MARKET FORESIGHTING

Stem Cells

September 2004

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Stem Cells – Summary (1)

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Definition & Details

Stem cells – are cells that have the capacity to self renew and differentiate into specialized cell types.

Market Dynamics & Emerging Markets

- Global mkt. size est. $8 bn for stem cell expansion services
- Total cell therapy market est. > $30 bn
- Future and emerging markets
  - Drug discovery tools – e.g., target screening, validation, ADMET
  - Therapeutics e.g. cancer, neurobiology, heart disease

Emerging Technologies & Platforms

- Renewal and differentiation control mechanisms
- Production and testing of cells with specific mutations in key genes
- Cell culture
- Regulation of cellular production
- Implantation techniques

Drivers & Trends

- New paradigm in regenerative medicine
- Repairing diseased or damaged tissues
- Need for cell based methods for testing efficacy and safety
- Population greying
- Substantial risk capital supplied by Governments
- Highly fragmented market

IP Landscape

- Geron (ES)
- WARF
- SCS (ES)
- Stemcell Inc
- ES Cell International (ES)
- Reneuron (Neural)
- Osiris (Mesenchymal)

Deal Space

- 15 deals in 2003
- Size of 1st round funding ranged from $10 mm to $13 mm (Cellerant & Neuronova AB)
- ViaCell most successful in raising financing through collaborations & VC investment

Challenges

- Technical
  - isolation
  - differentiation
  - propagation
- Political and ethical restraints
- Market acceptability
- Bio-manufacturing (scale-up and QA)

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Stem Cells – Summary (2)

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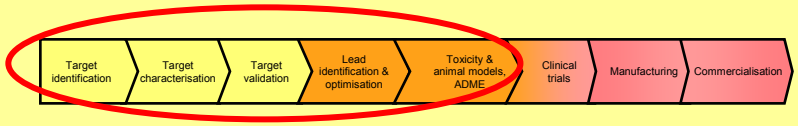
Value Chain and Business Models



- Almost all companies operate or provide services upstream of clinical development. Clinical research is progressing independently and aggressively of industry product development

Business models

- Therapies
- Reagents
- Cell banking
- Tools

Scottish Context

- Strength of stem cell base is strong
- Home to ISCR and Roslin – worldwide CoE in stem cell research
- 2 major stem cell companies linked to Scotland

Current and expected players & stakeholders

- Key players include Geron, ReNeuron, Osiris Therapeutics, Stem Cell Sciences
- Key stakeholders in the market include:
  - Pharma companies
  - Biotech companies
  - Academic institutes
  - Government
  - General Public

Market Demand

- **Discovery tools**
- **ADMET**
- **Therapeutics. Huge potential but initial focus likely to be in prevalent conditions with high unmet need such as Parkinson's, Diabetes and CHF**

Foresighting

Near-term Opportunity for Stem Cells

- Pharmaceutical drug development. E.g. cell models for;
  - ADMET
  - Screening drugs
  - Validating targets
  - Media and manufacturing

Specific Requirements

- Sufficient supply of sc
- Consistent and reproducible isolation kits for sc
- Standardisation of protocols
- Access to diverse set of stem cell source material
- Tools for *in vivo* tracking of sc
- Pooling of IP to enhance 'commercial viability'
- Supportive legislative environment

Gaps

- Markers for lineage commitment and plasticity
- Knowledge transfer form mouse to human
- Fully defined media
- Scale-up
- Key cell signalling pathways to be defined

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Stem Cells

SUPPORTING SLIDES

These slides are intended to support the summary slides. The ordering of this slide set does not lend itself to use as a presentation

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Stem Cells Supporting Information Contents

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Definition & Details

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Stem Cells

- Stem cells have both the capacity to self-renew as well as to differentiate into mature, specialized cells[1].

- There are four sources of stem cells;
  - The early embryo
  - The foetus
  - The placenta and umbilical cord
  - Other adult and foetal tissue such as bone marrow

(Please see the Glossary for a comprehensive description of terminology)

Source 1; http://www.isscr.org/glossary

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Overview

Embryonic stem (ES) cells derive from embryos (which can be created using *in vitro* fertilisation or cell nuclear replacement); cells from the inner cell mass are cultured on feeder cells (e.g. mouse fibroblasts). Alternatively, stem cells can be harvested from tissues rich in stem cells (e.g. foetal liver, umbilical tissue and blood), extracted, grown and concentrated in the laboratory. Adult stem cells can be isolated and cultured from adult tissue, such as bone marrow.

Stem cell research has substantial potential to produce novel (small molecule, biologic and cell) therapies for a range of illnesses including cardiovascular diseases (for example replacing damaged heart tissue), neurodegenerative diseases (for example replacing neurones), cancer (for example replacing bone marrow), diabetes (for example replacing islet cells) and the surgical repair of damaged tissues such as spinal cord. Additionally, stem cells could substantially impact drug discovery and pre-clinical research because of their potential for use as a platform technology in target identification, target validation, toxicity screening, and the generation of disease models.

However, stem cell research has received considerable media interest in recent years as it poses a number of ethical and legal challenges. Furthermore, the technology is still early in its development, and wide-spread therapeutic application of cell therapies based upon stem cell technologies is believed to be more than ten years away. (The aim of cell therapy is to replace, repair or enhance the function of damaged tissues or organs. It is related to and overlaps with several other established technologies, such as gene therapy, tissue engineering and regenerative medicine[2])

Source 2; http://www.pharmabiotech.ch/articles/20010905.pdf

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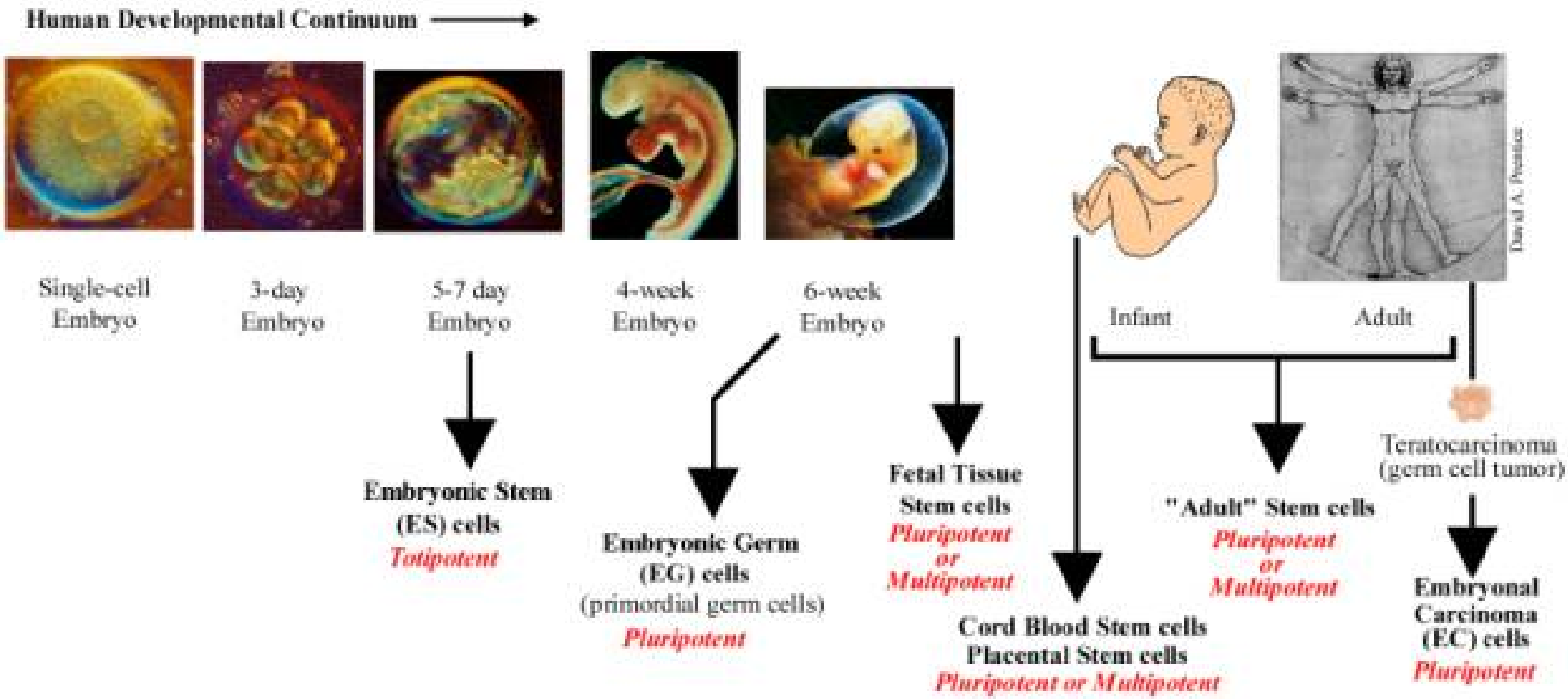
Stem Cells



Source; http://robby.nstemp.com/index.html

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Stem Cell Cultivation

- Once stem cells are extracted from their natural environment, they must be grown (expanded) to obtain sufficient quantities for experimental and therapeutic use; experimentally, embryonic stem cells have a greater capacity for self renewal (and consequently expansion on a therapeutic/commercial scale) than adult stem cells. In the case of bone marrow transplants, 70kg is reportedly the maximum body mass of patients in which the haematopoietic system can currently be practically repopulated because of the limited expansion potential of the haematopoietic stem cells. Cell expansion remains a practical issue for many stem cell lines of commercial or clinical interest.

- As all stem cells have the potential to divide, the culture of stem cells must be monitored closely to ensure that this process remains under control and that the cells do not undergo any unwanted changes, for example; the accumulation of chromosomal aberrations and other karyotypic abnormalities (which are often accompanied by reductions in the doubling time for cells grown in tissue culture). Some commentators suggest that the maximum practical time that human embryonic stem cells may be cultured *in vitro* is limited; however some lines have been cultured for over 70 passages without evidence of instability. The impact that industrial scale-up will have on the phenotype and subsequent utility of stem cell lines used for commercial or therapeutic purposes is unclear.

- Furthermore, unlike mouse embryonic stem cells (which can be routinely and reproducibly grown in fully defined media), the signalling mechanisms sufficient to maintain pluripotency in human embryonic stem cells are not currently fully defined. Human embryonic stem cells generally require support cells (feeder cells from either human or mouse) for growth to maintain their pluripotency; however, if cells are being grown for clinical use, they must be free from all contaminating pathogens. The current requirement for feeder cells may prove a regulatory issue unless it is resolved.

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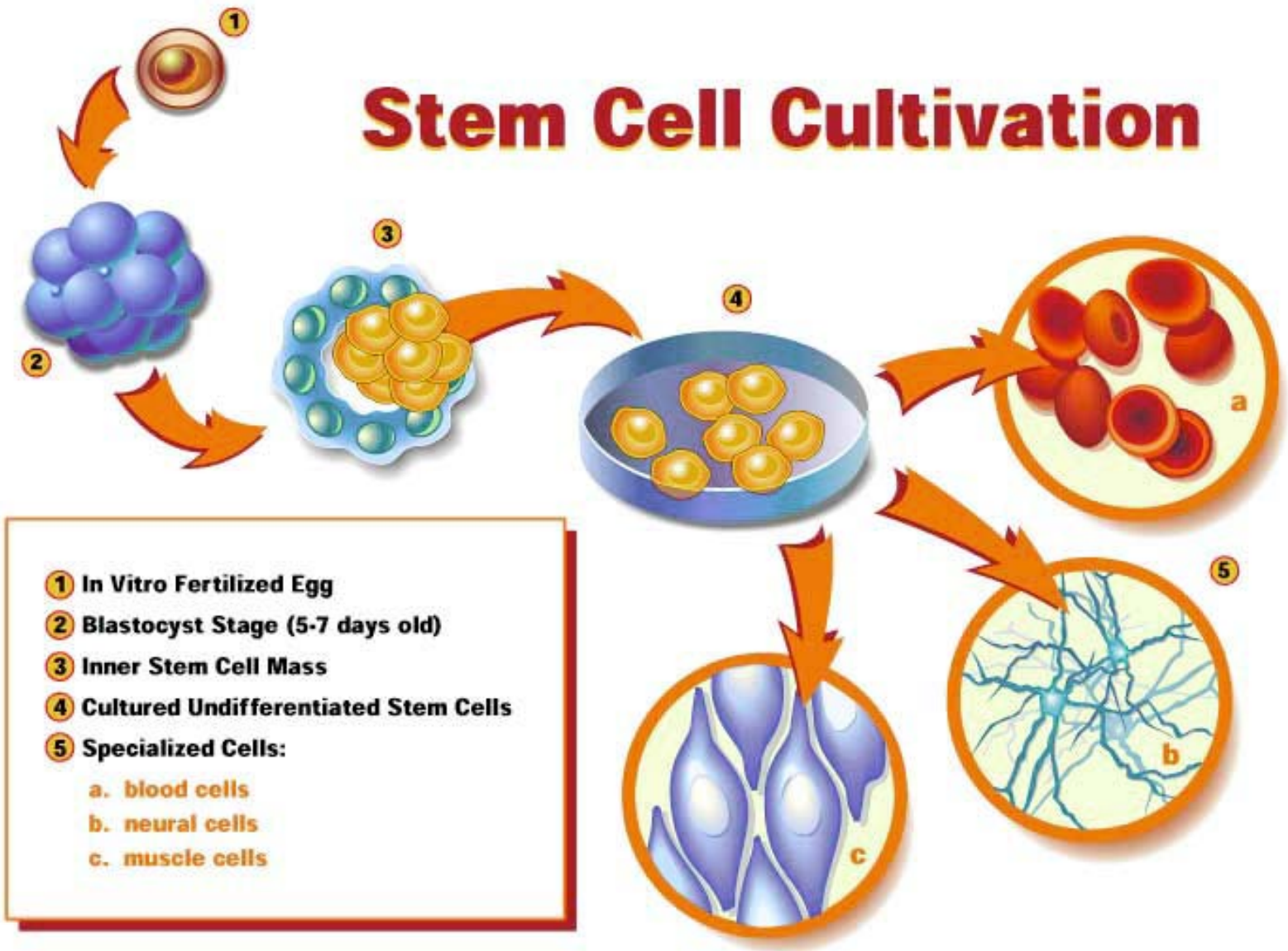

Source; http://robby.nstemp.com/index.html

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Bio-Manufacturing

- Currently, human stem cells are normally grown in the presence of feeder cells that supply essential factors that allow stem cells to retain their ability to self renewal
- Scale up currently possible for mouse ES cells and not human ES cells
- Synchronous differentiation in bioreactors will be challenging
- Adhering to GMP regulations, CFR21
  - Potency (defining cell activity, e.g. insulin-expressing cells/population of cells)
  - Identity (how many biomarkers required to define cell type?)
  - Purity (sorting/selection methodologies, removal of foreign agents, cell debris etc)
  - Safety (ensuring that no teratoma-producing cells are present in product)

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Directed Stem Cell Differentiation

- In the absence of a self renewal signal (or the activation of a pro-differentiation pathway), stem cells will differentiate into certain cell types, dependent upon the differentiation signals that they receive and their lineage commitment and plasticity. In the absence of LIF (and exogenous differentiation factors), wild type mouse embryonic stem cells spontaneously differentiate into cardiac myocytes *in vitro*. Human embryonic stem cells differentiate spontaneously *in vitro* into a range of cell types, and frequently give rise to cells with the properties of extra-embryonic endoderm. Treatment of human embryonic cell cultures with noggin (an antagonist of BMP2) induces the appearance of cells that give rise to neural precursors.

