Considerations in Product Development with Advanced Therapies and Cancer Vaccines

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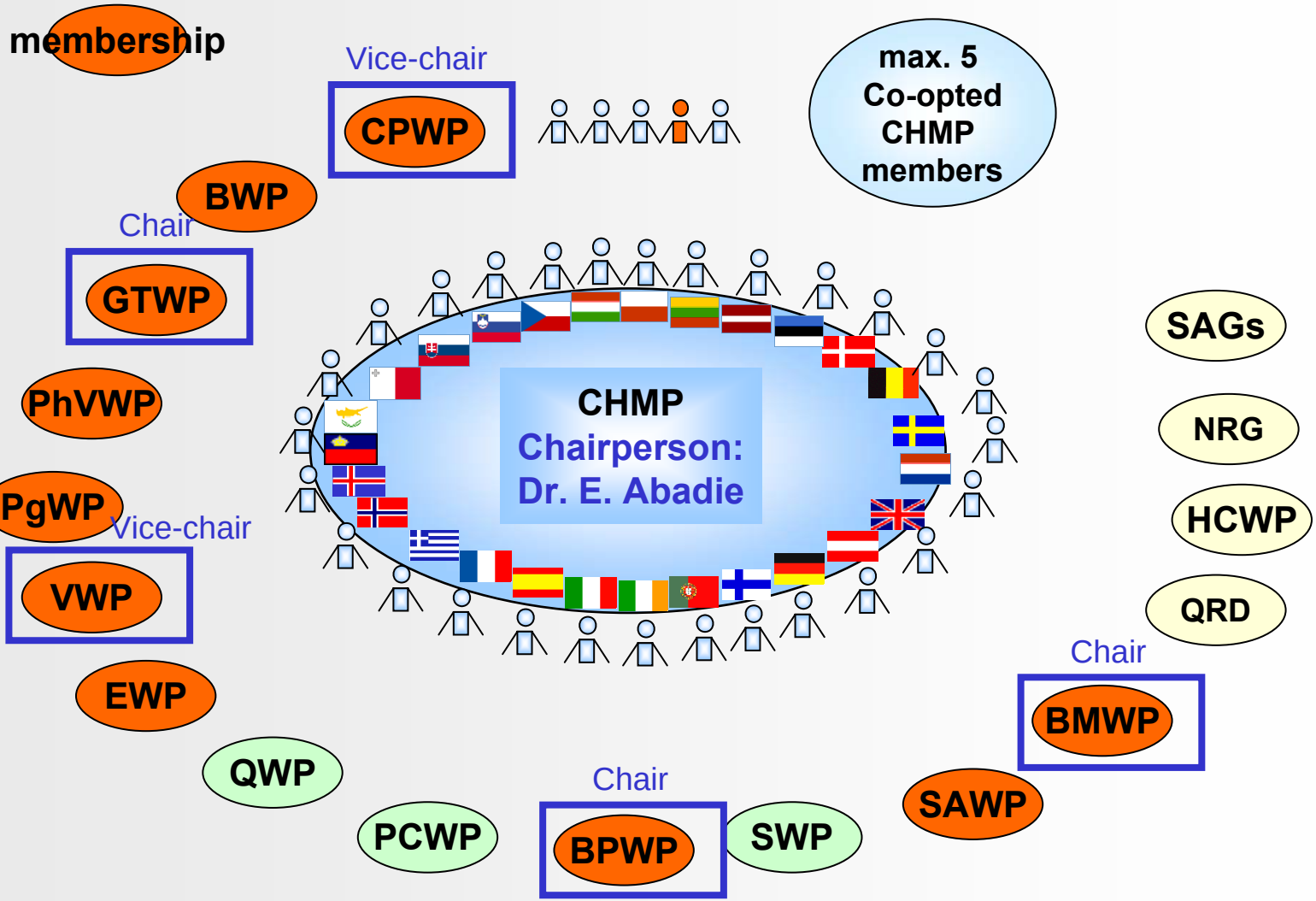
Federal Agency for Sera and Vaccines

- Responsibility for sera, vaccines, blood preparations, bone marrow preparations, tissue preparations, allergens, gene transfer medicinal products, somatic cell therapy products, xenogenic cell therapy products and blood components manufactured using genetic engineering
- Marketing authorization (national and EU)
- Clinical trial authorization (pure national responsibility)
- Batch control
- Pharmacovigilance
- Inspections (EMEA-GCP/GMP), support of regional authorities (manufacturing license, routine GMP inspections)
- Research in the fields of immunology, biotechnology, virology

