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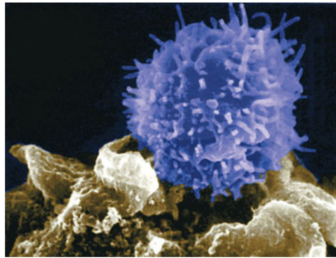
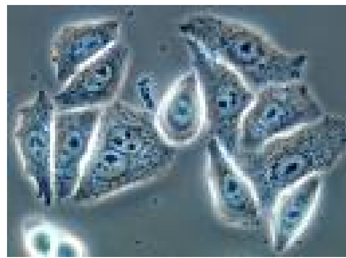

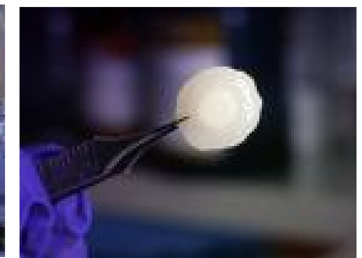

# Cell-based Medicinal Product - case study 1
# Cardioficticell

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# Disclaimer

- ✓ This case study is fully fictional and does not represent any real product under development
- ✓ The issues highlighted in the presentation, however, are built on the CAT experiences from different EMA processes e.g. from scientific advice
- ✓ The views expressed in this presentation are personal views of the speaker, and may not be understood or quoted as being made on behalf of the Committee for Advanced Therapies (CAT) or Committee for Medicinal Products for Human use (CHMP) or reflecting the positions of the CAT or CHMP. However, the regulatory requirements described in the presentation are based on the Regulation 1394/2007/EC, on technical requirements laid down in the revised Annex I, Part IV of Directive 2001/83/EC and on the EMEA/CHMP guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006).

# Cardioficticell

## Product

- 1 x $10^{10}$ viable bone marrow-derived stem cells / mL

## Indication

- treatment of heart failure

## Mode of action

- induction of cardiac repair (regeneration of cardiac tissue)

## Route of administration

- intramyocardial injections (max 10 injections)

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## Starting material

- ✓ 50 ml bone marrow aspirate

## Requirements for starting material

- ✓ donor testing according to Dir.2004/23/EC
  - HCV, HBV, HIV-1,2, syphilis, (HTLV-1)
  - additional testing (e.g. RhD, HLA, malaria, CMV, toxoplasma, EBV, *Trypanosoma cruzi*), case by case
- ✓ quality of the starting material
  - volume, amount of RBCs / hemolysis?
  - depends on the aspiration technique