- The signals that direct and drive differentiation of embryonic stem cells into different lineages remain poorly understood. However, there is some evidence that differentiation is not always irreversible; some adult stem cells can transdifferentiate from cell types characteristic of a particular tissue into cell types characteristic of another tissue (e.g. cells from a hematopoietic lineage into a neural lineage). This possibility could lessen the ethical and political impact of (embryonic) stem cell derived therapies because of the potential for deriving autologous cell types of the appropriate lineage for medical or industrial application, using transdifferentiation or innate plasticity in adult stem cells.

- Screens for biomolecules and small molecules that control stem cell fate are ongoing. In one, a high throughput phenotypic cell based screen, a kinase-directed combinatorial library was used to identify a small molecule modulator of glycogen synthase kinase-3 activity which induced neurogenesis in murine embryonic stem cells. Furthermore, screens are ongoing to identify factors that can induce osteogenesis in mesenchymal stem cells, and dedifferentiation factors that are active in muscle cells. These approaches complement ongoing functional screens for biomolecules active in driving differentiation in stem cells.

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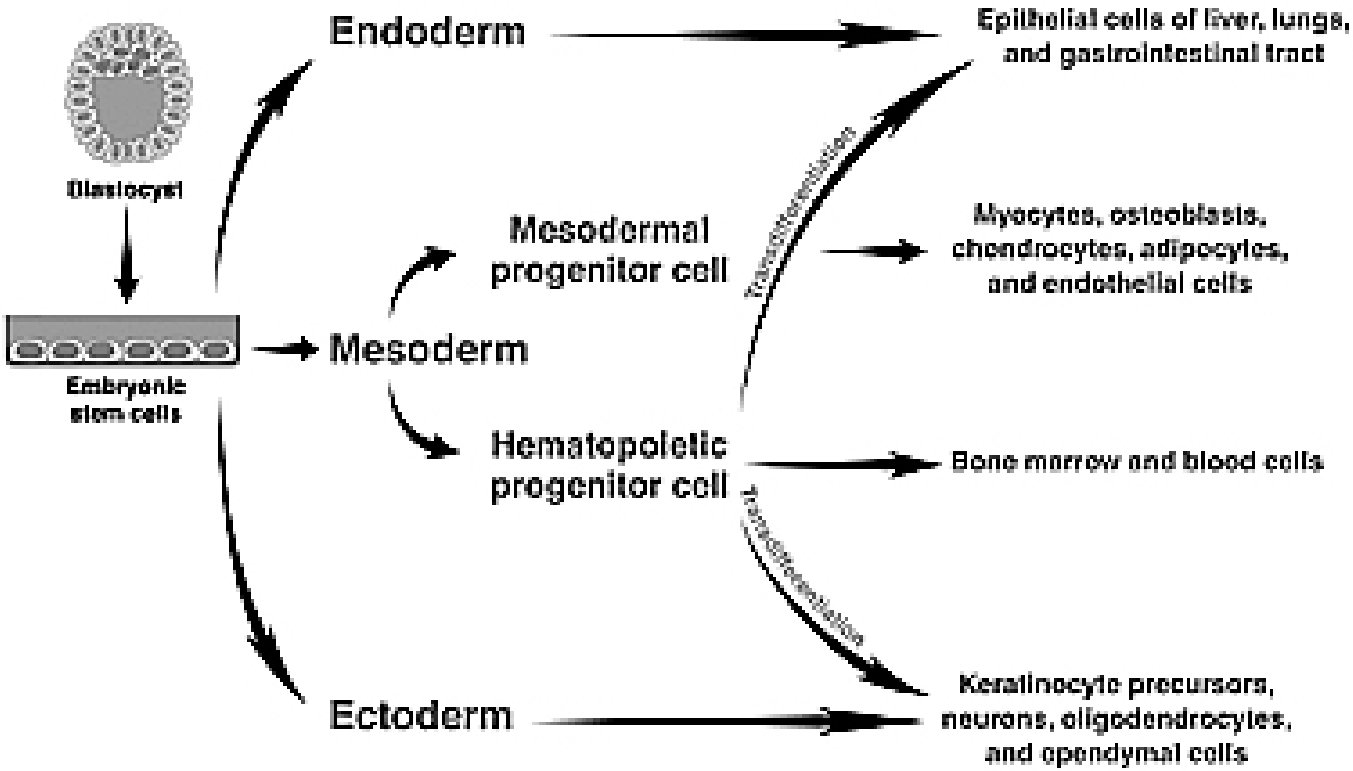
An illustration of ES stem cell differentiation



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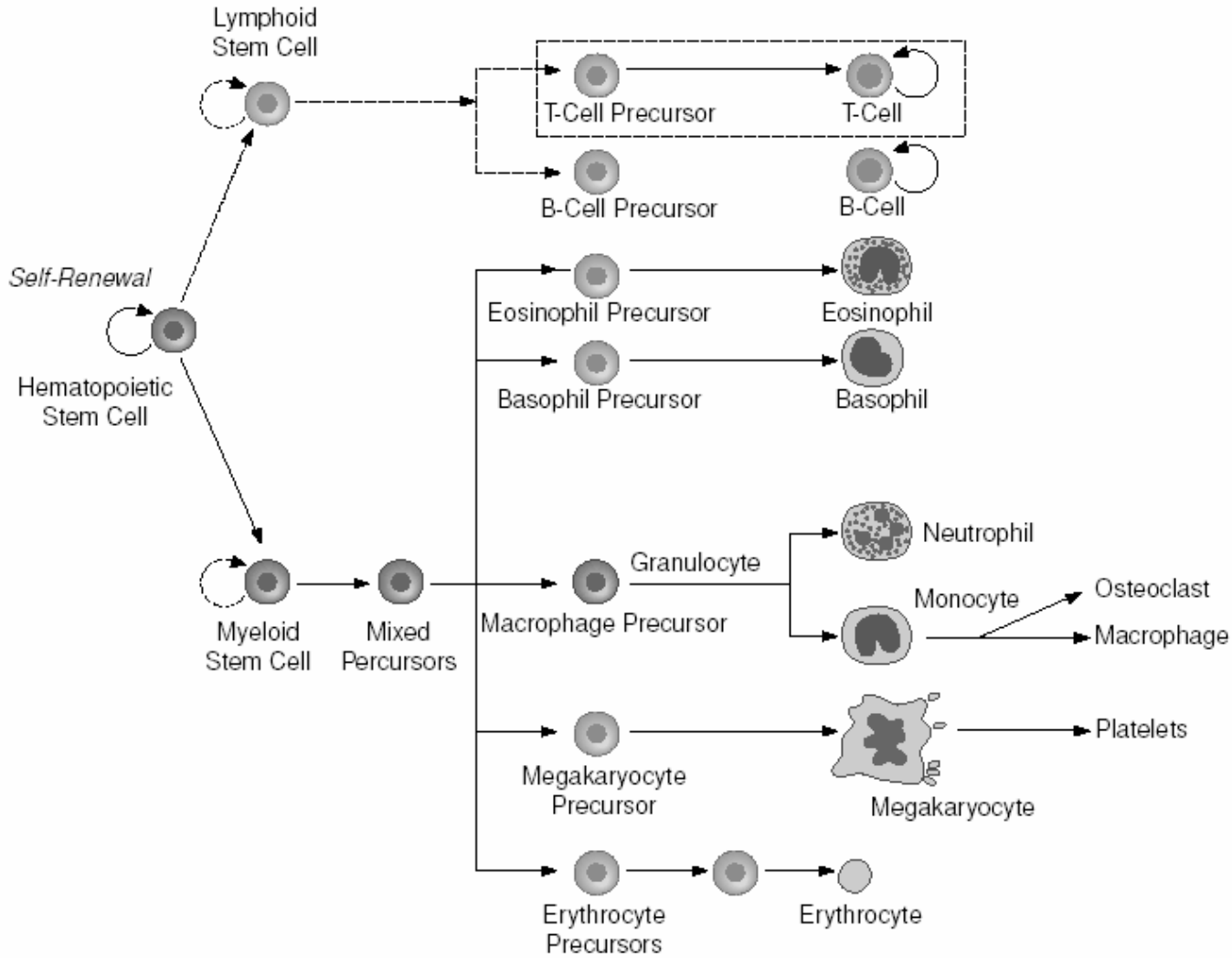
An illustration of adult haematopoietic stem cell differentiation



Source: "Stem cells and the future of medicine". Available at; http://books.nap.edu/catalog/10195.htm

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Avoiding at the 'hype'

- Human ES cells cannot yet efficiently give rise to endoderm-derived cell types, e.g. islets
- The media to grow sufficient quantities of ES cells have not yet been defined
- Human ES cells are not as tractable as mouse ES cells
- Developmental paradigms for the mouse may not directly translate into human development
- The external environment, e.g., O_2 concentrations, does affect differentiation
- Multiplexing of biomarkers is required to adequately characterize differentiated cell types, i.e., expression of nestin may not be sufficient to identify a cell as a neuron

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Adult Stem Cells

Pros

- The body will tolerate (not reject) an autologous stem-cell transplantation
- Already successful long-term treatment of patients with bone marrow stem cells
- Few specific ethical and legal restrictions as human embryos are not required
- High plasticity and suitable for many different applications
- Federal funding available

Cons

- In comparison to ES cells there is less experience with adult stem cells (bone-marrow derived stem cells being the exception)
- Adult stem cells are mainly multipotent rather than pluripotent (i.e. whilst they can differentiate into a wide variety of cell types, their lineage differentiation capabilities are more restricted relative to ES cells)
- Lack of markers and expansion protocols to isolate and enrich a single stem cell population derived from genuine stem cells
- Adult stem cells may carry more mutations than younger cells
- Isolation is difficult and expensive
- Culturing these cells is difficult due to lower proliferative capacities, expensive technical equipment, lack of standard expansion protocols and growth factors to maintain cells in an undifferentiated state

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Embryonic & Foetal Stem Cells

Pros	Cons
■ Relatively large numbers of cells are easy to isolate	■ Serious ethical concerns. Many countries do not allow research on embryos and ES cells; others only fund research within strict limits
■ Large proliferation capacity and amenable to genetic engineering	■ Risk of tumour formation after transplantation
■ ES cells could be less immunogenic than cell therapies derived from adult stem cells ■ Human ES cells are totipotent	■ No evidence to suggest that a terminally differentiated cell derived from an ES cell will behave the same as the adult derived cell
	■ Foetal cells obtained from the aborted foetus: ethical concerns and shortage of donors
	■ Embryos as a source of ES cells are limited, often only available from in vitro fertilisation clinics

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Umbilical Cord Blood Stem Cells

Pros	Cons
■ Cord blood is relatively easy to isolate and readily accessible	■ Multipotent and not pluripotent
■ Self-derived, genetically compatible cells and tissue for the donor and siblings	■ Efficient *ex vivo* multiplication of these cells is still a challenge: stem cells make up only a minor fraction of foetal tissue and the amount extractable from cord blood is only sufficient to treat children or young adolescents
■ Allogeneic transplants of result in surprisingly low rejection even in adult patients	■ Storage of cord blood for exclusive family use with private companies is relatively expensive
■ No extensive exposure to environmental factors, low risk of infectious diseases	
■ Larger proliferation capacities than adult stem cells	
■ Few specific ethical or legal concerns	
■ Viability following long-term storage confirmed	

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Ethics: Setting the Regulatory Environment

- Embryonic Stem (ES) cell research provokes much controversy, and attitudes to it are likely to be conditioned by one's view on the moral status of the embryo and when life begins.
- Because ES cell research is performed on cells derived from human embryos a few days old, which are destroyed during the process of extracting the cells, opponents argue that the research is unethical and ought to be banned.
- However, the fertilized eggs used in stem cell research would otherwise be discarded by the fertility clinics where they are stored because they are no longer needed for treatment. Rather than destroying the eggs, supporters argue, it makes moral and ethical sense to use them for research that could lead to treatments for diseases afflicting millions of people[1].

