blood Service.

Box 6
The history of stem cell transplantation in the cornea

The cornea is a clear, dome-shaped window covering the front surface of the eye. Inherited conditions, chemical, or thermal, injury in the cornea can cause visual impairment and even blindness. In 1971, Davanger and Evensen proposed that the corneal epithelium was renewed from a source of cells located at the limbus region of the cornea (Davanger & Evensen, 1971 *Nature* 229:560-561). They observed that pigment in heavily pigmented eyes migrated in lines from the limbus to the central cornea in healed corneal defects. In 1989, Cotsraelis and others reported the existence of slow-cycling limbal epithelial basal cells that retained radioactive label for long periods (Cotsarelis *et al.,* 1989 *Cell* 57:201-209). In laboratory culture, these limbal basal cells have the highest proliferative capacity, further supporting the existence of limbal stem cells (Ebato *et al*., 1988 *Invest. Ophthalmol. Vis. Sci.* 29:1533-1537; Pellegrini *et al*., 1999 *J. Cell Biol.* 145:769-782).

Over the last decade or so, a range of techniques have been developed to treat corneal defects, using stem cells taken from the limbus. Limbal autologous tissue transplantation involves the removal of multiple limbal biopsies from the patients healthy eye and transplanting them onto the damaged eye. However, this technique can only be used on patients with unilateral corneal defects and it carries the risk of inducing defects in the donor cornea. To avoid this problem, limbal grafts have been taken from cadaveric donors. Although results have been encouraging (Tsai & Tseng, 1994 *Cornea* 13: 389-400), the patient must still undergo long-term immunosuppression to avoid rejection of the transplanted tissue.

The culturing of cutaneous epithelium for skin grafting in burns victims has been successfully adopted to the culture of corneal epithelium (Lindberg *et al*., 1993 *Invest. Ophthalmol. Vis. Sci.* 34:2672-2679). Pellegrini and others reported that long-term restoration of damaged corneal surfaces with autologous cultivated human limbal stem cells (Pellegrini *et al*., 1997 *Lancet* 349: 990-993; Tsai *et al*., 2000 *New Engl J Med* 343:86-930.) Similar techniques have also been used with allogeneic limbal stem cell transplants (Daya *et al*., 2005 *Ophthalmology* 112: 470-477). Using culture expansion techniques, it is now possible for one cadaveric donor cornea to be used to treat at least ten patients. However, each of these techniques currently use growth-arrested mouse feeder cells and/or involve the use of animal-derived products to maintain limbal stem cells in culture.

Future challenges to improve limbal stem cell transplantation include: (1) a better understanding of the environmental niche into which the stem cells are transplanted, (2) identifying alternative sources of stem cells in the body for transplantation in the eye, & (3) developing safe, animal product-free culture systems for use in patients. With its unique optical properties and readily accessible location, the cornea should lead the way in helping us to develop other therapeutic applications for stem cells.

http://www.ucl.ac.uk/ioo/research/daniels.htm

Box 7
The history of skin grafting (keratinocyte transplantation).

Laboratory manipulation of human skin was first reported in 1898. Ljunggren was successful in returning skin back to donors after the pieces were kept in acetic acid for long periods of time. In the early 20th century scientists showed that it was possible to incubate skin in culture and for it to grow and produce epithelium and connective tissue. [Carrel & Burrows 1910]. Bornstein[1930] and Pinkus [1932] showed that keratinocytes were the main cells growing outwards from the original skin explants.

However, the 1940's and 50's led to the emergence of keratinocyte culturing as we know it today. In 1941, Medawar separated the epidermis from the dermis using the enzyme, trypsin. Later in 1952, Billingham and Reynolds showed that viable epithelial could be isolated after the successful division of epidermis from dermis, making it possible to culture the cells. However, this work was greatly advanced only as epidermal characterisation was developed in 1956 [Perry *et al.*] & 1957[Wheeler *et al.*]. In 1960, Cruickshank showed that the epidermal cells could proliferate in culture. Prunieras also made significant contributions to this field by demonstrating that keratinocytes could grow in the absence of supporting cells in the culture [Prunieras, 1965]. Improvements were made on this method by Karasek and Charlton in 1971[Karasek *et al.* J Invest Derm: 56: 205] when they showed that the epidermis separated by trypsin could be grown on collagen gels on a plastic substrate. This enabled the keratinocytes to be cultured into very large numbers.

Significant growth of keratinocytes in culture was shown in 1975 by Rheinwald and Green [J Rheinwald *et al.* Nature: 265: 421]. They were able to grow keratinocytes in colonies that eventually merged into a sheet, similar to skin. They made the keratinocytes proliferate on a plastic substrate with the support of the combination of growth factors and inactivated support cells from the mouse. This opened the doors to therapeutic applications of the keratinocyte grafts. [G Gallico *et al.* N Engl J Med:1984 Aug 16;311(7):448-51]. Further advances have been made in the nutritional requirements of the keratinocytes. The need for calcium was discovered by Hemming's research group [H Hennings *et al.* Cell:1980:19:245]. Later, trace elements [D Barnes *et al.* Anal Biochem:1980:102:225] and hormones such as transferrin, insulin and hydrocortisone [M Tsao et *al.* J Cell Phys:1982:110:219] were also shown to be important.

All these studies then led to the formulation of media which was specific to keratinocytes and did not require the need for animal support cells for keratinocyte proliferation [R Ham *et al.* C S H Conf Cell Prolif:1982:39-60]. This led to the growth of single layered non-differentiated keratinocytes, however with the addition of fetal bovine serum the cells would differentiate. Growing the cells in these two different ways made the application of keratinocyte grafts more practical for clinical application[M Pittelokow *et al.* Mayo Clin Proc:1986:61:771].

Courtesy of Dr Harry Navsaria, Queen Mary's London

2.2 Stem Cells & Cancer

Increasingly, stem cells are being implicated in tumour formation. It is now known that only a small fraction of the total number of cells which comprise a tumour are capable of forming another tumour and these cells show many of the properties of stem cells. In addition, the capacity for any tissue of the body to renew itself via stem cells correlates with the propensity of that tissue to develop cancer. For example, stem cells are readily found in the blood, skin and gut. Cancer commonly develops in these tissues. By contrast, stem cells are rare or absent from heart or skeletal muscle. Likewise, tumours in these tissues are rare. It is likely that we will learn much about the biology of cancer from stem cell research in the forthcoming decades. Indeed, stem cell research may help us to identify new drug targets which treat cancer via specific actions on stem cells.

2.3 Stem Cells in Drug Discovery

Other aspects of stem cell research may help us to develop new pharmaceuticals for other areas of medicine. For example, it has recently been shown that antipsychotics may work in patients via the stimulation of stem cells resident in the brain. This may allow us to develop new antipsychotics based on their specific ability to modulate the activity of neural stem cells.

Stem cells may also provide a valuable tool for traditional drug discovery and toxicology tests. For example, embryonic stem cells could be used to screen for drugs to treat the neurodegeneration found in Parkinson's disease. Stem cells would be grown in large numbers and then converted to neurons in culture. The neurons could be co-cultured with a neurotoxin which would ultimately kill the cells. However, the cells could simultaneously be exposed to a panel of chemicals in the hope of identifying lead compounds which might block the action of the neurotoxin and thus be neuroprotective.

A second use for stem cells in drug development lies in *predictive toxicology* testing. Stem cells could again be grown in large amounts and then converted, for example, into liver or heart cells in culture. The toxicity profile of lead compounds could be assessed using the physiological responses of the cultured cells. This would be likely to speed up pre-clinical assessments of new drugs. It should also serve to decrease, in due course, the number of animals needed for toxicology tests in the development of new pharmaceuticals.

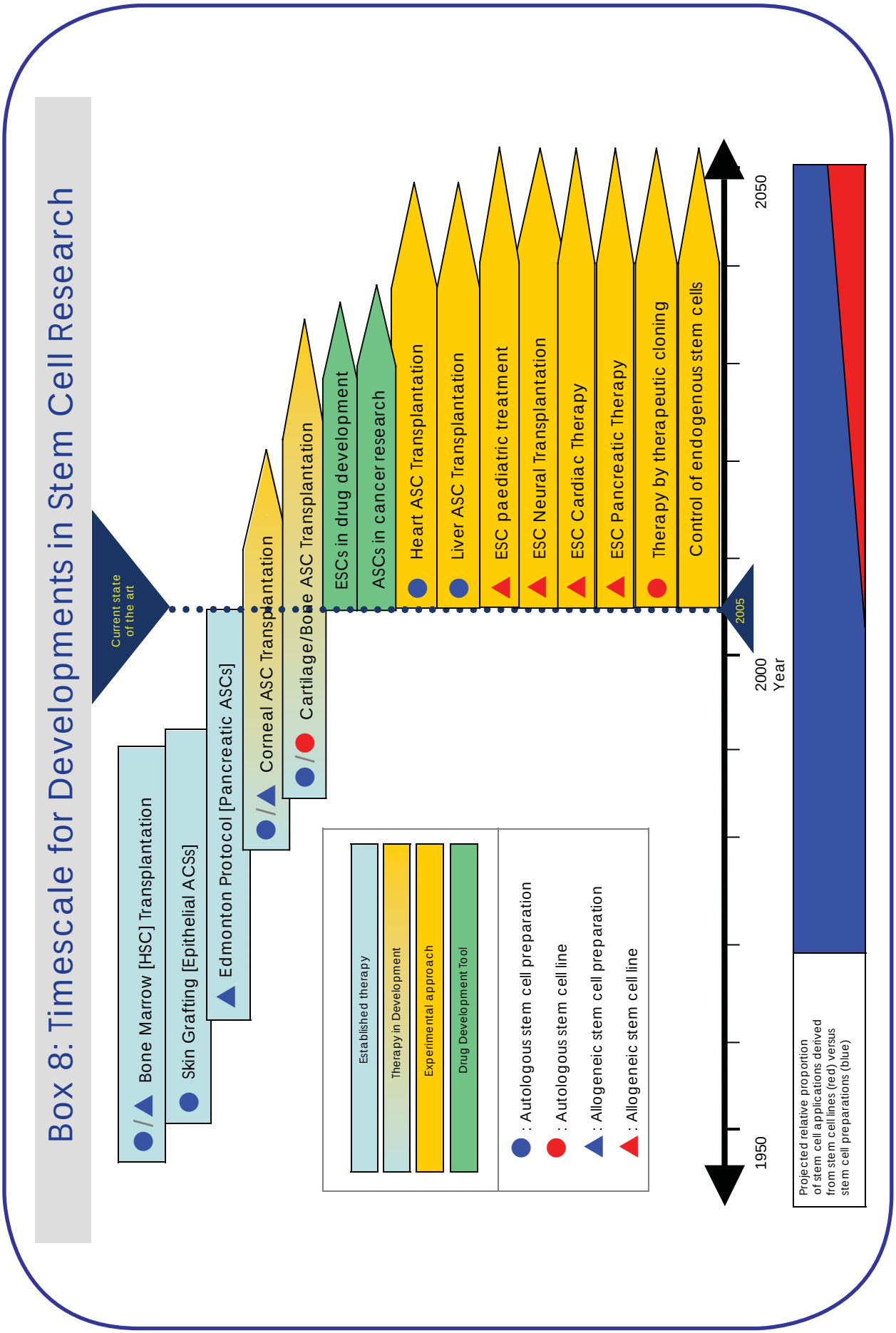
Section 3:
Challenges facing Stem Cell Therapy

3.1 Lessons from History

The development of future stem cell therapies is likely to mirror many of the historical aspects of pre-existing stem cell therapies [***See Boxes 4, 6 & 7***]. To that extent, there may be valuable lessons to learn from history. For instance, bone marrow transplantation arose from a desire to convert the basic understanding of immunology, radiation and cancer into clinical benefit for patients. Progress was painstakingly slow, and would not have occurred without experimentation in animals: first in mice, then in dogs. Its success required the parallel development of tissue-matching, materials technology, careful animal experimentation, antibiotics, chemotherapy and the technology of cell separation. Above all, perhaps, the successful development of bone marrow transplantation happened through the dedicated persistence and sustained support for several high-calibre groups of clinical scientists. As with previous stem cell therapies, future stem cell therapies are likely to develop at varying rates and with varying efficiencies [***See Box 8***], reflecting the breadth of problems encountered for each therapy along the way.

3.2 Classification of Stem Cell Therapy

Therapies using *stem cell preparations* that are not manipulated to any significant degree in the laboratory, such as in some types of corneal transplantation, are likely to develop more quickly. But these are also likely to have restricted clinical utility because the cells are not purified, only defined to a limited extent and consequently less controllable.


Box 8: Timescale for Developments in Stem Cell Research
Current state of the art
Bone Marrow [HSC] Transplantation
Skin Grafting [Epithelial ACSs]
Edmonton Protocol [Pancreatic ASCs]
Corneal ASC Transplantation
Cartilage/Bone ASC Transplantation
ESCs in drug development
ASCs in cancer research
Heart ASC Transplantation
Liver ASC Transplantation
ESC paediatric treatment
ESC Neural Transplantation
ESC Cardiac Therapy
ESC Pancreatic Therapy
Therapy by therapeutic cloning
Control of endogenous stem cells
2005
1950
2000
2050
Year
Established therapy
Therapy in Development
Experimental approach
Drug Development Tool
: Autologous stem cell preparation
: Autologous stem cell line
: Allogeneic stem cell preparation
: Allogeneic stem cell line
Projected relative proportion of stem cell applications derived from stem cell lines (red) versus stem cell preparations (blue)

Legend to Box 8:
Timescales for development of Stem Cell Therapies

Research leading to the first clinical applications of stem cells via bone marrow transplantation began before the 1950's. In the subsequent decades, skin grafting, corneal transplantation, cell therapy for the repair of cartilage and the Edmonton protocol for the treatment of diabetes by transplantation of pancreatic cells from cadavers have been developed to successfully treat patients. All exploit the properties of Adult Stem Cells.

Current stem cell treatments are derived, largely, from *stem cell preparations*. As stem cell research develops over the next decades, an increasing proportion of treatments are expected to take advantage of *stem cell lines*, reflecting an increased level of biological control and purity of stem cell therapies.

The current state of the art for stem cell research seeks to: (i) explore adult stem cells in non-homologous settings, such as the use of HSCs in heart repair; (ii) exploit further sources of stem cells, notably Embryonic Stem Cells, for the treatment of paediatric, heart, pancreatic, liver and brain conditions; (iii) use stem cell lines as tools in drug discovery and development; (iv) increase our understanding and treatment of cancer by further studies of endogenous adult stem cells; & (v) generate embryonic stem cells with the same nuclear genetic material to that of the patient using therapeutic cloning techniques, to avoid the potential rejection of cell therapies. Another ambitious goal for the field involves the use of endogenous stem cells, naturally resident in tissues of the human body, to direct the repair of damaged or diseased tissues. In all of the above examples, timescales are unknown and merely indicative.

Therapies derived from *stem cell lines* will require greater developmental time as the cells will be characterised and manipulated extensively in the laboratory before being transplanted into patients. However, because such therapies are likely to be highly defined, purified and controllable, they have the potential be applied in a broad range of clinical situations.

It is also likely that procedures using unmanipulated preparations of patients' own stem cells, known as *autologous stem cells*, will first be exploited in the clinic. This is because autologous cells are recognised by the patients immune system as "self", negating the possibility of rejection of the transplanted cells because of tissue mismatch. Autologous cells are also less likely to be a source of new infection to patients.

By contrast, therapies derived from donor stem cells, or *allogeneic stem cells*, pose increased risk of tissue mismatch and infection for recipient patients. Therefore, it is likely that allogeneic stem cell therapies will develop more slowly than autologous ones because of the greater level of laboratory characterisation required. Allogeneic stem cell therapy, with inherent risks of rejection following transplantation, will most likely require immunosuppressive drugs during treatment. Indeed, a further complication lies in the fact that different tissues appear to have differing abilities to elicit immune responses. For example, some tissues within the eye are believed to be immuno-privileged, and so allogeneic stem cell preparations, would not necessarily result in rejection of the transplanted cells.

Despite immunological drawbacks, allogeneic stem cell therapies are highly attractive for clinical applications, as they offer the potential of treating a wide range of conditions in a large number of patients. In this regard, it is worth remembering that the National Blood Service in the UK has considerable expertise in tissue-matching, *immunogenetics* and in developing the infrastructure needed to supply both autologous and allogeneic cell therapies.

It is also important not to over-emphasise the virtues of allogeneic therapy, as opposed to autologous therapy, or the use of stem cell lines over stem cell preparations. In reality, developments in all forms of stem cell therapy are mutually interdependent. The early development of treatments using autologous stem cell preparations is likely to inform the later progress of a range of treatments for regenerative medicine based on allogeneic stem cell lines.

3.3 Manipulation of Stem Cells

In addition to immunological issues, there are several significant technical hurdles to overcome before the promise of stem cell therapy can be fully realised.

We still cannot efficiently produce the very large quantities of cells from stem cell lines that would be required to treat patients. Cells behave very differently in their natural environment in the body as opposed to cell culture. When growing up in large volumes, they behave differently again. For instance, some cells need to be in contact with other cells to grow appropriately and some cells are highly sensitive to changes in oxygen levels when scaling up from growth in a small dish to a large vessel. Another concern lies in the genetic stability of stem cell lines which have been through numerous rounds of replication. With each cycle of growth, the possibility of mutations arising increases.

We still cannot efficiently differentiate stem cells in the laboratory into the large numbers of the desired cell types required to treat specific conditions. Currently, stem cell lines tend to be difficult to maintain and undergo random levels of spontaneous differentiation in culture. Even when stem cells can be successfully directed to differentiate in the laboratory, the proportions of the desired cell type are normally too low to be clinically meaningful.

Stem cells in the laboratory live in a highly artificial environment and are therefore likely to behave very differently when resident in the human body. Increasingly, animal studies reveal that the context, or *niche*, in which the stem cell finds itself is crucial to how it behaves. Stem cells are likely to behave entirely differently when not surrounded by the other cells and tissues with which they have evolved.

If embryonic stem cells were to be introduced directly into patients, they would be likely to form a type of tumour known as a *teratoma* which might exhibit malignant potential. Consequently, any therapy using embryonic stem cells would need to be based on purified cells which had been differentiated into the desired therapeutic cell type before transplantation. Even a small number of contaminating embryonic stem cells could represent a significant hazard to a patient. As yet, criteria for such purification procedures have yet to be established. By contrast, the threat of tumour formation from transplantation of adult stem cells is not thought to be significant, based on evidence from over 40 years of bone marrow transplantation.

The use of therapeutic cloning, or somatic cell nuclear replacement, raises a further set of technical challenges. Concerns exist over *epigenetic* effects caused by somatic cell nuclear replacement. In *reproductive cloning*, somatic cell nuclear replacement is used to create animal embryos which are then implanted in the uterus of a female and brought to term. The process of somatic cell nuclear replacement alters the epigenetic properties of the animal's DNA which in turn can lead to birth defects and physiological disorders in the cloned offspring. By the same logic, concerns exist over whether human stem cells derived by therapeutic cloning will show the same epigenetic defects, potentially limiting their therapeutic application, or worse still, rendering them unsafe for use in patients.

3.4 The Perception of Stem Cells

Aside from technical challenges, stem cell research can provoke strong ethical reactions. The vast majority of the UK public currently supports the use of embryonic stem cells in medical research. However, as stem cell research moves toward clinical application, negative perceptions may increase should problems arise in clinical trials. It is likely that adverse events in clinical research involving any one type of stem cell would affect the entire field. Consequently, clinical researchers will need to proceed to patients with even greater caution for stem cell research than in other areas of experimental medicine.

The above challenges make it difficult to predict exactly when new stem cell therapies are likely to be of benefit to patients. Clearly, much fundamental research is still required before we can be confident about clinical success. As with bone marrow transplantation, we are also likely to encounter unforeseen hurdles that impede exploitation of the full benefit of stem cells. It is important therefore to temper our hopes with realistic expectations and be patient. Otherwise, we are likely to do a disservice to stem cell research and the patients who will ultimately benefit from this early promise. With such reservations in mind, the last few years have seen sufficient progress in this area to allow cautious optimism that stem cell research will help to treat large numbers of patients in the forthcoming decades.

Section 4: The Global Landscape

4.1 THE INTERNATIONAL CONTEXT

4.1.1 The International Stem Cell Forum

In 2003, the UK's Medical Research Council convened an International Stem Cell Forum, bringing together nine international research agencies that had already shown an interest in working together to further stem cell research. The objectives of the Forum are to develop collaborative research across nations by encouraging the sharing of resources and data and by identifying schemes that would facilitate trans-national collaborations. Overall, the Forum aims to accelerate progress and improve global practice in stem cell research. The Forum, chaired by Professor Colin Blakemore, Chief Executive of the MRC, now consists of research agencies from sixteen countries.