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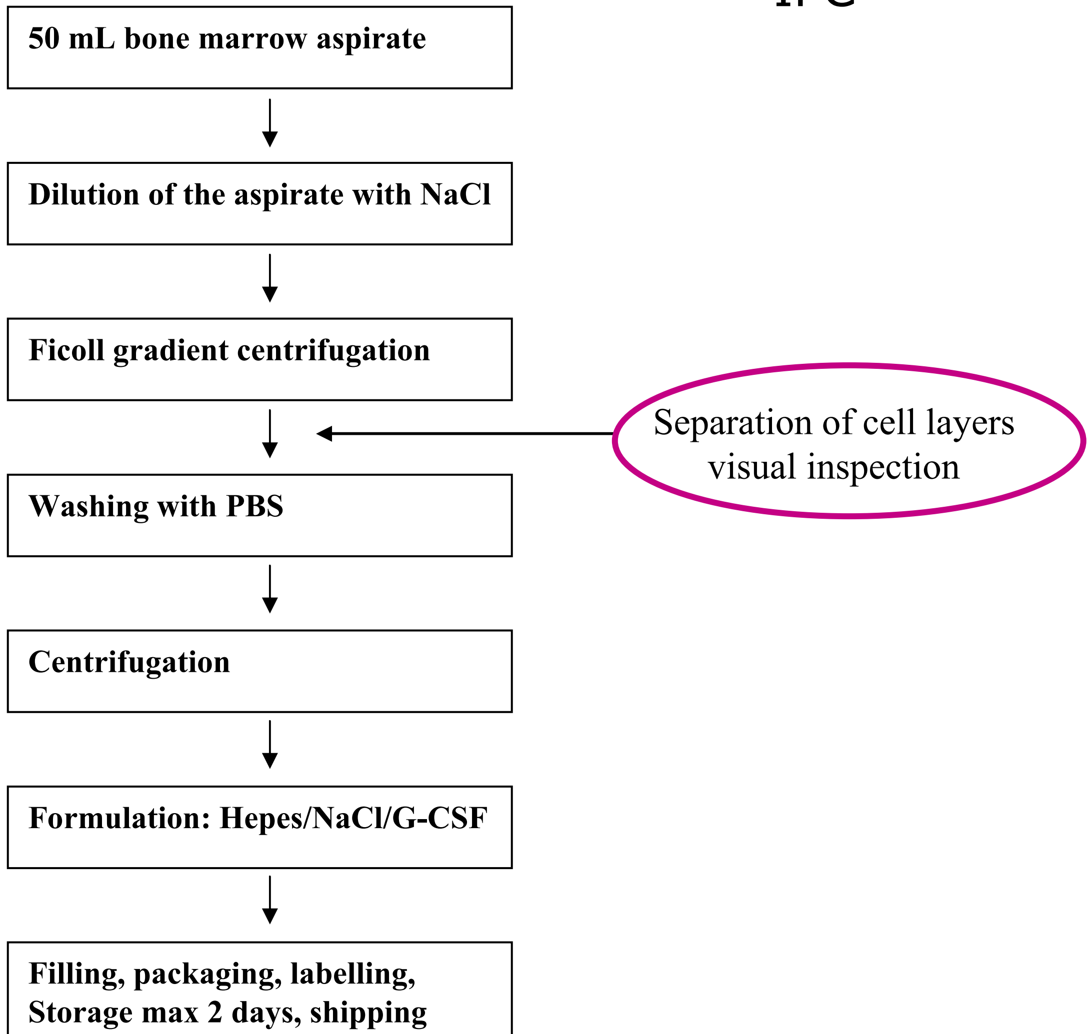
# Manufacturing process



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## Final product

- 1 x $10^{10}$ mononuclear cells in 1 mL Hepes/NaCl/G-CSF-buffer
- final composition
  neutrophils 20 - 50 %
  lymphocytes 20 - 40 %
  RBCs 5 - 50 %
  monocytes 10 - 20 %
  CD34+ cells 0 - 2 %
  CD133+ cells 0 - 1 %
- minimally manipulated cells for cardiac repair, DS=DP
- claim: hematopoietic stem cells are differentiated into cardiomyocytes

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# Release testing

| Test item | Test method | Specification |
|---|---|---|
| Cell viability | Trypan blue | > 80 % |
| Cell number | Trypan blue | ≥ 1 x $10^7$ cells |
| Identity CD 34<br>CD 133 | Flow cytometry<br>Flow cytometry | Positive<br>Positive |
| Potency CD34 + CD 133 | Flow cytometry | ≥ 2 % |
| Hepatitis B | PCR | Negative |
| Hepatitis C | PCR | Negative |
| Herpes 6, 7, 8 | PCR | Negative |
| Human parvovirus | PCR | Negative |
| HIV | PCR | Negative |
| Human polyoma virus | PCR | Negative |
| Sterility | Ph.Eur. | Negative |

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# Basic quality requirements

**GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS** EMEA/CHMP/410869/2006

**autologous / cell like or tissue like? / immunoactive? / proliferative or differentiated?**

Identity – markers, morphology, functionality
– test methods need to be specific for the cells / product