Membership of Paul-Ehrlich-Institut in EMEA Working Parties



Guidance for Advanced Therapy Products Including Cell-Based Cancer Vaccines

- Draft Guideline on GCP for ATMPs available from the European Commission (traceability, patient follow up, licensed tissue establishments)
- EMEA Guideline on Human Cell-Based Medicinal Products available since September 2008 (CMC, preclinical, clinical)
- No Guidance available for Cancer Vaccines in general
- EMEA Guideline on Potency Testing of Cell Based Immunotherapy Medicinal Products for the Treatment of Cancer

Diversity of Substances Used for Therapeutic Cancer Vaccination

Only some of the following are Advanced Therapy Products

- RNA (possibly defined as ATMP in the future)
- **DNA**
- Synthetic peptides
- Virus-like particles (e.g. Bacteriophage Q_{beta})
- Recombinant proteins
- Cell lysates
- **Somatic cells**

Products are often used together with novel adjuvants and formulations such as MPL, TLR, and liposomal formulations, respectively.

Definition of Somatic Cells Therapy Medicinal Products in the EU

L 159/46 EN Official Journal of the European Union 27.6.2003

COMMISSION DIRECTIVE 2003/63/EC

of 25 June 2003

amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use

... somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means. This manipulation includes the expansion or activation of autologous cell populations ex vivo (e.g., adoptive immuno-therapy)...

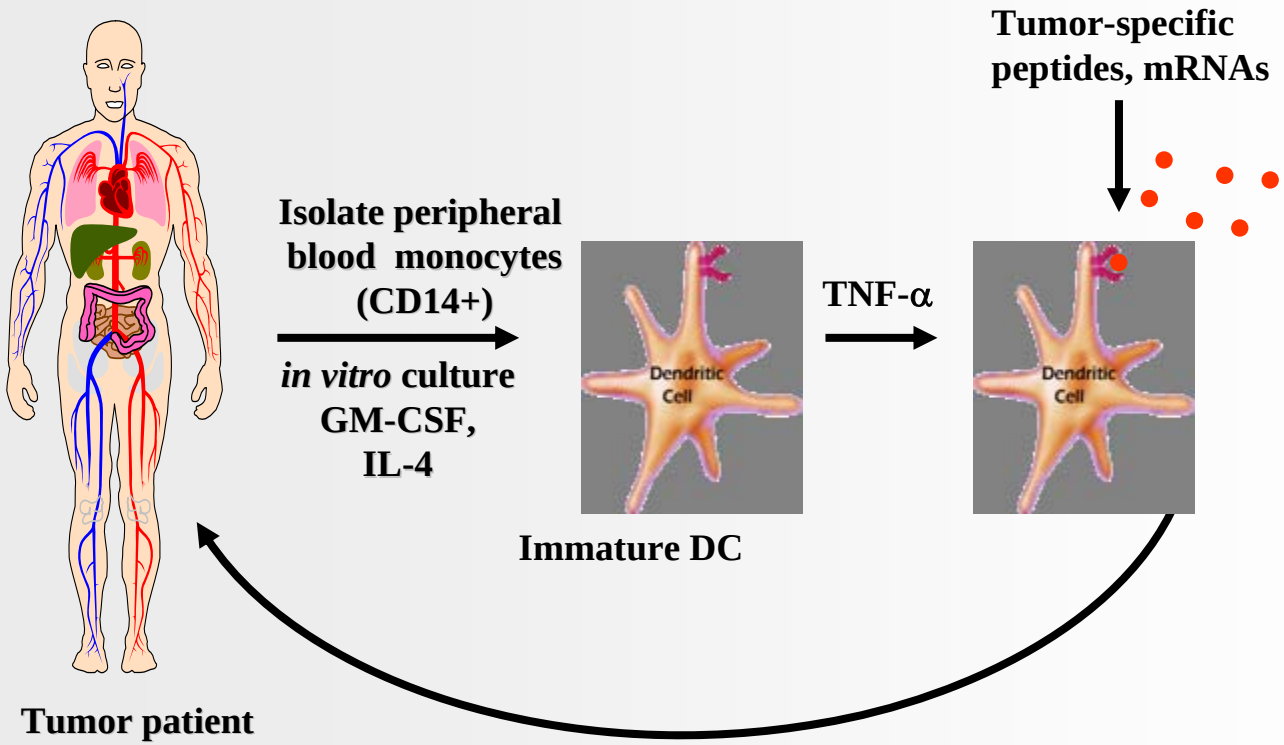
Substantial Manipulation of Cells According to Advanced Therapy Regulation 1394/2007/EC

