EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 March 2010
EMA/CAT/571134/2009
Committee For Advanced Therapies (CAT)

Reflection paper on stem cell-based medicinal products

Disclaimer: Please note that the present reflection paper has been developed to communicate the current status of discussions and to invite comments in the area of stem-cell based medicinal product development, where scientific knowledge is fast evolving and regulatory experience is limited.
The reflection paper shall be further discussed at the European Medicines Agency's public work shop on stem cell-based therapies to be held on 10 May 2010

Draft Agreed by Biologics Working Party and Safety Working Party	March 2010
Draft Agreed by Cell Products Working Party	March 2010
Adoption by Committee For Advanced Therapies (CAT) for release for consultation	12 March 2010
End of consultation (deadline for comments)	30 June 2010
Agreed by <WORKING PARTY>	<month year>
Adoption by <COMMITTEE>	<day month year>

Comments should be provided using this template.The completed comments form should be sent to veronika.jekerle@ema.europa.eu

Keywords	*Advanced therapy medicinal products, embryonic stem cells, induced pluripotent stem cells, adult stem cells, somatic stem cells, marketing authorisation application, quality, nonclinical, clinical considerations*

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1. Introduction (background)

Stem cells hold the promise for a limitless source of cells for therapeutic applications in various conditions, including metabolic, degenerative and inflammatory diseases, cancer and for repair and regeneration of damaged or lost tissue.
Various stem cell types can be isolated from different tissues of the human body, expanded and/or differentiated in *in vitro* culture conditions, and subsequently administered to patients.
Existing guidance on cell-based medicinal products (Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)) covers the general aspects of all cell-based products including stem cell advanced therapy medicinal products. In addition, in case of genetic modification of stem cells, the future guideline for genetically modified cells should be consulted (see Draft guideline on the quality, preclinical and clinical aspects of medicinal products containing genetically modified cells (EMEA/CHMP/GTWP/671639/2010)).

The aim of this reflection paper is to cover specific aspects related to stem cells based medicinal products as defined below.
This reflection paper shall apply to all types of stem cells regardless of their differentiation status at the time of administration. Stem cells that are not substantially manipulated and intended to be used for the same essential function in the recipient as in the donor as referred to in Article. 2 (1 (c)) of Regulation EC (No) 1394/2007 are out of the scope of this reflection paper. For a list of manipulations that are not considered substantially manipulated see Annex I of Regulation EC (No) 1394/2007.

Although the stem cells share the same principal characteristics of self-renewing potential and differentiation, stem-cell-based medicinal products do not constitute a homogeneous class. Instead, they represent a spectrum of different cell-based products for which there is a variable degree of scientific knowledge and clinical experience available. For example, while HSCs have been used for therapeutic purposes, this is not the case for human embryonic stem cells or induced pluripotent cells.

In addition, varying levels of risks are associated with specific types of stem cells. A risk-based approach according to Annex I, part IV of Dir 2001/83/EC is recommended for stem cell containing products.

This reflection paper is relevant to all medicinal products using stem cells as starting material. The final products may constitute of terminally differentiated cells derived from stem-cells, from pluripotent stem cells or even from a mixture of cells with varying differentiation profile.

1.1. Definition and identification of stem cells

Stem cells can be defined as cells with self-renewing capacity i.e. the capability of generating daughter cells and having multi-lineage differentiation capacity. Stem cells are capable to proliferate as stem cells in an undifferentiated form. For the purpose of this document, stem cells include:

- Embryonic stem cells (hESCs) derived from blastocysts;
- Adult or somatic stem cells including
    - Haematopoietic progenitor /stem cells (HSCs);
    - Mesenchymal/stromal stem cells (MSCs);
    - Tissue-specific progenitor cells with a more restricted differentiation capacity responsible for normal tissue renewal and turnover, such as neurons, intestine, skin, lung and muscle.

In addition, induced pluripotent stem cells (iPSs), and/or their intermediate stages, that are reprogrammed differentiated cells expected to re-acquire both the stemness and differentiation capacity of self-renewing embryonic stem cells, are also included.

1.2. Characteristics of different stem cell types

Embryonic stem cells can be maintained in *in vitro* culture conditions as established cell lines. hESCs are pluripotent and have the capacity to differentiate to virtually every cell type found in the human body. hESCs can be characterised by distinct set of cell surface markers, as well as marker genes for pluripotency. hESCs, when transplanted into a permissive host form teratoma, benign tumours consisting of various cell types derived from all three germ layers; endoderm, mesoderm and

ectoderm. hESCs can be differentiated *in vitro* using either external factors in the culture medium, or by genetic modification. However, *in vitro* differentiation often generates cell populations with varying degree of heterogeneity.