The Forum has taken forward a number of important issues that were identified as being of particular benefit to the advancement of stem cell research. These include:

I. International Stem Cell Initiative (ISCI): an international expert working group, led by Professor Peter Andrews (Sheffield University), to draw up globally agreed criteria for characterising stem cell lines derived in different laboratories. This information will form the basis of an International Human ES Cell Registry that will be hosted on the Forum Website. The ISCI held its first meeting in August 2005 to review the initial data being generated by the characterisation project. Some 60 delegates, representing all the 17 participating laboratories from around the world, as well as others with key interests, attended. The meeting was successful in bringing together many of the key participants in this newly emerging field to help shape the future of human ES cell research.

The ISCI represents the first attempt to compare and characterise many of the human ES cell lines derived so far. A second initiative is being developed that will build upon the first characterisation study to address several outstanding problems, such as genetic stability and culture conditions, which are fundamental to the future development of stem cell technology.

II. Ethical Landscape Working Group: One of the ISCF's key objectives is to help facilitate international harmonisation of ethical issues relating to use of stem cells in biomedical research. The Canadian Institute of Health Research set up an ethics sub-committee on behalf of the Forum to identify the ethical issues concerning stem cell research that are emerging throughout the world, and how these might best be addressed.

III. IPR Landscape Working Group: On behalf of the Forum the Australian National Health and Medical Research Council has developed a document about intellectual property (IPR) in stem cell science. This IPR 'landscape' document details the broad criteria for patenting stem cells throughout the world, identifying techniques that may be subject to patenting, highlights those patents already in existence, and explains how countries are attempting to ensure ongoing access to stem cell resources. The information provided will be key in encouraging further research and development world-wide.

IV. International Stem Cell Banks: The UK Stem Cell Bank will be leading on identifying best practice for stem cell banking protocols, including derivation, cryogenics and Good Manufacturing Process, and on how Stem Cell Banks worldwide can best interact and co-operate.

4.1.2 International Competition

The global position of stem cell research is becoming increasingly competitive. Research in the US, China, Singapore and South Korea is proceeding apace and with increasing levels of government support. Recent estimates suggest that Australia, China, Israel, Singapore, South Korea and Sweden are each currently investing between £10M and £90M in this area[3]. Perhaps most striking is the situation in the United States. Despite federal restrictions on embryonic stem cell research, the

3 Financial Times/Scientific American Special Report on "The Future of Stem Cells". July 2005

National Institute of Health in the USA spent $517M (£294M) on stem cell research in the fiscal year 2003. Additionally, individual US states are investing substantially in this area. For example, in November 2004, California voted to introduce Proposition 71 into its constitution. This committed $3B (£1.7B) over the next ten years for stem cell research in California.

The regulatory and funding climates in the most competitive countries in stem cell research are summarised below. Further details on global positions in stem cell research are available at: ***www.advisorybodies.doh.gov.uk/uksci/global***

4.1.2.1 AUSTRALIA

The future of stem cell research in Australia is currently being reviewed as the legislation governing the research is due for renewal. The current legislation, which makes therapeutic cloning illegal, has been in force since 2002 and the review must be completed by 19 December 2005. It is expected that the review will call for therapeutic cloning to be allowed.

Research involving stem cells is managed largely by the Australian Stem Cell Centre (ASCC) based at Monash University in Melbourne. The ASCC has links with many universities around Australia and around the world as well as links with corporate partners. Earlier this year, the Bio21 Institute was opened at the University of Melbourne. Bio21 is the Australian research base for Cygenics Ltd who, through their subsidiary Cordlife Pty Ltd, have moved some of their research from the USA to Australia.

Australian stem cell research has a largely therapeutic focus including research into haematopoiesis; cardiac regeneration and respiratory disease. As therapeutic cloning is illegal, the main technology platforms used are embryonic stem cells, obtained from surplus IVF embryos, adult stem cells, tissue repair and immunology. Funding for stem cell research is mainly from the Australian Government and state governments through various funding schemes with some coming from commercial partners.

The UK and Australia have a long history of scientific collaboration and stem cell research is one area that has been successful. However, there

is increasing scope to attract Australian researchers to the UK and to set up international collaborations, both for research and commercial purposes.

4.1.2.2 CANADA

Canada invests C$40M (£18.8M) annually on stem cell research. They have established the Canadian Stem Cell Network to co-ordinate research activity and fund major collaborations with a concentration along product development lines. The country has a long history of stem cell research, with current strengths in diabetes, neural research, cancer/blood, stem cell genomics, cardiac, muscle, stem cell bioengineering and ethics. Parliament passed an Act in March 2004 banning human cloning for reproductive or therapeutic purposes. The Assisted Human Reproduction Act allows Canadian researchers to derive new human stem cell lines from embryos left over after fertility treatment. To date, the generation of two human embryonic stem cell lines has been reported. Canadian research is primarily focused on adult stem cell work with some human embryonic stem cell research now underway.

On a global scale, Canadian spend on stem cell research is probably among the top ten nations but it is used more effectively than elsewhere because of its highly coordinated approach.

4.1.2.3 CHINA

The Chinese government has in recent years earmarked stem cell science for special investment, with the aim that China could take a leading role in a high-profile and potentially very important field at a time when Chinese biotechnologists in general are struggling to compete on innovation with their Western counterparts.

The result is a growing patchwork of well-funded teams in China's major cities researching stem cells from adult, fetal and embryonic sources, some connected to large hospitals. Many of these teams are carrying out work of international standing and publishing in Western journals. A recent mission to China from the UK was impressed with what it saw, judging facilities in the labs it visited to be "superb" and government support "excellent".

Overall, Chinese stem cell researchers are more focused on moving the science into the clinic than on understanding the basic mechanisms of stem cell biology. Scientists and clinicians are eager to pursue clinical trials of cell-based therapies and several such trials are now under way to treat brain injury, corneal disease and neurodegenerative illness. This focus reflects the Chinese government's wider approach to science, which is to concentrate funding on applied sciences rather than "blue skies" research.

The country faces fewer moral or public objections to the use of embryonic stem cells than many Western nations. The production of new human embryonic stem cell lines is legal, as is therapeutic cloning. Public opinion seems – as far as one can tell – to be largely positive and focused on the potential medical benefits.

4.1.2.4 CZECH REPUBLIC

The Czech Republic has a strong position in Stem Cell Research with seven 'stabilized' human embryonic stem cell lines derived at the Laboratory of Molecular Medicine in Brno. Molecular biology including stem cell research is one of the seven long-term research priorities of the Czech Republic. Funding from the Ministry of Health and other funding bodies is project oriented and so far, nobody counts expenditure on stem cells separately, so it is not possible at this time to provide accurate and comprehensive figures. A new government Bill regulating stem cell research passed through the government in July 2005 and will go to the Parliament with expected entry into force in July 2006. The legislation is liberal and in many ways mirrors the UK. The UK is perceived as a partner of choice and Czech researchers have many contacts with leading UK experts in stem cell research.

4.1.2.5 DENMARK

With an amendment to the existing Danish Act on Medically Assisted Procreation, it has been possible for Danish scientists to investigate human embryonic stem cells from national sources from September 1, 2003. Only stem cells derived from up to 14-day-old human embryos that are surplus to treatment by In Vitro Fertilisation. Danish embryonic stem cell research must be approved according to the rules of the scientific ethical committee system.

Since September 1 2003, academics have been expecting a strategy and funds for Danish stem cell research but, to date, this has not materialized. A significant part of Danish stem cell research is undertaken and coordinated by The Danish Centre for Stem Cell Research which was established in April 2002 based on nine existing research groups from universities and private research institutes. Denmark seems to be loosing ground in stem cell research due to lack of funding, but the existing researchers are well recognized globally and have published several findings of international quality.

4.1.2.6 FRANCE

France permitted research on the embryo and embryonic stem cells for the first time in July 2004, although somatic cell nuclear replacement and the creation of embryos for research remain forbidden. Licensing of embryo research will be the responsibility of a new Agence de Biomedecine. The Agency was established in May 2005, but the secondary legislation establishing its full licensing powers is still being prepared. In the interim, a temporary decree published last October establishes an ad hoc committee to consider applications to import, store and carry out research on embryonic stem cells.

French scientists are now trying to catch up, with a few world class groups in developmental biology and the neuroscience applications of stem cells. However, there is still only a small stem cell research community in France and there is no ring-fenced funding or national strategy. In December 2004, a report from the French Academy of Sciences concluded that the stem cell area required additional funding and clarity of strategy.

4.1.2.7 GERMANY

In June 2002, a majority in the German Bundestag (Lower House) agreed the German Stem Cell Act. This bans in principle the import and use of human embryonic stem cells, the production of which is outlawed in Germany. However, the import of human embryonic stem cells and research projects using human embryonic stem cells will be permitted under certain circumstances: (i) alternative forms of research have been exhausted; (ii) only stem cell lines created before 1 January 2002 are used which have come from surplus embryos created for reproduction; (iii) the aims of the research are worthy and of benefit for

society at large; (iv) applications have been assessed by a high-level ethics committee. There is a licensing authority, Robert Koch Institute in Berlin, to administer the system.

The German Research Foundation (DFG), Germany's Research Councils equivalent, produced an overview of its stem cell funding activities in early August 2005. Between 2000-2007, DFG allocations for stem cell research totalled over €70M (£48M). Of this, €60.37M (£41M) was spent on basic stem cell research between 2000-2005 and €10.1M (£7M) was allocated for stem cell clinical research between 2000-2007.

4.1.2.8 INDIA

The Indian government has realised the potential of this new technology in modern therapeutics and biomedical research. It is developing new policy, increasing funding and strongly recommends that stem cell research and its clinical applications be promoted in the country. Over 15 institutions are involved in stem cell research in India. Ethical guidelines are similar to those of the UK and opportunities exist for collaboration and attracting talent to the UK.

4.1.2.9 ISRAEL

Israel has no specific funding or research policy for stem cell research. The largest sum of money dedicated to stem cell research has been through the Ministry of Industry and Trade (MIT) in establishing a Cell Therapy consortium – with funding around $15M (£8.3M). Israel is considered a leader in stem cell research with strengths both in embryonic and adult stem cells. Areas of research include blood, bone, liver, pancreatic, heart and nerve cells. Israel has ten stem cell oriented companies. In March 2004, the Israeli Parliament extended until March 2009 the previous 5-year moratorium on genetic intervention for the purpose of human reproductive cloning. The UK is perceived both as having a sound regulatory system and as a major player in stem cell research.

4.1.2.10 JAPAN

The Japanese Government stance towards stem cell research is firmly in line with that of the UK. Two major factors underpin this. Firstly, Japan is keen to maintain its international scientific competitiveness in life sciences, while a nagging insecurity remains that, for all of its economic

and scientific stature, the country did not make a strong enough contribution to the human genome project. Secondly, the Government has a keen eye to the potential healthcare benefits that such research may bring for Japan's rapidly ageing population.

In line with this positive stance, huge investments have been made in national facilities and fundamental research. However, human embryonic stem cell research and clinical work has remained to a large extent held back by the slow development of the regulatory framework.

4.1.2.11 KOREA

The Korean Government has designated the development of Science & Technology as one of its top policy priorities. In 2004, it allocated US$5B (£2.59B) to support R&D activities - at least US$2B (£1.03B) is directly funded by government ministries, and industrial R&D contributes the rest.

The Ministry of Science and Technology (MOST) has also set up a National Innovation System, which aims to co-ordinate all the institutions, both public and private, that maximise the creation, application and dissemination of knowledge and information from the research base. As part of this innovation systems approach, MOST has identified '10 next-generation growth engines' - these are the ten key growth industries to be prioritised, including next generation biochemical products.

In parallel with these innovation initiatives is an effort to make science and engineering education and research more closely aligned to the needs of industry. Academic scientists and students will receive increases in remuneration and incentives to collaborate, for example by reforming their curriculum to support the S&T industries.

Korea is in a dynamic phase in regard to stem cell research with a supportive government. President Roh said that his government will not ban scientists from conducting research into stem cells and other bioengineering technologies, despite questions over the ethical issues involved. The Presidential adviser on science and technology, Dr Park Ki-young, also stressed the need for the government to guarantee

freedom for stem cell research. The Ministry of Health and Welfare (MOHW) announced on 12 January 2005 that it officially approved the research led by Dr Hwang Woo-suk in 2004 for the first time since the enactment of the 'Act on Bioethics and Safety'. His research is under the control of strict ethical standards set by the government and research institutes.

In July 2005, the government approved a research project by a local genetic engineering laboratory, the Maria Life Engineering Institute. The researchers will be involved in discovery of ways to develop human stem cells that can contribute to curing such illness as Parkinson's disease, spinal cord paralysis and senile dementia. This is the first case approved by the government for such a specific project on the use of human embryonic stem cells.

4.1.2.12 SINGAPORE

Stem Cell research is a major priority for Singapore and is undertaken in a number of government institutes and private companies, generally with significant government stakes. It has rapidly built up expertise in this area, mainly by importing overseas talent, attracted by state-of the-art facilities and significant research funding. Priorities include research on diabetes, heart and blood diseases, cancer and neurodegenerative conditions. Singapore has been responsible for a number of significant breakthroughs. Prof. Ariff Bongso of the National University of Singapore was amongst the first to derive embryonic stem cells from human embryos and also to grow human embryonic stem cells on human feeder rather than animal cells. More recently a Singapore company, CellResearch Corporation, has discovered a new source of stem cells from the outer lining of the umbilical cord.

Expenditure on Stem cell research in Singapore is estimated at around S$40-45m a year (~£13-15m). In July 2005 the British and Singaporean Prime Ministers signed a joint statement on science, engineering and technology which includes an initiative to encourage scientific collaborations and networks.

Stem cell research is identified as a priority area for forging new collaborations between the UK and Singapore. A UK-Singapore stem cell workshop was held in June 2004 at Imperial College and a DTI

GlobalWatch Mission visited Singapore in September 2004. These identified significant opportunities for collaboration with Singapore, in particular using Singapore's state-of-the-art facilities at the Biopolis. Collaborations have already developed or are under discussion resulting from these activities. A second UK-Singapore workshop on stem cell research is planned for 2006. In October 2005 Singapore will host a Keystone Symposium – the first to be held outside North America – on Stem Cells, Senescence and Cancer, dominated by US speakers. In addition to scientific collaboration, potential exists for encouraging Singapore's small but fast-growing biotechnology sector to consider the UK as a research partner and a gateway to Europe. Singapore's ethical and legal environment is similar to that of the UK, where reproductive cloning is banned but research on embryos up to 14 days old is allowed.

4.1.2.13 SWEDEN

Sweden is a world leader in stem cell research, with a regulatory & ethical environment similar to the UK. Increased international competition - and opportunities - are recognised resulting in strong marketing of "Swedish stem cell opportunities" and additional funds for medical (including stem cell) research. Their Research Council "Stem Cell Research Project" amounts to 75m Kr (approx £5.5m) for 2003-2008, but additional funds directed towards individual researchers increase this figure significantly to at least 257.3m Kr (£19m) for 2003-2008. This makes Sweden both a potential collaborator with and competitor for the UK.

4.1.2.14 SWITZERLAND

Switzerland is increasingly active in human embryonic stem cell research, but lack of critical mass in the Swiss research and the commercial spin-out community remains the biggest problem compared with the UK. However, swift passage into law of the pragmatic Swiss Federal Stem Cell Research Act this March and strength in adult stem cell research have opened up a window of opportunity for Switzerland to join international leaders in fundamental research and drug discovery.

There is currently no dedicated Swiss Federal funding programme or mechanism that specifically supports research projects with human

embryonic stem cells. However, since 1990 the Swiss National Science Foundation has funded many individual research projects that investigate adult stem cells. It has also committed budget to such research in other funding programmes.

It is estimated that some £ 2.5 million per annum of Swiss Federal budget is allocated to various projects in adult stem cell research in Switzerland. There is only one research project in Switzerland that works with human embryonic stem cells and this has been receiving a modest annual research budget from the Swiss National Science Foundation.

The Swiss State Secretariat for Education and Research is acutely aware of the opportunity offered by the new legislation now in force and is poised to set up and fund a dedicated new five year National Research Programme on Human Embryonic Stem Cell Research that may be launched as early as 2006. It is estimated that this will receive a new annual budget of about £1M over and above the Federal budget which is in place. Switzerland actively seeks bilateral collaboration with both the UK government and UK research to build the core of this new National Research Programme.

4.1.2.15 UNITED STATES OF AMERICA

The legislative positions of US States regarding stem cell research vary widely, ranging from laws in California, New Jersey, Massachusetts and Connecticut which encourage embryonic stem cell research, including therapeutic cloning, to South Dakota, which strictly forbids research on embryos regardless of the source.

Many states restrict research on aborted fetuses or embryos, but research is often permitted with consent of the patient. Almost half the states also restrict the sale of fetuses or embryos. Louisiana is the only state that specifically prohibits research on IVF embryos. Illinois and Michigan also prohibit research on 'live' embryos. Finally, Arkansas, Iowa, Michigan and North Dakota prohibit research on cloned embryos. Virginia's law also may ban research on cloned embryos, but the statute leaves room for interpretation because 'human being' is not defined and does not specify, whether human being includes blastocysts, embryos or fetuses. California, New Jersey, Massachusetts

and Rhode Island also have human cloning laws, but these laws prohibit cloning only for the purpose of initiating a pregnancy or reproductive cloning, but allow cloning for research. Missouri forbids the use of state funds for reproductive cloning but not for cloning for the purpose of stem cell research, and Nebraska prohibits the use of state funds for embryonic stem cells research.

Although the states are generally behaving in a partisan Republican/ Democrat manner when it comes to stem cell research, there are some controversies, such as in Massachusetts where the Republican governor had fought with and lost to Democratic legislators over the issue.

A number of states have pledged funding for stem cell research. California is leading these efforts and has pledged $3B (£1.7B) during the next decade for stem cell research. Other states such as Wisconsin have committed $375M (£213M), New Jersey $380M (£216M) and Illinois' comptroller has recommended that his state commit $1B (£568M). While states are trying to gather enough resources to recruit lead scientists in the field it remains to be seen if a brain drain to well funded states will occur and to what extent leading researchers and science will follow the money.

4.2 STEM CELL RESEARCH IN THE UK

In March 2005, The UK Stem Cell Initiative was established by the Chancellor, Rt. Hon. Gordon Brown, to produce a vision and strategy to keep the UK at the leading edge of global stem cell research over the next decade.

To achieve this aim, it is important to recognise that UK stem cell research currently has a number of strengths which need to be preserved and a number of weaknesses which need to be remedied. The weaknesses are likely to become increasingly evident as the applied benefits from stem cell research emerge. In order to highlight these elements, we have carried out a SWOT analysis for UK stem cell research [***See Box 9***].

Box 9
SWOT analysis of UK Stem Cell Research

Strengths

- Supportive and consistent Government position
- Enabling regulation for embryonic stem cell research
- Favourable ethical environment & public support
- World-class academic researchers in developmental and reproductive biology
- Strong climate of innovation in UK
- UK Stem Cell Bank
- National Blood Service
- Estimated £30M per annum investment in UK stem cell research from public and charity sector funding bodies
- Strong bio-processing initiative
- Strong clinical trials base and UKCRC

Weaknesses

- Gaps in UK funding for translational research
- Unknown business model & return on investment
- Lack of involvement by big pharmaceutical companies
- Lack of venture capital investment
- Lack of regulatory clarity for clinical use of stem cell therapies
- Lack of central co-ordinated strategy leading to "cottage industry" approach
- Smaller science base than US
- History of innovations being lost to the US for commercialisation phase
- Lack of clarity on Intellectual Property and Licensing Issues

Opportunities

- World leadership in embryonic stem cell therapies
- Enhanced drug development & cancer research
- Use NHS to drive clinical translation
- Redirect UK researchers from developmental biology to stem cell research
- Public investment matched by private funding
- Attract foreign skills as international hub
- Drive international agenda
- Attract international inward investment
- Develop international alliances

Threats

- Lack of infrastructure impedes clinical translation
- 'Brain-drain' to US & Far East
- Intellectual Property captured in US & Far East
- UK biotechnology sector weakens
- EU moves to limit stem cell research
- Clinical trial adverse events unravels public support
- NHS has to import expensive stem cell treatments for care of aging population

4.2.1 Strengths

The UK has a well-regarded and enabling policy environment where research using all sources of stem cells, from adult to embryonic, is supported. Ethical concerns surrounding research on adult stem cells are minimal. UK law on embryo research has evolved over 20 years through public and parliamentary debate [***See Box 10***] and a recent MORI poll has revealed that 70% UK public is supportive of the use of embryos in medical research[4].

4 http://www.mrc.ac.uk/index/public-interest/public-consultation/public-mori_human_embryo_survey.htm

Box 10
The regulation of embryo and stem cell research in the UK

The first baby to be born by In Vitro Fertilisation (IVF), Louise Brown, was born in the UK on 25th July 1978. The Inquiry into Human Fertilisation and Embryology, chaired by Baroness Warnock, was launched by the Government to consider the issues raised by this newfound ability to create human embryos outside the body. In 1984, the report from the Warnock Inquiry was published. It concluded that the human embryo had a special status and that research on human embryos should only be undertaken when there were no alternatives. But Warnock also found that an early embryo, less than 14 days old, was sufficiently different from a full human being that it might be used as a means to an end that was good for other human beings. To this day, the conclusions of report on the ethics of human embryo research remain widely acknowledged and respected internationally.

