Reflection paper on stem cell based medicinal products - introduction

Workshop on stem cell based therapies
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Regulatory framework
- need for additional guidance

- **Directive 2001/83/EC** Community code relating to all medicinal products for human use amendend by **Dir 2003/63/EC**
- **Regulation (EC) No 726/2004**
- **Regulation EC (No) 1394/2007** on advanced therapy medicinal products, amending Directive 2001/83/EC
  - Technical requirements in Annex I, part IV of Dir 2001/83/EC

- **Directive 2004/23/EC** setting standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissues/cells,
  - Technical requirements in **Directive 2006/17/EC** and **Directive 2006/86/EC**

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

- Due to the nature of stem cells additional safety concerns are pertained to them; need for additional guidance foreseen

  Reflection paper on stem cell-based medicinal products (EMA/CAT/571134/2009)

- This reflection paper covers only specific aspects related to stem cell based medicinal products

- Risk-based approach recommended

Scope

1. This reflection paper shall apply to all types of stem cells regardless of their differentiation status at the time of administration

2. This reflection paper is relevant to all medicinal products using stem cells as starting material

3. 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

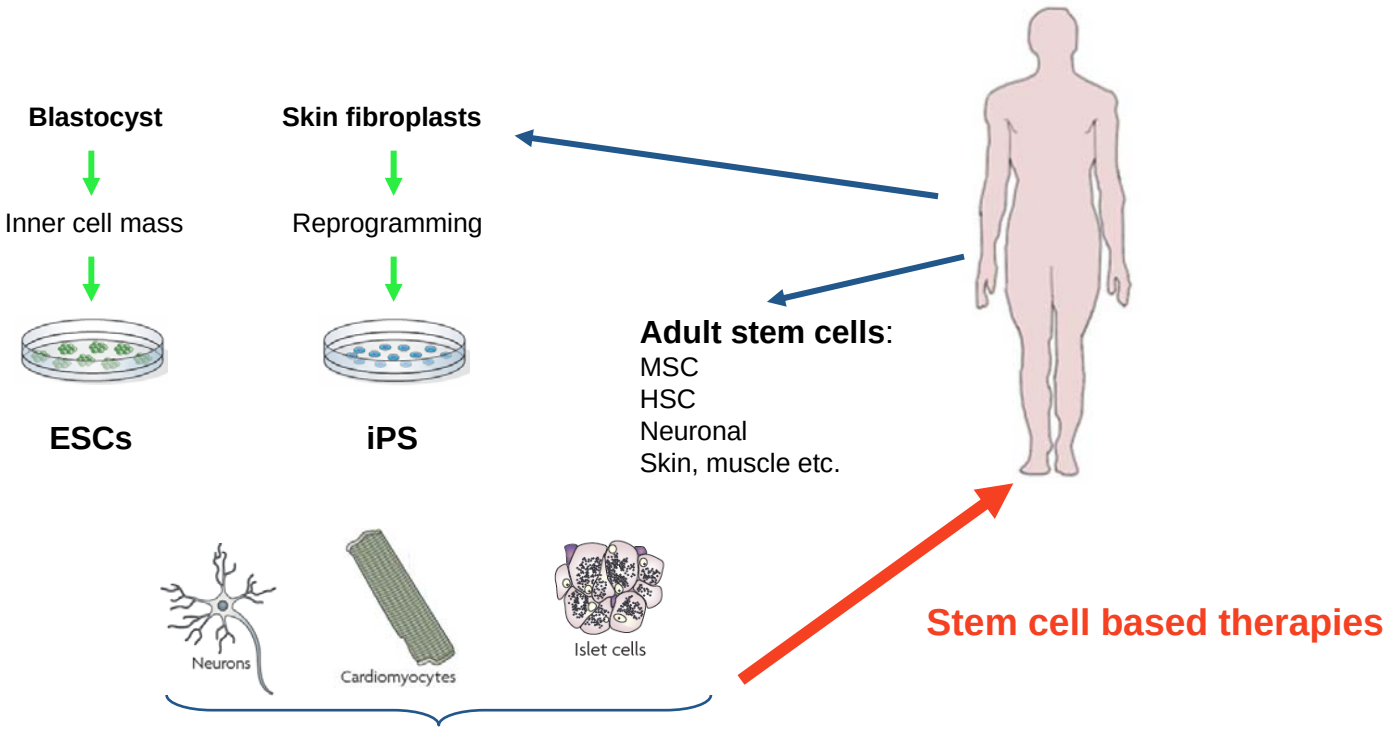
Definition and classification

Stem cells are cells with
- **self-renewing capacity**
- **multi-lineage differentiation capacity**

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

Induced pluripotent stem cells (iPSs), and/or their intermediate stages, that are reprogrammed differentiated cells