- Manipulations not considered substantial:

  — cutting
  — grinding
  — shaping
  — centrifugation
  — soaking in antibiotic or antimicrobial solutions
  — sterilization,
  — irradiation,
  — cell separation, concentration or purification,
  — filtering
  — lyophilization
  — freezing
  — cryopreservation
  — vitrification

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

Cell-Based Cancer Vaccine Using Substantially Manipulated Cells



Eligibility of Dendritic Cell-Based Cancer Vaccines to EMEA Procedure

EMEA/CHMP Conclusion for dendritic cell-based cancer vaccine:

"…falls into the class of advanced therapy medicinal products (Part IV of the annex to Directive 2001/83/EC as amended), and more specifically into the class of somatic cell therapy medicinal products."

How to Develop Cell-Based Medicinal Products?

Human Cell-Based Guideline

- Cell-Based Products should be developed on the basis of a risk analysis

- The results of the risk analysis should be used

  - to identify risk factors associated with the quality and safety of the product

  - determine the extent and focus of non-clinical and clinical studies

Some Risk Factors of Cell-Based Products

Human Cell-Based Guideline

- Origin (autologous vs. allogeneic)
- Ability to proliferate and differentiate
- Ability to initiate an immune response
- Level of cell manipulation (in vitro/ex vivo expansion/activation/genetic manipulation)
- Mode of administration (ex vivo perfusion, local, systemic)
- Duration of exposure (short to permanent)
- Combination product (cells + bioactive molecules or structural materials)
- Availability of clinical data on or experience with similar products

Reflection Paper on the practical application of the risk-based approach for cell-based products will be published by EMEA