Subsequent to the Warnock report, The Human Fertilisation and Embryology Authority (HFEA) was established under the HFEA Act 1991. This HFEA subjects all embryo research in both the private and public sector to a robust system of case-by-case review before any license to permit research is issued. No research is allowed on embryos over 14 days old. At the time of the 1991 Act, embryo research was restricted to the study of infertility, miscarriage and congenital disease. In 2000, the Chief Medical Officer published *Stem Cell Research: Medical Progress with Responsibility,* to take account of contemporary developments in embryonic stem cell research. Following this report and widespread debate in both houses of Parliament, the HFEA legislation was amended in 2001 to allow the use of embryos for stem cell research. The HFEA can license the derivation of stem cells from embryos that are: (i) surplus to IVF requirements, or (ii) created by IVF specifically for research purposes, or (iii) created by therapeutic cloning.

In voting in favour of this legislation, the House of Lords established a Select Committee on Stem Cells to examine the range of ethical issues in this area. In 2002, that Select Committee published a detailed report supporting this decision. It stated: "We strongly believe that therapeutic cloning research should be allowed to continue in countries, like the UK, which have reached a national consensus on this issue and which have a rigorous and effective system of regulation of embryo research." At the same time as approving stem cell research, including techniques such as therapeutic cloning, Parliament recognised that cloning for reproductive purposes (reproductive cloning) was entirely unacceptable. The UK was one of the first countries to ban reproductive cloning via The Human Reproductive Cloning Act 2001, which provides for up to ten years' imprisonment and an unlimited fine on conviction. Without doubt, the enabling and consistent regulatory environment is currently one of the strongest assets to UK stem cell research. Indeed, overseas researchers have been attracted to the UK precisely because of its coherent regulatory framework covering all forms of stem cell research in the public and private sector.

The UK has a strong history of discovery in stem cell research, indicative of a robust base of world-class academic researchers in developmental and reproductive biology. Amongst many landmark achievements in UK stem cell research were the first isolation of mammalian embryonic stem cells at Cambridge in 1981, the first cloning of a mammal at the Roslin Institute in 1997 and the first identification of the stem cell 'immortality' gene, *Nanog*, at the Institute for Stem Cell Research (ISCR) in Edinburgh in 2003.

In terms of infrastructure, the UK has already established a national stem cell bank, "The UK Stem Cell Bank", which was launched in May 2004. The first of its kind in the world, the bank makes ethically sourced, well-characterised stem cell lines available to researchers and is a repository for all types of stem cell lines from embryonic, foetal and adult tissues. As part of the conditions of a HFEA license to derive an embryonic stem cell line, researchers must agree to deposit the line in the UK Stem Cell Bank so that it can be made available to other researchers in the UK. The independent steering committee of the UK Stem Cell Bank, operated via the MRC, oversees deposits and withdrawals from the bank and ensures that stem cell lines are used in keeping with UK legislation.

The National Blood Service (NBS) also provides a comprehensive range of infrastructure services, in order to support haemopoietic stem cell transplantation. These services include: (i) the searching of national and international registries for unrelated haemopoietic stem cell donors; (ii) the collection of stem cells from blood; (iii) umbilical cord blood banking; (iv) the processing and cryopreservation of stem cells; and (v) immunogenetic and histocompatibility testing.

In particular, the Cord Blood Bank of the NBS continues to add to the UK's resources for transplantation, processing 1,000 cord blood donations during the year. The policy of the NBS to collect cord units from ethnic minorities has resulted in 42% of the cord blood donations being derived from these groups.[5]

5 http://www.blood.co.uk/pdfdocs/annual_report_2004.pdf

Financial support for UK stem cell research, via a broad spectrum of funding agencies is considerable. UKSCI estimates that Government and charitable research funding agencies are currently spending between £21M and £31M per annum in the UK [***See Box 11***]. Direct investment from industry in UK stem cell research is more difficult to establish with any degree of accuracy. The above figures are therefore likely to underestimate total spend in the UK. With that caveat in mind, extrapolating from these amounts indicates that the UK will invest over £300M in stem cell research over the next decade. In addition, the UK already has a number of funds to support large-scale capital investment beyond the scope of Research Councils and Universities [***See Box 12***], which could be exploited to develop any major infrastructure requirements for stem cell research.

Box 11
Estimated UK investment in stem cell research

	£££	
Organisation[1]	**2003/04**	**2004/05**
Research Councils[2]	11,368,269	15,378,451
Dept Trade & Industry[3]	0	1,857,866
Dept Health (NHS R&D and National Blood Service)	N/A	6,500,000
Regional Development Authorities	750,000	2,050,000
Wellcome Trust[4]	6,591,028 (2003)	5,129,286 (2004)
Association of Medical Research Charities	2,896,545	N/A
Scotland	76,147	127,180
Ireland	159,525	158,397
Wales	N/A	N/A
Total	**21,841,514**	**31,201,180**

Notes:

1. Figures are intended to present a general overview of the level of funding for stem cell research in the UK and do not include research funded by industry/commercial sector. The figures given here relate to research specific to stem cells, and may exclude other projects, such as bioprocessing, which have direct relevance to stem cells. The amount each Research Council or funding agency will spend on stem cell research will depend on the quality/number of applications relating to stem cell research received. It is not possible to collate exact figures for the years given due to differences between organisations including: the funding periods, the way research is classified, & the way spend is planned. N/A = figures not available.

2. BBSRC has funded two Career Development Stem Cell Fellowships in each of the past two financial years, and will be doing so again this year. MRC administers this scheme, and BBSRC funds by invoice. Last year's two awards were as follows: Stavridis, Dundee (£142,148) & Durcova-Hills, Cambridge (£161,936).

3. The figures for DTI are part of the Technology Programme "Succeeding Through Innovation". In April 2004 DTI Innovation Group called for proposals for collaborative research and development in stem cell technology as part of the 2nd call of the Technology Programme "Succeeding Through Innovation". Three stem cell research projects, jointly worth £10M, were successful and will share £4.9 million in DTI grants. All three projects are led by companies spun out from UK universities; Novathera Ltd, ReNeuron Ltd and Stem Cell Sciences (UK) Ltd. Other partners are predominantly small and medium sized enterprises and academic research groups, reflecting the early stage of development of this sector.

4. The Wellcome Trust has also committed £3 million over five years towards a £6 million partnership with the Juvenile Diabetes Research Foundation (JDRF) in an effort to promote the UK's contribution to stem-cell research.

Box 12
Capital Research Investment Funds for the UK Science Base

1. Large Facilities Capital Fund

Maintaining access to leading edge large-scale experimental facilities is a key element of ensuring that UK scientists remain at the forefront of their individual fields of research. Such facilities present particular challenges due to their very high cost to build and operate. These facilities often have a substantial European or Global dimension and are frequently multi-disciplinary. Consequently, regular funding methods (for example, wholly through a research council) may not be suitable. The Large Facilities Capital Fund is a centrally held DTI fund of about £100M p.a., managed by OST, to which Research Councils can bid for money to build exclusively UK facilities or to support UK participation in large facilities projects in the EU and beyond. Decisions on who receives funding, and how much, are taken by OST following an initial exercise by RCUK which lists potential projects in priority order. This prioritisation exercise typically takes place every two years and one will be undertaken one at the end of 2005. Projects will only be considered in this prioritisation exercise if they have been included on the Large Facilities Road Map, which is scheduled for publication by RCUK later in the summer, and if they begin capital construction phase between 2007/08 and 2009/10.

2. Science Research Investment Fund (SRIF)

Science Research Investment Fund (SRIF) was set up to help address the under-investment in HEI research infrastructure. SRIF1 announced in the 2000 spending review was a partnership with the Wellcome Trust and covered the period 2002-03 and 2003-04 and totalled £675m from DTI and HEFCE. This funding was distributed by a formula and it was for universities rather than the funding departments to decide how they spent their allocations. A separate SRIF stream of £150m from the Wellcome Trust was invested in replacement or refurbished buildings for sciences within the Trust's remit drawn from top-rated but unmet JIF bids. A further £75m of Wellcome SRIF funding was set aside for biomedical science project related equipment/refurbishment and administered through the Wellcome Trust's normal project grant process.

SRIF2 was announced as part of the July 2002 Spending Review. The main SRIF2 fund (building on the £675m fund for SRIF1) is worth £950m and will be paid out between April 2004 and March 2006 – distribution again being based on a formula. This is wholly Government funded (DTI £570m, DfES £380M). SRIF2 placed a sharper responsibility on Universities to ensure that research is funded on a sustainable basis. In 2004, an independent review showed that institutions were using SRIF funds effectively on projects that will address the backlog on science research infrastructure. They indicated that without SRIF the research base would have continued to deteriorate, and there could have been significant adverse impacts in terms of lost opportunities, reduced productivity, failure to attract key staff and pose a long-term threat to the health of UK science. The review concluded that the results of their case studies show that there is still a considerable backlog on investment need and that SRIF probably needs to continue for a further few years. As a result, the Government announced SRIF3 as part of the 2004 Spending Review amounting to £1bn of Government funds (£600m DTI, £400m DfES). Allocations to universities were announced by HEFCE in January 2005 and universities had until about May 2005 to submit their proposals. Institutions will be expected to explain how their proposals take account of the Science and Innovation Investment Framework, which includes making institutions' expertise and facilities more open to access by business, as well as how proposals fit with their own sustainable research strategies. The bids are under review with a view to projects starting from April 2006 – March 2008.

The Government has sponsored a number of previous programmes to develop the applied biosciences in the UK. In particular, the Bioscience Innovation and Growth team report (BIGT) recommended that the UK build a strong bioprocessing sub-sector. In direct response to this, the BioIndustry Associaton was awarded funding of £3M through DTI's Technology Programme, to establish a National Bioprocessing Knowledge Transfer Network, "bioProcessUK"

The key aim of bioProcessUK is to foster community development of the sector by developing a robust network that encourages effective partnerships between academia and industry and facilitates increased exchange of best practice, people, knowledge and experience. The Network also acts as a forum for a coherent industry voice to inform government policy making, such as areas of focus for DTI's Technology Programme, through applying professional benchmarking techniques and market analysis.

BioProcessUK is currently determining the bioprocessing needs of the emerging cell therapy sector to get the views of industry, academia and regulators. Their recommendations are likely to include exchange of best practice between the established biopharmaceutical industry, emerging cell therapy companies and the academic scientific base. BioProcessUK will host a series of industry-led Special Interest Group workshops to achieve this.

Other recommendations may be for further initiatives in translational science, linking basic research with clinical research, by assisting academics and emerging companies. An example of this in the cell therapy area would be to promote better understanding of Quality Assurance and Regulatory Compliance needs for the production of clinical trials materials.

As stem cell research approaches early phase clinical trials, guidance on standards applying to the development of stem-cell derived products for characterisation, culture and storage, and how these are integrated into the regulatory framework would be useful and helpful in determining any requirement for new standards.

Following a discussion meeting with industry and research base representatives, the DTI has commissioned work to map, guide and inform industry and researchers of the critical path requirements from research to clinical trial within the UK, with reference to EU and US markets. It is intended that the output will be published as a Publicly Available Specification for the application of stem cell therapies in the UK, early in 2006. The project draws together leading organisations including the National Institute of Biological Standards and Control (NIBSC), the Medicines and Healthcare products Regulatory Agnecy (MHRA), the Laboratory of the Government Chemist (LGC) and the BioIndustry Association (BIA) to produce a collaborative guidance for the UK. The British Standards Institute (BSI) will impartially facilitate this project and industry, academia and other organisations are encouraged to contribute to the project to ensure that all views are considered and that the resulting document is a valuable tool for those developing therapies in this area.

The UK Clinical Research Collaboration (UKCRC) emerged from the work of BIGT. UKCRC is a partnership of organisations united by the shared aim of establishing the position of the UK as a world leader in clinical research by harnessing the power of the NHS. It has been based on the successful model of the National Cancer Research Institute (NCRI). The Collaboration includes representatives from the main funding bodies for clinical research, academic medicine, the NHS, regulatory bodies, representatives from industry and patients. The ultimate goal underpinning the UKCRC is to create a clinical research environment that will benefit patients and the public by improving national health, increasing national wealth, and enriching world knowledge.

4.2.2 Weaknesses

Whilst the funding climate for stem cell research is generally favourable, many researchers have drawn our attention to the fact that funding for the translation of stem cell research into clinical interventions currently receives less priority than basic research by funding bodies. During the pioneering phases of any new medical treatments, there are often substantial gaps in our knowledge, leading to a perception that the research is 'high-risk.' Because translational research is often

"non-hypothesis-driven", there is a belief that it tends to perform less well in conventional funding approaches. Stem cell research is also multidisciplinary in nature, requiring a high degree of collaboration. This tends to mean that publications for translational stem cell research involve a large number of authors, with the contribution of any one particular researcher being less apparent. For these reasons, translational stem cell research can be an unattractive activity for university departments, as it is perceived to be less likely to receive a favourable evaluation in the Research Assessment Exercise. But it is important to recognise that we must foster those who pioneer the applied aspects of our strong basic science base, if we are to make significant contributions to global development of stem cell research.

Currently, there is also a lack of clarity on intellectual property, patenting and licensing issues amongst stem cell researchers. It will be important for the Government to work towards clarifying the position with regard to the UK, European and world wide patents around stem cells and associated technologies. For instance, the UK Patent Office and the European Patent Office appear to have divergent views about the possibility of patenting human embryonic stem cells.

Irrespective of the patent position, it is important that any necessary licensing of stem cell lines or techniques should promote the principles being developed by the Organisation for Economic Cooperation and Development (OECD). Namely, that licensing practices should increase rather than decrease access to inventions for research purposes and that commercial considerations in public research activities should not unduly hinder the academic freedom of researchers. One way to achieve this would be to pool IP rights amongst patent holders so that patents could be licensed broadly.

On a global level, there is evidence that the investment from the venture capitalist community and major pharmaceutical & healthcare companies will not be readily forthcoming for stem cell research. This is most likely to be due to their perception that stem cell research is financially high-risk, with an unknown timeframe for and level of return on investment, an unknown business model, and the potential for unravelling of public support upon any high-profile adverse reactions in clinical trials. In addition, the lack of regulatory clarity on the clinical

application of stem cells makes the commercial sector even more wary of investing in this area.

With a smaller science base in stem cell research than, e.g. the USA, some strategic coordination of UK stem cell research is desirable. To date there have been a number of programmes designed to achieve this, such as the Funders' Forum. However, if the UK is to make optimal use of its stem cell resources further efforts at coordinating funding bodies and the research community need to be made.

4.2.3 Opportunities

In the United States of America, Italy and Germany, there are considerable restrictions on embryonic stem cell research. By contrast, the UK has a strict, but facilitating, regulatory system that allows all forms of stem cell research, including therapeutic cloning, to take place under license. Therefore, the UK is, in this respect, in a position of strength to become a world leader in embryonic stem cell research. Because the UK Government has been supportive of all types of stem cell research, the opportunities for cross-fertilisation between the sub-disciplines of stem cell research are greater in the UK than elsewhere. This means that there is an opportunity for the UK to be more interdisciplinary and engage in research beyond the development of stem cell therapies for regenerative medicine, including the use of stem cell lines in drug discovery and in understanding the processes leading to cancer.

In terms of infrastructure, the UK has two considerable opportunities. The first is to use the National Health Service to expedite clinical research and innovation in a strategic approach, coordinated at a national level. The second is to facilitate the entry of further numbers of world-class researchers from developmental and reproductive biology into stem cell research, by increasing investment in this area. With an increasingly attractive stem cell research base, the UK also has an opportunity to attract the best stem cell researchers from abroad. In addition, the pharmaceutical and healthcare industries are likely to focus their stem cell research activities in close proximity to the international centres of excellence in stem cell and clinical research, such as the UK.

Any increased strength in stem cell research is likely to entice other nations into forming strategic alliances with the UK, where complementary expertise and interests can be exploited to the maximum benefit of both parties.

4.2.4 Threats

Although there are many reasons to be cautiously optimistic about the future of UK stem cell research, there is also no reason for complacency as there are a number of significant threats. At present, there is a lack of infrastructure within the UK science base to develop stem cell therapies for use in patients. For example, there are no national facilities to develop sufficient quantities of stem cell therapy material for use in clinical trials. Current funding mechanisms appear to favour hypothesis-driven, intellectually-based research at the expense of translational and clinical stem cell research. This poses a threat to the UK's ability to innovate, as many of the techniques and applications needed to produce stem cell therapies could be developed overseas. Thus, the UK could fail to capture important IP rights.

A related issue concerns the potential for the UK to lose a significant portion of its stem cell researchers to countries overseas. This threat could manifest itself for two reasons. Support for certain aspects of stem cell research could be underfunded in the UK, compared to other nations. Alternatively, with the substantial levels of investment in stem cell research seen in some overseas locations, for example, California, researchers from the UK could be attracted to these locations. In such a scenario, this would have a doubly-negative effect on the UK research base. Firstly, the UK would lose expertise and skills in this area. Secondly, commercial exploitation of discoveries that could have taken place in the UK will be lost. This threat is significant. It could result in a diminished capacity of the UK to capture intellectual property rights and, ultimately, undermine the entire capacity of the UK commercial biotechnology sector to innovate.

Another threat to UK stem cell research comes from regulatory uncertainty. At present, a significant proportion of regulation comes in the form of proposals from the European Union. Given the divergence at national level in Europe over stem cell research, there is a danger

that such regulation would place inappropriate restrictions on such research in the UK.

As basic research progresses to clinical research over the next decade, an increasing number of very ill patients will be exposed to potentially effective stem cell therapies. However, it is likely that many of these patients will experience adverse reactions during the course of this research, based on their pre-existing medical condition and not the therapy *per se*. Nevertheless, it is likely that such adverse reactions will be widely reported in the media and may lead to a loss of public confidence in stem cell research. Such a scenario has already taken place in another high-profile area of experimental medicine, gene therapy. It will be important for the UK to examine carefully the lessons learned from our experiences of gene therapy research to plan for such a scenario.

Finally, the UK faces a threat based on health economic issues. If we fail to capitalise on our current position of strength in stem cell research to develop stem cell therapies and technology, there is a danger that the National Heath Service will have to pay significantly greater amounts than it otherwise would have done in order to import stem cell expertise and products from overseas.

4.3 ANALYSES OF INTELLECTUAL PROPERTY

One way to determine the potential levels of innovation which are likely to result from stem cell research is to examine patenting activity in this area. We commissioned Scientific-Generics, part of The Generics Group (Cambridge, UK) to conduct such an analysis. Using the term "stem cell", searches were performed on patents that have been filed anywhere in the world since 1993[6]. This analysis was designed to identify:

(I) Prominent UK and global organisations in stem cell research, as judged by the citation levels of their patents in other patents;
(II) Patents with significant impact on stem cell research, as judged by the by the citation levels of those patients in other patents; &
(III) International trends in patenting activity over the last decade.

There are a considerable number of limitations and caveats associated with this approach. In particular, this study is a relatively superficial quantitative analysis of patenting activity, which takes no separate account of qualitative differences in patents. Nor does it take account of differences in the quality of approval processes between different patent offices in the US, Europe and rest of the world. Nonetheless, it does represent a useful initial guide to global trends in 'stem cell' patenting.

(I) Our analysis revealed that the organisations which were most prolific in the UK in generating patents from stem cell research were, in rank order:

1. The Roslin Institute, Edinburgh (BBSRC-sponsored);
2. Pfizer;
3. Medical Research Council;
4. University of Sheffield;
5. Cancer Research Technology Ltd.;
6. University of Edinburgh; &
7. The Babraham Institute (BBSRC-sponsored).

6 Only patents filed either in the US, the European Patent Office or under the PCT were included, based on pervious experience indicating that patents taken only to the national stage do not usually represent significant inventions.

Globally, our analysis identified the following organisations, ranked in order, as the most prolific in generating patents from stem cell research:

1. Incyte Corporation
2. Human Genome Sciences Inc.
3. Pfizer Inc.
4. Amgen Inc.
5. Roche Holding Ltd.
6. University of California Office of Technology
7. Wyeth
8. University of Massachusetts
9. Millenium Pharmaceuticals
10. Johns Hopkins University
11. Novo Nordisk A/S
12. Novartis AG
13. Chiron Corp.
14. Osiris Therapeutics, Inc.

Of potential concern, none of these organisations from our global analysis are UK-based.