1. http://www.news.harvard.edu/gazette/2004/04.22/99-StemOver.html

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Regulatory Issues

- Stem cell therapies are stretching the regulatory guidelines currently in place for cell therapies and therefore many agencies are in the process of developing their guidance
- Standardisation/QC methodologies for culturing under common good practice will be vital to ensure a reproducible and safe outcome where stem cells are to be used therapeutically as well as in Pharma discovery programmes
- Stem cell banks holding collections of stem cells need to be established as these will provide a characterised and standardised source of ethically obtained cultures for researchers
- The FDA and other regulatory agencies are likely to classify embryonic stem cell products grown with the support of mouse feeder cells as xenografts and therefore a production process avoiding non-human cells would be preferable

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Regulatory Issues contd.

- A number of safety issues will also need to be addressed including:
  - How genetically stable are the cells after extended culturing *in vitro* and after transplantation
  - Do cells maintain their function e.g. do cells continue to produce insulin
  - The purity of the cells, i.e., are they free from contaminating cells?
  - Potential for tumour formation - the graft growth rate in patients cannot be controlled easily and only limited technologies are available for killing the grafts should anything goes wrong
  - Control of the graft disposition – the need for migration of the stem cells to the target site appears to be critical for efficacy but can also turn out to be a disadvantage since the cells could also migrate to other parts of the body where they may cause unwanted effects
  - Immunosuppressant regimens might be required for allogeneic cell transplants
  - Potential contamination with viruses or other infectious agents

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United States

- Following an August 2001 announcement by President Bush, federal funding for stem cell research has been restricted to approximately 78 stem cell lines – those created prior to August 2001 from embryos donated for *in vitro* fertilization.
  - No federal funds are to be used to investigate other cell lines or to create new ones.
  - Privately-funded research in the US is not subject to the same restrictions as federal funding and privately funded groups can and have generated new ES cell lines
- Organisations such as the Coalition for the Advancement of Medical Research and the Juvenile Diabetes Research Foundation have argued strenuously against US policy, pleading instead for more public funding.
- The National Institutes of Health (NIH) awarded about $20m for work on ES cells in 2003, compared with almost $300m for work in adult stem cells, which do not require federal approval for funding. In contrast, around $200m of private funding went into ES cell research worldwide.
- In July 2004 the government announced plans to open a "national bank" to better grow the only ES cells eligible for government-funded research. In addition, the NIH plans to spend $18m over four years to establish three "centers of excellence" to speed up research on the currently available cell lines.
- Individual states have the authority to pass laws permitting human ES cell research using state funds. Unless Congress passes a law that bans it, states may pay for research using human ES cell lines that are not eligible for Federal funding.[1] Both California and New Jersey have passed laws supporting ES cell research.
- Although federal law remains silent on the topic of therapeutic cloning, the President's Council on Bioethics has recommended a moratorium on the practice. The Bush administration remains opposed to both therapeutic and reproductive cloning. In contrast John Kerry has promised to increase federal funding and open up the field.

1. http://stemcells.nih.gov/info/faqs.asp#states

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United Kingdom

- UK legislation covering cloning and stem cells is set out in a series of Acts:
  - The creation of embryos for certain limited research purposes was made legal under the Human Fertilization and Embryology Act 1990.
  - The Human Fertilization and Embryology (Research Purposes) Regulations 2001 extended the permitted use of the embryo to include research to improve the understanding of treatment of serious diseases.
  - The Human Reproductive Cloning Act (2001) prohibits reproductive cloning.

- In the UK research embryos are not allowed to develop beyond 14 days (this includes research which may generate embryonic stem cells). The Human Fertilization and Embryology Authority (HFEA) is responsible for controlling the creation and use in research of embryos up to 14 days. All embryo research, whether publicly or privately funded, must be approved and licensed by the HFEA.

- In May 2004, five UK research councils announced a £16.5m investment in SC research and in the same month the UK stem cell bank opened, the first of its kind in the world. This is a central facility that characterizes and stores ethically sourced, quality controlled adult, fetal and embryonic stem cell lines, and makes them available for medical research and clinical applications.

- In August 2004, the HFEA granted a therapeutic cloning license to the University of Newcastle's Centre for Life allowing the centre to create human embryonic stem cells for one year using cell nuclear transfer.

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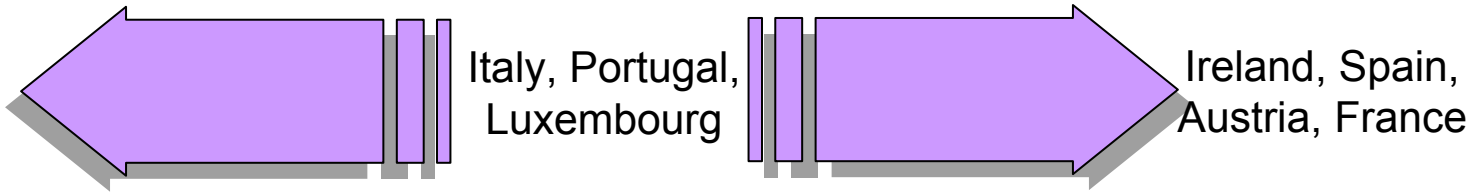
EU/Member States



Law permits creation of human embryos for generation of stem cells

No specific legislation regarding human embryo research

Ban on creation of human embryos for research and for the procurement of stem cells from human embryos

- The European Union itself currently does not regulate the field of stem cell research. However, the European Parliament has taken a more restrictive position, expressing opposition to the creation of embryos for research purposes and calling for the European Union to take control in this area.
- The Parliament has backed the public funding of research on ES cells derived from existing embryos or foetal tissue, though such research can only take place in EU countries which legalise it themselves.
- Individual European states have differing legal frameworks; e.g. Italy has no law and Germany has outright ban (see EU legislative spectrum above).

Source: http://www.europa.eu.int/comm/research/biosociety/pdf/catalogue_stem_cells.pdf

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Asia

Japan

- A Japanese law was enacted in 2001 to regulate the use of cloning technology. It prohibits the production of human embryos.
- However, new legislation permitting therapeutic cloning is expected after a key bioethics advisory body voted in June 2004 to recommend lifting a ban on the practice. These recommendations have since been endorsed by the Council for Science and Technology Policy.

Singapore

- There are currently no legal restrictions governing embryonic stem cell research in Singapore. In February 2002, the country's Bioethics Advisory Committee (BAC) made recommendations regarding embryonic stem cell research to the Life Sciences Ministerial Committee. The Singapore Government has accepted BAC's recommendations and legislation is now being drafted.
- BAC supports ES cell research subject to strict regulation on the methods used to generate ES cells. It does allow the cloning of human embryos for certain research purposes. Only embryos less than 14 days old are used.
- Singapore is currently forging ahead with plans to spend £300m on Biopolis, a cutting-edge science park focused on stem cell technology.

Korea

- In February 2004, a team of Korean scientists were the first to create a line of human embryonic stem cells in the laboratory using somatic cell nuclear transfer (therapeutic cloning).

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Australia

- Australia has two principal Acts (The Research Involving Human Embryos Act 2002 and the Prohibition of Human Cloning Act 2002) that establish a strong regulatory framework to prohibit human cloning, and to regulate the uses of excess human embryos created though assisted reproductive technology.
- In Australia it is possible to derive embryonic stem cells from human embryos that are left over from approved IVF programmes. This can only occur under a license and with the full consent of the embryo donors.
- The use of existing stem cell lines is permitted in Australia under the approval of institutional human research ethics committees.

Israel

- In 1999, the Knesset (Israeli Parliament) enacted the Prohibition of Genetic Intervention (Human Cloning and Genetic Modification of Reproductive Cells) Act. This Act, renewed in 2004 for a further five-year period, prohibits human reproductive cloning. However, there is no law in Israel to regulate human embryonic stem cell research and attitudes are generally permissive towards such research, with several hES cell lines being created.
- In October 2002, the Israel Stem Cell Therapy Consortium was initiated. The consortium, which is being primarily funded by the Israeli Ministry of Industry and Trade (current budget is $15-20m), will combine the efforts of companies (such as Gamida-Cell), academic groups and hospital research centres to develop generic technologies for industrialized stem cell therapy.

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International Stem Cell Forum

- The International Stem Cell Forum (ISCF) is made up of 14 funders of stem cell research from around the world, including the NIH and the UK MRC. It was founded in January 2003 to encourage international collaboration and funding support for stem cell research, with the overall aim of promoting global good practice and accelerating progress in this vitally important area of biomedical science.

- ISCF Members have agreed a set of key principles that determine their approach to stem cell research, which are:
  - Opposition to human reproductive cloning
  - Use of adult somatic human stem cells as well as embryonic human stem cells
  - The generation of embryonic human stem cell lines should be minimised
  - International harmonisation of ethical and intellectual property right issues.

- One ISCF initiative is a working group looking at regulations for intellectual property rights in the different countries active in stem cell research. The group is now drawing up a global IPR landscape document to help prevent researchers infringing existing patents on stem cell technology, and to help them protect their own IPR where appropriate. This document should be ready later in 2004.

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Key Scientific Questions Remaining to be Answered:

- What causes stem cells to maintain themselves in an undifferentiated state?
- What cues do cells use to tell them when to stop or start dividing?
- What genetic (intrinsic) and environmental (extrinsic) signals affect differentiation?
- What physiological properties guide the functional integration of newly generated tissues into existing organs?
- Are there functional differences between *in vitro* and *in vivo* derived cells?

Source: "Stem cells and the future of medicine". Available at; http://books.nap.edu/catalog/10195.html
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Technical Overview - state of play

- Isolation
  - Labour intensive, lab-based and not yet amenable to scale-up
- Growth – see slide 12
  - Characterisation is limited
  - Scale up is problematic
    - Mouse ES cells scale up tractable
    - Mouse adult stem cells have restricted expansion potential
    - Human ES cells grow poorly
    - Human adult stem cells have restricted expansion potential
  - Growth medias not fully defined for commercial use

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Technical Overview – Cont.

- Manipulation
  - Endogenous reporters (e.g. tagged IRES-GFP) are available
  - Targeting of genes by homologous recombination is currently routine in mouse ES cells. (Homologous recombination is theoretically possible in all stem cells; however, poor growth and thus insufficient biomass makes this challenging)
  - Differentiation
    - Small molecule screens
    - Biomaterials and manipulation of the extra-cellular environment (niche)
    - Biological screens (e.g. functional assays)
  - Nuclear reprogramming for therapeutic cloning (e.g. somatic cell nuclear transfer – illustrated on the next slide)

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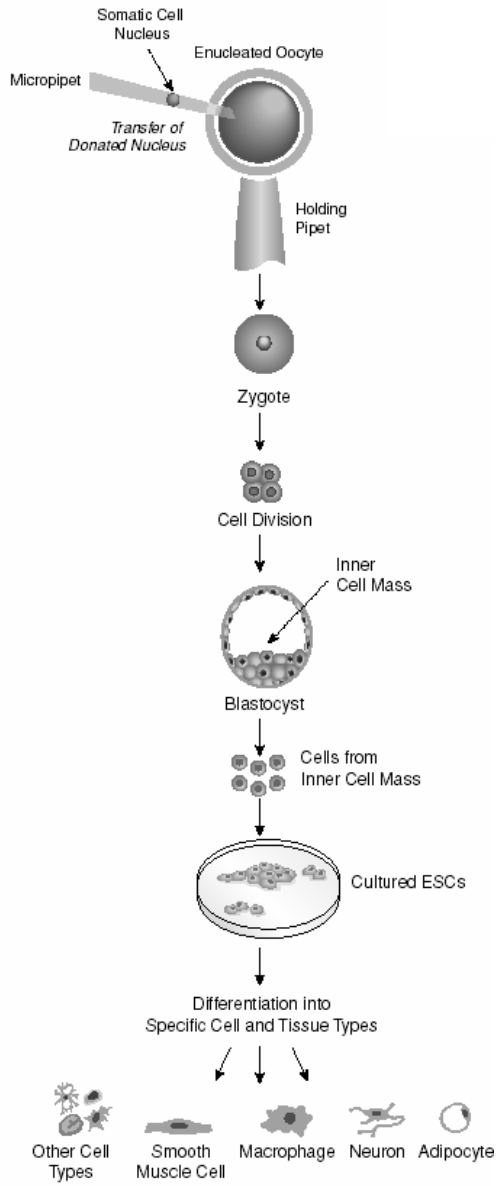
Somatic Cell Nuclear Transfer

- Somatic-cell nuclear transfer (SCNT) can be used to generate animal clones, i.e. genetically identical organisms.
- The SCNT process involves removing the nucleus of an egg cell (oocyte) and replacing it with the genetic material (i.e. nucleus) from a single adult cell.
- If this 'renucleated' oocyte is implanted into the womb of an animal then the offspring and donor providing the nucleus are usually described as 'clones'. However, it should be noted that they share only the same nuclear DNA; they do not share the same mitochondrial DNA, unlike genetically identical twins.
- This technique can be used to isolate embryonic stem cells. Essentially the stem cells can be extracted from the blastocyte that is formed from the renucleated oocyte in the same way as embryonic stem cells are isolated from blastocytes that are no longer required for *in vitro* fertilisation.
- In theory the stem cells isolated from the developing eggs can be used to produce cells or tissue that would match those of the original donor perfectly (and importantly would not be rejected by the donor).
- Validation of this technique came with the pioneering work by Ian Wilmut *et al* and the generation of the cloned sheep "Dolly". Clearly, human SCNT would have an huge impact and a Korean team has already claimed to have generated a line of human embryonic stem cells in the laboratory. However, problems encountered during Dolly's life mean that from both a scientific and ethical stance SCNT should only be used for therapeutic cloning (blastocyte not allowed to develop into an embryo) and not reproductive cloning.



