Federal Institute for Vaccines and Biomedicines

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Cell-based immune therapies – regulatory pathway and critical issues

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Agenda

- Regulatory framework for cellular immune therapies
- Regulatory requirements for CAR T-cells: quality and non-clinical aspects
- Issues of concern
- Guidance

Cellular immune therapies

➢ Non-ATMP

➢ Advanced Therapy Medicinal Product (ATMP)

1. cells are not intended to be used for the same essential function(s) in the recipient and the donor (non-homologous use)

OR

2. cells have been subject to substantial manipulation so that relevant biological characteristics, physiological functions or structural properties have been al

Manipulations not considered as substantial:
- Cutting and grinding
- Shaping and centrifugation
- Sterilization/irradiation
- Filtering/lyophilization
- Cell separation, purification, concentration
- Freezing/cryopreservation
- Soaking in antibiotic/antimicrobial solutions

ATMPs - Definition

TISSUE ENGINEERING PRODUCT

SOMATIC CELL THERAPY MEDICINAL PRODUCT

is a biological medicinal product which

(a) is substantial manipulated or used in non-homologous way AND

(b) is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues

GENE THERAPY MEDICINAL PRODUCT

means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence AND

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence

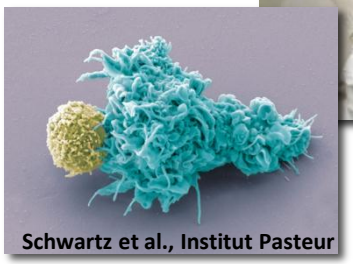
Gene therapy medicinal products shall not include vaccines against infectious diseases.

Cellular immunotherapies

SOMATIC CELL THERAPY MEDICINAL PRODUCT

- CTLs or NK cells for adoptive immune therapy
- RNA or peptide-loaded DC
- fused tumor cells/DC hybrids
- MSCs for GvHD treatment

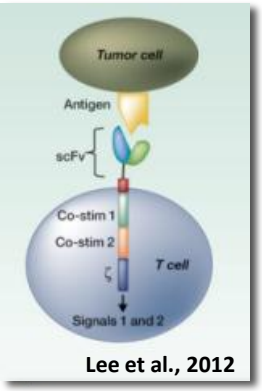

Dendreon Corp.


Schwartz et al., Institut Pasteur

Orisis Therapeutic Inc.

GENE THERAPY MEDICINAL PRODUCT

- Genetically modified tumor cells
- RNA-loaded DC
- Transgenic TCR gene modified cells
- CAR T-cells



Lee et al., 2012

www.mologen.com

Regulatory landscape in Europe

Marketing authorisation (incl. conditional, exeptional)

- Centrally authorised by the European Commission
- Evaluation via Committee of Advanced Therapies (CAT) + CHMP
- Detailed in Regulation EC/726/2004 and Directive 2001/83/EC

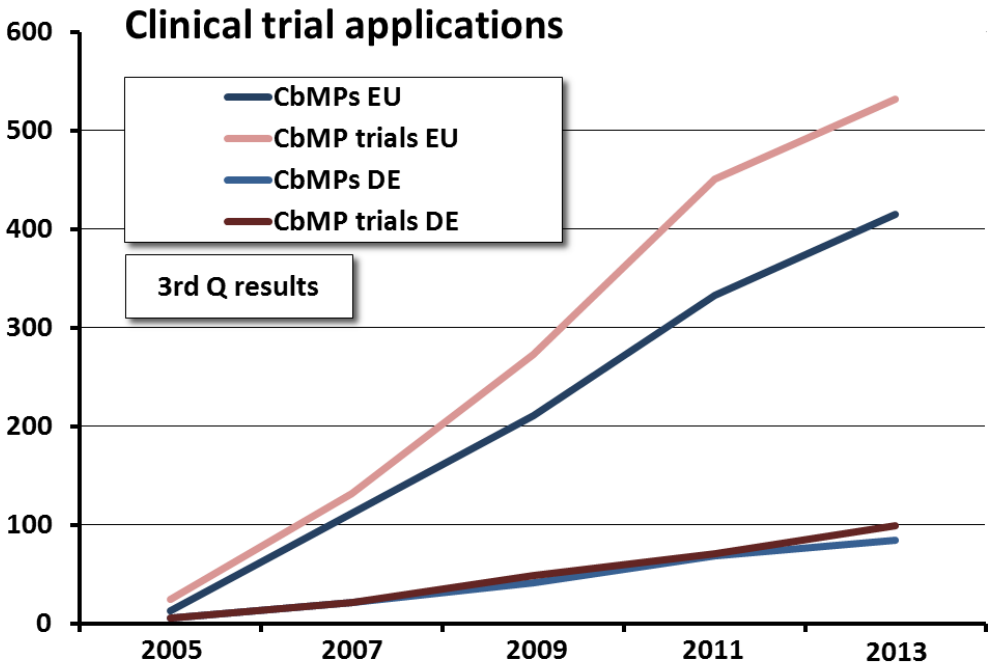
Hospital exemption

- Nationally authorised
- Restricted to ATMPs prepared on an non-routine basis for an individual patient used under professional responsibility