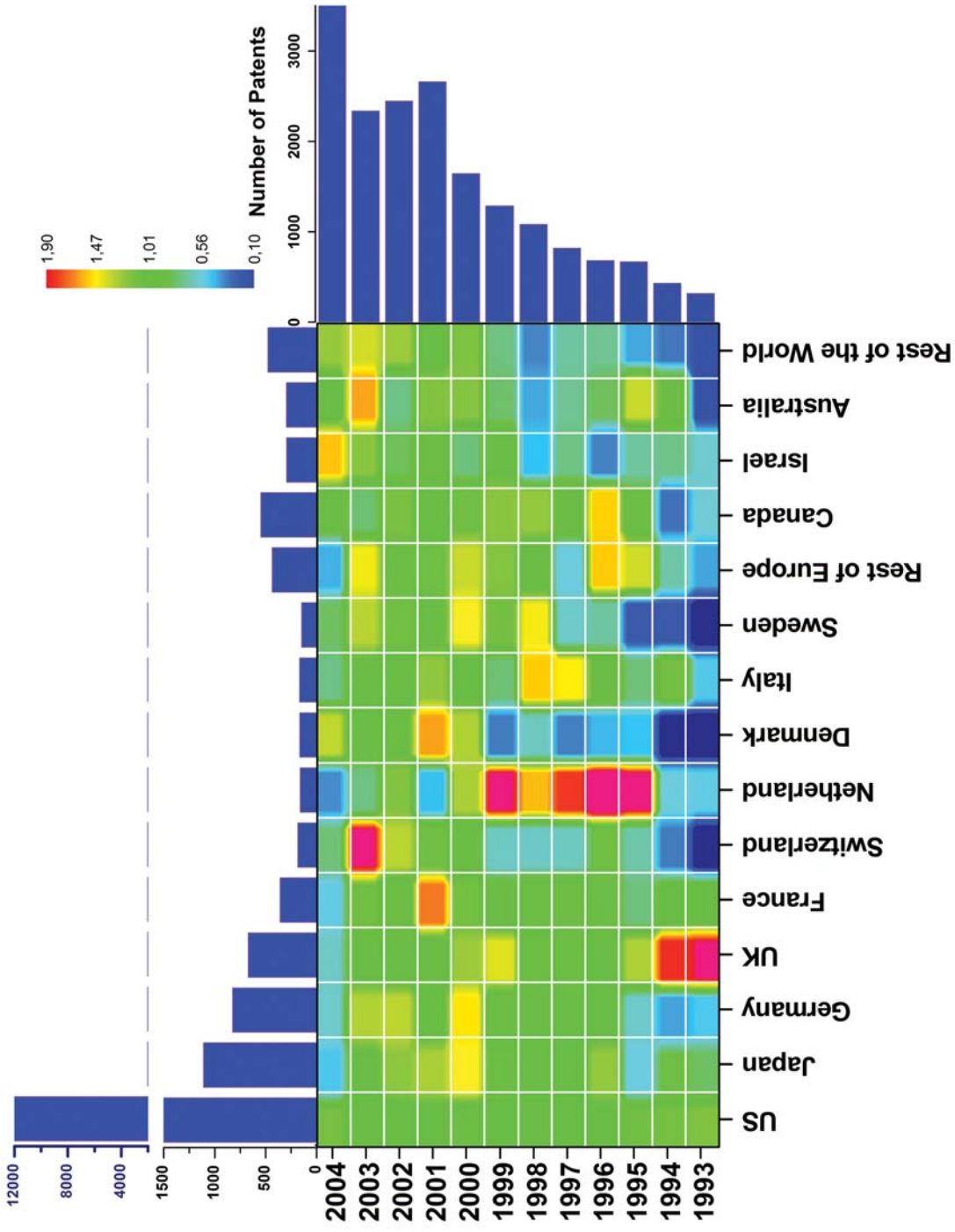
(II) Our analysis also identified sixteen of the most influential patents for stem cell research, when ranked by their number of citations in other patents. Twelve of these belonged to organisations from the USA, three to organisations from the UK and one to a Canadian organisation. This is somewhat reassuring, as the UK is proportionally well-represented in terms of influential 'stem cell' patents. Further details on these patents are presented in ***Annex 5***.

(III) Lastly, we examined international trends in stem cell patenting activity over the last decade [***See Box 13***]. The US, UK, Japan and Netherlands were active in stem cell patenting at the beginning of the 1990s. As with other areas of technology, the US has been consistently dominant in this area. However, Japan and Germany are significantly under-represented in stem cell patents. By contrast, UK inventors have a reasonable share, 3.8%, of the total 17,800 'stem cell' patents since 1994.

However, since 2004 there has been a significant upturn in the level of patenting activities in the US. In addition, several other countries are patenting in the stem cell field more aggressively than before, including Israel, Australia, Canada, Denmark, Switzerland, Italy and Sweden. The 'Rest of the world', with Korea and China accounting for 50% of that figure, is also significantly accelerating its patenting activity. By contrast, stem cell patenting activities in the UK, Germany, Japan and France do not show any corresponding increase.

Overall, the UK has obtained a proportionate amount of intellectual property over the last decade, although many of the UK patents were filed in the early 1990's. It seems likely that other countries will continue to accelerate their patenting activities in this area. Consequently, at least some additional levels of strategic outlay for UK stem cell research should be helpful in ensuring that the UK continues to capture levels of intellectual property in this area that are proportionate to our investment.

Box 13
International Activity in Stem Cell Patenting



Legend to Box 13:
International Activity in Stem Cell Patenting

Patents filed since 1993 were searched using the term "stem cell." We identified 17,800 patents meeting this criterion. The number of patents were further sub-divided by "Assignee Country" (Horizontal axis) and "Priority Date" (Vertical axis). A ratio of patenting activity, ranging from 0.1-1.9, was calculated for each country over each of the years 1993-2004. In the "Hotspot" diagram, colour coding illustrates this ratio of patenting activity using 1,000 bands, each representing 0.1% of the range of values. The colours run from black (lowest patenting activity) through the spectrum to red (highest patenting activity). The figures in each cell are doubly normalised on both axes, so that exceptionally low and high levels of activity are apparent.

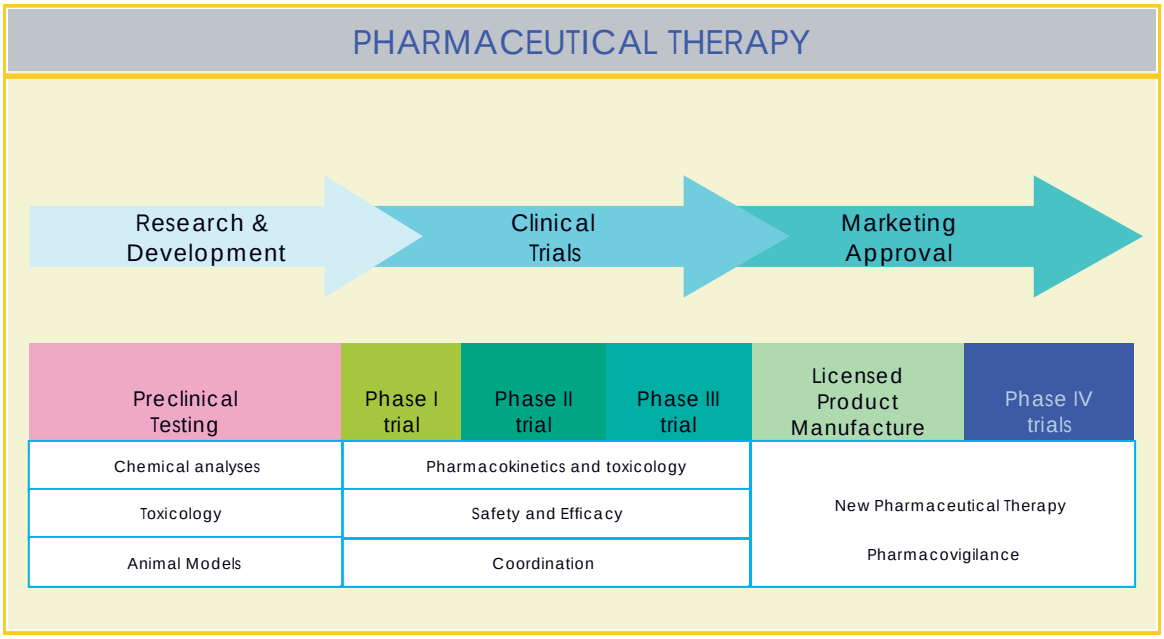
Section 5: Investment Strategy

5.1 RESEARCH CAPACITY

The requirements for the development of stem cell therapies for regenerative medicine are very different from those of more traditional pharmaceutical medicines. This is because any stem cell therapy contains living material and needs to be manufactured, processed and stored in entirely different ways to pharmaceuticals. In the pharmaceutical industry, medicines have been successfully developed over a number of decades through a well-established 'pipeline', which allows the safety and efficacy of drugs to be evaluated at each stage of development [***See Box 14***]. Because this is a tried and trusted approach to drug discovery, the research infrastructure needed to support this pipeline is either already in existence or is readily supported by investment from industry.

Because stem cell therapy is a less developed aspect of medicine than pharmaceutical discovery, there is no established pipeline for the development of stem cell therapies. However, each of the steps required in the development of novel stem cell therapies can be predicted. UKSCI foresees the development of a range of stem cell therapies in the UK via the pipelines of ***Box 15***.

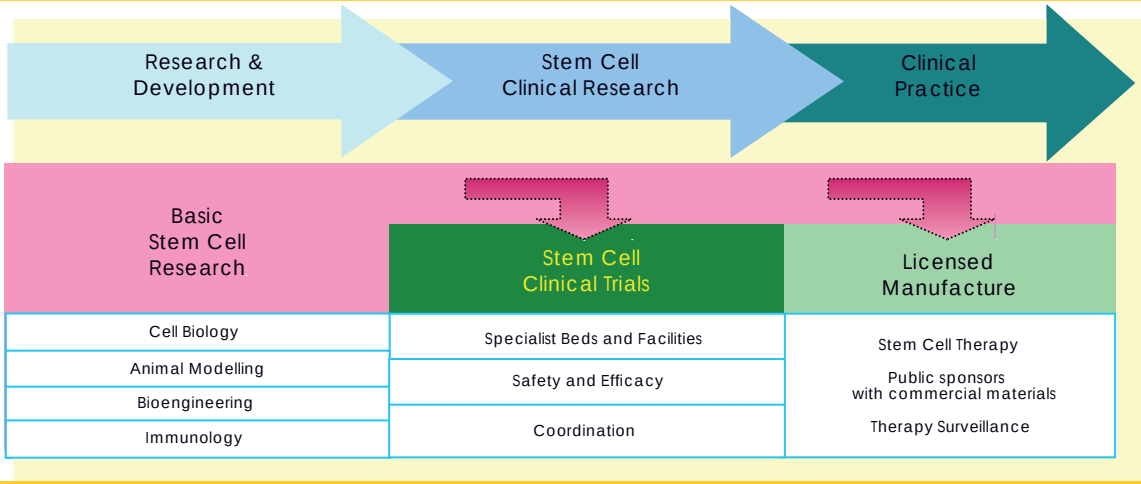
Box 14
The Drug Development Pipeline



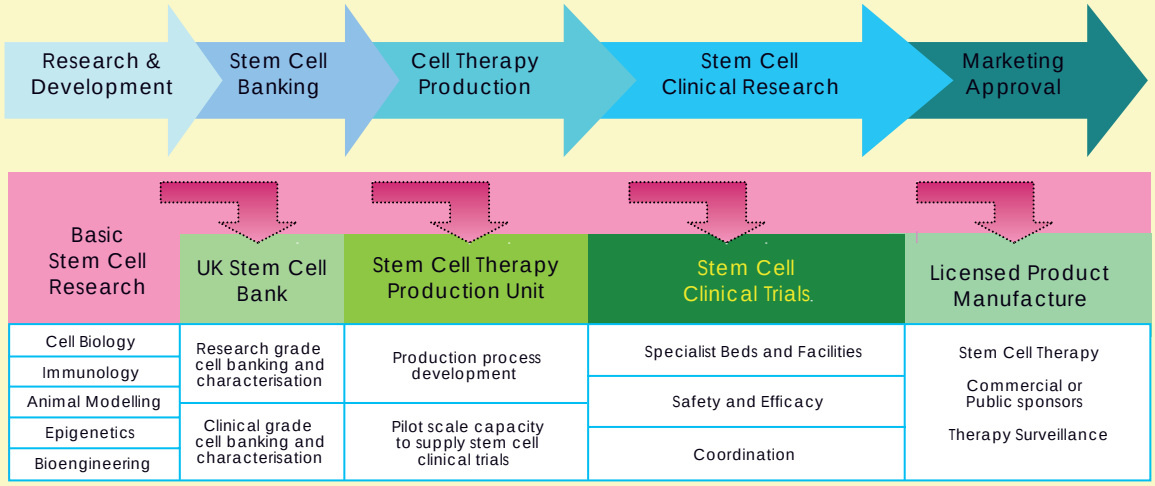
Compounds are tested in the laboratory during the research and development stages. Successful lead candidate drugs are next tested on patients in clinical trials. In Phase I trials, the safety and pharmacological activity of compounds is examined in a small number of people. If proven safe and tolerable, drugs are tested on a greater number of patients in Phase II trials. If the drug shows both efficacy and continued safety, it then passes to Phase III trials, involving a large number of patients. The results from the Phase III trials are used to determine whether the drug can receive a licence from the regulatory agency, which would allow it to be marketed and prescribed by doctors. Marketed drugs continue to be monitored for safety in both the general patient population and in specific 'post-marketing' studies, known as Phase IV trials.

Box 15
Stem Cell Therapy Development Pipelines

(I) THERAPIES PRODUCED FROM STEM CELL PREPARATIONS



(II) THERAPIES PRODUCED FROM STEM CELL LINES



See legend on next page

Legend to Box 15:
Stem Cell Therapy Development Pipelines

Stem cell therapies can be produced from two sources: stem cell preparations, Box 15(I), or stem cell lines, Box 15(II).

Stem cell preparations are isolated from a donor or the patient themselves, as in bone marrow transplantation. Stem cells may sometimes be purified from the preparation before being transplanted into the patient. By contrast, stem cell lines are generated from stem cells that have been derived from donors but grown to homogeneity in laboratory culture. Lines are banked as pure frozen stocks. They can later be expanded to large numbers in the laboratory, differentiated into the therapeutic cell type and transplanted into patients.

During the Research & Development stages, innovations from Basic stem cell research (pink) play a vital role in identifying potentially relevant clinical targets. This area impacts upon all stages of the development of stem cell therapies (indicated by purple arrows). All stem cell therapy requires an understanding of cell biology, bioprocessing and studies in animal models. Allogeneic therapies, as either stem cell preparations or stem cell lines, require knowledge of immune system responses to the transplanted cells.

Stem Cell Banking stages are required to maintain the security and quality of supply of stem cell lines. The UK Stem Cell Bank ensures that cell lines have suitable ethical provenance, are screened for relevant infectious agents and characterised to an appropriate degree. Cell lines can be produced to sufficient quality for clinical or laboratory research applications. At Cell Therapy Production stages, Stem Cell Therapy Production Units develop processes to grow stem cells to a volume which can supply the demand for the large numbers of cells to treat patients in clinical trials.

At Stem Cell Clinical Research stages, the safety and efficacy of stem cell therapies derived from both stem cell lines and stem cell preparations are assessed in Stem Cell Clinical Trials. Trials require specialist beds and facilities to monitor the response of patients to treatment. Clinical research requires a considerable degree of coordination, both in managing individual trials and in strategic analyses of funding areas for grant-awarding agencies and policy-makers.

Stem cell preparations tend to have little commercial value and develop as treatments from publicly-sponsored research. As their use reaches Clinical Practice, devices that facilitate the use of these therapies are manufactured under license from the commercial sector. By contrast, therapies developed from stem cell lines have commercial value in themselves and are manufactured as products under license, once they have received Marketing Approval from regulatory agencies. New stem cell therapies are kept under surveillance after marketing approval, to detect any adverse reactions that were not observed during clinical research stages.

We have used this diagrammatic representation of the stem cell therapy development pipeline extensively throughout this section of our report to highlight, via red boxes, how each of our recommendations are designed to contribute to the overall development of UK stem cell therapy. For the sake of simplicity, illustrations accompanying our recommendations refer solely to therapies derived from stem cell lines [***See Box 15(II)***]. Where relevant, recommendations will be equally applicable to therapies derived from stem cell preparations [***See Box 15(I)***].

In fulfilment of our terms of reference [***See Annex 2***], recommendations are also accompanied by estimates of their cost over the period 2006-2015. For most of our recommendations, it is has proved impossible to estimate a single precise figure for costs over such a timeframe. Therefore we have generated two complementary estimates of costs depending upon whether the field of stem cell research grows relatively slowly (Low Trajectory) or relatively rapidly (High Trajectory).

5.1.1 Public-Private Consortium

From our consultations with the pharmaceutical, biotechnology and healthcare industries, the idea of the development in the UK of a broadly-based consortium to advance pre-commercial aspects of stem cell research has emerged. Because such a consortium would provide focus, increased competitiveness, critical mass, industry participation, IP clarity and license accessibility, it appears likely that it would be widely supported by the commercial sector.

There are a number of models for how such a consortium could be operated, but one attractive approach, worthy of consideration, would be for the UK Government to establish a limited company and invite members of the commercial sector to become shareholders. Such an idea for Government participation in a limited company is not without precedent [***See Box 16***].

Involvement of shareholders could be contingent upon their financial, intellectual property or technical contributions to the new company. Funding from the shareholders could be substantial, of the order of tens of millions of pounds in total, and would be used to commission the highest quality research from suitable universities and institutions

to develop stem cell tools in drug development. Because the UK Government would be a major shareholder, it would be incumbent upon the new company to commission, wherever possible, research within the UK.

In return for their commitment, shareholders would be entitled to use the intellectual property obtained from the company's research portfolio, for example, in their own drug development programmes. The company could be founded on the principle that any IP it owned would be widely licensed within academia to promote stem cell research as efficiently as possible. In addition, any external commercial organisations wishing to exploit IP generated by the new company would require licenses and have to pay royalties to the company, yielding a potential financial return on the shareholders investment.

Box 16
Diamond – A Public-Private Partnership in Research

Diamond Light Source is a new scientific facility currently being built in South Oxfordshire on the Harwell Chilton science campus. This giant machine, called a synchrotron can be described as a series of 'super microscopes'. It is housed in a futuristic doughnut-shaped building which covers the area of 5 football pitches. Diamond will ultimately host up to 40 cutting edge research stations, supporting the life, physical and environmental sciences.

Diamond Light Source Ltd is a company limited by shares. It has two shareholders, the Council for the Central Laboratory of the Research Councils (CCLRC), on behalf of the Govenment, and the Wellcome Trust. CCLRC contribute 86% of the funding and the Wellcome Trust 14%. The company was established following a Joint Venture Agreement (JVA) between the two parties, along with an overarching agreement between the DTI and CCLRC and a "Heads" agreement between DTI and the Wellcome Trust. The JVA was written with the express possibility of other shareholders coming forward; none have done so and it is now exceedingly unlikely that they will. The JVA initially covered the first phase of Diamond with an "in principle" agreement for Phase 2; when Phase 2 was subsequently agreed, amendments were made to the JVA.

Diamond, as a company, employs its own staff and completes its own accounts. Governance is via the Diamond Board of Directors, which comprises nominations from CCLRC and the Wellcome Trust and some independents, including an independent chairman. The Diamond Board have all the normal responsibilities for a company, and Diamond's accounts are separate from those of CCLRC and are not integrated into CCLRC's accounts. The JVA determines the total cost for construction of Diamond and its initial beamline suite (Phase 1), and now amended also includes the cost for Phase 2 (additional beamlines). That funding is therefore in control of the Board. However, Diamond is currently planning for the operational phase, for which both shareholders are committed in principle via the JVA but for which there is as yet no agreed budget. So CCLRC and the Wellcome Trust have an additional role as "funders", and decisions on levels of funding have to be agreed with those funders separate from any decision of the Board.

The DTI remains closely involved in the Diamond project through a 4-way meeting at official level (DTI, CCLRC, Wellcome Trust, Diamond) held before each Board meeting.

We have considered a number of possible areas where the consortium could focus its work. We have concluded that the development of stem cells as *predictive toxicology* tools in conventional drug development, as outlined in ***Section 2***, is worthy of pursuit. This option is attractive as it would increase the efficiency and effectiveness of the development of new pharmaceuticals and minimise the use of animals in this context. To achieve such an objective, stem cell lines would be grown to large volume in culture, then differentiated into the appropriate cell type, such as liver or heart cells, for toxicology testing. New candidate pharmaceuticals could be first tested on these cell cultures and any toxic effects accurately gauged using existing cell biological techniques. The realisation of this kind of technology would require the development of processes to:

(i) Scale-up the growth of stem cell lines,
(ii) Control the differentiation of stem cells into the desired cell type for toxicology testing, &
(iii) Purify and characterise the cultured cells.