Source: "Stem cells and the future of medicine". Available at; http://books.nap.edu/catalog/10195.html

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Clinical Challenges to Overcome

- Bio-Manufacturing
  - Generating sufficient amounts of qualified and safe material
- Carcinogenesis
- Immunogenicity
- Appropriate application of technology and having an understanding of aetiology of the targeted disease

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Clinical Challenges – current state of play

- Approved clinical applications using adult stem cells
  - Bone marrow stem cells (BMSC) expansion
  - Carticel® (autologous cultured chondrocytes), marketed in the United States and Europe by Genzyme Biosurgery is the only approved stem cell therapeutic product. It employs a commercial process to culture a patient's own (autologous) cartilage cells, known as chondrocytes, for use in the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral, or trochlear) caused by acute or repetitive trauma in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure

- Clinical research applications using adult stem cells
  - RA (Northwestern University, Chicago)
    http://www.nlm.nih.gov/medlineplus/news/fullstory_19724.html
  - Repairing heart muscle
    http://news.bbc.co.uk/2/hi/health/3658927.stm
  - Foetal neuron cell transplants for Parkinson's
    http://www.ninds.nih.gov/health_and_medical/pubs/parkinson_workshop_proceeding.htm

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Carcinogenesis

Human ES cells injected into mice can produce a benign tumour made up of diverse tissues. This response is believed to be related to the multipotency of the undifferentiated cells in the *in vivo* environment.

It remains too early to tell if it will be appropriate to use human ES cells directly in regenerative medicine. A great deal must be elucidated about how the body controls the differentiation of stem cells. Further, the behaviour of ES cells implanted in a specific organ has not been well studied.

Source: “Stem cells and the future of medicine”. Available at; http://books.nap.edu/catalog/10195.html

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Immune Rejection

Regenerative medicine is likely to involve the implantation of new tissues in patients with damaged or diseased organs. A substantial obstacle to the success of transplantation of any cells, including stem cells and their derivatives, is the immune-mediated rejection of foreign tissue by the recipient's body. In current stem cell transplantation procedures with bone marrow and blood, success can hinge on obtaining a close match between donor and recipient tissues and on the use of immuno-suppressive drugs, which often have severe and life-threatening side effects.

To ensure that stem cell-based therapies can be broadly applicable for many conditions and individuals, new means to overcome the problem of tissue rejection must be found. Although ethically controversial, nuclear re-programming, a technique that produces a lineage of stem cells that are genetically identical to the donor, promises such an advantage. Other options for this purpose include genetic manipulation of the stem cells and the development of a very large bank of embryonic stem cell lines. In conjunction with research on stem cell biology and the development of stem cell therapies, research on approaches that prevent immune rejection of stem cells and stem cell-derived tissues should be actively pursued.

Source: "Stem cells and the future of medicine". Available at; http://books.nap.edu/catalog/10195.html

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Appropriate application of technology and understanding the complexity of disease

- Having a good understanding of disease aetiology
- E.g. correcting somatic mutations:
  - Source of DNA - 'Diseased'
    - Adult stems cells (immune system tolerance)
    - Nuclear transfer to egg – autologous ES stem cell (immune system tolerance)
  - Source of DNA - 'Corrected'
    - Nuclear transfer to egg – allogeneic ES stem cell (immune rejection a possibility)
- Potential immune issues e.g. the immune destruction of pancreatic islets in diabetes may also destroy introduced stem cells or impact their therapeutic potential
- Depending on the indication, treatments need not be curative *per se* as improvements to quality of life may be sufficient for regulatory approval

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The current patent environment in Canada and the United States is fairly favourable to granting patent rights in most areas of stem cell research while Europe has much more restrictive provisions. For example, in Europe it is not possible to patent animal and plant varieties and inventions whose commercial exploitation would be contrary to "*ordre public*" (morality). In addition, the human body and its gene sequences are excluded from patent protection as are patents on processes for modifying the germ line genetic identity of human beings, while processes for cloning human beings and uses of human embryos for industrial or commercial purposes are prohibited on the ground that such processes are contrary to "*ordre public*". The lack of patentability of certain inventions may deter research and development in a particular jurisdiction.

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As the field matures, pooling of IP and/or cross licensing may be required for commercialization. The companies who have a dominant intellectual property position in stem cells are:

- Geron
- Advanced Cell Technologies
- PharmaStem Therapeutics, Inc
- ES Cell International
- ReNeuron
- Osiris Therapeutics
- Aegera Therapeutics
- Bioheart
- Stem Cell Sciences
- Stemcell Inc
- WARF – Wisconsin Alumni

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Market Dynamics & Emerging Markets

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Market Risk and Reward

Research tools e.g. Tagged primary cells, *in vitro* molecules (media additives), as discovery tools

Molecules that can direct the differentiation of stem cells *in vivo* e.g. Donor-matched cell therapies

Cell therapies

Value **Success**

$ **Higher probability**

$$

$$$$ **Lower probability**

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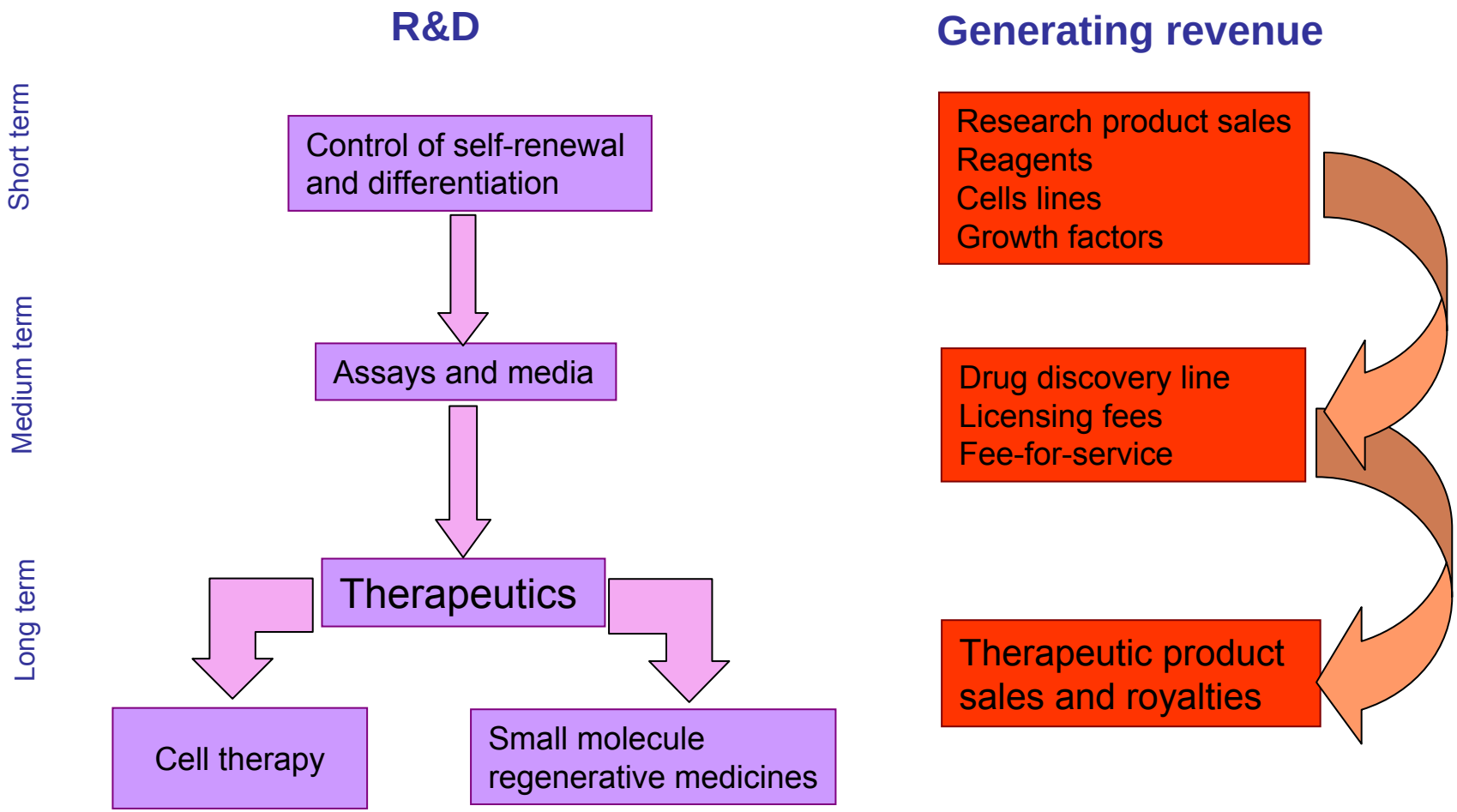
Generic Business Models



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- Reagents Manufacturers and CMOs
  - *E.g. Stem Cell Technologies Inc., Molecular Medicine Inc. and Invitrogen*
- Discovery/Screening
  - *E.g. development and contract screening using validated assays*
- Device Driven
  - *Develops devices to isolate, separate, and possibly expand stem cells e.g. titanium mesh support for new bone production. Examples include Aastrom, Baxter, Eligix and CellExSys*
- Adult Autologous Therapy – differentiated cells
  - *Uses a proprietary process to generally isolate, characterize, and expand adult stem cells. Examples include Bioheart, Verigen and co.don*

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- Adult Allogeneic Therapy – stem cells

  Uses a proprietary process to isolate, characterize, and expand adult stem cells that differentiate following implantation or injection in vivo. Examples include Osiris Therapeutics.

- Productised Therapy – differentiated cells

  Uses a proprietary process to isolate, characterize, and expand foetal or adult stem cells. Committed cells are derived from the specific tissue and are immortalized to create cell lines or "drugs". Examples include Stemcells, CellFactors, Neuronyx and Neuralstem.

- Productised Therapy – stem cells

  Uses a proprietary process to isolate, characterize and expand embryonic or neonatal stem cells. The cell population is then stimulated to differentiate and cell lines are created. Examples include Kourion, ES Cell International and Bresagen.

- Cell Banking

  Banks placental and cord blood stem cells to produce a reservoir of stem cells for autologous and possibly allogenic use in the future. There may be a need to examine/bank multiple cells lines form different ethnic backgrounds. Examples include Anthrogenesis, Netcord and ViaCord.

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Stem Cells in Drug Discovery

- Primary screening
- Toxicology
- Target validation screens
- Efficacy screens

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Stem Cells v Primary Cells

- Primary cells are often difficult to grow and manipulate
  - Stem cells can be used to derive specialized cell types for drug/toxicology screening, e.g. currently, human hepatocytes are currently sourced from cadavers, or from diseased livers
  - Stems cells can be used to create terminally differentiated cells with endogenous target genes tagged with fluorescent markers to permit real-time screening. For example, neurons are notoriously difficult to grow and to manipulate in culture and transfection procedures often kill them.

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Near term realization

- The following slides highlight potential clinical applications of stem cell technologies. However, we believe that the utilization of human ES cells in cell-based screens will:
  - facilitate our understanding of the requirements for clinical application
  - provide the necessary tools for:
    - expansion of genetically stable ES cells
    - Control of efficient differentiation into given lineages

The timeframe for ES stem cell therapeutics is likely to be 10 years

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Oncology

- The ability of stem cell and other cell therapies to impact the medical management of cancer depends primarily on their functional capacity to repopulate organs or tissues damaged by cancer treatments (for example the haematopoietic system) or through the stimulation of the immune system to eradicate disease.

- Cell therapies involving dendritic cells that function as antigen-presenting cells can be manipulated *ex-vivo* to up-regulate the immune response to disease. Disease-specific T cells can also be collected and expanded *ex-vivo* to increase the immune systems response.

- The current use of BMSC therapy proves 'proof of concept' for stem cell therapy in the cancer setting.

Source; Decision Resources & D&MD Publications

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Cardiovascular Disease

- Cardiovascular disease remains the leading cause of mortality in the United States and accounts for more than 40% of deaths each year. Myocardial infarction (MI) and congestive heart failure (CHF) both contribute substantially to this mortality. MI triggers the formation of scar tissue which is one of the causes of CHF.

- Recent improvements in treating MI have increased the number of patients living with CHF. Patients in NYHA class III and class IV CHF could benefit substantially from cell therapies. Total Medicare payments associated with CHF currently exceed $3.6 billion in the US. Associated drug costs account for $1.4 billion of this, with patients in classes III and IV CHF (i.e. those most likely to receive cell therapies) accounting for approximately 66% of these costs. Stem cells offer the possibility of providing cardiomyocytes for the repair of cardiac scar tissue.

- Companies with cardiovascular programmes include; Bioheart, Genzyme Biosurgery, Osiris Therapeutics, and Kourion. These focus on characterising methods for heart muscle regeneration using autologous skeletal muscle cells, autologous bone marrow cells derived from stromal cells and ES cells.

- However, questions remain about the ability of exogenously derived cardiomyocytes to integrate appropriately (electrically) into the heart. These treatments may lead to improvements in left ventricular ejection fraction and patient quality of life scores but may increase risk of atrial fibrillation and potentially stroke.

Source; Decision Resources & D&MD Publications

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Central Nervous System Disorders - 1

- Currently, patients suffering from Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), and stroke have limited, and frequently ineffective, treatment options. Furthermore, the continued "greying of the population" in the developed world will increase the healthcare burden associated with providing long-term care for patients afflicted with CNS disorders.

- The CNS market potential of cell therapies is broad and substantial. The most common cause of dementia in the elderly is the neurodegenerative condition AD. Approximately 4 million people are affected by AD in the United States; AD is responsible for 100,000 deaths per year.

- PD affects between 115,000 and 155,000 patients in the United States, and up to 5 million people worldwide; associated medical expenses in the US alone exceed $5 billion, with current drug costs totalling $1.6 billion. The commercial potential of new methods for treating PD is estimated to be in excess of $10 billion.

