Regulation of advanced blood cell therapies

• Clinical trials using cell-based products
• Substantially manipulated cells and cells for non-homologous use
• Quality, safety and non-clinical aspects
• The future
Types of cellular blood products

- transfusion medicine
  - erythrocytes
  - thrombocytes
  - leukocytes
  - granulocytes

- stem cell containing products
  - blood-derived
    - peripheral blood
    - chord blood
  - bone marrow-derived
haematopoietic reconstitution and transfusion medicine

stem cell containing products from the bone marrow
Stem cells for haematopoetic reconstitution (CD34+) from blood or bone marrow

- known
  - Blood stem cell transfer for cancer treatment (chemotherapy, radiation therapy)
  - DLI - Donor Lymphocyte Infusion (GvHD)

- rather new
  - blood system disorders (ß-thalassemia, other haemoglobinopathies)
  - immune system disorders (SCID, ALD, etc.)

- allogeneic cells can be banked
- autologous cells are often used directly or after short manipulation
Cell-therapy medicinal products

- Liver repair
  allogenic liver cell suspension for treatment of acute sepsis or inherited metabolic liver failure

- Immunotherapy
  CTLs or NK cell transfer for adoptive immunotherapy

- Cell-based therapeutic vaccination
  - peptide-loaded DCs used as tumor vaccines to induce immunity towards tumor-associated antigens
  - fused tumor/DC hybrid cells
haematopoietic reconstitution and transfusion medicine

stem cell containing products from the bone marrow

somatic cell therapy; tissue engineering
Tissue engineering products
Non-clinical proof-of-concept needed, e.g., for cardiovascular applications to treat heart infarction

- Which kind of cells are appropriate for the treatment of the disease?
- What is the hypothesis for the mechanism of action?
- What is the appropriate manipulation of the cells?
- Are their cell surface markers to be used as specifications?
- Is there an appropriate animal model to show regeneration?
Stem cells from blood or bone marrow offer new treatment possibilities

- Pluripotent stem cells offer the possibility of a renewable source of replacement cells and tissues to treat a myriad of diseases, conditions, and disabilities including
  - Parkinson's disease,
  - amyotrophic lateral sclerosis,
  - spinal cord injury,
  - burns,
  - heart disease,
  - diabetes,
  - GvHD
  - and arthritis
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Regulation (EC) No. 1394/2007 on ATMP

Tissue Engineered Medicinal Product

Contains or consists of engineered cells or tissues of human or animal origin, or both.

Having properties for, or is used in or administered to human beings with a view to replace, repair or regenerate a human tissue

The cells or tissues may be viable or non-viable.

May contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices.
Cells or tissues shall be considered engineered if they fulfil **at least one** of the following points:

- Have been subject to **substantial manipulation**, so that their original biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are altered.

- The cells or tissues are **not intended to be used for the same essential function** or functions in the recipient as in the donor.

- The cells or tissues form **part** of a combined medicinal product.

**Manipulations not considered as substantial manipulations:**

- Cutting and grinding
- Sterilization / irradiation
- Cell separation, purification, concentration
- Soaking in antibiotic / antimicrobial solutions
- Shaping and centrifugation
- Filtering / lyophilization
- Freezing / cryopreservation
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Advanced blood cell therapy products: regulations in common with other blood products

- allogeneic
  - appropriate donor selection (HLA compatibility)
  - viral and microbial safety
  - storage, preservation/banking and transport

- autologous
  - microbial safety
  - storage, preservation/banking and transport

- manufacture
  - GMP
  - manipulations
  - specifications/quality
  - identity
  - sterility
CBMPs – quality aspects

Genetic stability – Do you know your cells?

– Technique of choice: GTG, FISH, subtelFISH, SKY, SNP-Array, …?

P0: Karyotype: 46,XX

P20: Karyotype: 41, X, -X, -1, + del(1)(q10→qter), t(2;13)(qter→p21::q22→qter), + t(2;13)(pter→p21::q22→pter), t(3;5)(pter→q29::q33→qter), -4, -8, + t(8;9)(qter→q11::p12→pter), + t(8;9)(p10→p21::p12→p10), + t(8;12)(q11;p12), del(9)(q10→qter), -9, -10, -11, -13, -14

from: Heidrun Holland, TRM, Leipzig
CBMPs – Challenges (III)

Potential (long-term) safety issues of CBMPs

- Infections
- Inflammation
- Immunogenicity
- Immunosuppressive action
- Inappropriate differentiation
- Malignant transformation
- In vivo durability of biomaterials or device part
Risks associated with mode of administration

- intra-ventricular and intra-cerebral applications
- endoscopic applications
- catheter applications
- i.v.
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Challenge: iPS cells
A Breakthrough in Cell Biology
New cell types for potential broad therapeutic applications?

Why are iPS cells useful?

- New tools for studying development and function
- Development of disease models
- Discovering and testing new drugs
- Novel cell-based therapies?
  - Patient specific iPS lines could overcome problem of immune rejection
  - Avoid most ethical considerations associated with hES cells

ATMP Clinical Trial Applications within EU & Germany 3Q 2005 to 2Q 2009

trials

- Cell Ther. EU
- Gene Ther. EU
- Cell Ther. DE
- Gene Ther. DE
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Back-up slides
Tissue-Engineered Products

- Cartilage repair
  Autologous chondrocyte transplantation (ACT)
  1st & 2nd & 3rd generation products

- Skin regeneration
  Different skin cells (keratinocytes, fibroblasts)
  in combination with a sheet-like matrices/scaffolds
  Acute wounds, diabetic foot skin ulcers

- Bone regeneration
  Osteoblasts or bone-marrow-derived stem cells combined
  with ceramic-based scaffolds or biomaterials

- Cardiovascular regeneration
  Stem cells for heart regeneration
  Engineered autologous/allogeneic blood vessels or heart
  valves

- Complete organ engineering
  Artificial liver
  Artificial engineered trachea
Borderline Products

BM-SC, expands

(autolog) / allogen

Treatment of akute GvHD in Steroid-nonresponding Patients

Quelle: M. Bornhauser, Dresden