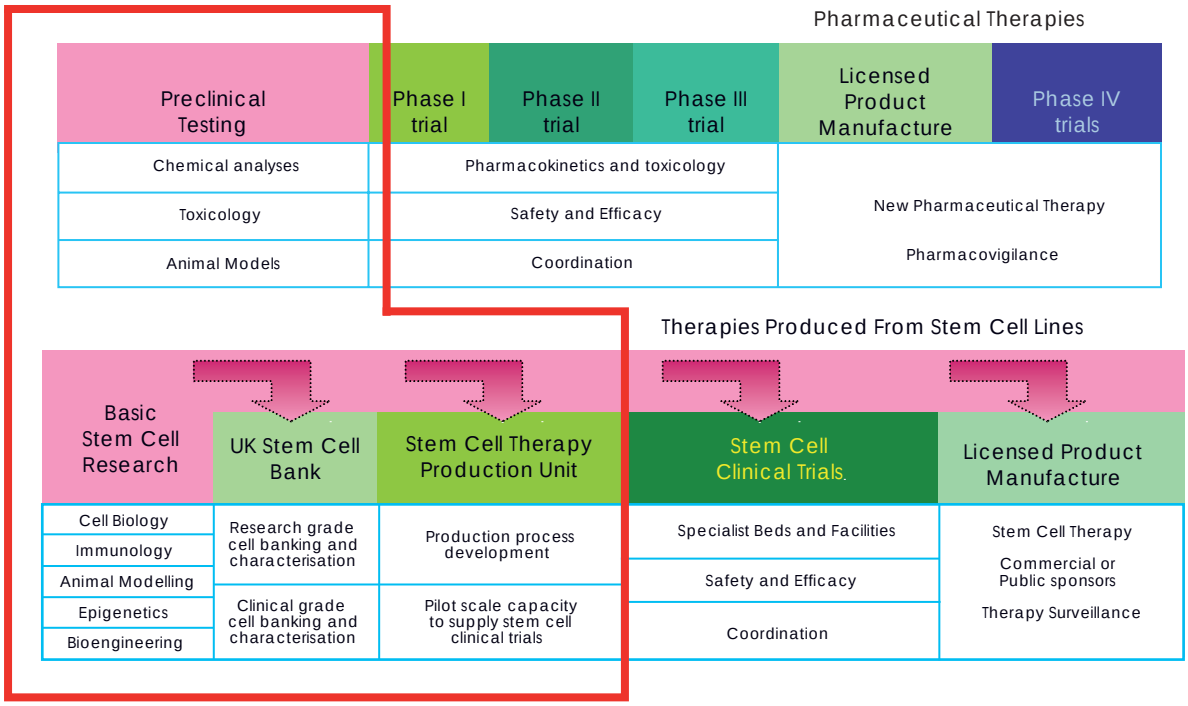
It is possible that much of the understanding and intellectual property captured during the development of these processes will be equally applicable to the development of stem cell therapies. Therefore, strategic investment in this area would likely expedite the development of the entire spectrum of stem cell research.

Such research is viewed by industry as highly desirable and valuable, but nonetheless, pre-competitive. Some members of the industry are still concerned about entering this research area on their own because of the potential negative effects on their markets in countries with less tolerant attitudes than the UK to embryonic stem cell research. However, some members of the industry were supportive of participation *en masse* in such a consortium specifically to negate this possibility. Should the Government encourage the establishment of such a consortium in the UK, with some initial UK Government investment, then much of the stem cell technology and associated IP would likely be first captured within the UK stem cell research base.

Another potential area of specialisation for the consortium could be the development of placental or umbilical cord stem cell banking services and therapies. However, within the time constraints of this report, we have been unable to examine the case for this in sufficient detail.

Perhaps most importantly a public-private consortium focusing on the understanding required for the use of stem cells in predictive toxicology would help develop technology to improve the safety and range of conventional pharmaceuticals and expedite the development of stem cell therapies for regenerative medicine.This would contribute to stem cells having a positive impact on patient's health sooner rather than later.

Recommendation 1: The UK Government should establish a public-private partnership to develop predictive toxicology tools from stem cell lines.



Projected Cost Range of UKSCI Recommendation 1: £16.4 – 31.3M

LOW TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Management costs[1]	0.2	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Costs of research[2]	0.5	1	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Cost per year	0.7	1.3	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8

HIGH TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Management costs[3]	0.5	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Costs of research[2]	0.5	1	2	3	3	3	3	3	3	3
Cost per year	1.0	1.7	2.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7

[1]Based on recruitment of a Chief Executive to develop commercial partners, business planning, research portfolio development planning and scientific advisory board, along with additional funding for administrative assistance and office space. Further funding for management team to come from commercial partners.

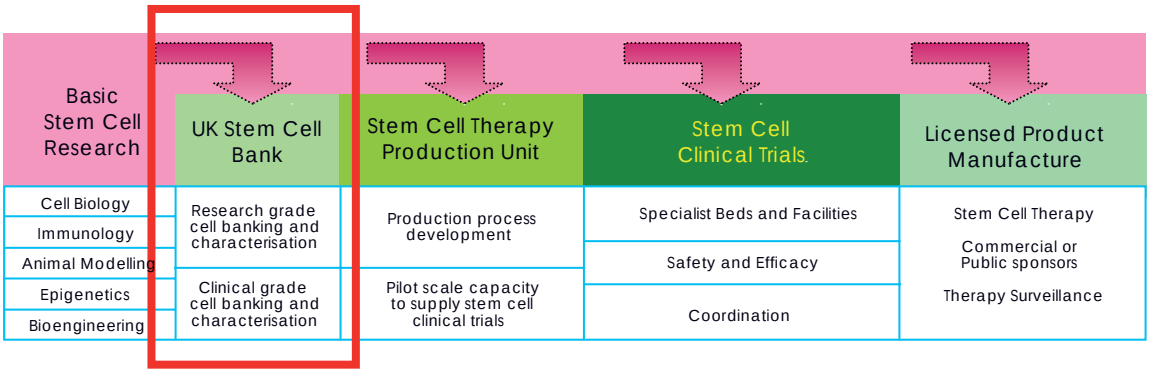
[2]Figures represent seed Government funding to commission research. Further substantial investment to fund research to be contributed from commercial partners. Costings profiled for each research project to span three years.

[3]Includes salaries for Chief Executive, Finance Officer, Legal Officer, administrative assistance and office space.

5.1.2 Stem Cell Banking

The UK Stem Cell Bank is co-funded by the BBSRC and MRC. It plays a crucial role in ensuring the ethical provenance, quality and secure supply of stem cell lines in the UK. The Bank also contributes to the development of stem cell technology in general and to a stem cell therapy development programme by providing centrally-based expertise in the handling and storage of stem cell lines. The Stem Cell Bank is currently synonymous with embryonic stem cell lines. In the future, it should ensure that it develops expertise in the handling and storage of stem cell lines from all sources, including adult stem cells. The Bank should also ensure that it can accommodate the anticipated increase in requests for withdrawals of stem cell lines over the next decade. In addition to this anticipated increase in transactions, the Bank should become the international centre in the development of stem cell banking protocols, processes and techniques, such as in cryogenics, infection control and Good Manufacturing Practice (GMP).

Recommendation 2: *The UK Stem Cell Bank* should be consolidated in new permanent facilities adjacent to its current site and its operational and development costs should be secured for the next decade.



Projected Cost Range of UKSCI Recommendation 2: £17.0 – 20.8M

LOW TRAJECTORY (£M):

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Capital building costs[1]	3.4	0	0	0	0	0	0	0	0	0
Operational costs[2]	1	1	1	1.1	1.1	1.1	1.2	1.2	1.2	1.2
Development costs[3]	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3
Cost per year	4.6	1.2	1.2	1.3	1.3	1.4	1.5	1.5	1.5	1.5

HIGH TRAJECTORY (£M):

Year	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Capital building costs[1]	4.5	0	0	0	0	0	0	0	0	0
Operational costs[2]	1	1	1	1.2	1.2	1.2	1.3	1.3	1.3	1.3
Development costs[3]	0.4	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5
Cost per year	5.9	1.4	1.4	1.6	1.6	1.7	1.8	1.8	1.8	1.8

[1] SIngle cost expenditure in 2006 to finance permanent facilities for UK Stem Cell Bank.

[2] Maintenance and supply of stem cell lines, salary support, and administration costs, profiled to increase with demand by 2009.

[3] Costs for the development of techniques and protocols in cryogenics, infection control and GMP, profiles to increase in cost by 2011.

5.1.3 Centres of Excellence

The discussions we had as part of this review impressed upon us the multidisciplinary nature of stem cell research, the long-term nature of the endeavour and the relatively small cadre of scientific, clinical and technical staff involved in the UK. Moreover, there is in stem cell research a requirement for somewhat repetitive development and maintenance work for which it is difficult to obtain grants when proposals are in competition with those incorporating novel, hypothesis driven science. Accordingly, high quality, internationally competitive research in the UK will develop in locations that make a, strategic, long-term committment to such research and fund it with contributions from all possible sources. We believe Centres of Excellence in UK stem cell research will evolve in the coming years and play vital roles as:

- locations within the UK where the best researchers can interact and share their ideas, talents and energy;
- dedicated and specialised facilities for multiple aspects of stem cell research;
- hothouses for the specialised training needed to expand the cadre of UK stem cell researchers; and
- infrastructure to attract internationally acclaimed stem cell research groups to the UK.

Central to the rationale for Centres of Excellence is the recognition that there is a considerable danger that a shortage of human resources at all levels will limit the overall capacity for growth of UK stem cell research over the next decade. In particular, it will be critical to ensure that sufficient training opportunities exist for post-graduate and post-doctoral researchers so that they can be attracted to long-term careers in this area. Centres of Excellence should provide such opportunities. In addition, we note that there is a large body of internationally-acclaimed researchers working on developmental and reproductive biology in the UK. In order to increase the number of stem cell researchers in the UK it should be possible to entice some of these into stem cell research. Again, Centres of Excellence should provide the locations and facilities capable of achieving this.

Finally, in terms of existing UK stem cell researchers, it is vital that every effort is made to avoid the loss of these key personnel. One of the principle threats to UK stem cell research comes from international competition. With very substantial levels of funding in California, Singapore, China and South Korea, there are concerns that UK researchers, particularly younger ones, will be attracted to working in these overseas economies. The resultant loss of skilled personnel and intellectual property rights could adversely affect the entire UK biotechnology sector. Encouragingly, the UK is already perceived by both researchers in the UK and abroad as providing a first class regulatory envinment for stem cell research. However, we are aware of one recent instance of a key scientist moving abroad in respose to substantial funding being made available elsewhere. Providing core funding for Centres of Excellence should help combat this.

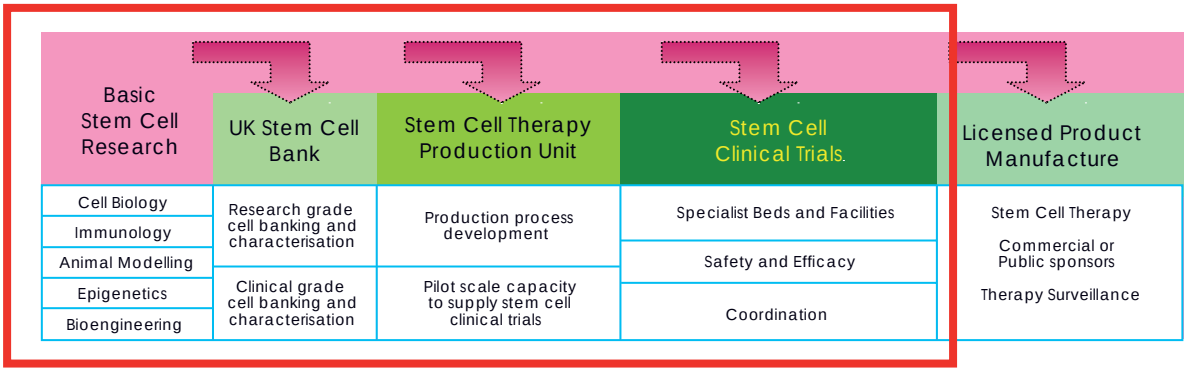
In March 2005, the Academic Subcommittee of the Modernising Medical Careers and UK Clinical Research Collaboration published a report aimed at improving the academic career prospects for medically-qualified researchers in the UK. The committee, chaired by Dr Mark Walport, Director of the Wellcome Trust, set out a clear training pathway for doctors wishing to pursue academic careers. The report's recommendations were supported by £2.5M committed by the Department of Health to pilot the establishment of an integrated academic training programme as a foundation for the academic clinicians of the future. Drawing on the lessons from the Walport report, there is a critical need for contributions from clinical scientists in the early stages of the development of stem cell therapies within the UK research base. Based on their clinical knowledge of the therapeutic area, medically-qualified researchers are best placed to optimise the design and of development of new treatments for patients. The Department of Health should ensure full implementation of the Walport report and funding bodies should prioritise the recruitment of medically-qualified researchers, to be embedded within basic and translational groups in the UK Centres of Excellence in stem cell research.

During the preparation of this review, we have become aware of the possibility of a number of top international scientists in stem cell research moving to the UK. We commend the efforts of Universities and funding bodies to enable these recruitments to occur. Whilst we

recognise that some funds for recruitment are available, for example, via allocations from the Higher Education Funding Council for England (HEFCE), the MRC's Strategic Appointments Awards or the Wellcome Trust's Principal Research Fellowship Scheme, there is a limit to how far this can be achieved without additional resources. Nevertheless, it is of critical importance to be able to grasp these opportunities during the relatively short time they are available. They provide an addittional means of increasing the numbers of scientists involved in stem cell research in the UK. Such researchers are only likely to be attracted to and thrive in Centres of Excellence.

It will be important for the Research Councils to resource the development of such Centres of Excellence if we are to foster an environment in the UK that is conducive for the development of ideas from "bench to bedside". Centres of Excellence should be monitored jointly by the relevant Research Councils, so that excellence in the necessary biological, engineering, social science and the arts and humanities can be recognised. Key to their success will be the availability of sufficient and adequate NHS support for clinical studies. Therefore, additional resources should be requested in Spending Reviews, as necessary.

Recommendation 3: The Research Councils should monitor the emergence of Centres of Excellence in stem cell research, designate them as such and strengthen them with core funding.



Projected Cost Range of UKSCI Recommendation 3: £36 – 70M

LOW TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Centres Of Excellence[1]	2	2	2	2	4	4	4	4	4	4
Recruitment of internationally-acclaimed research groups[2]	2	2	0	0	0	0	0	0	0	0
Cost per year	4	4	2	2	4	4	4	4	4	4

HIGH TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Centres Of Excellence[3]	2	2	4	4	6	6	8	8	10	10
Recruitment of internationally-acclaimed research groups[4]	2	2	2	0	0	2	0	0	2	0
Cost per year	4	4	6	4	6	8	8	8	12	10

[1]Based on two rounds of designation of UK Centres of Excellence in stem cell research in 2006 & one in 2010.

[2]Based on the recruitment of two internationally-acclaimed research groups, one in 2006 & one in 2007.

[3]Based on five rounds of designation of UK Centres of Excellence in stem cell research in 2006, 2008, 2010, 2012 & 2014.

[4]Based on the recruitment of five internationally-acclaimed research groups, one each in 2006, 2007, 2008, 2011 & 2014.

5.1.4 Cell Therapy Production Units

Currently, there are a number of infrastructure components from the stem cell therapy development pipeline, which are missing from, or are limited in, the UK. Therapies involving stem cell lines will require facilities to allow researchers to develop processes to produce clinical grade batches of cells for use in clinical trials. Our vision for UK stem cell research is to include the development of therapies for regenerative medicine, so we must ensure that the infrastructure for every component of this envisaged pipeline is in place.

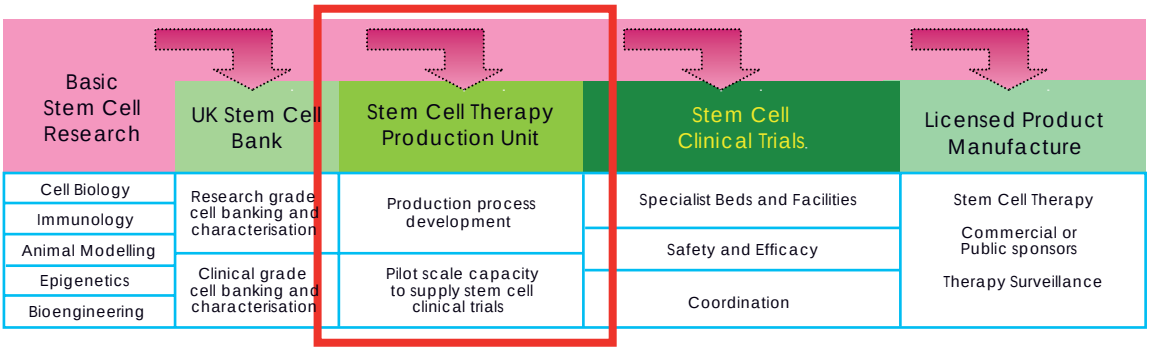
The infrastructure to produce large volumes of cells for clinical trials is essential to the successful development of stem cell research. It will eventually be important to develop multiple national facilities at centres of excellence to maximise the potential for demonstrating proof-of-concept in any particular stem cell therapy.

Such facilities should provide a vital, and currently missing, infrastructural component to a number of research centres and will allow ideas for new treatments to be developed from "bench to bedside." The facilities should be capable of developing processes required to produce clinical grade material derived from both adult and embryonic sources of stem cells and producing pilot-scale clinical grade material for use in clinical trials.

It will be essential to ensure that these facilities are staffed appropriately or their use will be extremely limited. These facilities will act as training centres in the UK for the development of the technical skills base in cell therapy. The availability of long term funding for posts in these facilities will attract technical staff to careers in cell-based therapy.

Until allogeneic stem cell therapy is applied to a range of illnesses in patients, UKSCI believes that the commercial sector is unlikely to fill these infrastructural gaps in the pipeline by investment. It therefore falls to Government, the Research Councils, the National Blood Service and other funding bodies to build this capacity within the UK.

Recommendation 4: Research Councils and funding bodies should support the development of stem cell therapy production units at UK Centres of Excellence in stem cell research.



Projected Cost Range of UKSCI Recommendation 4: £12.2 – 43.4M

LOW TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Capital building costs[1]	2	0	0	0	0	0	0	0	0	0
Operational costs[2]	0	1	1	1	1.2	1.2	1.2	1.2	1.2	1.2
Cost per year	2	1	1	1	1.2	1.2	1.2	1.2	1.2	1.2

HIGH TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Capital building costs[3]	3	0	3	0	3	0	3	0	3	0
Operational costs[2]	0	1	1	2	2.2	3.2	3.4	4.4	4.6	5.6
Cost per year	3	1	4	2	5.2	3.2	6.4	4.4	8.6	5.6

[1]Based on the development of one Cell Therapy Production Unit in the UK in 2006.

[2]Cell Therapy Production Units' operational costs profiled to increase four years after establishment by 20%.

[3]Based on the development of five Cell Therapy Production Unit in the UK between 2006-2015.

5.2 RESEARCH SUPPORT

UK stem cell research receives considerable financial support from a broad spectrum of funding agencies. In relative terms, current levels of funding for UK stem cell research are competitive internationally, with the exception of the significant federal and state funding in the USA [***See Section 4***]. Over the next decade, the anticipated expansion in the UK stem cell research base will increase the demand for funding in this area in the UK.

5.2.1 Basic stem cell research

Funding bodies believe that the current resources have funded high-quality proposals for stem cell research and that this has been effective in initiating research in this area. We have estimated that the Research Councils are currently spending £15M per annum on this [***See Box 11***]. However, the overall funding of the science base is restricted and stem cell research requires continuing long term investment and is relatively expensive.

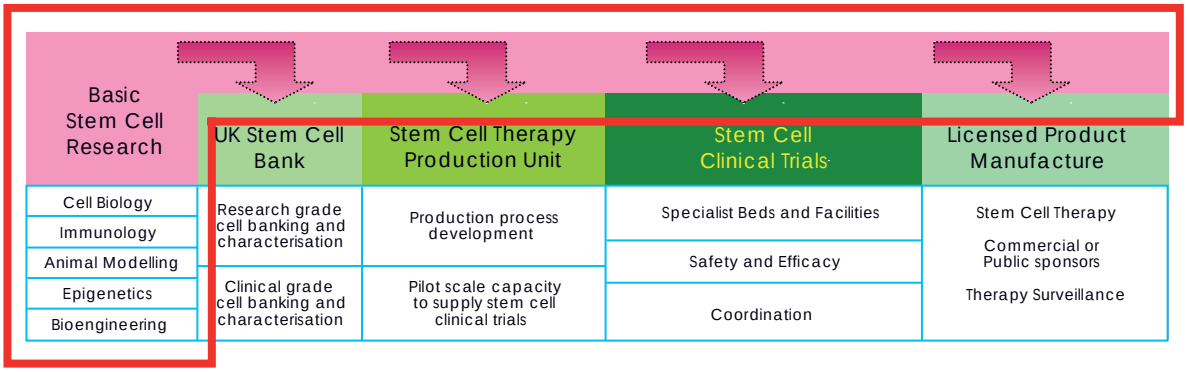
Basic stem cell research will contribute to all stages of stem cell technology and therapy development. It will form the bedrock for any innovation, from which crucial intellectual property rights can be established. High priority should, therefore, be given to integrated research programmes that are interdisciplinary and directed towards the conversion of basic stem cell research into clinical appliciations.