Source; Decision Resources & D&MD Publications

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Central Nervous System Disorders - 2

- HD afflicts approximately 25,000 people in the United States. Each year an additional 1,500 patients are diagnosed with the disease. Currently about 20,000 patients are in the late stages of the disease.
- Stroke is the third-leading cause of death in the United States and the leading cause of long-term disability. Each year, 60,000 people experience new or recurrent stroke.
- Spinal cord injury affects 500,000 in the United States. There are 10,000 new cases each year.
- Companies with CNS programmes include; BresaGen, CellFactors, CyThera, IsoTis, Kourion, Layton Biosciences, Macropore, Neuralstem, Neuronyx, Osiris Therapeutics, Proneuron, and Stem Cells.
- The use of regenerative stem cell therapies for CNS disease and/or trauma has substantial potential. However, until the aetiologies of the disease, e.g. Alzheimer's, or a comprehensive understanding of nerve re-wiring is understood, it may prevent meaningful development of therapeutics.

Source; Decision Resources & D&MD Publications

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Musculoskeletal Disorders and Rheumatoid Arthritis (RA)

- Articular cartilage covers the ends of bones at the joint interface and allows bones to move easily. Over time, injury and use can damage the cartilage, causing the bones to rub against each other, resulting in pain and immobility. To treat cartilage injury and chronic osteoarthritis, physicians perform approximately 1 million arthroscopic procedures and 350,000 knee and hip replacement surgeries in the United States each year. These costly surgeries (approximately $25,000 each) often result in substantial morbidity. Joint replacement is considered a poor choice for people younger than 50 because of the relatively short life of the replacements (10-15 years). Alternative treatments for joint disorders, particularly cartilage repair and replacement, represent a growing market for cell therapies with little, if any, competition from other types of products.

- Several companies market cartilage cell therapy, and more products are being developed. In 1997, Genzyme Biosurgery introduced the first cell therapy product in the United States—Carticel autologous chondrocytes. Verigen, co.don, and Fidia market cell based therapies for cartilage repair in Europe. Companies with cartilage and/or bone cell therapy programs include; Aastrom, Bio Tissue Technologies, Cell Factors, co.don, Fidia, Genzyme Biosurgery, IsoTis, Isto Technologies, Kourion, Osiris Therapeutics, Tigenix, and Verigen.

- In August 2004, an inter-sibling adult stem cell transplant reportedly resulted in cure of RA. However, commercialisation of allogeneic transplants in adults remains a problem due to bio-manufacturing.

Source; Decision Resources & D&MD Publications

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Metabolic Disorders - 1

- In the United States, the Centres for Disease Control estimates that 16 million people have diabetes, of whom 50% are undiagnosed. Worldwide, more than 135 million people are affected by this disease. By the year 2025, the World Health Organisation estimates that the diabetic population will have grown to 300 million.

- Non-insulin-dependent (type 2) diabetes is the most common, affecting approximately 90% of the diabetic population. In the United States, more than $45 billion in direct costs is spent on treating diabetes each year. Indirect costs, which include medical costs, disability and work loss bring the total to an estimated $92 billion per year.

- Diabetes is also associated with numerous complications, such as cardiovascular disease, stroke, kidney diseases, blindness and diseases of the CNS. Stem cell technologies offer the potential to provide non-immunogenic insulin-producing pancreatic islet cell implants that will restore some pancreatic function, alleviating the need for insulin injections. The utility of these approaches in type II diabetics, where numerous ethical pharmaceutical treatments are available, is unclear.

- The success of islet transplants, using material isolated from cadavers, in alleviating clinical symptoms of severe disease (type 1) indicates that a plentiful supply of islets, generated from stem cells, could address the severe unmet medical need in this indication. However, to date it has not been possible to derive the appropriate developmental lineage from human ES cells and much work still needs to be done to understand the relevant differentiation pathways.

Source; Decision Resources & D&MD Publications

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Metabolic Disorders - 2

- In the United States, chronic liver disease is the tenth most common cause of death. Viral hepatitis is the most common cause of chronic liver disease. An estimated 1.3 million people suffer from chronic hepatitis B virus (HBV), another 2.7 million are diagnosed with hepatitis C virus (HCV) and 70,000 people have hepatitis D virus (HDV) infections. Each year, liver insufficiency results in 300,000 hospitalizations and liver failure cause 30,000 deaths.
- Currently, the only treatment options for patients with acute insufficiency of the liver is an organ transplant. For the 17,500 people in the U.S. awaiting liver transplants annually, only about 5,000 donor livers become available. The cost of a liver transplant is approximately $150,000. The complication and difficulties that result from liver transplantation include lifelong immunosuppression, potential for rejection, long hospitalization, and lack of organ availability. Cell therapy should present patients with a more attractive treatment option: the implantation of nonimmunogenic liver cells, which would reduce the cost to the patients and increase the number of patients who can be successfully treated.
- Companies with hepatocyte programmes include; CyThera, ES Cell International, Geron, StemCells, and VitaGen.
- Transplanted livers are still susceptible to infection from the recipient's residual latent/persistent viral infection. However, it may be possible to modify hepatocytes and render them resistant to infection.

Source; Decision Resources & D&MD Publications

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Primary Immunodeficiencies

- Stem cells could be used in the treatment of virtually all primary immunodeficiency diseases. Presently, more than 70 different forms of congenital and inherited deficiencies of the immune system have been recognised. These include diseases such as severe combined immunodeficiency disease, Wiskott-Aldrich Syndrome, and the autoimmune disease lupus. The immune deficiencies suffered as a result of acquired immune deficiency syndrome (AIDS) following infection with the human immunodeficiency virus are also relevant here.

- At press time, 25 people in the United States had undergone stem cell transplants for lupus. The majority of stem cell transplant patients are doing well; however, two of the lupus patients died due to complications of the procedure. The risk of complications - including serious infection, bleeding, blood clots and the failure of the new immune system to take hold - is a major downside of stem cell transplants.

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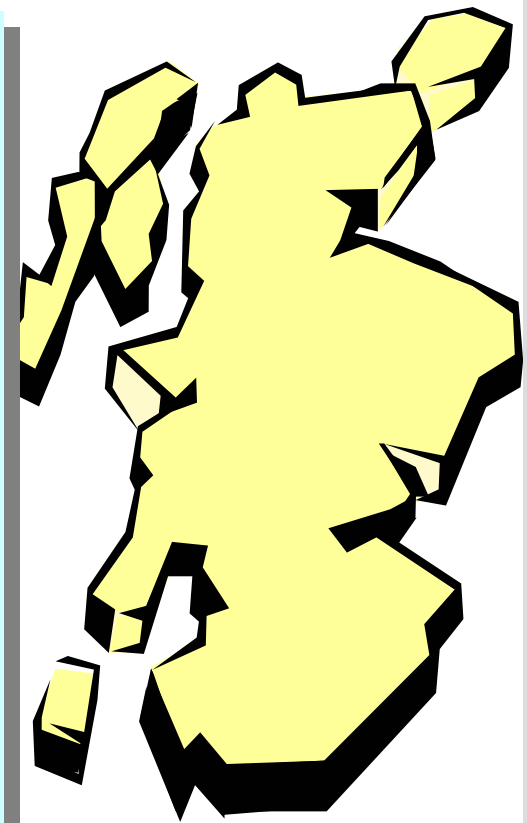
The Scottish stem cell base is strong

Commercial

- Geron closely involved with Roslin & Scottish Research groups
  - Obtained rights to nuclear transfer technology through acquisition of Roslin Bio-Med
  - Research collaboration with Roslin focusing on understanding molecular mechanisms of reprogramming
  - Collaboration with CXR to produce human ES cell derived hepatocytes
- Stem Cell Sciences – Japanese / Australian/UK
  - Global head office in Edinburgh
  - Preferred commercial partner for ISCR



Academia

- The largest academic cluster in the Europe
  - –ISCR and Roslin
- Institute for Stem Cell Research (ISCR)
  - –Worldwide CoE in stem cell research & technology
  - –Houses 9 research groups exploiting genetic manipulation technologies to investigate;-
    - Pluripotent mouse & human embryonic stem cell
    - Tissue stem cells in the embryo
    - Transcriptional & epigenetic determinants of cell fate
  - –£1mm grant from MRC
  - –$1.25 mm grant from NIH
  - – Lead coordinator in a ~£8 mm framework 6 project
  - – Focus on ES cell biology
- First to demonstrate nuclear reprogramming – Dolly the Sheep
- Scottish Stem Cell Network

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What are the opportunities in stem cells in the next 10 years

" in regeneration of organs….particularly organs comprising of terminally differentiated cells e.g. brain, heart etc. *Biotech*

"…in pharmaceutical drug development particularly in use of hepatocytes for safety…." *Pharma*

"….in pharmaceutical drug development particularly as tools for target validation…." *Pharma*

"….for use directly as therapeutics, the potential for stem cells is still far from reality…" *Pharma*

".. researching the use of factors driving endogenous stem cells to grow and differentiate……" *Pharma*

"..have a big role in drug discovery specifically for screening drugs and validating drug targets – key activities for drug discovery…" *Pharma*

What are the major gaps in the market

"Good consistent reproducible isolation methods……if a company could come up with a reproducible isolation and characterisation kit" *Biotech*

*"…*A lot work still needs to be done in stem cell around the underlying mechanisms and controls……." *Biotech*

*"…*A major need in the market is the requirement to understand how to manipulate stem cells indirectly through the use of growth factors and other external agents…this is to encourage endogenous stem cells to develop rather than having to extract etc… " *Biotech*

" ..A tracking mechanism such that stem cells can be permanently labelled before injecting into animals – can track what it does, where it goes, what happens when you add certain modulators ……." *Biotech*

*"…..*Standardisation of protocols and isolation methods for stem cell extraction and expansion……" *Pharma*

What are the greatest barriers to be overcome

"..lack of definite knowledge around stem cells. – without this knowledge cannot control or manipulate the sc." *biotech*

"… Availability of embryonic stem cells…our company works on foetal stem cells but availability of the quantities required is an issue." *Pharma*

" …. Standard protocols for generating hepatocytes in sufficient quantities to be of real use to companies …" *Pharma*

" ….Lack of protocols means that supplies are unlikely to be homogenous….." *Pharma*

*"….*Evidence for stem cells as therapeutics is very anecdotal and not at all clear ……" *Pharma*

*"….*As a therapeutic, despite all the 'hype' surrounding potential in treating diseases, much work has yet to be done and unlikely to see SC as therapeutics for many years……..even for practical purposes one cannot yet access sources which are reproducible, of consistent quality and of sufficient quantity to support work in the area of transplantation……."

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An Overview of the Company Landscape

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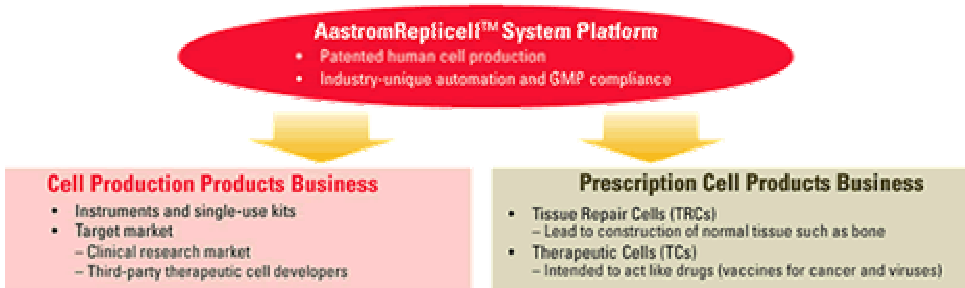
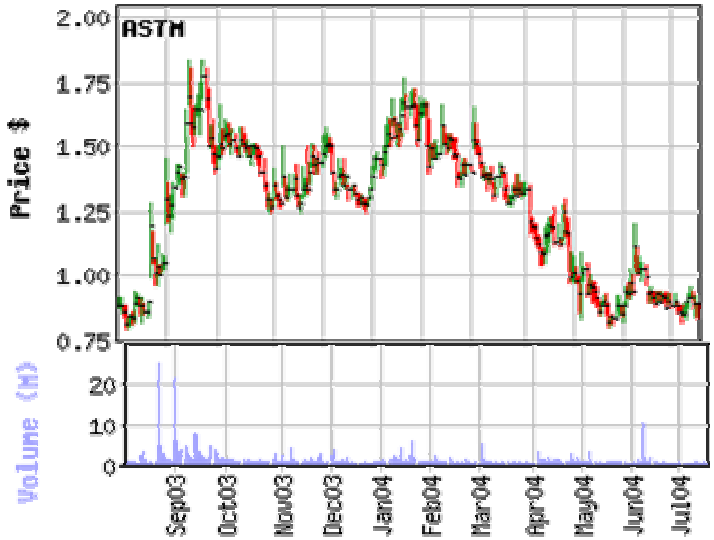
Aastrom BIOSCIENCES INC

The Cell Therapy Company

NasdaqSC: ASTM

Aastrom Biosciences' AastromReplicell equipment is used to grow bone marrow cells and umbilical cord cells to replace cells damaged by cancer treatments and other diseases, including osteoporosis. The system is designed to be less costly, faster, and less invasive than traditional cell-replacement methods such as blood transfusion and bone marrow harvesting. AastromReplicell is sold in Europe and has been approved in the US for research and investigational use; the EU has also approved its human dendritic cell production kit.





In April 2004, Aastrom announced that it received a Phase I Small Business Innovation Research (SBIR) grant from the National Institutes of Health (NIH) National Cancer Institute. The $124,000, 8-month study is designed to demonstrate the feasibility and advantages of using Aastrom's proprietary technology to expand T-lymphocytes, or T-cells, from patients' tumours or peripheral blood for a treatment against malignant melanoma.

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AEgera Therapeutics is a private oncology company aiming to extend and enhance the lives of cancer patients. Aegera, through its expertise in controlling apoptosis, is developing new therapeutics to significantly enhance existing cancer treatment paradigms. Aegera aims to have two new oncology drugs in the clinic by the end of 2004, developing exciting proof-of-principle for multiple line extension opportunities, and has a rich development pipeline and significant business development potential. (Source; AEgera).