Clinical trials

- Nationally regulated (German Drug Law, 3rd Notification on the clinical trial of medicinal products for human use)
- Voluntary harmonisation procedure (VHP)
- Clinical Trials Regulation repealing Directive 2001/20/EC (proposed approval date mid 2014)

CBMPs applications in EU & Germany



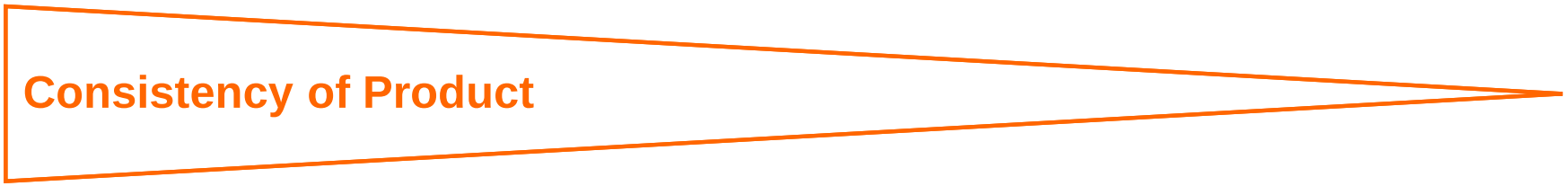
Approved cell therapies

- ChondroCelect (TiGenix)
- Maci (Genzyme)
- **Provenge (Dendreon)**

Cell Therapy MPs	3Q 2005	3Q 2007	3Q 2009	3Q 2011	3Q 2013	
trials/products	25/13	132/112	292/211	451/333	532/415	EU
cancer immunotherapy	3	45	92	141	169	
trials	6	14	32	48	69	Germany
cancer immunotherapy	1	2	8	12	18	

Regulatory aspects of CAR T-cells

plasmid DNA naked complexed	genetically modified microorganism	replication-competent virus	replication-deficient virus vector	genetically modified cell lines	genetically modifed primary cells