If we are committed to making a contribution to the field in the international context, we must accept the need to fund basic stem cell research to a significant degree. If the UK Stem Cell Bank is to be fully resourced, internationally acclaimed researchers are to be recruited to the UK, Centres of Excellence are to be supported and the benefits of stem cell therapies are to be realised, then more resources for UK stem cell research through conventional channels will be required. Otherwise, other parts of the UK science base will suffer.

While we cannot expect to invest the levels of funding in stem cell research that are being proposed by California, $3B over ten years, the UK Government should be prepared to commit to respond to Spending

Review bids for basic stem cell research. It is impossible to predict how much might be required, but for the purposes of our indicative costings, we estimate that a profiled increase of £5 - 21M per annum will be required over the next decade.

Recommendation 5: The Government and Research Councils should strengthen the levels of funding for basic stem cell research over the next decade.



Projected Cost Range of UKSCI Recommendation 5: £200 – 272M

LOW TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Existing commitment to Basic Stem Cell Research[1]	15	15	15	15	15	15	15	15	15	15
New Funding for Basic Stem Cell Research[2]	5	5	5	5	5	5	5	5	5	5
Cost per year	20	20	20	20	20	20	20	20	20	20

HIGH TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Existing commitment to Basic Stem Cell Research[1]	15	15	15	15	15	15	15	15	15	15
New Funding for Basic Stem Cell Research[3]	5	5	7	9	11	13	15	17	19	21
Cost per year	20	20	22	24	26	28	30	32	34	36

[1]Based on the estimated spending by Research Councils on stem cell research in 2005 **[See Box 11]**.

[2]Based on additional spending by Research Councils on stem cell research of £5M per annum between 2006 & 2015.

[3]Based on spending by Research Councils on stem cell research increasing from £5M per annum in 2006 and 2007 and, profiled to increase to £21M per annum by 2015

5.2.2 Translational & Clinical Research

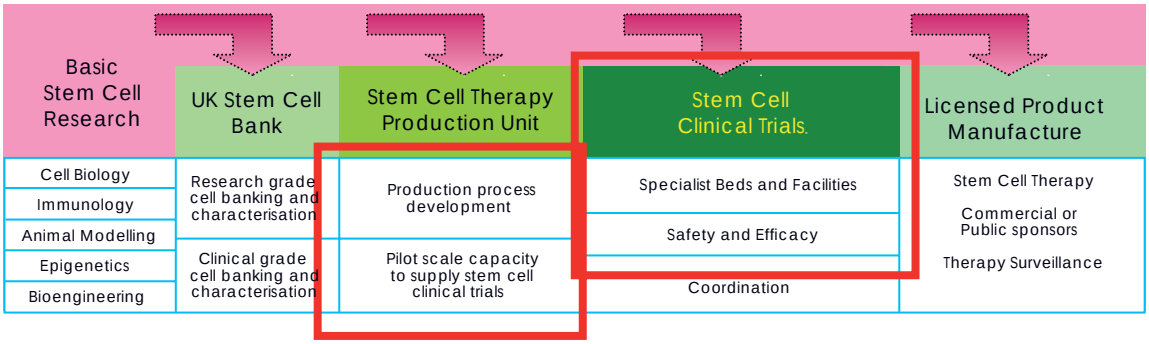
The majority of translational research in the next five years is likely to involve adult stem cells. It is expected that there will be an increasing number of embryonic stem cell applications in the subsequent years. The expertise gained earlier from the development of adult stem cell therapies will expedite the development of therapies involving embryonic stem cells. It is therefore essential that the UK is supportive of early clinical stem cell research trials, provided they are of sufficient quality. This will help to develop our breath of expertise and knowledge of clinical aspects of stem cell research.

The UK Stem Cell Foundation (UKSCF) has been established specifically to fund translational and clinical stem cell research in the UK and seeks to raise substantial funds (up to £10M per annum) from private donations in order to promote this research. The Foundation recognises the emerging potential of stem cell research to create health benefits in the UK and is determined that these opportunities should not be lost. It has suggested that the Government matches the private money raised pound-for-pound.

Consideration should be given to this proposal, as it would effectively halve the cost to the public purse of funding such translational and clinical research in the UK. The research proposed must be of high quality and to ensure this, the UKSCF and the MRC are jointly developing specific selection criteria and a combined review process for the funding of translational stem cell research proposals. If UKSCF/MRC successfully develop this joint process, the Government could administer this new funding via a UKSCF/MRC collaboration. Public money would be allocated to the MRC for the specific purpose of matching UKSCF funding for translational and clinical stem cell research projects.

Should such a partnership prove possible, then it would undoubtedly contribute to the development of stem cell therapy in the UK by providing much needed support for research aimed at clinical application within two years.

Recommendation 6: The Government should provide funding for clinical and translational stem cell research over the next decade at a level matching that raised by the UK Stem Cell Foundation (UKSCF), up to a maximum of £10M per annum, and administer it via a UKSCF/Medical Research Council collaboration.



Projected Cost Range of UKSCI Recommendation 6: £83 – 87M

LOW TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
UK Stem Cell Foundation[1]	2	5	7	9	10	10	10	10	10	10
Cost per year	2	5	7	9	10	10	10	10	10	10

HIGH TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
UK Stem Cell Foundation[2]	2	5	10	10	10	10	10	10	10	10
Cost per year	2	5	10	10	10	10	10	10	10	10

[1]Based on a profiled increase in fund-raising by the UKSCF, that requires matching funding of £10M each year by 2010.

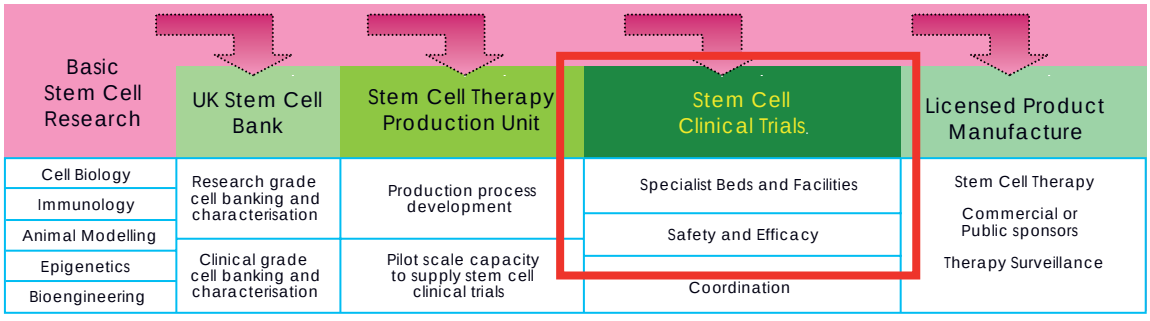
[2]Based on the UKSCF raising funds of £10M (or over) each year from 2006 to 2015.

The new allocation of money to the UKSCF raises a second issue with respect to public funding for translational and clinical stem cell research. These studies are likely to fail if the NHS is unable to support the additional costs of these experimental therapies. Therefore, It will be critical to increase funding of NHS R&D.

As well as the 'Direct Research Costs', the cost of clinical research in the NHS is composed of 'Service Support Costs', which are the extra costs associated with care and monitoring of patients in clinical trials, and the 'Excess Treatment Costs', which are the costs of providing the experimental treatment above those of the standard regimen. Retrospective analyses of clinical research in the NHS reveals that Service Support Costs and Excess Treatment Costs are each equivalent to the Direct Research Costs. That is, the cost of clinical research in the NHS is twice that of the Direct Research Costs.

In 2004, a major increase in the overall NHS R&D allocation was made but, subsequently, much of this increase has been delayed. Should the Government wish to support stem cell clinical research, then the new NHS R&D resource previously promised will have to be restored and additional money to meet the full NHS costs of stem cell trials will need to be made available. We estimate this latter requirement will grow to £32M per annum over the next decade.

Recommendation 7: The Department of Health must ensure that the promised increase in R&D resources is forthcoming and furthermore, that the full NHS costs of stem cell clinical research trials within the NHS are supported with extra funding from each Spending Review over the next decade to match the increase in research grants and activity.



[1]Projected Cost Range of UKSCI Recommendation 7: £265.6 – 278.4M

LOW TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Full NHS Cost[2]	6.4	16	22.4	28.8	32	32	32	32	32	32
Cost per year	6.4	16	22.4	28.8	32	32	32	32	32	32

HIGH TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Full NHS Cost[3]	6.4	16	32	32	32	32	32	32	32	32
Cost per year	6.4	16	32	32	32	32	32	32	32	32

[1]The Full NHS Cost of clinical research is composed of Service Support Costs and Excess Treatment Costs, both of which are the same as Direct Research Costs. Figures are based on funding raised by UKSCF being equivalently matched by public money, as in Recommendation 6. UKSCF estimate that 80% of their funding will support of clinical trials in the NHS. Therefore, the cost per year has been calculated according to the formula: **[Full NHS Cost]= 2 X [0.8 X (Funding raised by UKSCF + Matching public funding to UKSCF)]**.

[2]Based on a profiled increase in fund-raising by the UKSCF that requires matching funding of £10M each year by 2010.

[3]Based on a profiled increase in fund-raising by the UKSCF that requires matching funding of £10M each year by 2008.

5.3 REGULATION

The regulatory environment is arguably the single most important factor underpinning the global prominence of UK stem cell research. It will be critical to ensure that the UK's favourable regulatory climate for embryonic stem cell research is maintained over the next decade and, furthermore, extended to include the appropriate level of oversight of clinical applications.

5.3.1 Regulation of Stem Cell Lines

The regulation of embryo research to derive embryonic stem cell lines is an important activity and continues to be carried out effectively by the HFEA. We welcome the fact that the 15 year old legislation underpinning the work of the HFEA is currently under review by the Department of Health. The HFEA should continue to regulate the use of embryos for stem cell research and satisfy itself that these embryos are being treated in an appropriate manner, consistent with legislation.

However, it is important to recognise that the act of destroying the blastocyst, or early stage embryo, is what presents us with an ethical challenge. Once an embryonic stem cell line has been established, any ethical quandary over the status of the embryo should no longer exist. Logically, the embryonic stem cell line should be treated like any other cell line in the laboratory.

The independent Steering Committee of the UK Stem Cell Bank currently oversees, on a purely voluntary basis, the deposit and withdrawal of stem cell lines from the Bank on a case-by-case basis. This level of self-regulation of embryonic stem cell lines is currently appropriate and proportionate. As the field of stem cell research evolves and expands in the next few years, it is likely that a case-by-case review of each transaction to and from the Bank will seem excessive. It would seem prudent for stem cell researchers to register with the Bank and to submit an annual summary report on the use of stem cell lines from the Bank. It would therefore seem appropriate for the Bank to charge researchers an appropriate handling fee to cover the costs of withdrawals of stem cell lines from the Bank.

5.3.2 Regulation of Animal Experimentation

An important element in the development of bone marrow transplantation was careful experimentation in animal models. Likewise, for new stem cell therapies to be developed in the future, it will be necessary to conduct some experiments in animal models before proceeding to patients. Perhaps the use of human/animal *chimeras* exemplifies the situation most clearly.

Here, human stem cells are introduced into adult or developing animals and the contribution of the human cells to the animal's physiology assessed. These kind of experiments include studies of the human *haematopoietic* system by its reconstitution, with human haematopoietic stem cells, in adult mice.

It may also be possible to use human/animal chimeras to improve the safety profiles of pharmaceuticals in patients by generating 'humanised' organs, such as the liver, in animals for toxicology experiments. As described in ***Section 3***, if embryonic stem cells were to be injected directly into patients, they would most likely cause tumours, known as teratomas. Stem cell therapies will need to be composed exclusively of differentiated cells of the type appropriate to the therapy. It will be vital to test cell therapy preparations in animals for the absence of contaminating embryonic stem cells in order to ensure that they cannot cause teratomas in patients.

Currently, there is a lack of clarity amongst researchers over the roles of the Department of Health, HFEA, Home Office and Steering Committee of the UK Stem Cell Bank in regulating animal experimentation in stem cell research.

5.3.3 Regulation of Stem Cell Therapy

Stem cell therapies are likely to be developed that cover the full spectrum of risk to patients: from almost inert biomaterial and autologous cells, through to pluripotent, virally-modified cells. Importantly, cell therapy can be used in either a *homologous* or non-homologous setting. In a homologous stem cell transplantation,

stem cells are themselves native to the target tissue being repaired. An example of homologous stem cell transplantation would be the use of haematopoietic stem cells from bone marrow to restore the haematopoietic system, or the use of corneal stem cells to repair the cornea. In a non-homologous stem cell transplantation, the stem cells originate from outside of the target tissue of repair. An example of non-homologous stem cell transplantation would be the use of haematopoietic stem cells from bone marrow to repair the heart muscle following infarct.

Current studies to test the safety of pharmaceuticals and medical devices may be insufficient for complex live cells. As a result, there is an opportunity for the UK to create a distinctive competence in the field of risk mitigation in stem cell therapy, to influence and inform UK preclinical evaluation and ethics approval processes, and to become a leading country to accelerate patient benefits from these technologies. It is therefore incumbent upon the UK to influence appropriately the development of European policies in this area.

To ensure that stem cell therapies are regulated in a proportionate and flexible way, the Medicines and Healthcare Products Regulatory Agency, Department of Health, HFEA and new Human Tissue Authority should also liaise closely with the biotechnology and healthcare industries. It will be essential for these groups to work together to ensure that legislation, particularly from the European Union, such as the proposed Tissue Engineering Regulation, is as seamless as possible and facilitates, rather than hinders, the developments of effective new treatments for the benefit of patients. Because stem cell therapies are likely to be developed through very different routes than pharmaceuticals, and in a highly iterative manner, it is important that they be regulated in the appropriate way, with sufficiently flexibility to mitigate against the varying degrees of risks from the full range of cell therapy products.

The Food & Drug Administration of the United States of America appear to have adopted a sensible approach to the flexible regulation of these kinds of cell-based therapies. For example, a more substantial level of review is applied to cell therapy products used in non-homologous settings than to the same products used in homologous settings.

The House of Lords Select Committee on stem cells recommended that the Government should consider establishing a specialist Research Ethics Committee (REC) to oversee clinical trials involving embryonic stem cells. The Select Committee suggested that such a specialist committee could either be created specifically for the purpose or that the remit of the Gene Therapy Advisory Committee (GTAC) could be extended. We recommend the former.

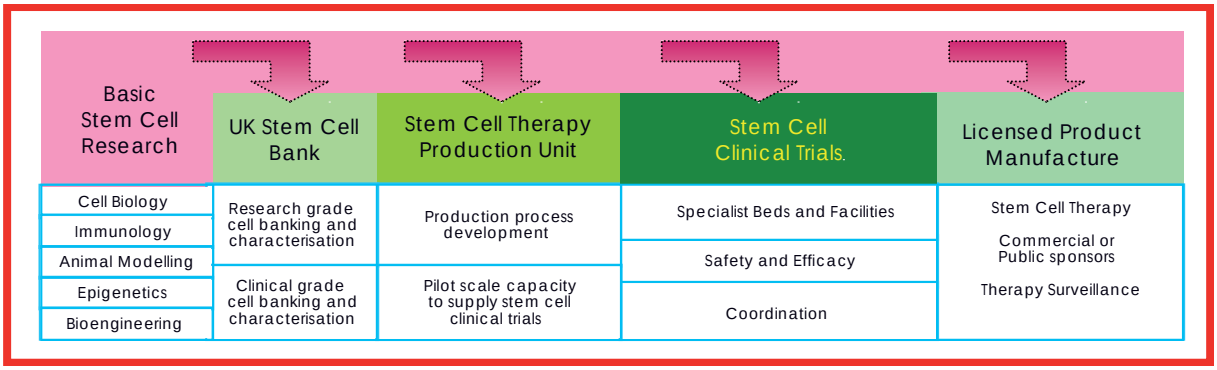
As with GTAC, approval of the new committee would be instead of, and equivalent to, that of a non-specialist REC. Therefore, it would not impose any additional regulatory burden on stem cell researchers. On the contrary, the new committee should help to standardise the ethical review of stem cell clinical trials, providing clarity across the UK. Given the high profile nature of stem cell research, the committee will act to maintain public confidence in this area as the field matures into an established branch of medicine.

The new committee's remit should include clinical research involving embryonic stem cells, adult stem cells and other forms of cell therapy.

Clinical applications involving the *homologous* use of stem cells would not require approval by this specialist ethics committee. However, non-homologous stem cell transplantation raises much greater safety and ethical concerns. All of these types of applications should be formally reviewed by the new ethics committee.

Sensible regulation is key to maintaining public support for this area of research. It will be critical for the Government to inform the development of appropriate regulation of stem cell research by taking into account any changes in public attitudes. Ultimately, the benevolence of the public will determine the level of participation of patient volunteers in stem cell clinical trials. We therefore strongly encourage the close liaison of parties involved in developing regulation and public dialogue on stem cell research (Recommendations 8 & 11).

Recommendation 8: The Government should continue to ensure that regulation of stem cell research is risk-based and proportionate and does not stifle the development of the full range of safe and effective new cell therapies for the benefit of patients. In particular, (i) the Department of Health should establish a specialised research ethics committee for stem cell clinical research; (ii) the Government should clarify the regulatory requirements for the use of animals and animal cells in human stem cell research; & (iii) for the *in vitro* use of embryonic stem cell lines, researchers should be registered with, and submit an annual research summary report to, the UK Stem Cell Bank.



Projected Cost of UKSCI Recommendation 8: £5M

COST (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Stem Cell Therapy Specialised Ethics Committee expenditure[1]	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cost per year	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

[1]Based on figures from similar Government Scientific Advisory Committees in the life sciences.

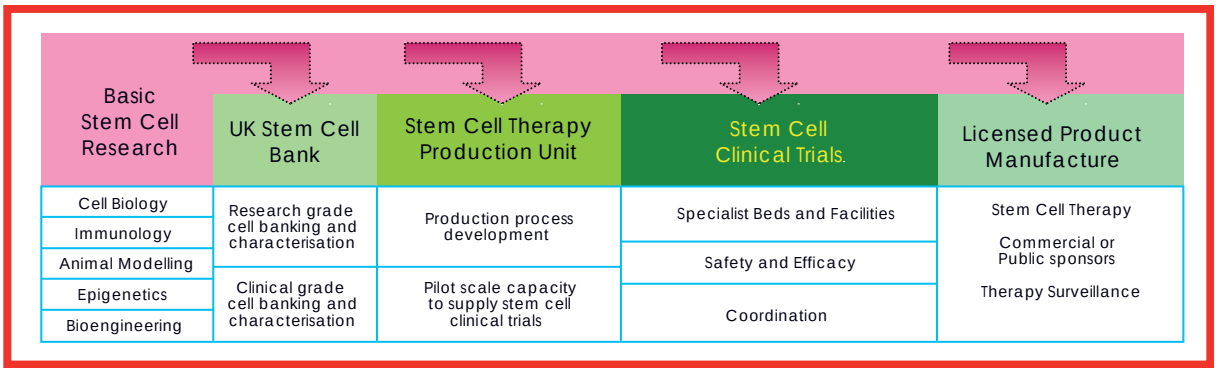
5.4 COORDINATION & COMMUNICATION

5.4.1 Strategic Coordination

As outlined in ***Section 4***, a number of countries offer strengths in stem cell research which are complementary to those of the UK. The Government currently has a number of disparate programmes that promote UK stem cell research and gather information on research globally, such as the DTI *Globalwatch* missions, *UK Trade and Investment* and the *Science and Innovation Network* of the Foreign & Commonwealth Office. Global strategic alliances between the UK and other countries in areas of mutual interest in stem cell research should be developed in a coordinated fashion, based on input from all relevant Government Departments and the Research Councils. The Department of Health, Department of Trade & Industry, Foreign & Commonwealth Office, Research Councils and other relevant Government bodies should coordinate activities to consolidate the global position of UK stem cell research, including via the development of strategic alliances with other countries that have complementary interests to the UK.

Because of the multidisciplinary nature of stem cell research, the Research Councils should continue to work closely together to develop cross-functional research programmes, such as in bioengineering. It continues to be essential for the Research Councils to coordinate their activities if we are to see maximum value for our investment in this area. One of the work streams of the UK Clinical Research Collaboration involves experimental medicine. It would seem a natural progression for the UKCRC to coordinate the efforts of the Research Councils and charitable funding bodies that support stem cell research.

Recommendation 9: The *UK Clinical Research Collaboration* should help to (i) coordinate organisations supporting stem cell research, including all of the relevant Research Councils and the UK Stem Cell Foundation and (ii) ensure that the *National Health Service* is optimally engaged in this area.