AEgera also has an exclusive license for the use of stem cells derived from skin, as an autologous source of tissue for treatment of nervous system disorders. Skin-derived Pre-cursor Cells (SKPs) can be expanded in culture, differentiated into neural cells and transplanted into the damaged nervous system to enhance functional recovery in spinal cord injury and Parkinson's disease. SKPs can also serve as model systems for the introduction of disease causing human genes and screening of drugs for neuroregeneration. Patents are pending on the isolation and expansion of SKPs, exemplified with appropriate differentiation protocols and genetic markers of differentiation.
Ultimately, AEgera aim to produce cellular therapeutic products for the regeneration and functional restoration of damaged and diseased tissue. AEgera are also testing if SKPs can give rise to cells originating from the mesoderm (bone, cartilage, etc) and the endoderm (pancreas, thyroid gland, etc). Cells (differentiated or non-differentiated) are being tested in animal models for their ability to survive, and to functionally restore a diseased organs. Exclusive rights to this adult stem cell technology are available for licensing, with multiple discussions currently under way.

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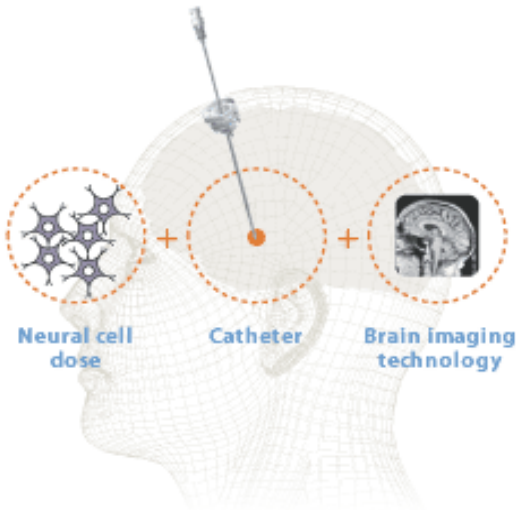
BresaGen has offices and laboratories in Adelaide, Australia and Athens, Georgia USA and is represented by two divisions, Protein Pharmaceuticals and Cell Therapy. Bresagen's cell therapy research and development programme takes the company's proprietary position in embryonic stem cell differentiation and applies it to the treatment of neurodegenerative disease and gene based disorders. The division also has an extensive program developing catheter and imaging technology for neurosurgical cell delivery. Following the appointment of administrators and restructuring in spring 2004, Vasogen announced the completion of a merger with Cythera in July 2004 (Source; Bresagen)

BresaGen's Cell Therapy division has three major programmes:

•cell differentiation based in Adelaide, Australia
•human stem cell based in Athens, GA, USA
•catheters and imaging based in North America.

BresaGen holds several proprietary positions in the area of ES cell isolation and controlled differentiation. BresaGen also holds proprietary positions in delivery devices and surgical techniques for administering cells This is built around a specially developed catheter designed to maximize the viability of therapeutic cells during implantation, together with imaging technology that tracks the placement of a catheter in the brain.

BresaGen envisages an integrated product made up of a defined dose of nerve cells, the catheter delivery device and imaging software for accurate administration of cells in a transplant area.



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CELLERANT THERAPEUTICS

Cellerant Therapeutics Inc. is a clinical-stage biotechnology company using haematopoietic factors to develop therapies for autoimmune diseases, cancer and haematologic disorders.

Cellerant has licensed stem cell isolation and purification technology from Novartis and discoveries related to progenitor cells and stem cell expansion from Stanford University.

Cellerant's technology portfolio is focused on the regulation of, and components of the haematopoietic system. Cellerant’s intellectual property include cells and cell factors throughout the hematopoietic lineage, and near-term technologies include highly purified hematopoietic stem cells (HP-HSCs) and common myeloid progenitor cells (CMPs).

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CellFactors plc

CellFactors is a tissue engineering company, generating human cell lines and products from them. CellFactors lead programme is Skeletex™, a material that can regenerate bone. CellFactors aim is to generate a variety of cell-derived materials for different therapies. CellFactors was founded in 1997, building upon seven master patents based around harnessing human cell lines and their derivatives for therapies. £1.6m of external investment was raised in 2000 to establish a commercial operation, and a further £2.4m was raised the following in 2001. 2003 saw £2.6m invested.

Skeletex™ is a biological material derived from human cells that induces bone to grow; it has the potential to increase the strength of weak or damaged bones, or to create new bone where required.
To date, CellFactors has proved (in pre-clinical tests) that Skeletex™ has bone-inducing properties, and that in principle, the material can be made to a commercial scale, and in a regulatory-appropriate manner.

CellFactors is developing Skeletex™ for use in conjunction with existing orthopaedic devices and prosthetics as well as for dental applications.

Additionally, CellFactors owns a collection of neural cell lines that can be used as research tools, called NeuCell. These are conditionally immortalised human neural cell lines derived from key areas of the brain and spinal cord. The cell lines each provide an easy to use, physiologically relevant research tool for diverse neuroscientific research and development processes in pharmaceuticals.

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Curis focus on developing products that regenerate and restore tissues; this approach is based upon naturally occurring proteins that initiate and regulate tissue and organ formation. Curis is developing therapeutics - based on proteins which regulate nerve development - as a possible treatment for Parkinson's and stroke.

Other disease targets include cancer (Curis is partnering with Genentech for its oncology R&D), hair loss, and kidney disease (Ortho Biotech is the company's partner for this target). Curis' interest in stem cell based research included the directed differentiation of adult stem cells into insulin producing cells (work emanating from Doug Melton's Laboratory). In December 2002, Patent rights related to the hES programme for developing cell therapies for the treatment of diabetes transferred to ES Cell International , in return for an equity stake in that company. This transfer, in combination with reductions in the stem cell based drug discovery programme, reflect Curis's attempts to rationalize their drug development process and the waning of its interest in ES cells. Nevertheless, Curis continue to develop small molecule and biologic modulators that direct differentiation of stem cells into specific cell fates. In June 2004, Curis announced the use of a small molecule Hedgehog signalling pathway agonist to promote the generation of new motor neurones. Under this protocol, ES cells are exposed to a Hedgehog agonist and retinoic acid directing differentiation into motor neurons. These ES derived motor neurones are believed to have potential therapeutic utility as replacement cells to reconstitute damaged neural systems. In addition, sonic hedgehog is known to drive differentiation of dopaminergic neurons from ES cells[1].

1; http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12767935

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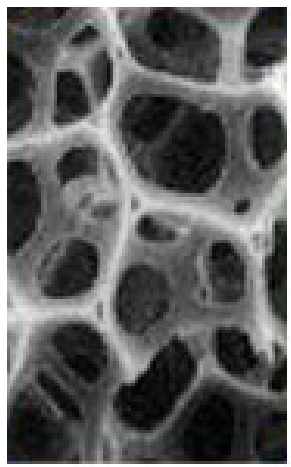
Cytomatrix is a development stage company focused on commercializing cell therapies. Cytomatrix' core technology is a cell growth matrix, termed "The Cytomatrix", that enables cells to grow in three dimensions. Cytomatrix' initial focus is on diseases in which hematopoietic cells, such as stem cells and lymphocytes, play a role.
The Cytomatrix is a three-dimensional cell growth scaffold which is highly porous, highly biocompatible and allows cells to grow in 'tissue-like' environment.

Cytomatrix' cell therapy product line includes:

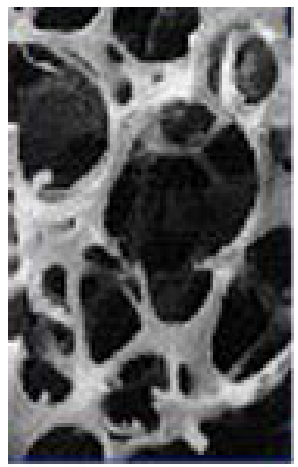
- TranStem, a system for expanding the number of autologous blood stem cells for bone marrow transplantation

- TransCord, a system for expanding the number of blood stem cells obtained from donated umbilical cord blood samples prior to transplantation into the recipient patient

- RegenImmune, a system for producing fresh T cells from blood stem cells to fight a broad array of diseases, including infections and cancer.



Cytomatrix



Bone Marrow

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DeveloGen is a drug discovery company with R&D interests in type 1 diabetes as well as for type 2 diabetes, obesity and metabolic syndrome.

DiaPep277 -- currently in phase 2 clinical trials- acts to protect the insulin producing beta cells from auto immune destruction in type I diabetes.

Developen's Pax4 program aims to promote regeneration of beta cells. DeveloGen aims to treat type 1 diabetics, by protecting and regrowing the beta cells.

- Pax4 is a critical regulator of pancreatic development
- Pax4 function is sufficient for beta cell development
- Pax4 knockout mice fail to develop beta cells and are unable to produce insulin. Mice which specifically over-express Pax4 in the pancreatic epithelium generate additional islets
- Pax4 efficiently differentiates mouse embryonic stem cells into glucose responsive and insulin-secreting cells. After transplantation, these insulin-secreting cells are able to normalize blood glucose levels of diabetic mice and protect the animals from hyperglycemic episodes

DeveloGen is pursuing a drug discovery programme, to identify small molecules which function as Pax4 activators *in vivo*.

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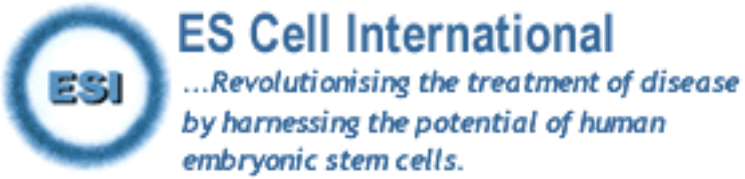

ES Cell International (ESI) is a regenerative medicine company and provider of products and technologies derived from human embryonic stem (hES) cells. ESI owns six of the nineteen hES cell lines currently listed on the US National Institutes of Health Stem Cell Registry, and offers hES cells, associated reagents, and training to researchers, worldwide. ESI is developing therapies based on regenerating human tissue using cells and/or proteins derived from hES cells. ESI's therapeutic focus is Diabetes, with additional basic research in neurology, cardiology and haematology. ESI is working to identify the stimuli controlling self-renewal and/or directed differentiation of hES cells, using genomic, proteomic and high throughput testing approaches.

ESI was incorporated in Singapore in July 2000, with SGD$17m in seed capital provided by Life Science Investments Ltd, a subsidiary of the Singapore EDB, and ES Cell Australia Ltd (ESCA), an Australian investment consortium.

Other shareholders in ESI include an Australian founding scientist, Curis and the three founding research organisations; Monash University (Australia), Hadassah University (Israel), and the National University of Singapore (Singapore).

ESI has arrangements with Quark Biotech Inc, based in Chicago and Tel Aviv, to undertake gene and protein discovery related to factors controlling hES cell renewal and differentiation.

ESI has also entered into a number of material transfer agreements (MTAs) with academic and commercial groups in North America, Europe and Australasia, for the provision of hES cells in return for access to any resultant IP emerging from their use.

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genzyme Biosurgery

Genzyme Biosurgery, a division of Genzyme Inc., develops and markets biologically based products for osteoarthritis relief, adhesion prevention, hernia repair, cartilage repair, cardiothoracic surgery, and severe burn treatment.

Epicel (cultured epidermal autografts) was approved by the FDA for the treatment of severe burns in 1987. Epicel consists of sheets of autologous keratinocytes co-cultured with irradiated murine cells to form cultured epidermal autografts.

Carticel® (autologous cultured chondrocytes), uses a commercial process to culture a patient's own cartilage cells for use in the repair of symptomatic cartilage defects of the femoral condyle (medial, lateral, or trochlear) caused by acute or repetitive trauma in patients who have had an inadequate response to a prior arthroscopic or other surgical repair procedure.

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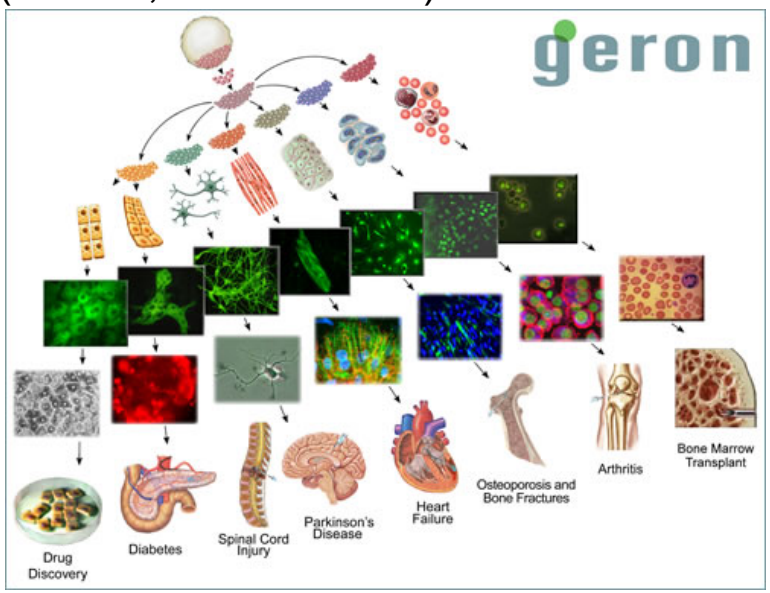
geron

Geron is focusing its development efforts on lead anticancer drug candidate GRN163, which inhibits telomerase preventing apoptosis. Geron is also continuing its work with hESCs to develop neural cells that could be implanted to treat Parkinson's disease and other neurodegenerative disorders; heart muscle cells that could treat various cardiovascular conditions; and pancreatic islet cells that may restore insulin production in patients suffering from type I diabetes. (Source; Hoovers.com)



Geron are developing therapeutics based on differentiated cells derived from hESCs, including neural cells for spinal cord injury and Parkinson's disease, cardiomyocytes for heart disease, pancreatic islet ß cells for diabetes, osteoblasts for osteoporosis, chondrocytes for osteoarthritis, and hematopoietic cells for blood diseases and to prevent immune rejection of the other cell types. Geron are testing six different therapeutic cell types in animal models. In three of these cell types, functional recovery was observed in treated animals. As of May 2004, it appears likely that the first clinical trial will focus on treatment for acute spinal cord injury. (Source; Geron)

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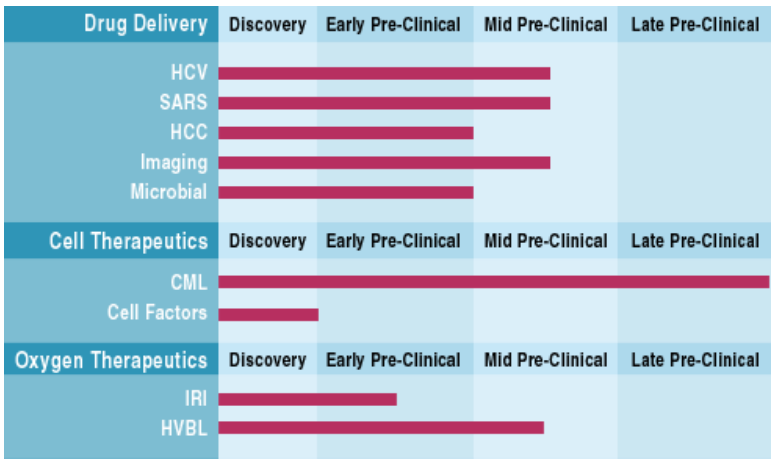
HEMOSOL

Hemosol Inc. is developing Hemolink, a haemoglobin replacement used to treat acute anaemia caused by chemotherapy or surgery. Hemolink, which is made by purifying, then modifying human red blood cells, obviates the need for donor red blood cell transfusions. Trials are ongoing for cardiac procedures. Hemosol is also developing other drugs, including a blood-based treatment for hepatitis C and liver cancer, as well as an anti-oxidant to prevent tissue damage due to reperfusion.