Mesenchymal/stromal stem cells (MSCs) are primarily derived from bone marrow stroma or adipose tissue. Additionally, MSCs have been isolated from numerous other tissues, such as retina, liver, gastric epithelium, tendons, synovial membrane, placenta, umbilical cord and blood. They have a multi-lineage differentiation capacity and can be directed towards for example chondrogenic, osteogenic and adipogenic cell lineages. MSCs can also be differentiated towards e.g. neurons, astrocytes, tenocytes, and skeletal myocytes.

Haematopoietic stem cells (HSCs) are able to give rise to differentiated cells of all haematopoietic lineages, myeloid and lymphoid, either in the hemopoietic bone marrow or in the thymus. In the adult body, HSCs are localized in the bone marrow and found at a lower frequency circulating in the peripheral blood. At low frequency they may be found also in other tissues (liver, spleen and muscle) but their origin and relevance for the normal haematopoiesis have not yet been fully clarified at the moment. HSCs are mobilized to the blood compartment after treatments with intensive chemotherapy and/or growth factors. These stem cells are also found in the placental and cord blood at birth in concentrations similar to adult bone marrow one's.

Tissue specific stem cells have a more limited differentiation capacity and normally produce a single cell type or a few cell types that are specific to that tissue.

Induced pluripotent stem cells (iPSs) are artificially generated stem cells. They are reprogrammed from somatic adult cells such as skin fibroblasts. iPS cells share many features of hESCs; they have self-renewing capacity, are pluripotent and form teratoma. Increasingly iPS cells are being produced from different adult cell types. Their differentiation capacity seems to be dependent on the cell type and age of the cells from which the iPS cells were reprogrammed. There is a knowledge gap to be addressed with respect to alterations of some regulatory pathways, differences in gene expression and in epigenetic control. These characteristics may result in tissues chimerism or malfunctioning of the cells.

2. Quality Considerations

2.1. General

Stem cell preparations normally constitute a complex mixture of cell types or of cells with varying differentiation capacity and multiple differentiation stages. Their differentiation capacity *in vivo* and mode of action may strongly depend on the conditions and time of *in vitro* culture, such as the use of growth factors or serum, separation methods, cell confluency etc. Due to their plasticity and large differentiation potential it is essential that the preclinical and clinical studies are being performed with well defined and characterized stem cell preparations that are produced via a robust manufacturing process and quality control to ensure consistent and reproducible quality of the final product.
Embryonic stem cells and iPS cells should be lineage-committed before administration to the patient due to their associated tumourigenicity risks.

2.2. Starting materials

For hESCs, the history of the cell line derivation and cell banking, including the raw material used during production, need to be carefully documented. Viral safety of the cells should be addressed; this is particularly important in cases where results from donor testing are not available.

The origin and sampling procedure of the starting material to isolate the stem cells is critical for the yield and homogeneity of the final cell population. Therefore the selection of appropriate markers to standardise isolation conditions, heterogeneity of the cell population and yield need to be addressed.

2.3. Manufacturing process

Manufacturing often involves the following steps depending on the starting material:

- Procurement of tissue or cells and processing to yield a a well predefined/characterised cell suspension;

- Reprogramming of terminally differentiated cells (iPS cells);
- Expansion under conditions supporting growth of undifferentiated cells;
- In vitro differentiation of the cells;
- Purification of the intended biologically active cell population (*e.g.* removal of undifferentiated pluripotent cells, immunoselection).

Expanded stem cells are always substantially manipulated and are often administered in a differentiated state.
However it is acknowledged that multipotent stem cells may be administered into the patients after expansion. In such cases the potential for tumourigenicity might demand additional testing during process validation.
The choice of relevant markers to control the critical manufacturing steps is dependent on the intended purpose of the application. A risk assessment should be part of designing the therapeutic strategy. For instance, tumourigenic risk of ectopic grafting is much higher for pluripotent cells than for lineage-committed cells.