Cell purity – relevant cells, ratio of viable to non viable

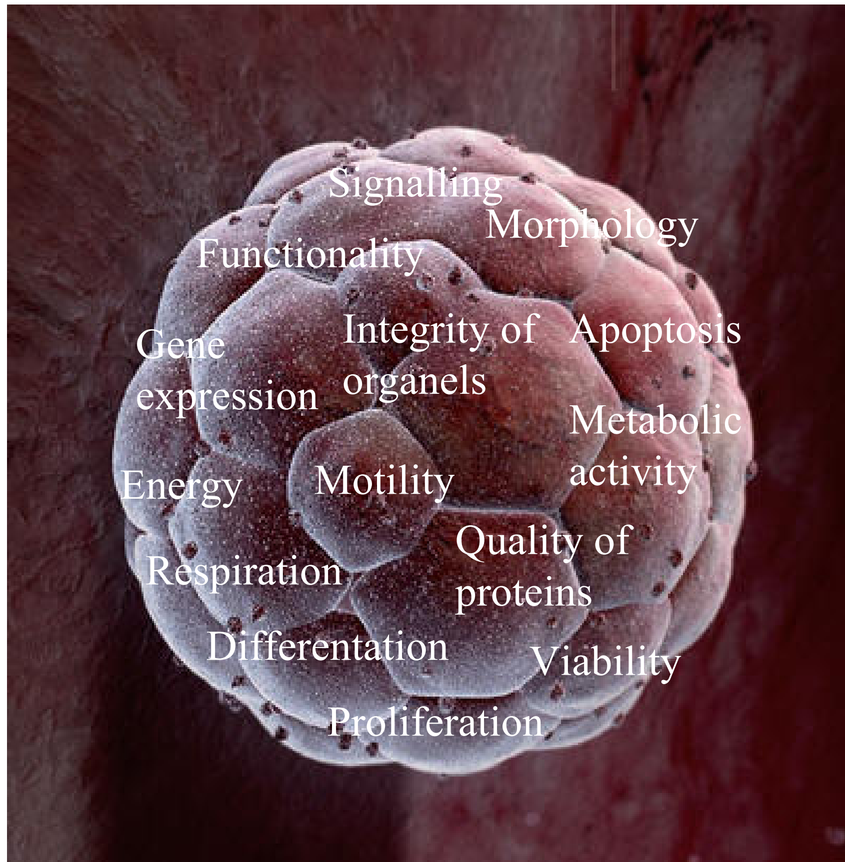
Impurities - product / process – related, unwanted cells, degradation products, adventitious agents, bioactive reagents

Potency – according to intended function, related to biological activity
– should detect clinically meaningful changes in the product
– required for comparability,consistency and stability

**Tumourigenicity , Karyology / Genetic Stability, Biocompatibility**

Release specifications for final products or intermediates : identity, purity / impurities, potency, sterility, cell viability and total cell number (dose)

# Critical parameters of cells?




Critical parameters of most MPs are related to molecular integrity;

Critical parameters of cells

- should safeguard both structural and functional integrity of the cells

-should be able to reflect changes in complexed, dynamic and viable entities

# Identity

- ✓ what are the cells that contribute to the therapeutic effect?
  - → is the MoA related really to cardiac regeneration? Which cells could possibly create new tissue in the heart? Proof that HSCs transdifferentiate to cardiomyocytes? Or is the activity related to mesenchymal stem cells (neovascularisation?)? If yes, there are no assays in batch release to detect the MSCs or control their activity
  - → is the MoA related to a paracrine effect? If yes, which cells could the ones needed for this activity? What are possible molecules to be followed?

→ product needs further characterisation!

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# Purity / Impurities

- ✓ product- related impurities?
  → cells needed for therapeutic activity vs. cells that have negative impact? Cell fragments, dead cells?

- ✓ process-related impurities?
  → Ficoll traces? Antibiotics used in any of the media?

→ product needs further characterisation!

- ✓ impurities may be assessed as part of process validation and if the removal of impurities is robust, they do not need to be analysed at release

- ✓ viral testing does not need to be repeated, if the donor testing and microbiological testing of raw materials is adequate

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# Potency

- ✓ poor potency assay proposed; what is the mechanism of action or expected biological activity of the cells that are needed for the therapeutic effect?
- ✓ in early development, potency can be measured by markers, but for MA functional assays are needed. These assays play a key role in evaluation of consistency, comparability and stability
- ✓ for paracrine effect, e.g. secretion of important cytokines, growth factors or other relevant molecules may provide a good potency assay. If HSCs/MSCs are expected to differentiate into cardiomyocytes or vascular epithelial cells, characterisation data and potency testing should support this claim

→ product needs further characterisation!
→ proper, justified and validated potency assay(s) required!