Hemosol is also developing technology to expand human gamma delta T cells, a rare type of T cell with broad potential in the treatment of cancer and infectious diseases. Hemosol has succeeded in expanding highly purified populations of T cells from small samples of peripheral blood, permitting the reinfusion of large numbers of the therapeutic cells back into patients (HRC 302). Hemosol has regulatory approval to conduct a Phase I clinical trial to use autologous, *ex vivo* expanded T cells in patients with chronic myelogenous leukemia. If effective, the T cell therapy should have application in many other forms of cancer, as well as in the treatment of certain types of infection. Other types of T cells including CD4+ and CD8+ cells, as well as natural killer cells, may be grown using Hemosol technology.

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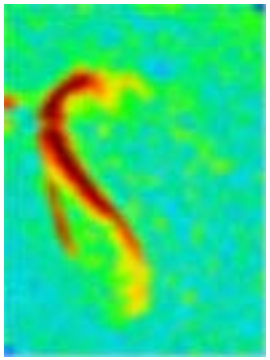

Kaleidos Pharma Inc. is developing a family of naturally occurring cytokines, including its lead product, TGF alpha, for GI mucositis and for therapy of Parkinson's disease.

TGF alpha stimulates resident adult stem cells to proliferate and respond to injury signals released by diseased or damaged tissue. These stem cells, present in most organs of the body, migrate to the area of disease or trauma, and regenerate functional tissue. Additionally, TGF alpha is a modulator of bone marrow (CD34+) stem cells. Bone marrow stem cells reportedly have broad potential to differentiate into other tissues of the body including neural, liver, and cardiac. Kaleidos assert that, because TGF alpha modulates these pluripotent stem cells, they have a broad platform of drug discovery to treat several disease conditions.

Treatment with TGF alpha, which has been shown to cause the generation of new dopamine-producing neurons in a relevant animal model, significantly reverses Parkinson’s symptoms. Currently, TGF alpha is being tested in a primate model of Parkinson’s disease. Kaleidos expects to file an IND to begin human clinical trials in 2004. The NIH has indicated that it will likely fund and conduct these first human trials.

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MacroPore Biosurgery is specifically targeting spine and orthopedic bone repair and cardiovascular disease. MacroPore aim to deliver autologous, point-of-care cell therapy systems for the regeneration and repair of damaged tissues and are developing a proprietary system to isolate and concentrate autologous, homologous-use, regenerative cells found in adipose tissue. These cells can reportedly be harvested (in high quantity) safely and with minimal discomfort to the patient so that a therapeutic dose of cells can be provided back to that patient in real-time, without exposing those cells to a cell culture process.

Macropore's most advanced research and development programme is in the repair of cardiovascular tissues that are damaged after a heart attack, and the problems of disease transmission and rejection associated with donor tissue. Areas of potential clinical application for Macropore's regenerative cell therapies include disorders of the nerve, muscle, bone, cartilage, and heart.

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NeuroNova

NeuroNova is engaged in the discovery and development of drugs and therapeutic cells for the treatment of central nervous system disorders such as Parkinson's disease, Alzheimer's disease and stroke.

NeuroNova's research is focused on Therapeutic Neurogenesis; the restoration of normal CNS function by stimulating stem/progenitor cells in the brain to generate new neurons. NeuroNova also has capability in Cell Therapy; which seeks to reverse neurological deficits through transplantation of cultured adult human neural stem/progenitor cells.

NeuroNova has developed a drug discovery platform, driving its research programmes in both drug and cell therapy. The Company has several projects in different phases of discovery and pre-clinical development and additional activities classified as exploratory projects.

In September 2003, NeuroNova announced a collaboration with Lundbeck to study the effect of chemical compounds on precursor cells of the adult mouse brain.

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NeurOnyx is developing therapeutics based upon the ability of adult bone marrow-derived stem cells to repair, regenerate and remodel tissue in acute and chronic disease settings. NeurOnyx has developed a unique population of human adult bone marrow-derived stem cells (hABM-SCs) and processes for their isolation and expansion; these have efficacy in animal models of myocardial infarction, spinal cord injury and stroke. NeurOnyx can produce up to 1 x 10^{17} cells from a single bone marrow aspirate in four passages without the need for immortalizing agents or a murine feeder layer. This level of expansion should provide NeurOnyx with the ability to produce commercial quantities of pharmaceutical-grade hABM-SCs.

NeurOnyx' lead programme, in collaboration with Centocor/Johnson & Johnson, is focused on the use of hABM-SCs for cardio-related disease applications. NeurOnyx are also conducting research relating to other indications including spinal cord injury, stroke, diabetes and musculo-skeletal disorders.

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- Founded in 1992, Osiris is a privately owned company focusing on developing its proprietary adult, human Mesenchymal Stem Cells (MSC) derived from bone marrow.
- Osiris has a 118,000 sq.ft. facility in Baltimore and currently has approx. 70 employees.
- Osiris has demonstrated that multi-potent MSCs have the ability to engraft and selectively differentiate, based on the tissue environment, to various tissue lineages, including muscle, bone, cartilage, marrow stroma, fat and neural tissue (Osiris has developed culture conditions to induce differentiation of hMSCs).
- Adult sourced cells such as MSCs do not in contrast to embryonic stem cells suffer from uncontrolled growth and political/ethical concerns. In addition MSCs are also non-immunogenic. Osiris believes that these properties and the ability to produce "off-the-shelf" MSCs gives it a competitive advantage over companies developing autologous and allogeneic-matched cell therapies.
- Unlike hematopoietic stem cells that do not propagate well in culture, hMSCs can be greatly expanded while retaining their ability to differentiate. Therefore, collection of only a small amount of bone marrow is necessary to provide a starting material ready for expansion. The hMSCs are isolated and grown from the marrow in Osiris' clinical manufacturing facility (also housed in Baltimore).
- The company has a series of clinical programmes:
  - The two lead programmes (both Phase II) are investigating the use of MSC to support treatment of blood cancers treated using peripheral blood and cord blood bone marrow transplantation after chemotherapy and/or total body irradiation. The goals are to reduce the time to engraftment and the incidence of graft-versus-host-disease (GVHD).
  - The company's cardiac programme (reached Phase I) is studying the use of MSCs to regenerate cardiac tissue post acute myocardial infarction and in congestive heart failure. Osiris has entered into a strategic alliance with Boston Scientific for the development and commercialisation of its cardiac products.
  - Osiris has earlier stage programmes evaluating MSCs in orthopedics (repairing damaged knee tissue and promoting new jaw bone formation in preparation for dental implants) and CNS (tissue regeneration in the brain) applications.
- Osiris' technology is protected by 38 issued US patents, including a MSC composition of matter patent allowed in the US and in Europe.

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Quark Biotech Inc. is developing therapeutics to treat cancer and other metabolic and fibrotic diseases. The company's product, QC-BT16 treats dyslipidemia and other disorders related to Metabolic Syndrome and is in Phase II clinical trials. Its product QC-BT2000 is designed to treat Type 2 Diabetes and Metabolic Syndrome. The company is also developing products to combat chronic kidney disease, end stage renal disease, diabetic retinopathy (disorders of the retina that can cause blindness), and diabetic nephropathy (debilitating conditions of the kidney associated with diabetes).

Quark have several research programmes in stem cells; from basic research to understand the cellular events that lead to cell specialization to gene discovery to uncover growth factors and to systems to screen drugs and small chemicals. In addition, Quark are using stem cell based technologies to inform a drive programmes in disease of bone and cartilage (including osteoporosis, osteoarthritis and bone healing), Oncology (including protection from cancer therapy side effects, breast cancer, skin cancer, liver cancer, kidney cancer, prostate cancer and cancer fibrosis), ischemic and vascular diseases (including stroke, atherosclerosis, retinopathy, and heart failure) and type II diabetes.

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ReNeuron

ReNeuron is developing neural stem cell technologies for cell transplantation treatments for major brain diseases such as stroke, Parkinson's disease and Alzheimer's disease. Additionally, ReNeuron is developing Stem Cells (its ReNcell product) for drug discovery and for use as biosensors.

ReNeuron's stem cells reportedly have the capability to form neural networks suitable for use in biosensors. Biosensors are currently being developed to detect harmful agents in the event of bio-terrorism attacks, and could also potentially serve as drug screening tools.

Additionally, ReNeuron are providing human neural stem cell lines for commercial and academic research *in vitro*. ReNcell lines have the following characteristics

Readily expandable in serum free defined media
Human neural stem cell lines
Multipotential
Derived from cortex and ventral mesencephalon
Adapted for all common laboratory formats including 96-well plates, chamber slides and cover slips
Fast growing - doubling time about 48 hours
Screened for adventitious agents
Differentiate *in vitro*
Generate high neuronal content *in vitro*
Transfectable
Compliant with high-throughput multi-well and single cell drug discovery applications

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StemCell Technologies

The Cell Experts™

StemCell Technologies provides specialized cell culture media and cell separation products that support medical research in cancer, hematology, immunology, cell transplantation, gene therapy, and developmental biology and a wide range of research applications. Additionally, StemCell Technologies can provide an array of cytokines, antibodies, tissue culture reagents, as well as services including contract assays, proficiency testing, and training. StemCell's lead product, MethoCult™, is a media for hematopoietic progenitor assays. StemCell also offers training courses and coordinates a global proficiency testing program for hematopoietic progenitor assays, and provides contract assay services to the biotechnology and pharmaceutical industry.

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Stem Cell Sciences

Stem Cell Sciences UK Ltd (SCS UK) is a wholly owned subsidiary of SCS Holdings Ltd, an Edinburgh based stem cell company. Stem Cell Sciences Ltd was first founded in 1994 as an Australian biotechnology Company, but now SCS Ltd is also an operating subsidiary of SCS Holdings Co. The company group has a leading intellectual property (IP) and technology position in the area of stem cells, particularly embryonic stem (ES) cells and has an exclusive, perpetual, world-wide licensing agreement with the University of Edinburgh.

Dr Peter Mountford, CEO
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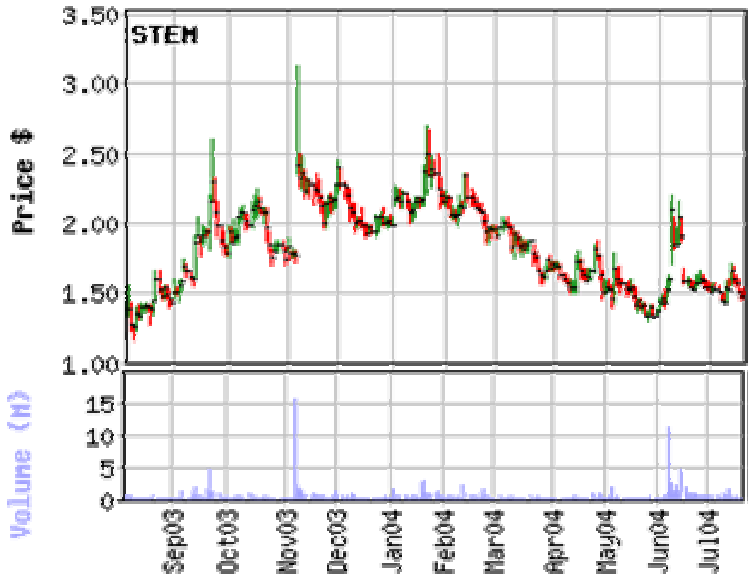
STEMCELLS INC.

Stem Cells Inc. is developing cell-based therapies to treat injuries to and diseases of the central nervous system (CNS) such as Parkinson's and Alzheimer's disease, as well as liver and pancreas diseases and injury. It is researching stem cell and progenitor cell (cells that have developed from stem cells) therapies to repair or repopulate neural or other tissue damaged or lost due to disease or injury. StemCells has discovered markers for CNS stem cells and a way to reproduce them for transplant. The company has outsourced R&D on insulin-producing islet stem cells for use in liver and kidney repair.