2.4. Characterisation and quality control

2.4.1. Identity

Identity of stem cells is defined by their self renewal capacity (proliferation) and the expression of specific markers. Starting materials are often mixed cell populations (*i.e.* bone marrow, fat tissue, umbilical cord blood) and procurement and production can have a considerable impact on the final cell population. Therefore, the identity of the intended cell population(s) needed for the therapeutic effect needs to be carefully defined and characterised.
Several cellular markers indicative of either cell type, pluripotency, lineage commitment or terminal differentiation can be used to establish identity. The cell identity markers should be specific for the intended cell population(s) and should be based on an understanding of the biological or molecular mechanism of the therapy. Ideally the combination of markers to be used should be able to distinguish between the different differentiation states or cell types. The use of mRNA level based markers as surrogate test is possible, provided that a validated correlation with protein marker expression has been established.

2.4.2. Purity

The identification of the mode of action of a stem-cell based product needs to be accompanied by the attempt to maximise this active moiety in the medicinal product and a reduction and avoidance of cells that do not contribute or negatively impact on the therapeutic activity and safety.
Whenever possible, these attempts should aim at the elimination of undesired cells. It is recognized, that stem cells might not be accessible to cell separation for lack of appropriate surface markers. The minimum requirement however, is the demonstration of consistency of the medicinal product and a comprehensive strategy is required to achieve this goal, including the choice and preparation of starting material, in process control and release testing.

2.4.3. Potency

The potency of a stem cell-based product should be measured with analytical methods that are capable to define biological activity, number and differentiation status of the cells needed for the intended use.
The design of a potency assay can vary depending on the product and it may comprise both functional tests and marker-based assays. Ideally, the assay should be (semi)quantitative and show correlation with the intended therapeutic effect. Understanding the biological or cellular mechanism of action/therapeutic action will provide a solid basis for developing reliable potency tests.
Examples of positive selection criteria:

- Expression of lineage commitment markers
- Expression of pre-differentiation markers
- Expression of terminal differentiation markers
- Expression of relevant biological substances (e.g. recombinant protein, glyco- or lipo-protein, growth factors, cytokines etc.)
- Formation of cell/ extra cellular matrix/ structures
- Altered adhesive or non-adhesive properties, cell interaction (e.g. immune activation/inhibition)

2.4.4. Tumourigenicity

The differentiation state, pluripotency or lineage commitment and culture conditions of the intended cells has important implications for identifying the potential risks (e.g. tumourigenic potential). Undifferentiated / multipotent cells have a relatively high potential risk of tumour formation, which

should be carefully addressed during product development. The amount of proliferative and/or undifferentiated cells in the final product should be limited and justified. Where multipotent cells are to be administered to the patient, the Applicant should propose a strategy to minimise the risk of tumourigenicity.

2.4.5. Process validation

During product development / characterisation and validation of the manufacturing process, genotypic instability, tumourigenicity and phenotypic profile of the intended cell population should be demonstrated for each intermediate. Special attention should be paid to the use of growth factors and reagents that may have different impact on different cells in the original cell population.

3. Non-clinical Considerations

3.1. Animal models

Animal models reflecting the therapeutic indication i.e. disease models would be ideal but in practice availability of such models may be limited. Small animal models may not be useful for surgically implanted cell products, for long-term evaluation of tissue regeneration and repair and safety follow-up. In such cases, large animal models may be preferable. Large animal models may be required in situations where the size of the animal is relevant for appropriately studying the clinical effect (e.g. regeneration of tissue).

Ideally, human cells should be used for proof-of-concept and safety studies. This would often necessitate use of immunocompromised animals in which, however, some aspects, such as persistence or functionality may not be optimally translated to predict *in vivo* behaviour of transplanted cells. Homologous animal models may often provide the most relevant system for not only proof-of-concept but also for safety testing. However, uncertainty of the equivalence between animal and human stem cells or factors involved in the differentiation process may limit the predictiveness of such a model. If homologous animal models are used the equivalence between human and animal stem cells should be shown.

For the testing of the potential to form teratomas and/or tumours of a stem cell product, a genetically immunocompromised animal model, or a humanised animal model (e.g. animal model with a humanised immune system) are preferred. The use of immunosuppressant may influence tumour formation (inherent property of immunosuppressants), whereas in an immunocompetent animal model the host immune system may reject/kill the administered stem cell product thus causing a failure of engraftment of the product and leading to a (potentially) false negative outcome of the study.

The duration of animal studies should be adequate to cover evaluation of long-term effects.