Desired characteristics

- Proliferation in undifferentiated state
- Limitless expansion
- Renewable source of cells for therapeutic purposes
- Multilineage differentiation capacity
- Directed production of virtually all cell types

Self-renewal

Differentiation

Migration

Risks

- Uncontrolled proliferation
- Teratoma formation
- Tumorigenicity
- Unintended differentiation
- Migration to ectopic locations

Quality-related issues

Starting materials

- History of cell line derivation and cell banking
- Origin and sampling procedure critical for yield and homogeneity

Manufacturing process

- Complex process including procurement and processing of cells, (reprogramming), expansion, differentiation and purification steps
- Choice of markers for critical steps

Quality-related issues (2)

Characterisation and quality control

Identity

- Specific markers indicative of cell type, pluripotency, lineage commitment,terminal differentiation to distinguish between the differentiation stages and/or cell types

Purity

- Reduction and elimination of undesired cells
- Demonstration of consistency

Potency

- Potency test should define biological activity, number and differentation status of cells needed for intended use
- Should correlate with the intended therapeutic effect

Quality-related issues (3)

Tumourigenicity

- Risk of tumourigenicity linked to the differentiation status
- The amount of proliferative and/or undifferentiated cells in the final product should be limited and justified

Process validation

- Process validation should include genotypic instability, tumourigenicity and phenotypic profile of the intended cell population

Non-clinical issues

Animal models

- Animal model should reflect the therapeutic indication; availability of disease models limited
- Large animal models
  - For long-term evaluation of tissue regeneration and repair, and safety follow-up
  - When size of the animal is relevant for the clinical effect
- Proof-of-concept studies
  - with human cells in an immunocompromised host
  - With equivalent animal cells in a homologous animal model
- Duration of studies should cover evaluation of long-term effects
- More than one animal species or strains may be necessary to cover different aspects
- Supplementary or alternative testing using *in vitro* tests

Non-clinical issues (2)

Biodistribution and niche

- Many stem cell types have the propensity to home to distant locations
- Differentiation and function of stem cells are dependent on and affected by the microenvironment
- Formation of ectopic tissue due to multi-lineage differentiation capacity
- Local non-physiological or toxic effects mediated by distributed cells
- Suitable methods for tracking of stem cells

Differentiation *in vivo*

- Expected differentiation *in vivo*
- Unintended differentiation

Non-clinical issues (3)

Tumourigenicity and genomic stability

- Intrinsic tumourigenic potential of ESCs and iPS cells (teratoma formation)
- Effect of culture conditions and extensive manipulation on the genomic instability
  - Prolonged *in vitro* culture
  - Rate of proliferative growth
  - Mechanical/enzymatic passaging
- Most sensitive models to be used for tumourigenicity evaluation

Immune rejection and persistence

- Elimination of cells due to immune rejection
- Persistence of cells; efficacy/safety

Clinical issues

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

Pharmacodynamics

- Mode of action which may be directly dependent on the stem cell population, molecules secreted by the cells or their engraftment in the host tissue, should ideally be confirmed in clinical trials
- Biomarkers capable of following the differentiation status of the stem cells at time of administration and during *in vivo* follow-up of the cell population needed
- In cases where suitable homologous animal models or other relevant preclinical models are not available additional clinical endpoints for efficacy and safety should be included

Clinical issues (2)

Pharmacokinetics

- Clinical biodistribution should be evaluated depending on the risk profile of the product and its mode of administration and localisation for administration
- The effect of different administration procedure, doses/cell numbers should be addressed during the preclinical and confirmed during the clinical studies
- Evaluation of time to engraftment and to achieve the clinical outcome
- Concern related to stem cell proliferation *in vivo*

Clinical issues (3)

Dose-finding studies

- The effective range of stem cells and/or stem-cell derived cells administered should be defined; when possible minimally effective dose should be defined
- Where formal dose-finding is not feasible it might be appropriate to begin an initial human clinical trial with a dose that could have a therapeutic effect and is justified on the basis of available nonclinical evidence for safety

Clinical issues (4)

Clinical efficacy

- Clinically meaningful endpoints related to the pharmacodynamic effect should be used
- Appropriate structural and morphological endpoints may be necessary in order to study regeneration, repair or replacement of a tissue
- Pivotal clinical study design
- The need for and duration of Post-Authorisation long term efficacy follow-up should be identified during the clinical studies

Clinical issues (5)

Clinical safety

- Stem cell-specific safety concerns
  - Tumourigenicity
  - Persistence and ectopic localisation of stem cells due to their self-renewal potential
- Safety follow-up can be combined with a parallel efficacy follow-up
- Suitable surrogate end points may be used for safety follow-up

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