Program	Focus	Status	Near-Term Goal
Human Neural Stem Cell	Neurodegenerative	Preclinical	Establish Strategic Alliances, IND
	Genetic Disorders	Research	
Liver Stem Cell	Injury, Cancer, Hepatitis	Research	Isolate and patent stem cell
Pancreatic Stem Cell	Type I Diabetes	Research	Isolate and patent stem cell

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ViaCell

ViaCell Inc. is developing cellular treatments for cancer, genetic diseases, immune deficiencies and neurological diseases using the company's patented cell expansion technology. ViaCell also owns and operates Viacord, an umbilical cord blood stem cell storage company. In December 2003, ViaCell, Inc. announced a collaboration and license agreement with Amgen Inc. that provides ViaCell with licenses to certain cellular growth factors and provides Amgen with the right to collaborate with ViaCell to develop and commercialize cellular therapy products resulting from the collaboration. Amgen will also purchase $20 million of equity in ViaCell as part of the transaction.

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VistaGen Therapeutics Inc. is focused on developing drug therapies for treatment of CNS disorders while simultaneously generating operating income through strategic collaborations involving its core embryonic stem cell technologies for drug discovery and development in fields outside of epilepsy and other CNS disorders.

In November 2003, VistaGen announced acquisition of Artemis Neuroscience, Inc., a privately-held biopharmaceutical company developing drug candidates for epilepsy, neuropathic pain and other CNS disorders. Through the acquisition, VistaGen added AV-101 to its drug pipeline, a indirectly acting NMDA receptor antagonist candidate in late-stage preclinical development for epilepsy. In January 2004, VistaGen announced that the U.S. National Institutes of Health's (NIH) National Institute of Neurological Disorders and Stress (NINDS) awarded the company a $379,000 Phase 1 Small Business Innovation Research (SBIR) grant entitled “Development of 4-Chlorokynurenine to Treat Epilepsy.” This grant will be used to advance the development of AV-101.

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WiCell Research Institute, Inc.

WiCell Research Institute Inc. is non-profit organization established in October 1999 to advance stem cell research. Through internal research efforts in collaboration with other research institutions, WiCell aims to uncover the full potential of stem cells. Most of the costs of expanding, distributing, and shipping cells are subsidized by WiCell to insure the widest possible access to their technology.

WiCell offers industry access to stem cells for use in internal research and subsequent commercialization undertakings under two separate licensing agreements:

Industry Research License

- Includes materials (non-human ES cells and human ES cells)
- Allows for internal research on ES cells, differentiation to any cell type, and derivation of new cells lines
- Defines parameters for commercialization of products

Industry Commercial License

-Allows for product development and commercialization
-Defined by cell type (cardiomyocytes, osteoblasts, etc) and application (screening, research products, etc)
- Non-exclusive
- All fields available - except heart, neural, and pancreatic cells for cell therapy and diagnostic applications

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Xcellsyz uses novel cell-based technologies to create unmatched human and animal cell lines, models and cell-based assays to advance its own drug discovery and development programmes for diabetes and obesity, with an option of out-licensing and partnering collaborations with pharmaceutical and biotechnology companies. As well as developing its own patents, Xcellsyz is active in looking for novel technology which it will license in to compliment its activities.

In June 2004, Xcellsyz, announced a non-exclusive deal to license their conditionally immortalised, human skeletal muscle cell lines to Boehringer Ingelheim for evaluation and drug discovery research.

In March 2004, Geron Corporation and Xcellsyz Ltd announced that Geron had granted Xcellsyz a nonexclusive license to Geron's human telomerase reverse transcriptase (hTERT) technology for research applications and the development of research products.

Xcellsyz' CEO, Brad Hoy, was formally a Senior Director of Geron Biomed.

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Stem cell lines that are eligible for federal funding

Name	Derivations	Available Lines
BresaGen, Inc., Athens, Georgia * The cells in line BG04/hESBGN-04 failed to expand into undifferentiated cell cultures.	4	3*
Cell & Gene Therapy Research Institute (Pochon CHA University), Seoul, Korea	2	
Cellartis AB, Göteborg, Sweden * Cell line SA03/Sahlgrenska 3 withdrawn by donor.	3	2*
CyThera, Inc., San Diego, California * The cells failed to expand into undifferentiated cell cultures.	9	0*
ES Cell International, Melbourne, Australia	6	6
Geron Corporation, Menlo Park, California	7	
Göteborg University, Göteborg, Sweden	16	
Karolinska Institute, Stockholm, Sweden * The cells failed to expand into undifferentiated cell cultures.	6	0*
Maria Biotech Co. Ltd. – Maria Infertility Hospital Medical Institute, Seoul, Korea	3	
MizMedi Hospital—Seoul National University, Seoul, Korea	1	1
National Centre for Biological Sciences/Tata Institute of Fundamental Research, Bangalore, India	3	
Reliance Life Sciences, Mumbai, India	7	
Technion-Israel Institute of Technology, Haifa, Israel	4	3
University of California, San Francisco, California	2	2
Wisconsin Alumni Research Foundation, Madison, Wisconsin	5	5

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- **Embryonic stem cell**
  Also called ES cells, embryonic stem cells are cells derived from the inner cell mass of developing blastocysts. An ES cell is self-renewing (can replicate itself), pluripotent (can form all cell types found in the body) and theoretically is immortal.
- **Human embryonic stem cell**
  A stem cell that is derived from the inner cell mass of a blastocyst and can differentiate into several tissue types in a dish. They are similar to embryonic stem cells from the mouse; however, in the mouse, it is possible to inject those cells into a blastocyst, to make a new mouse, while this is not, and should not, be possible in humans for ethical reasons. Human embryonic stem cells are harder to grow than mouse embryonic stem cells.
- **Embryonic germline cells**
  Embryonic germline cells, also called EG cells, are pluripotent stem cells derived from the primitive germline cells (those cells that give rise to eggs and sperm). Their properties are similar to those of embryonic stem cells.
- **Umbilical cord stem cells**
  Hematopoietic stem cells are present in the blood of the umbilical cord during and shortly after delivery. These stem cells are in the blood at the time of delivery, because they move from the liver, where blood-formation takes place during fetal life, to the bone marrow, where blood is made after birth. Umbilical cord stem cells are similar to stem cells that reside in bone marrow, and can be used for the treatment of leukemia, and other diseases of the blood. Efforts are now being undertaken to collect these cells and store them in freezers for later use. However, one problem is that there may not be enough umbilical cord stem cells in any one sample to transplant into an adult.
- **Adult stem cells**
  Stem cells found in different tissues of the developed, adult organism that remain in an undifferentiated, or unspecialized, state. These stem cells can give rise to specialized cell types of the tissue from which they came, i.e., a heart stem cell can give rise to a functional heart muscle cell, but it is still unclear whether they can give rise to all different cell types of the body.

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- **Mesemchymal stem cell**
  Also known as bone marrow stromal cells, mesenchymal stem cells are rare cells, mainly found in the bone marrow, that can give rise to a large number of tissue types such as bone, cartilage (the lining of joints), fat tissue, and connective tissue (tissue that is in between organs and structures in the body).
- **Neural stem cell**
  A type of stem cell that resides in the brain, which can make new nerve cells (called neurons) and other cells that support nerve cells (called glia). In the adult, neural stem cells can be found in very specific and very small areas of the brain where replacement of nerve cells is seen.
- **Hematopoietic stem cells**
  The precursors of mature blood cells that are defined by their ability to replace the bone marrow system following its obliteration (for example, by g-irradiation) and can continue to produce mature blood cells.
- **Allogeneic transplantation**
  Cell, tissue or organ transplants from one member of a species to a genetically different member of the same species.
- **Autologous transplantation**
  Cell, tissue or organ transplants from one individual back to the same individual. Such transplants do not induce an immune response and are not rejected.
- **Heterologous**
  Not homologous or uniform. In the context of cells, heterologous is a mixed or divergent cell population or of a divergent origin.
- **Histocompatible**
  A tissue or organ from a donor (the person giving the organ or tissue) that will not be rejected by the recipient (the patient in whom the tissue or organ is transplanted). Rejection is caused because the immune system of the recipient sees the transplanted organ or tissue as foreign and tries to destroy it. Tissues from most people are not histocompatible with other people. In siblings, the probability of histocompatibility is higher, while identical twins are almost always histocompatible.

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- **Blastocyst**
  A very early embryo consisting of approximately 150 cells. The blastocyst is a spherical cell mass produced by cleavage of the zygote (fertilized egg). It contains a fluid-filled cavity, a cluster of cells called the inner cell mass (from which embryonic stem cells are derived) and an outer layer of cells called the trophoblast (that forms the placenta).
- **Bone marrow stromal cell**
  Also known as mesenchymal stem cells, bone marrow stromal cells are a mixed population of cells derived from the non-blood forming fraction of bone marrow. Bone marrow stromal cells are capable of growth and differentiation into a number of different cell types including bone, cartilage and fat.
- **Ectoderm**
  The outer of three germ layers of the early embryo that gives rise in later development to the skin, cells of the amnion and chorion, nervous system, enamel of the teeth, lens of the eye and neural crest.
- **Endoderm**
  The inner of three germ layers of the early embryo that gives rise in later development to tissues such as the lungs, the intestine, the liver and the pancreas.
- **Mesoderm**
  The middle of three germ layers that gives rise later in development to such tissues as muscle, bone, and blood.
- **Homologous recombination**
  A technique used to inactivate a gene and determine its function in a living animal. The process of homologous recombination is more efficient in embryonic stem cells than in other cell types. It is achieved by introducing a stretch of DNA that is similar or identical (homologous) to part of a gene and to some of the DNA surrounding the gene, but different (not homologous) to a specific section of the gene. The DNA is then introduced into the stem cells and the stretch of homologous DNA will recognize the similar sequences of the gene within the cell, and replace it. But the cell is then left with a piece of DNA in the gene that has the wrong sequence and this interrupts the function of the gene. The gene is then said to be knocked out. From these embryonic stem cells, an entire mouse can be made by injecting the altered stem cells into a blastocyst, and implanting the blastocyst into a female mouse. This is one way to make genetically manipulated mice and other animals with altered gene function. These experiments are crucial to understand how specific genes work and interact in living animals.

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Stem cells have different properties depending upon their origin;

- **Totipotent**
  Stem cells that can give rise to all cell types that are found in an embryo, foetus, or developed organism, including the embryonic components of the trophoblast and placenta required to support development and birth. The zygote and the cells at the very early stages following fertilization (i.e., the 2-cell stage) are considered totipotent.

- **Pluripotent**
  Stem cells that can become all the cell types that are found in an implanted embryo, foetus, or developed organism, but not embryonic components of the trophoblast and placenta (these are usually called extra-embryonic). These stem cells are present in embryonic and foetal tissue.

- **Multipotent**
  Stem cells whose progeny are of multiple differentiated cell types, but all within a particular tissue, organ, or physiological system. For example, blood-forming (hematopoietic) stem cells are single multipotent cells that can produce all cell types that are normal components of the blood. These stem cells are present in adult animals in most/all organs.

- **Unipotent**
  Stem cells that self-renew as well as give rise to a single mature cell type; e.g., spermatogenic stem cells.

- **Progenitor**
  A progenitor cell, often confused with stem cell, is an early descendant of a stem cell that can only differentiate, but it cannot renew itself anymore. In contrast, a stem cell can renew itself (make more stem cells by cell division) or it can differentiate (divide and with each cell division evolve more and more into different types of cells). A progenitor cell is often more limited in the kinds of cells it can become than a stem cell. In scientific terms, it is said that progenitor cells are more differentiated than stem cells.

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Cell type

A specific subset of cells within the body, defined by their appearance, location and function. There are approximately 220 different cell types, all of which derive, *in vivo,* from stem cells.

- **Adipocyte:** the functional cell type of fat, or adipose tissue, that is found throughout the body, particularly under the skin. Adipocytes store and synthesize fat for energy, thermal regulation and cushioning against mechanical shock
- **Cardiomyocytes**: the functional muscle cell type of the heart that allows it to beat continuously and rhythmically
- **Chondrocyte**: the functional cell type that makes cartilage for joints, ear canals, trachea, epiglottis, larynx, the discs between vertebrae and the ends of ribs
- **Fibroblast**: a connective or support cell found within most tissues of the body. Fibroblasts provide an instructive support scaffold to help the functional cell types of a specific organ perform correctly.
- **Hepatocyte**: the functional cell type of the liver that makes enzymes for detoxifying metabolic waste, destroying red blood cells and reclaiming their constituents, and the synthesis of proteins for the blood plasma
- **Hematopoietic cell**: the functional cell type that makes blood. Hematopoietic cells are found within the bone marrow of adults. In the fetus, hematopoietic cells are found within the liver, spleen, bone marrow and support tissues surrounding the fe tus in the womb.
- **Myocyte**: the functional cell type of muscles
- **Neuron**: the functional cell type of the brain that is specialized in conducting impulses
- **Osteoblast**: the functional cell type responsible for making bone
- **Islet cell**: the functional cell of the pancreas that is responsible for secreting insulin, glucagon, gastrin and somatostatin. Together, these molecules regulate a number of processes including carbohydrate and fat metabolism, blood glucose levels and acid secretions into the stomach.

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- **Lineage commitment**

  Lineage commitment involves activation of lineage-specific genes, stabilization of a lineage-specific gene expression program, and inhibition of inappropriate characteristics. If a cell is able to differentiate into its committed fate even in the presence of factors/environments that would normally be expected to drive cells along fates, the commitment step is considered irreversible.

- **Differentiation**

  The process of development with an increase in the level of organization or complexity of a cell or tissue, accompanied with a more specialized function. of specialized cell types from precursor cells .

- **Transdifferentiation**

  The ability of a particular cell of one tissue, organ or system, including stem or progenitor cells, to differentiate into a cell type characteristic of another tissue, organ, or system; e.g., blood stem cells changing to liver cells[1].

- **Plasticity**

  A phenomenon used to describe a cell that is capable of becoming a specialized cell type of different tissue. For example, when the same stem cell can make both new blood cells and new muscle cells[2].

1. http://www.isscr.org/glossary 2. http://www.isscr.org/glossary

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