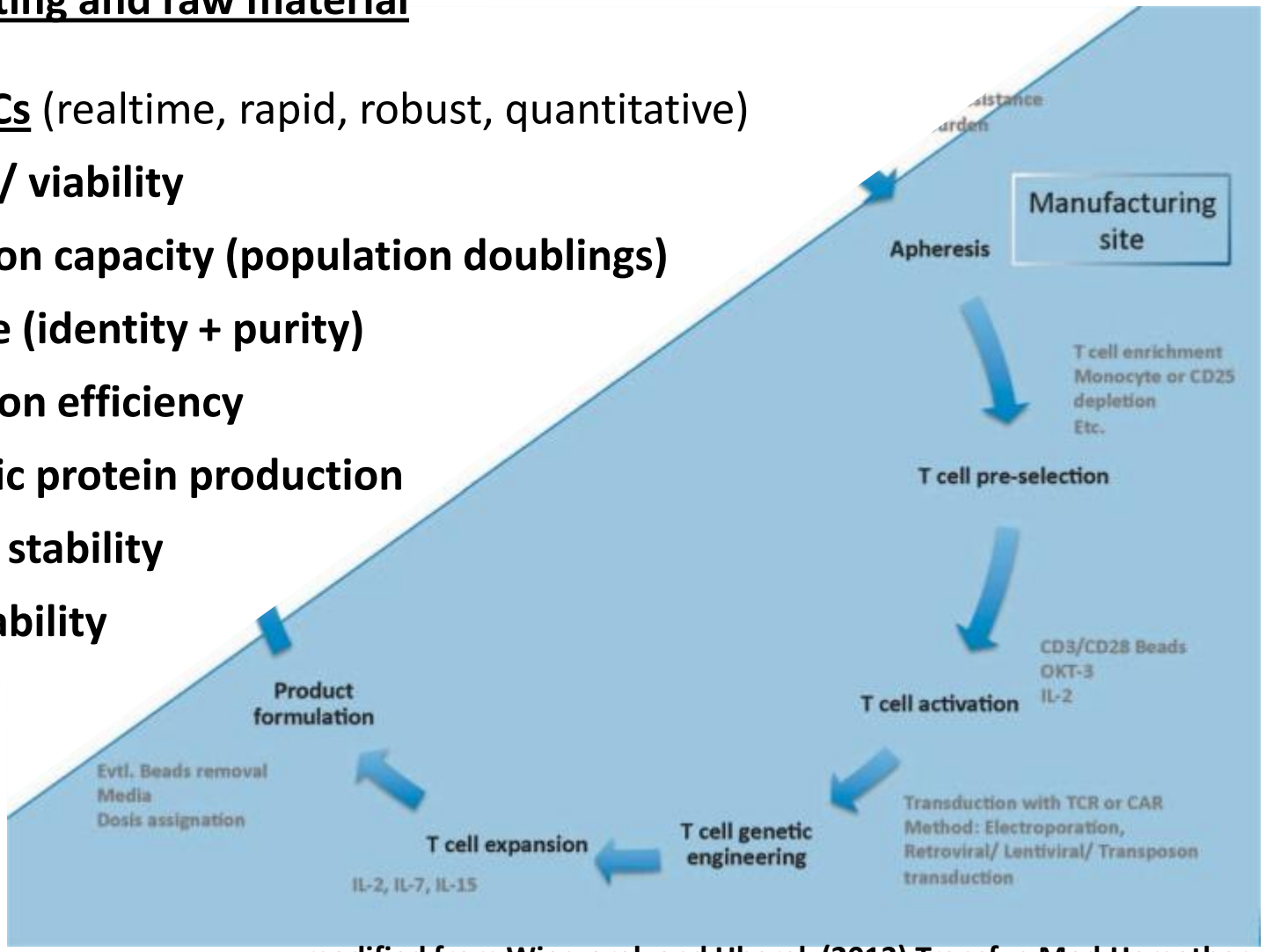


Manufacturing aspects

Quality of starting and raw material

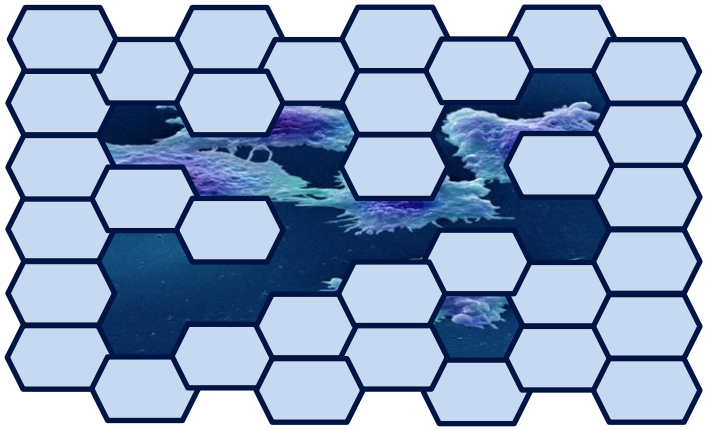
Meaningful IPCs (realtime, rapid, robust, quantitative)

- **cell count / viability**
- **proliferation capacity (population doublings)**
- **phenotype (identity + purity)**
- **transduction efficiency**
- **therapeutic protein production**
- **functional stability**
- **genetic stability**
- **sterility**



modified from Wieczorek and Uharek (2013) Transfus.Med.Hemother.

TCR /CAR T-cells – Characterisation and QC



- Mycoplasma (EP 2.6.7)
- Endotoxin (EP 2.6.14)
- Sterility (EP 2.6.27)
- **Cell viability / total cell number**
- **Identity / Purity**
  - **Multiple specific markers indicative of cell type**
  - **Vector presence**
  - **Reduction or elimination of undesired cells**
  - **Demonstration of consistency**
- **Impurities** (Product/process-related)

TCR /CAR T-cells – Characterisation and QC

- **Number of transduced (therapeutically active) cells**
- **Transgene expression levels**
- **Average copy number/cell, integration site mapping in case of targeted integration**
- **Absence of RCV, modifying enzymes (TALENs, transposons, ZFNs)**
- **Potency**
  - **(Ideally) reflects biological activity, should correlate with intended therapeutic effect. (At least) shows consistency of the product.**
- **Stability**
- **Other**
  - **Conditions of transport**
  - **In use stability**

Aims of non-clinical studies

- proof-of-principle including mode of action
- biodistribution of the cell therapy to identify potential target organs of toxicity
- identification of toxic effects including immunotoxicity and tumorigenicity
- estimation of clinical starting dose
- identification of patient eligibility criteria
- identification of clinical monitoring parameters

CAR T-cells – non-clinical aspects

PHARMACOLOGY:

- ✓ dose dependent therapeutic efficacy, e.g. using tumor bearing animal models
- ✓ activation and proliferation capacity of CAR T-cells
- ✓ MoA - effect mediated by CAR (target blocking, transduced vs. untransduced cells, specificity)

PHARMACOKINETICS:

- ✓ distribution, engraftment and persistence of CAR T-cells
- ✓ capability of IMP to migrate to target area
- ✓ duration and level of CAR expression
- ✓ parameters should mimic clinical situation

CAR T-cells – critical safety issues

- **On-target / off-tumor toxicity**
  - low level antigen expression in non-target tissues
  - use of high affinity CARs
- **Off-target/off-tumor toxicity**
  - Presence of similar epitopes detected by CAR, rather an issue of transgenic TCR ??
- **Identification of a safe clinical dose**
  - In vivo expansion of administered cells
  - Excessive T-cell proliferation
- **TLS**
- **Cytokine release syndrome**
- **GvHD (use of allogeneic T-cells)**
- **Insertional oncogenesis** (criticality dependent on vector, integration events, cell impurity levels)

Points to consider .....

..... when addressing safety of CAR T-cells

- Use of suitable animal models, or justify
- Use of batches comparable to clinical batches (e.g. composition of cell types, % transduced cells etc.)
- Use of model tumors reflecting clinical TAA expression levels
- Clinical data with similar CAR might be supportive
- Provision of an appropriate safety strategy re. CAR T-cell elimination (suicide gene, tags, regulated CAR expression/activity, mABs)

Regulatory guidance for CIMT

London, 30 May 2008
Doc. Ref. EMEA/CHMP/GTWP/125491/2006

GUIDELINE ON SCIENTIFIC REQUIREMENTS FOR THE ENVIRONMENTAL RISK ASSESSMENT OF GENE THERAPY MEDICINAL PRODUCTS

London 30 May 2008
EMEA/CHMP/GTWP/125459/2006

GUIDELINE ON THE NON-CLINICAL STUDIES REQUIRED BEFORE FIRST CLINICAL USE OF GENE THERAPY MEDICINAL PRODUCTS

London, 10 October 2007
Doc. Ref. EMEA/CHMP/BWP/271475/2006

GUIDELINE ON POTENCY TESTING OF CELL BASED IMMUNOTHERAPY MEDICINAL PRODUCTS FOR THE TREATMENT OF CANCER

London, 21 May 2008
Doc. Ref. EMEA/CHMP/410869/2006

GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS

London, 22 October 2009
Doc. Ref. EMEA/CHMP/GTWP/60436/2007

GUIDELINE ON FOLLOW-UP OF PATIENTS ADMINISTERED WITH GENE THERAPY MEDICINAL PRODUCTS

Regulation of ATMPs

Case by case decision on requirements
Employment of a tailored approach
Allowing sufficient flexibility for product developments

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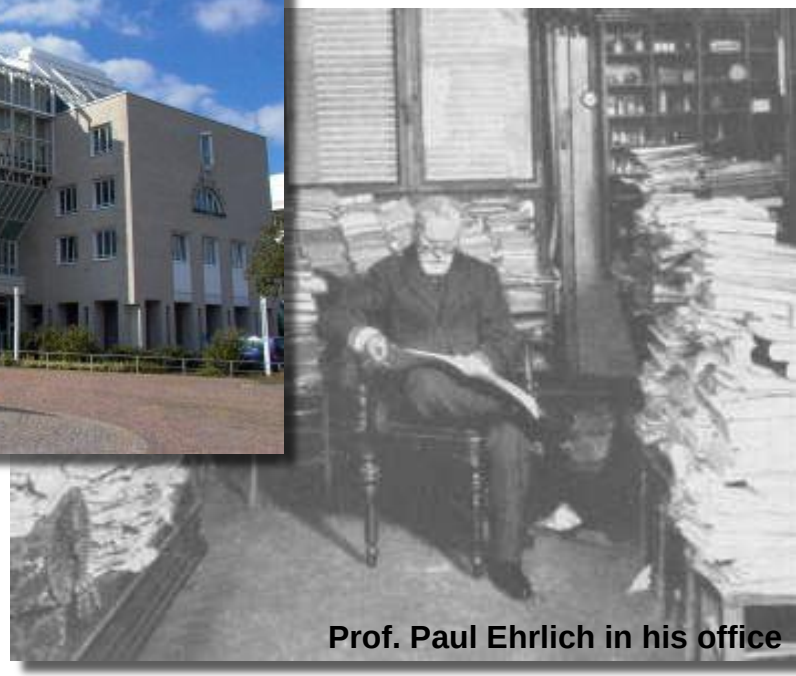

Prof. Paul Ehrlich in his office

Thank you !

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