Non-clinical evaluation for stem cell-based medicinal products may need to be more substantial than for cell based medicinal products containing differentiated cells only. In order to adequately evaluate different aspects including proof of concept, biodistribution, immune rejection and safety, more than one animal species or strains might be needed. *In vitro* testing may provide additional and/or alternative ways to address some specific aspects.

3.2. Biodistribution and niche

Biodistribution studies of stem cells are considered highly important, particularly in cases of i.v. administration of the product. Suitable methods for tracking of stem cells should be applied, e.g. introducing marker genes or labelling of cells. Many stem cell types have the propensity to home to distant locations, e.g. recruitment of bone marrow-derived MSCs to the site of injury. MSCs have also been shown to locate to metastatic sites. Differentiation and function of stem cells are dependent on and affected by the microenvironment (niche). A major risk associated is the formation of ectopic tissue due to the cells' intrinsic capacity to differentiate along several lineages. This risk will be substantially increased after systemic application of the cells, thereby allowing the distribution to distant sites. Besides ectopic tissue formation local non-physiological or toxic effects might be mediated by distributed cells such as immune suppression by MSCs.

3.3. Tumourigenicity and genomic stability

Teratoma formation is a characteristic of embryonic stem cells and induced pluripotent stem cells, making them intrinsically tumourigenic. For example, undifferentiated mouse embryonic stem cells can produce malignant teratocarcinomas in the brains at the site of implantation. It has been reported in the literature that after prolonged *in vitro* culture human adipose-derived MSCs and murine bone marrow-derived stem cells can become tumourigenic. Culture conditions, such as feeder cells may substantially influence the genomic stability of stem cells. For example, human embryonic stem cells grown on mouse feeder cells and passaged by enzymatic means are more prone to karyotypic changes.

In contrast, when using more stringent culturing conditions, i.e. human feeder cells and passaging by mechanical means, it has been show that hESCs can retain their chromosomal integrity. Therefore it appears essential that stem cell preparations that have undergone substantial *in vitro* manipulation such as vigorous proliferative growth, are evaluated for both their tumourigenicity and chromosomal stability before the first clinical use. The choice of the most appropriate and sensitive model for tumourigenicity studies should take into account the characteristics, the manipulation conditions of stem cells, the route of administration as well as the intended clinical use.

3.4. Differentiation in vivo

The expected differentiation process and function *in vivo* should be studied carefully to substantiate the desired mode of action. Stem cells might not differentiate in the expected way at the intended location. This for example has been shown for MSCs intended to differentiate into the cardiac or vascular lineage, and found to induce profound calcifications in the infarcted hearts.

3.5. *Immune rejection and persistence*

While embryonic and HSCs transplantation requires careful HLA matching between donor and recipient, MSCs are generally considered as being immune privileged. Nevertheless, allogeneic MSCs are known to be immunogenic in immune competent murine models, leading to rapid clearance from the peripheral blood. It appears important, therefore, to evaluate the risk of stem cell elimination due to an induced immune response. Immune rejection might be acceptable in cases where limited persistence is intended, for example during temporary immune suppression via MSCs, but it might preclude the desired long term efficacy in other cases.

4. Clinical Considerations

Generally, the clinical development plan should follow corresponding EU guidance on medicinal product and specific relevant guidance for the diseases to be treated.

Nonclinical evidence on the proof-of-principle and safety of the stem-cell based product in a relevant animal model is expected before administration to humans. This is particularly important when the stem cells have been extensively manipulated *ex vivo* or where a systemic administration is proposed. In those cases, where sufficient proof-of-concept and safety cannot be established in the nonclinical studies, e.g. due to justified difficulties in finding an appropriate animal model, the evidence should be generated in clinical studies by including additional end points for efficacy and safety, respectively. For first in man studies the principles of the Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07) might be considered.

For these products two specific relevant clinical issues are perceived, namely specific safety and long term efficacy concerns.

4.1. Pharmacodynamics

The clinical trials should ideally confirm the mode of action identified during the preclinical studies. Such mode of action may be directly dependent on the stem cell population, molecules secreted by the cells or their engraftment in the host tissue.

The stem cells may be in various differentiation stages at the time of administration. The selected biomarkers should be capable of following the differentiation status of the stem cells at time of administration and during *in vivo* follow-up of the cell population.

It should be noted that the follow-up of efficacy and safety is highly dependent on the mode of action related to either their pharmacological, immunological and/or metabolic effect (Cell therapy medicinal product) or regenerative, repair and/or replacement effect (Tissue engineered product).