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# Confounding aspects that may hamper potency testing

- ✓insuffcent knowledge on the active component(s)
- ✓limited sample size / shelf life (autologous, primary cells)
- ✓unknown mode of action / lack of appropriate biological atribute
- ✓structural and functional complexity of the product
- ✓interfering substances / G-CSF

# Cell number / dose and viability

✓ dose is defined through non-clinical and clinical studies

✓ should take into account non-viable cells & cellular impurities in the product

✓ final product defined as $1 \times 10^{10}$ viable cells/mL. As viability is $\geq$ 80 %, the max cell number may be $1.2 \times 10^{10}$ cells/mL. What is the actual dose to be administered? How is the specification in line with the dose ($\geq 1 \times 10^{7}$ cells)? Is the inter-individual variability reflected in the spec? Limits for the actual dose to be administered should be set and the specification should be set so that a minimum acceptable dose is ensured at release

→ Final cell dose and cell number specification need to be defined!

# Consistency

- ✓ high inter-individual variability in starting material, company claims it is impossible to define exact cell composition
- ✓ consistency does not mean that every batch has to be exactly the same; consistency means that there are limits set for variability and the limits are qualified through NC and C studies (correlation between composition and safety/efficacy)
- ✓ Without a consistent product can one expect consistent results from non-clinical and clinical studies?

→ high variability and final cell composition need to be justified by NC and C data (RBA) or the bone marrow aspiration technique and/or production process improved / standardised to improve consistency and narrow down the specification limits for cell composition!

# Other relevant quality issues?

- ✓ tumourigenicity? Autologous, minimally manipulates cells
  → RBA, NC, C
- ✓ biocompatibility? Injection device –catheter and needle?
  → compatibility studies at quality level needed (dose)
- ✓ aseptic manufacturing process, GMP issues?
- ✓ stability evaluation / formulation?
- ✓ quality control system
  - → what tests should be as IPCs and/or release tests?
  - → what aspects could be solved through process validation?
- ✓ quality of the excipients (G-CSF!!) and impact on cells during storage / transportation?

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# Non-clinical development

- ✓ proof-of-principle
  → unclear functionality, variability of the product
  → further PD studies are needed
- ✓ toxicological effects predictive of the human response
  → autologous product; toxicity mainly related to G-CSF?
  → persistence and biodistribution of the cells important?
- ✓ information to select safe / efficacious dose
  → further elaboration on dose both at Q and NC level needed
- ✓ support to the route of administration
  → impact of several injections to heart?
- ✓ support duration of exposure and duration of follow-up
  → administration issues, fate of cells?

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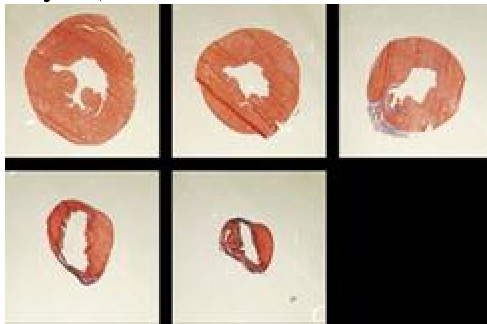
# Clinical development

- ✓ dose finding and proof-of-concept for MAA
  → hampered by poorly defined and controlled product, inconsistent production
- ✓ safety evaluation
  → autologous cells, minimally manipulated (RBA), G-CSF?
- ✓ proof of efficacy
  → high product variability, minimal PoC and PoE
  → patient population/indication, number of patients?
  → end-points? Morbidity-related or also structural/functional?
  → study design? Controlled, blinded study? Comparator?
  → follow-up? Risk management activities?
- ✓ establish a link from the quality of the cells to the clinical outcome (root cause of treatment failures?)

# What lies behind a therapeutic effect?

## Injection Induces Myocardial Regeneration Without Stem Cells

July 24, 2009



July 24, 2009 – Injured heart tissue normally can't regrow, but researchers at Children's Hospital Boston have now laid the groundwork for regenerating heart tissue after a heart attack without the use of stem cells, in patients with heart failure, or in children with congenital heart defects.

In the July 24 issue of Cell, they show that a growth factor called neuregulin1 (NRG1), which is involved in the initial development of the heart and nervous system, can spur heart-muscle growth and recovery of cardiac function when injected systemically into animals after a heart attack.

Thank you for your attention!