Projected Cost of UKSCI Recommendation 9: £1M

COST (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
UKCRC expenditure[1]	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Cost per year	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

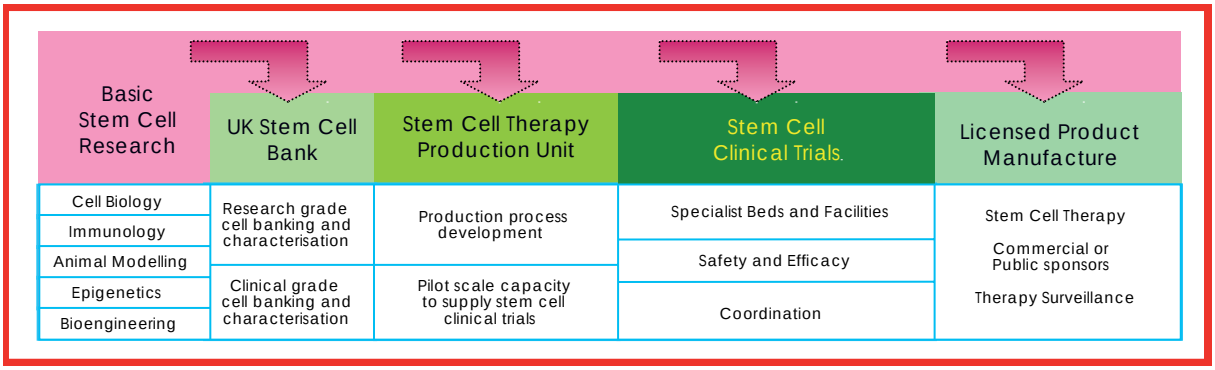
[1]Based on costs of administering of a sub-committee of UKCRC for coordination of stem cell research funders.

5.4.2 The UK Stem Cell Cooperative

One of the crucial elements currently missing from UK stem cell research is a national cooperative, network or forum, for the interaction of scientists, clinicians, ethicists, policy-makers, regulators and commercial organisations with an interest in stem cell research. Stem cell researchers have recognised the need for such associations and established them at regional levels, such as the Scottish Stem Cell Network, the East of England Stem Cell Network and the London Regenerative Medicine Network. A UK-wide cooperative would promote the exchange of ideas and actively facilitate collaboration within both the public and private sectors across the breadth of UK stem cell research.

The UK Stem Cell Cooperative should host regular meetings and establish efficient mechanisms to exchange information and ideas in the area. The Cooperative should also work with the International Stem Cell Forum on the characterisation of stem cell lines, the ethical landscape and intellectual property issues.

Recommendation 10: The Government should allocate additional funding to establish *The UK Stem Cell Cooperative*, to maximise the cross-fertilisation between those involved in the sub-disciplines of UK stem cell research.



Projected Cost Range of UKSCI Recommendation 10: £4.6 – 6M

LOW TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
UK Stem Cell Cooperative[1]	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5
Cost per year	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5

HIGH TRAJECTORY (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
UK Stem Cell Cooperative[2]	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Cost per year	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6

[1]Based on expenditure for annual national scientific conference, regular regional meetings, internet site, administrative costs.

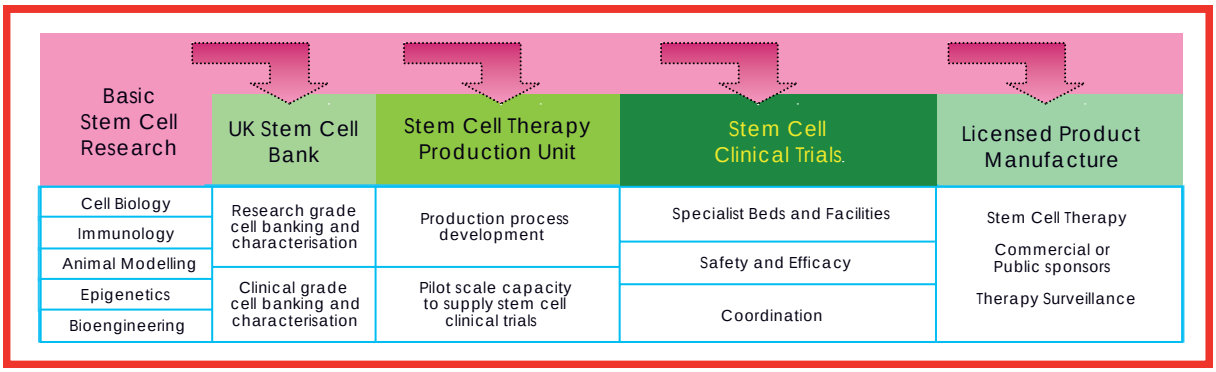
[2]Based on expenditure for annual international scientific conference, regular regional meetings, internet site, administrative costs.

5.4.3 Public Dialogue

The majority of the UK public are currently supportive of stem cell research, as judged in recent opinion polls and via parliamentary debate. However, as research moves towards the clinic it will be important to ensure that the public is kept aware of developments in a balanced and fair manner. As with all clinical research, the safety of treatments is unknown until clinical research takes place. Any adverse events in stem cell clinical research could unravel public support for this technology.

In accordance with the Council for Science & Technology's 2005 report entitled "Policy through dialogue" , it will be critical for the regulation of stem cell research to take due account of public changes in attitude towards this area. Of key importance in the dialogue with the UK public are (i) the ethical issues surrounding the derivation and laboratory use of embryonic stem cell lines (ii) the use of animal experimentation in stem cell research and (iii) the benefits and risks of stem cell therapies.

Recommendation 11: The Research Councils, charitable funding bodies, and Government Departments should develop a sustained and coordinated programme of public dialogue on stem cell research over the next decade.



Projected Cost of UKSCI Recommendation 11: £5M

COST (£M):

Year	*2006*	*2007*	*2008*	*2009*	*2010*	*2011*	*2012*	*2013*	*2014*	*2015*
Annual Public Meeting[1]	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Educational Programmes[2]	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Cost per year	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

[1]Based on expenditure for one annual meeting on stem cell research for a lay audience.

[2]Based on the development of literature and regional workshops on stem cell research for a lay audience.

5.5 SUMMARISED COSTINGS

In this report, we have made 11 recommendations to act as a strategic guide for public and charity sector investment in UK stem cell research over the next decade. Whilst these recommendations have been designed as a cohesive and comprehensive package of measures, UKSCI believes that the implementation of each one should, by itself, enhance UK stem cell research and, therefore, merits consideration. In the table below, we have summarised the total costs for our programme of recommendations over the next ten years and have projected these to cost in the range of £41M to £104M per annum. We have calculated that pre-existing public and private sector funding bodies' investment to support ongoing research efforts in this area is likely to account for approximately £30M per annum over the next decade [***See Box 11***]. We propose that the UK should maintain this level of investment in ongoing UK stem cell research activity and make an additional investment, ranging from approximately £11M to £74M per annum over the next decade, specifically to supplement the new endeavours proposed in this report. Clearly these cost estimates will need to be updated periodically during the next decade, not least to determine whether the increase in resources required is following a high or low trajectory.

As well as direct funding from Government, Research Councils and private sector funding bodies, UK investment could be augmented from a number of public and private funding sources and enterprises [e.g. ***See Boxes 12 & 16***]. With this level of investment in stem cell research, it is probable that a significant portion of discovery and innovation in the entire field of stem cell research will take place in the UK.

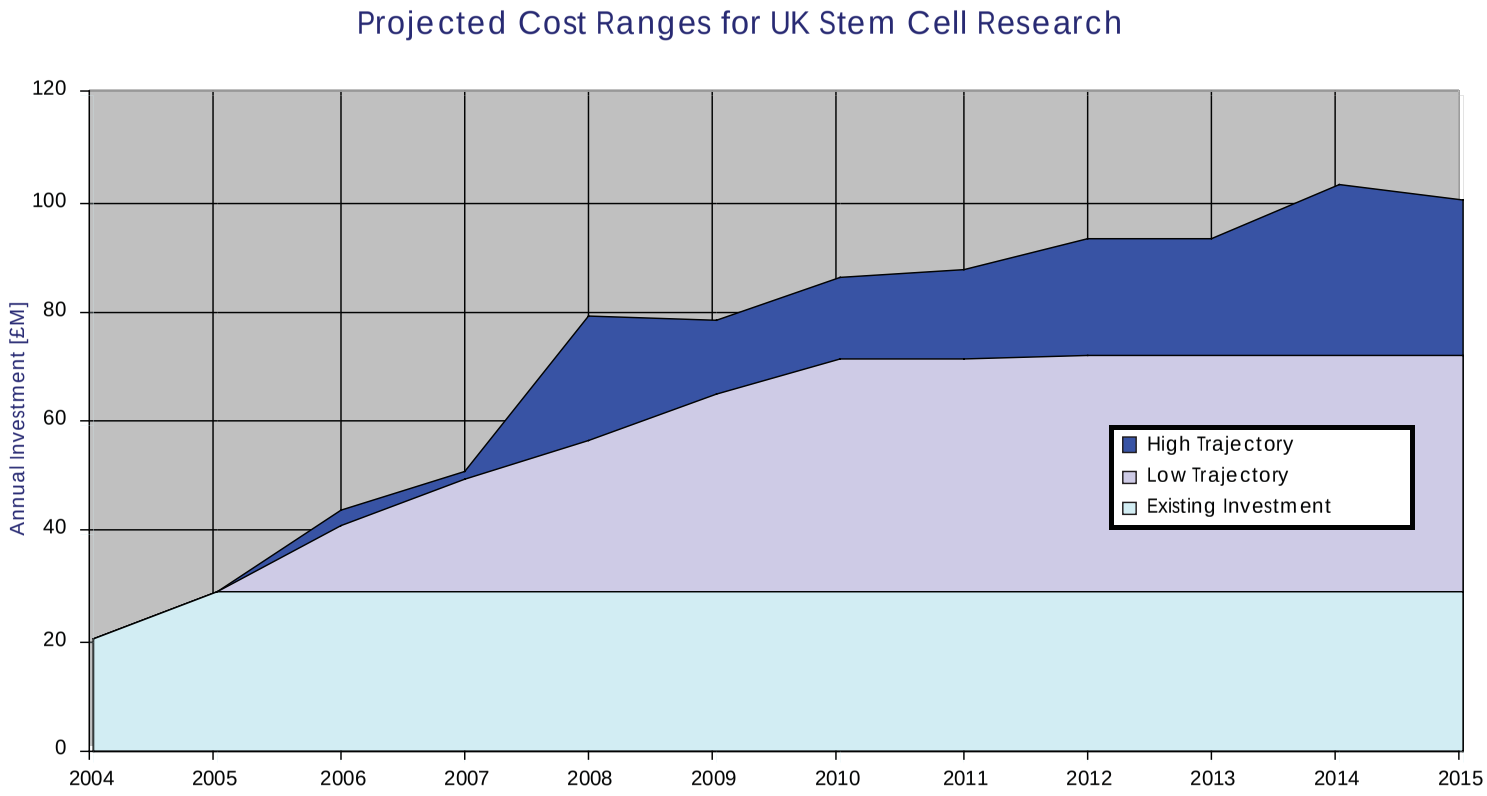
Grand Table for Projected Total Cost Ranges of UKSCI Recommendations

LOW TRAJECTORY (£M):

		Year									
Recommendation:	**Cost over 10 years:**	***2006***	***2007***	***2008***	***2009***	***2010***	***2011***	***2012***	***2013***	***2014***	***2015***
1 [Public-Private Consortium]	16.4	0.7	1.3	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
2 [UK Stem Cell Bank]	17	4.6	1.2	1.2	1.3	1.3	1.4	1.5	1.5	1.5	1.5
3 [Stem Cell Centres of Excellence]	36	4	4	2	2	4	4	4	4	4	4
4 [Cell Therapy Production Units]	12.2	2	1	1	1	1.2	1.2	1.2	1.2	1.2	1.2
5 [Basic Stem Cell Research]	200	20	20	20	20	20	20	20	20	20	20
6 [UK Stem Cell Foundation]	83	2	5	7	9	10	10	10	10	10	10
7 [Full NHS Costs]	265.6	6.4	16	22.4	28.8	32	32	32	32	32	32
8 [Regulatory Measures]	5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
9 [UK CRC]	1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
10 [UK Stem Cell Cooperative]	4.6	0.4	0.4	0.4	0.4	0.5	0.5	0.5	0.5	0.5	0.5
11 [Public Dialogue]	5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total cost:	645.8	41.2	50	56.9	65.4	71.9	72	72.1	72.1	72.1	72.1

HIGH TRAJECTORY (£M):

		Year									
Recommendation:	**Cost over 10 years:**	***2006***	***2007***	***2008***	***2009***	***2010***	***2011***	***2012***	***2013***	***2014***	***2015***
1 [Public-Private Consortium]	31.3	1.0	1.7	2.7	3.7	3.7	3.7	3.7	3.7	3.7	3.7
2 [UK Stem Cell Bank]	20.8	5.9	1.4	1.4	1.6	1.6	1.7	1.8	1.8	1.8	1.8
3 [Stem Cell Centres of Excellence]	70	4	4	6	4	6	8	8	8	12	10
4 [Cell Therapy Production Units]	43.4	3	1	4	2	5.2	3.2	6.4	4.4	8.6	5.6
5 [Basic Stem Cell Research]	272	20	20	22	24	26	28	30	32	34	36
6 [UK Stem Cell Foundation]	87	2	5	10	10	10	10	10	10	10	10
7 [NHS R&D Costs]	278.4	6.4	16	32	32	32	32	32	32	32	32
8 [Regulatory Measures]	5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
9 [UK CRC]	1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
10 [UK Stem Cell Cooperative]	6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
11 [Public Dialogue]	5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total cost:	819.9	44	50.8	79.8	79	86.2	88.3	93.6	93.6	103.8	100.8



The graph above plots projected annual investment in UK stem cell research from 2004-2015. 'High Trajectory' and 'Low Trajectory' plots are based on figures from the "Grand Table for Projected Total Cost Ranges of UKSCI Recommendations". Annual investment figures for 2004 & 2005 are based on figures in *Box 11*. 'Existing Investment' plots investment in UK stem cell research based on the maintenance of 2005 levels of spending between 2006-2015.

ANNEX 1:
MEMBERSHIP OF THE UK STEM CELL INITIATIVE

Chairman:

- Sir John Pattison DM FRCPath FMedSci

Panel Members:

- Professor Colin Blakemore, Chief Executive, Medical Research Council (Alternate: Dr Diana Dunstan);
- Professor Julia Goodfellow, Chief Executive, Biotechnology & Biological Sciences Research Council;
- Professor Sally Davies, Director of R&D, Department of Health;
- Dr Mark Walport, Director, The Wellcome Trust;
- Dr Fiona Watt, The Academy of Medical Sciences;
- Ms Diana Garnham, Chief Executive, Association of Medical Research Charities;
- Dr Peter Mountford, Chief Executive, Stem Cell Sciences Ltd.;
- Dr Peter Arnold, Director of Technology, Smith and Nephew (UK);
- Dr David McCauley, Chief Executive, UK Stem Cell Foundation;
- Sir Christopher Evans, Trustee, UK Stem Cell Foundation;
- Lord May of Oxford, Trustee, UK Stem Cell Foundation;

Secretariat:

- Dr John Connolly, Department of Health

ANNEX 2: TERMS OF REFERENCE

- To develop a ten-year vision for UK stem cell research, which seeks to make the UK the most scientifically and commercially productive location for this activity over the coming decade, and which commands the support of public and private research funders, practitioners and commercial partners.

- To present a costed plan to Government and business for implementation over 2006-2015, to inform future public spending reviews and private sector investment planning.

- To identify options for better coordinating and leading UK stem cell research and commercial translation in the coming years.

- To report back to Government (DTI, Department of Health, HM Treasury) by Pre-Budget Report 2005 (anticipated late autumn 2005)

ANNEX 3: SUMMARY OF UKSCI CONSULTATIONS

Between March and September 2005, the Chairman and Secretariat of UKSCI have attempted to consult widely with the academic and commercial sectors who have an interest in stem cell research. Below is a synopsis of this activity.

A. Meetings with the UK research community:

13th April: Dr Stephen Minger, Kings College London; Dr Chris Mason, University College London & Professor Robin Ali, University College London.

20th April: Dr John Martin, University College London, Dr Anthony Marthur, Barts and the London NHS Trust, Dr Jonathon Hill, Guy's, King's and St Thomas School of Medicine, Professor Eric Alton, Imperial College London, Professor Martin Rothman, Barts and The London NHS Trust.

27th April: Site visits to, Edinburgh University & The Roslin Institute, Scotland.

28th April: Site visit to researchers from the University of Newcastle, the Newcastle Centre for Life & University of Durham.

4th May: Dame Julia Polak, Imperial College, London; Professor Roger Pedersen, Cambridge University; Dr Brian Salter, University of East Anglia.

12th May: Site visit to the UK Stem Cell Bank at NIBSC

23th June: Professor Ian McKenzie, Professor Malcolm Alison, Dr Nick Wright and Dr Harry Navsaria, Institute of Cell and Molecular Science, Queen Mary's School of Medicine and Dentistry, Barts and the London.

21st July: Professor Mike Hoare and Dr Chris Mason. The Advanced Centre for Biochmeical Engineering, University College London.

9th August: Site visit to the University of Oxford, Department of Obstetrics & Gynaecology and the MRC Molecular Haematology Unit.

15th August: Site visit to the National Blood Service, Collindale, London.

1st September: Site visit to the National Institute of Medical Research, Mill Hill, London

20th September: Site visit to the University of Sheffield.

B. Meetings with the UK commercial sector.

24th August: Meeting with representatives from the Bioindustry Association, GlaxoSmithKline, Smith and Nephew, Pfizer, Astrazeneca, Merck, Epistem, Axordia, Stem Cell Sciences, ReNeuron, Avalar, Intercytex, Javelin Ventrues, CellCentric.

31st August: Roger Ashby, StemCell Ventures

C. Written comments from UK Universities.

We wrote to all 121 UK Universities (www.universitiesuk.ac.uk), asking them to input to our Initiative. We received 31 responses from the following:

University of Bristol;
University of Dundee;
University of Edinburgh;
University of Glasgow;
Heriot-Watt University;
University of Bath;
University College London;
University of York;
Imperial College London;
University of Oxford;
University of Southampton;
Brighton and Sussex Medical School;
University of Sheffield;
Durham University;
University of Essex;
University of Newcastle Upon Tyne;
Cardiff University;
Oxford Brookes University;
University of Manchester;
London South Bank University;
University of East Anglia;
Northumbria University;
University of Nottingham;
University of Surrey;
University of Aberdeen;
Queen's University Belfast;
Kings College London;
University of Central Lancashire;
Queen Mary, University of London;
University of Strathclyde; &
The London School of Economics and Political Science.

D. Written comments from individuals.

We received written comments from the following individuals:

Professor Manuel Galinanes, University of Leicester.
Dr Ged Brady, Epistem Ltd;
Professor Peter Dunhill, University College London;
Professor Dennis McGonagle, Leeds General Infirmary;
Dr Chris Mason, University College London
Dr Robert A. Goldstein, Juvenile Diabetes Research Foundation International

ANNEX 4:
GLOSSARY OF TERMS

Allogeneic: Cells or tissue obtained from donors for use in recipient patients.

Autologous: Cells or tissue obtained from the patient themselves.

Basic research: Science in pursuit of knowledge, rather than specifically directed towards application.

BBSRC: The Biotechnology and Biological Science Research Council.

Bioengineering: The laboratory processing of cells and tissues.

Blastocyst: The 4-6 day old embryo, consisting of 100-200 cells, before implantation in the uterus.

BSI: British Standards Institute.

Chimera: Organism composed of two genetically distinct types of cells.

Clinical research: Research in patients and healthy volunteers.

Cryogeneics: Science of the preservation of biological samples at very low temperatures.

Differentiation: The process of maturation of stem cells into specialised cell types of the body.

DfES: Department for Education and Skills

DH: Department of Health.

DTI: Department of Trade and Industry.

Endogenous: Originating from within an animal.

Epigenetic: Long-term effects on cells without permanent alteration to the genetic material.

EPSRC: The Engineering and Physical Sciences Research Council.

FCO: Foreign and Commonwealth Office.

GMP: Good Manufacturing Practice, a standard of quality for the production of clinical material.

Haematopoietic: pertaining to cells of the blood, derived from bone marrow.

HFEA: Human Fertilisation and Embryology Authority.

Histocompatibilty: Compatibility of tissues or cells from a donor with the tissue type of the recipient patient.

Homologous transplantation: Cells or tissue transplanted back into the same tissue type from which they were originally derived.

Immunogenetics*:* The genetics of the immune system.

Inner Cell Mass: A set of cells in the blastocyst that give rise to the cells and tissues of the embryo.