In cases where suitable homologous animal models or other relevant preclinical models are not available, additional clinical endpoints to address the effect of the microenvironment on the stem cell product may be needed.

4.2. Pharmacokinetics

It is acknowledged that it may be challenging to perform biodistribution studies in humans (fate of the stem cell transplant in the body). However, depending on the risk profile of the product and its mode of administration and localisation for administration, these studies may be important. There should be ways to follow the cells during the clinical studies, they should be utilised. Possible markers / tracers should be evaluated and justified.

The presence of the administered stem cells in places other than the intended should be investigated. The effect of different administration procedure, doses/cell numbers should be addressed during the preclinical and confirmed during the clinical studies.

For ATMPs based on stem cells, it is important to evaluate the time to engraftment and to achieve the clinical outcome in order to correctly define the cell population required for such an *in vivo* effect.
A particular feature of stem cell-based medicinal products is that the number of cells may increase with time due to their renewal potential. Accordingly, there has been substantial theoretical concern that a very minor contamination, perhaps even a single proliferating cell with deleterious properties, could possibly be clinically important and may need to be addressed in a non-clinical model through the use of immuno-suppressed or constitutively immuno-deficient animals and/or appropriate clinical follow-up.

4.3. Dose finding studies

The effective range of stem cells and/or stem-cell derived cells administered should be defined during dose finding studies, unless justified. A safe and effective treatment dose should be identified, and where possible, the minimally effective dose should be determined.
Where formal dose-finding is not feasible such as for indications requiring administration of the product in vulnerable sites (e.g. CNS, myocardium), it might be appropriate to begin an initial human clinical trial with a dose that could have a therapeutic effect as long as it is justified on the basis of available nonclinical evidence for safety.

4.4. Clinical efficacy

In general, clinical trials to study efficacy should follow the relevant available guidance in the target indication. Clinically meaningful endpoints related to the pharmacodynamic effect of the product should be used.
It is acknowledged that in the field of regenerative medicines additional appropriate structural and morphological endpoints may be necessary in order to study regeneration, repair or replacement of a tissue.
If pivotal clinical studies differ significantly from studies conducted for other medicinal products in the same indication, the Applicant is advised to discuss the design and end points of the studies with the authorities in order to optimise the remaining development of the stem cell-based medicinal product in view of an application for marketing authorisation (MAA).
The need for and duration of Post-Authorisation long term efficacy follow-up should be identified during the clinical studies, also taking into consideration results from non-clinical studies.

4.5. Clinical safety

In general the same safety requirements as for other medicinal products shall apply. For stem cell-based products the following unique risk factors are envisioned and should be addressed by the Applicant.

An important safety concern is the capability of hESCs to form teratomas. Although these tumours are benign, their formation in anatomically sensitive locations, such as the CNS, joint spaces or the conduction apparatus of the myocardium, is nevertheless a serious safety concern. Likewise, the risk for ectopic engraftment in non-target tissues should be addressed.

In case of observed tumour formation, it should be investigated whether this is due to the administered product or endogenous tumour formation (e.g. genetic analysis).

Another safety concern is that the self-renewal characteristics of these (iPSC / hESC) cells makes it probable that some cells with sufficient plasticity persist in any stem-cell-derived product, no matter how efficient the process used to induce them to differentiate into a cell population with the desired characteristics or how effective the method used to remove undesired cells from the final product.
The number of stem cells circulating in the patient can be much higher than physiological levels and this may pose a safety concern as their distribution in the body could be abnormal. The timing of the administration in case of i.v. injection should be guided by the preclinical biodistribution results and optimised in order to minimize the presence of the product in non target tissues/ organs.
Caution is needed with stem cell products that have been developed solely using non-clinical homologous model and where all cellular and molecular interactions are found to be functional based on a homologous setting. In first-in-man studies, specific safety end points may need to be defined based on theoretical considerations and in order to detect early any toxicity arising from potential contaminants in the final product.
The safety follow-up can be combined with a parallel efficacy follow-up. Suitable surrogate end points may need to be validated since the clinical safety and efficacy may be apparent only first after several years.

4.6. Pharmacovigilance

Specific safety issues, including lack of efficacy, should be evaluated in long term follow-up. The duration of follow-up should be envisioned according to the intended therapeutic effect and should also contain a specific surveillance plan for the assessment of long-term safety and unique risks associated with the administration of stem cells. For tissue engineered products for which long term efficacy is claimed a prolonged post-marketing follow-up might be required.