IP: Intellectual Property.
LGC: Laboratory of the Government Chemist.
Mesenchymal Stem Cells: A specific class of adult stem cells.
MRC: Medical Research Council.
NBS: National Blood Service.
NCRI: National Cancer Research Institute.
NHS: National Health Service.
NIBSC: National Institute for Biological Standards and Control.
Niche: The physiological environment in which a cell lives.
OST: Office of Science & Technology, Department of Trade & Industry.
PCT: Patent Cooperation Treaty
Predictive toxicology: Pre-clinical experiments to ascertain any toxic effects of drugs to guide subsequent research in patients or healthy volunteers.
Puripotent: The potential of a stem cell to differentiate into all types of specialised cell in the body.
R&D: Research and Development.
REC: Research Ethics Committee.
Regenerative medicine: The use of stem cells to repair damaged or lost tissue.
Reproductive cloning: Generation of live offspring by somatic cell nuclear replacement.
Scale-up: The conversion of small numbers of cells into large cultures.
Self-renewal: The ability of stem cells to generate new copies of themselves.
Somatic cell nuclear replacement: The replacement of the unfertilised nucleus from an egg with a nucleus from a body cell, leading to the development of an embryo.
Stem Cell: A cell that can self-renew and differentiate into a variety of specialised cell types.
Stem Cell Line: A stable population of stem cells maintained in culture for successive generations.
Stem Cell Preparation: An extract from patients containing stem cells.
Teratoma: Malignant tumour derived from embryonic stem cells.
Therapeutic cloning: Generation of embryonic stem cells from embryos produced by somatic cell nuclear replacement.
Tissue Engineering: The use of cells and biomaterials to generate new tissue to replace diseased of damaged ones.

Translational research: Science bridging basic and clinical research which is directed towards specific application.
UKCRC: UK Clinical Research Collaboration.
UKSCF: UK Stem Cell Foundation.
UKSCI: UK Stem Cell Initiative.

ANNEX 5:
INFLUENTIAL PATENTS IN STEM CELL RESEARCH

The table below contains summary details on the most important patents in stem cell research. Patents were identified by a search of various patent databases using the term "stem cell", with the level of importance determined by the levels of citation in other patents. The analysis corrected for the age of the patent using a re-based citation count, similar that that used for ranking scientific publications.

Publication Number	Assignee Name	Assignee Country	Title	Abstract	Family Patent Numbers	Priority Date
US5192553	Biocyte Corporation	USA	Isolation and preservation of fetal and neonatal hematopoietic stem and progenitor cells of the blood and methods of therapeutic use	The present invention relates to hematopoietic stem and progenitor cells of neonatal or fetal blood that are cryopreserved, and the therapeutic uses of such stem and progenitor cells upon thawing. In particular, the present invention relates to the therapeutic use of fetal or neonatal stem cells for hematopoietic (or immune) reconstitution. Hematopoietic reconstitution with the cells of the invention can be valuable in the treatment or prevention of various diseases and disorders such as anemias, malignancies, autoimmune disorders, and various immune dysfunctions and deficiencies. In another embodiment, fetal or neonatal hematopoietic stem and progenitor cells which contain a heterologous gene sequence can be used for hematopoietic reconstitution in gene therapy. In a preferred embodiment of he invention, neonatal or fetal blood cells that have been cryopreserved and thawed can be used for utologous (self) reconstitution.	AT137974E AU2610288A1 DE3855301C0 DE3855301T2 EP343217A1 EP343217B1 JP3501207T2 JP8000069B4 SG46352A1 US5004681 US5192553 US6461645 US6569427 US6605275 WO8904168A1	12/11/1987

US6436701	Babraham Institute (BBSRC-sponsored)	UK	Derivation of pluripotential embryonic cell lines from ungulate species	A method of selecting and growing pluripotential embryonic stem cells isolated from an ungulate species blastocysts of embryos that develop by way of an embryonic disc is disclosed. The method comprises growing blastocysts in tissue culture growth medium which includes both heat-inactivated new born calf serum and heat-inactivated fetal calf serum; disaggregating the blastocysts either after spontaneous hatching or after mechanical removal of the zone pellucida; growing stem cell colonies from the disaggregated cells in issue culture growth medium; selecting stem cell colonies by morphological characteristics; and growing the selected stem cells in tissue culture growth medium. The cells are round cells, tightly packed with large nuclei in relation to cytoplasm, and fairly prominent nucleoli. They grow in tightly adherent coloedes and as the colonies get larger the cells tend to flatten out in the center of the colony. The outer, less flattened cells of a larger colony or all the cells of a smaller colony without central flattening are readily disaggregated by trypsinization into small spherical cells which have a bright phase contrast appearance, and if observed after a short time of incubation at 37.degree. C. they show lobular pseudopodia.	AU650616B2 AU4321789A1 BR8907666A EP435928A1 GB8822158A0 GB8918203A0 JP450090972 NZ230723A US6436701 US2002187549A1 WO9003432A1	21/09/1988
US5486359	Osiris Therapeutics, Inc.	USA	Human mesenchymal stem cells	Isolated human mesenchymal stem cells which can differentiate into more than one tissue type (e.g. bone, cartilage, muscle or marrow stroma), a method for isolating, purifying, and culturally expanding human mesenchymal stem cells (i.e. "mesenchymal stem cells" or "hMSCs"), and characterization of and uses, particularly research reagent, diagnostic and therapeutic uses for such cells. The stem cells can be culture expanded without differentiating. Monoclonal antibodies specific for human mesenchymal stem cells and the monoclonal hybridoma cell lines (ATCC nos. 10743-10745) that synthesize and secrete these monospecific antibodies, and uses of the monoclonal antibodies for diagnostic and/or therapeutic purposes.	AT239072E AU669850B2 AU2252492A1 AU4704196A1 AU5958996A1 CA2111845AA CA2111845C DE69233029T2 DK592521T3 EP592521A1 EP592521A4 EP592521B1 EP13612267A2 EP13612267A3 ES2198403T3 JP7500001T2 US5197985 US5226914 US5486359 US5733542 US5811094 US5837539 US6010696 US6087113 WO9222584A1 WO9623058A1 WO9638482A1	16/11/1990

US5199942	Immunex Corporation	USA	Method for improving autologous transplantation	There is disclosed a method for autologous hematopoietic cell transplantation of patients receiving cytoreductive therapy, comprising: (1) obtaining hematopoietic progenitor cells from bone marrow or peripheral blood from a patient prior to cytoreductive therapy; (2) expanding the hematopoietic progenitor cells ex vivo with an ex vivo growth factor selected from the group consisting of interleukin-3 (IL-3), steel factor (SF), granulocyte macrophage-colony stimulating factor (GM-CSF), interleukin-1 (IL-1), GM-CSF/IL-3 fusion proteins and combinations thereof, to provide a cellular preparation comprising an expanded population of progenitor cells; and (3) administering the cellular preparation to the patient concurrently with or follwoing cytoreductive therapy. The inventive method optionally comprising a preliminary treatment with a recruitment growth factor to recruit hematopoietic progenitor cells into peripheral blood and a subsequent treatment with an engraftment growth factor to facilitate engraftment and proliferation of hematopoietic progenitor cells administered in the cellular preparation. The invention further provides a hematopoietic progenitor cell expansion media composition comprising cell media, an ex vivo growth factor, and autologous serum.	AU665955B2 AU2179392A1 CA2109699AA EP587754A1 EP587754A4 JP6508613T2 US5199942 WO9221402A1	17/06/1991

US5750376	NeuroSpheres Holdings Ltd.	Canada	In vitro growth and proliferation of genetically modified multipotent neural stem cells and their progeny	A method for producing genetically modified neural cells comprises culturing cells derived from embryonic, juvenile, or adult mammalian neural tissue with one or more growth factors that induce multipotent neural stem cells to proliferate and produce multipotent neural stem cell progeny which include more daughter multipotent neural stem cells and undifferentiated progeny that are capable of differentiating into neurons, astrocytes, and oligodendrocytes. The proliferating neural cells can be transfected with exogenous DNA to produce genetically modified neural stem cell progeny. The genetic modification can be for the production of biologically useful proteins such as growth factor products, growth factor receptors, neurotransmitters, neurotransmitter receptors, neuropeptides and neurotransmitter synthesizing genes. The multipotent neural stem cell progeny can be continuously passaged and proliferation reinitiated in the presence of growth factors to result in an unlimited supply of neural cells for transplantation and other purposes. Culture conditions can be provided that induce the genetically modified multipotent neural stem cell progeny to differentiate into neurons, astrocytes, and oligodendrocytes in vitro.	AT208495E AT221117E AT230795E AT234353E AT240389E AT262912E AU665012B2 AU683023B2 AU687785B2 AU697894B2 AU703729B2 AU714837B2 AU715246B2 AU716811B2 AU2242592A1 AU3515295A1 AU3836695A1 AU3836795A1 AU4924197A1 AU5147493A1 AU5367694A1 AU6098394A1 AU8056194A1 CA2113118C CA2113118AA CA2147162C CA2147162AA CA2148138C CA2148138AA CA2155024C CA2155024AA CA2175992AA CA2200709AA CA2204630AA CN1141058A CN1170434A CN1170435A DE69233061C0 DE69233061T2 DE69232147C0 DE69232147T2 DE69332759C0 DE69332759T2 DE69431993C0 DE69431993T2 DE69433661C0 DE69433661T2 DE69523771C0 DE69523771T2 DK594669T3 DK664832T3 DK669973T3 DK728194T3 DK783693T3 EP594669A1 EP594669B1 EP664832A1 EP664832B1 EP669973A1 EP669973B1 EP681477A1 EP681477A4 EP681477B1 EP728194A1 EP728194B1 EP783693A1 EP783693B1 EP792349A1 EP792350A1 EP1130394A1 EP1298202A2 EP1298202A3 EP1329499A2 ES2116746T3 ES2180547T3 ES2189807T3 ES2190401T3 ES2198404T3 ES2218524T3 FI935929A0 FI935929A FI951677A0 FI951677A FI952022A0 FI952022A FI953569A0 FI953569A FI961855A0 FI961855A FI971168A0 FI971168A FI971955A0 FI971955A FI971956A0 FI971956A JP3583778B2 JP6509225T2 JP8502172T2 JP8502652T2 JP8505762T2 JP9507747T2 JP10505754T2 JP10509319T2 JP10509592T2 NO940056A0 NO940056A NO951378A0 NO951378A NO951617A0 NO951617A NO952985A0 NO952985A NO961859A0 NO961859A NO971245A0 NO971245A NO972170A0 NO972170A NO972171A0 NO972171A PT664832T PT669973T PT783693T US5750376 US5851832 US5980885 US5981165 US6071889 US6294346 US6399369 US6497872 US2003049837A1 US2003082515A1 US2003095956A1 US2003109008A1 WO9301275A1 WO9409119A1 WO9410292A1 WO9416718A1 WO9513664A1 WO9609543A1 WO9615224A1 WO9615226A1	08/07/1991

US5453357	Vanderbilt University	USA	Pluripotential embryonic stem cells and methods of making same	The present invention provides a non-mouse pluripotential embryonic stem cell which can: (a) be maintained on feeder layers for at least 20 passages; and (b) give rise to embryoid bodies and multiple differentiated cell phenotypes in monolayer culture. The invention further provides a method of making a pluripotential embryonic stem cell comprising administering a growth enhancing amount of basic fibroblast growth factor, leukemia inhibitory factor, membrane associated steel factor, and soluble steel factor to primordial germ cells under cell growth conditions, thereby making a pluripotential embryonic stem cell.	US5453357 US5670372 US5690926 US2004071672A1	08/10/1992
US6146888	The University of Edinburgh	UK	Method of enriching for mammalian stem cells	Mammalian stem cells are obtained and maintained in vitro whose genome has at least one nucleic acid construct encoding an antibiotic resistance gene operatively linked to a promoter specific for mammalian stem cells. The preferential expression of the antibiotic resistance gene in the stem cells results in the preferential survival of the stem cells in the presence of antibiotic.	AT187491E AT247171E AU67823382 AU678234B2 AU745043B2 AU3435799A1 AU6542694A1 AU6542794A1 CA2161088AA CA2161089AA CA2325800AA DE69422034C0 DE69422034T2 DE69433034C0 DE69433034T2 DK695361T3 EP695351A1 EP695351B1 EP695361A1 EP695361B1 EP1115840A2 EP1403376A2 GB9308271A0 GB9807935A0 IL109381A0 IL109381A1 IL109382A0 IL138937A0 JP9500004T2 JP9500005T2 JP2251124612 NZ265090A NZ265091A NZ507281A SG41951A1 SG48698A1 US6146888 US6150169 US6878542 US2005196858A1 WO9424274A1 WO9424301A1 WO9953022A2 WO9953022A3 ZA9402719A ZA9402720A	21/04/1993

US6147276	Roslin Institute, Edinburgh/ The Minister of Agriculture, Fisheries and Food/ Biotechnology and Biological Sciences Research Council	UK	Quiescent cell populations for nuclear transfer	A method of reconstituting a mammalian embryo involves transferring the nucleus from a quiescent donor cell into a suitable recipient cell. The donor cell is quiescent, in that it is caused to exit from the growth and division cycle at G1 and to arrest in the G0 state. Nuclear transfer may take place by cell fusion. The reconstituted embryo may then give rise to one or more mammals. The invention is useful in the production of transgenic mammals as well as non-transgenics of high genetic merit.	AT199115E AU716956B2 AU716956C AU6831096A1 BR9610034A CA2229568AA CN1202084A C29800608A3 DE69611793C0 DE69611793T2 DK849990T3 EP849990A1 EP849990B1 EP930009A1 EP1005789A2 EP1005789A3 ES2155197T3 GB2318578A1 GB2318578B2 GB2318578B GB2331751A1 GB2331751A GB2331751B2 GB2331751B GB9517780A0 GB9802915A0 GB9802915A GB9824304A0 GB9824304A HK1004938A1 HK1019394A1 HU9900234AB IL123298A0 JP2050672T2 NO980845A0 NO980845A NZ316149A NZ334288A PL325331A1 SG75155A1 SI849990T1 US6147276 US2005010966A1 WO9707669A1 ZA9607390A	31/08/1995
US5753506	CNS Stem Cell Technology, Inc.	USA	Isolation propagation and directed differentiation of stem cells from embryonic and adult central nervous system of mammals	The present invention reveals an in vitro procedure by which a homogeneous population of multipotential precursor cells from mammalian embryonic neuroepithelium (CNS stem cells) can be expanded up to 10.sup.9 fold in culture while maintaining their multipotential capacity to differentiate into neurons, oligodendrocytes, and astrocytes. Chemically defined conditions are presented that enable a large number of neurons, up to 50% of the expanded cells, to be derived from the stem cells. In addition, four factors--PDGF, CNTF, LIF, and T3--have been identified which, individually, generate significantly higher proportions of neurons, astrocytes, or oligodendrocytes. These defined procedures permit a large-scale preparation of the mammalian CNS stem cells, neurons, astrocytes, and oligodendrocytes under chemically defined conditions with efficiency and control. These cells should be an important tool for many cell- and gene-based therapies for neurological disorders.	AU7558498B2 AU2934197A1 AU6158699A1 AU7289898A1 CA2257068AA CA2343571AA EP915968A1 EP923640A1 EP1115841A1 EP1115841A4 JP2252606T2 US5753506 US6040180 US2002064873A1 WO0017323A1 WO0017323C2 WO9744442A1 WO9850525A1	25/09/1996

US5945577	University of Massachusetts, as represented by its Amherst Campus	USA	Cloning using donor nuclei from proliferating somatic cells	An improved method of nuclear transfer involving the transplantation of donor differentiated cell nuclei into enucleated oocytes of the same species as the donor cell is provided. The resultant nuclear transfer units are useful for multiplication of genotypes and transgenic genotypes by the production of fetuses and offspring, and for production of isogenic CICM cells, including human isogenic embryonic or stem cells. Production of genetically engineered or transgenic mammalian embryos, fetuses and offspring is facilitated by the present method since the differentiated cell source of the donor nuclei can be genetically modified and clonally propagated.	AU742363B2 AU742840B2 AU2211499A1 AU6014598A1 AU8374598A1 BR9806872A BR9811659A CA2277192AA CA2317494AA CN1248288A CN1248288T CN1265600T EP1015572A2 EP1017423A1 EP1017423A4 EP1045635A1 EP1045635A4 IL130829A0 IL133785A0 JP2150936T2 JP2151296 4T2 NZ336612A NZ502124A US5945577 US6215041 US6235969 US6235970 US2001039667A1 US2002010949A1 US2002012655A1 US2002035737A1 US2002073439A1 US2004120934A1 US2004180041A1 US2004194159A1 US2005074439A1 US2005108785A1 WO9830683A2 WO9830683A3 WO9901164A1 WO9934669A1	10/01/1997
US6011197	Infigen, Inc.	USA	Method of cloning bovines using reprogrammed non-embryonic bovine cells	The present invention relates to cloning technologies. The invention relates in part to immortalized and totipotent cells useful for cloning animals, the embryos produced from these cells using nuclear transfer techniques, animals that arise from these cells and embryos, and materials, methods, and processes for establishing such cells, embryos, and animals.	AU745334B2 AU6688098A1 BR9808192A CA2282722AA EP973871A1 JP2251251 0T2 NZ337495A NZ510930A US6011197 US6395958 US6603059 US2003070186A1 WO9839416A1	06/03/1997
US6528245	University of South Florida	USA	Bone marrow cells as a source of neurons for brain and spinal cord repair	Bone marrow stromal cells (BMSC) differentiate into neuron-like phenotypes in vitro and in vivo, engrafted into normal or denervated rat striatum. The BMSC did not remain localized to the site of the graft, but migrated throughout the brain and integrated into specific brain regions in various architectonic patterns. The most orderly integration of BMSC was in the laminar distribution of cerebellar Purkinje cells, where the BMSC-derived cells took on the Purkinje phenotype. The BMSC exhibited site-dependent differentiation and expressed several neuronal markers including neuron-specific nuclear protein, tyrosine hydroxylase and calbindin. BMSC can be used to target specific brain nuclei in strategies of neural repair and gene therapy.	AU3888699A1 DE69926639C0 EP1096941A1 EP1096941B1 JP2251354 5T2 US6528245 US2002146821A1 WO9956759A1	07/05/1998

US6326201	Curis, Inc.	USA	Pancreatic progenitor cells, methods and uses related thereto	The present invention relates to a substantially pure population of viable pancreatic progenitor cells, and methods for isolating such cells. The present invention further concerns certain therapeutic uses for such progenitor cells, and their progeny.	AU36979A5 AU179245A5 AU780794B2 AU5203060AA CA2362593AA CA2418381AA EP1175487A2 EP1309673A2 IL144654A0 JP2253877?2 US6326201 US6610535 WO0047720A2 WO0047720A3 WO0212452A2 WO0212452A3	10/02/1999
WO0121767A2	Morphogen Pharmaceuticals, INC.	USA	Pluripotent embryonic-like Stem Cells, Compositions, Methods and Uses Thereof.	The present invention relates to pluripotent stem cells, particularly to pluripotent embryonic-like stem cells. The invention further relates to methods of purifying pluripotent embryonic-like stem cells and to compositions, cultures and clones thereof. The present invention also relates to a method of transplanting the pluripotent stem cells of the present invention in a mammalian host, such as human, comprising introducing the stem cells, into the host. The invention further relates to methods of \Alt;i\Agt;in vivo\Alt;/i\Agt; administration of a protein or gene of interest comprising transfecting a pluripotent stem cell with a construct comprising DNA which encodes a protein of interest and then introducing the stem cell into the host where the protein or gene of interest is expressed. The present invention also relates to methods of producing mesodermal, endodermal or ectodermal lineage-committed cells by culturing or transplantation of the pluripotent stem cells of the present invention.	AU76115A5 EP1218489A2 JP2450400?T2 NZ518601A US20040332?4A1 WO0121767A2 WO0121767A3 WO0121767C2	24/09/1999
WO0111011A2	REYES, Morayma	USA	Multipotent adult stem cells and methods for isolation	The invention provides isolated stem cells of non-embryonic origin that can be maintained in culture in the undifferentiated state or differentiated to form cells of multiple tissue types. Also provided are methods of isolation and culture, as well as therapeutic uses for the isolated cells.	AU66218A5 CA2381292AA EP1226233A2 IL147990A0 JP2350607?T2 NZ517002A US20051815?2A1 WO0111011A2 WO0111011A3 WO0111011C2 ZA201125A	10/11/1999

WO0139784A1	The General Hospital Corporation	USA	Pancreatic Stem Cells and their use in transplantation.	Methods and compositions are described for the treatment of type I insulin-dependent diabetes mellitus and other conditions using newly identified stem cells that are capable of differentiation into a variety of pancreatic islet cells, including insulin-producing beta cells, as well as hepatocytes. Nestin has been identified as a molecular marker for pancreatic stem cells, while cytokeratin-19 serves as a marker for a distinct class of islet ductal cells. Methods are described whereby nestin-positive stem cells can be isolated from pancreatic islets and cultured to obtain further stem cells or pseudo-islet like structures. Methods for ex vivo differentiation of the pancreatic stem cells are disclosed. Methods are described whereby pancreatic stem cells can be isolated, expanded, and transplanted into a patient in need thereof, either allogeneically, isogeneically or xenogenically, to provide replacement for lost or damaged insulin-secreting cells or other cells.	AU118173A5 AU778929B2 CA2392615AA CN1423563A CN1423563T EP1257282A1 EP1257282A4 IL149933A0 JP2352332T2 US6866843 US6923959 US2001024824A1 US2001046489A1 US2002164307A1 US2003031657A1 US2003082155A1 WO0139784A1 WO0326584A2	06/12/1999

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