The Guideline on the safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008) should be considered.

5. References

Regulation EC (No) 1394/2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use Dir 2001/83/EC and amendments.

Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)

Draft guideline on the quality, preclinical and clinical aspects of medicinal products containing genetically modified cells (EMEA/CHMP/GTWP/671639/2010)

Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)

Guideline on the safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008)

ANNEX 1.Glossary

Adult stem cell—See **somatic stem cell**.
Blastocyst—A preimplantation embryo of about 150 cells produced by cell division following fertilisation. The blastocyst is a sphere made up of an outer layer of cells (the trophoblast), a fluid-filled cavity (the blastocoel), and a cluster of cells on the interior (the inner cell mass).
Cord blood stem cells—See Umbilical cord blood stem cells.
Ectoderm—The outermost germ layer of cells derived from the inner cell mass of the blastocyst; gives rise to the nervous system, sensory organs, skin, and related structures.
Embryonic stem cells—Primitive (undifferentiated) cells derived from a 5-day preimplantation embryo that are capable of dividing without differentiating for a prolonged period in culture, and are known to develop into cells and tissues of the three primary germ layers.
Embryonic stem cell line—Embryonic stem cells, which have been cultured under *in vitro* conditions that allow proliferation without differentiation for months to years.
Endoderm—The innermost layer of the cells derived from the inner cell mass of the blastocyst; it gives rise to lungs, other respiratory structures, and digestive organs, or generally "the gut"
Epigenetic changes —Changes in gene expression caused by mechanisms other than changes in the DNA nucleotide sequence,
Feeder layer— Feeder cells produce proteins and other substances needed to support growth of stem cells.
Germ layers—After the blastocyst stage of embryonic development, the inner cell mass of the blastocyst goes through gastrulation, a period when the inner cell mass becomes organized into three distinct cell layers, called germ layers. The three layers are the ectoderm, the mesoderm, and the endoderm.
Haematopoietic stem cell—A stem cell that gives rise to all red and white blood cells and platelets.
Induced pluripotent stem cell (iPS)—A type of pluripotent stem cell artificially derived from an adult somatic cell.
Inner cell mass (ICM)—The cluster of cells inside the blastocyst. These cells give rise to the embryo and ultimately the fetus.
Mesenchymal stromal/stem cells—Multipotent non-haematopoietic stem cells found in a variety of tissues such as bone marrow stroma, umbilical cord blood and adipose tissue, capable of producing cell types of eg. osteogenic, chondrogenic and adipogenic lineages,
Mesoderm—Middle layer of a group of cells derived from the inner cell mass of the blastocyst; it gives rise to bone, muscle, connective tissue, kidneys, and related structures.
Microenvironment (niche)—The molecules and compounds such as nutrients and growth factors in the fluid surrounding a cell in an organism which play an important role in determining the characteristics of the cell.
Multipotent—Having the ability to develop into more than one cell type of the body. See also **pluripotent** and **totipotent**.
Neural stem cell—A stem cell found in adult neural tissue that can give rise to neurons and glial (supporting) cells. Examples of glial cells include astrocytes and oligodendrocytes.
Pluripotent—Having the ability to give rise to all of the various cell types of the body.
Progenitor cells—Undifferentiated cells that have a capacity to differentiate into a specific type of cell. In contrast to stem cells. The most important difference between stem cells and progenitor cells is that stem cells can replicate indefinitely, whereas progenitor cells can only divide a limited number of times.
Self-renewal—The ability of stem cells to replicate themselves in an undifferentiated form
Somatic (adult) stem cells—undifferentiated cells found in many organs and differentiated tissues with a limited capacity for both self renewal and differentiation. Such cells vary in their differentiation capacity, but it is usually limited to cell types in the organ of origin. (See also **progenitor cell**).
Teratoma—A benign tumour consisting of cell types derived from all three embryonic germ layers

Totipotent—Having the ability to give rise to all the cell types of the body plus all of the cell types that make up the extraembryonic tissues such as the placenta. (See also **Pluripotent** and **Multipotent**).

Trophectoderm—The outer layer of the preimplantation embryo in mice.

Umbilical cord blood stem cells—Stem cells collected from the umbilical cord at birth that can produce all of the blood cells in the body (haematopoietic).