Quality of Cell-Based Medicinal Product at Release

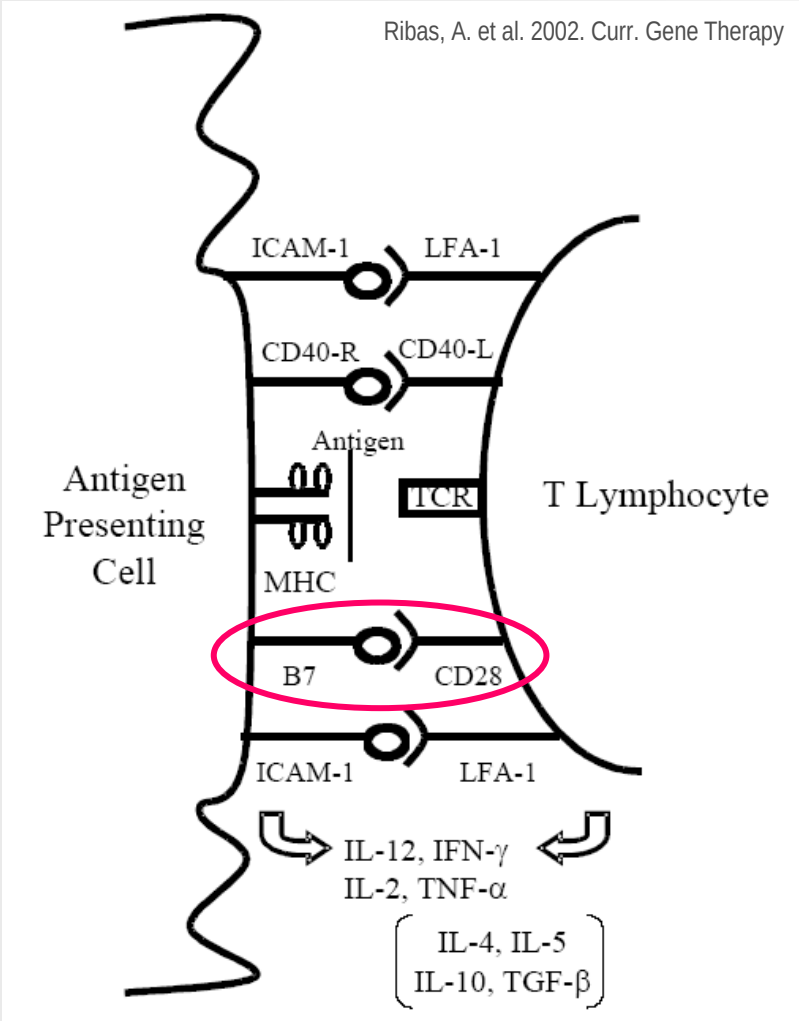
Human Cell-Based Guideline

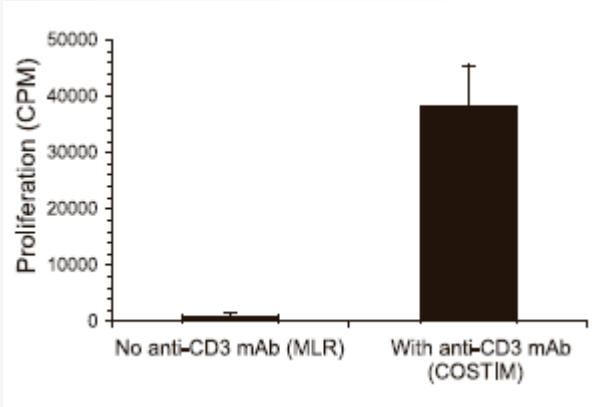
- Identity (CD marker by FACS etc.)
- Purity (consider contaminating cells, control consistency of complex cellular preparations)
- Cell number
- Sterility
- Viability
- Potency

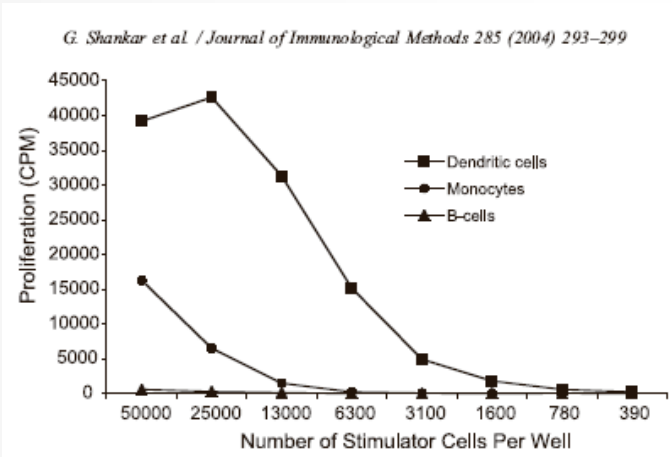
Guideline on Potency Testing of Cell Based Immunotherapy Medicinal Products for the Treatment of Cancer

- Acknowledges that complex and laborious potency assays are not suitable for release testing of product. Such potency testing rather to be used for product characterization
- Surrogates can be tested such as co-stimulatory molecule expression in case of dendritic cells
- Correlation of surrogate with real biological activity has to be shown

Measure Expression of Costimulatory Molecules as Surrogate for Potency of Dendritic Cells







Principles of Preclinical Development for Cell-Based Medicinal Products

Human Cell-based Guideline

- Conventional requirements as detailed in Directive 2001/83/EC may not always be appropriate
- Deviations from these requirements need to be justified
- The scrutiny applied during non-clinical testing should be proportional to the risk expected to be associated with clinical use

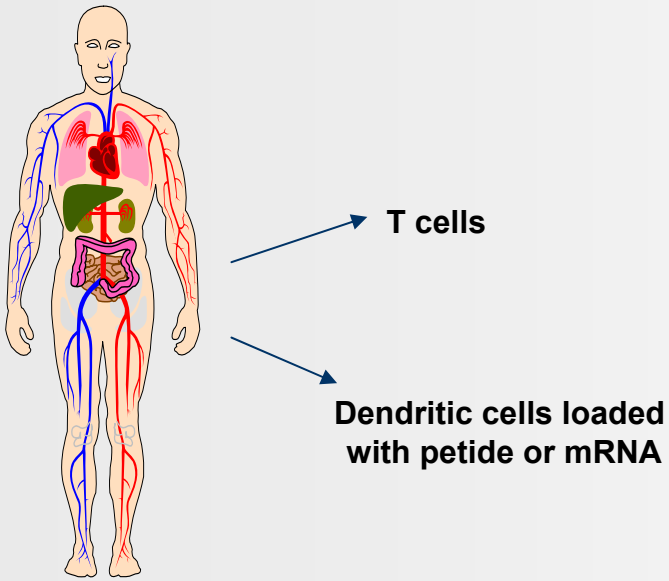
Non Clinical Development - General Aspects

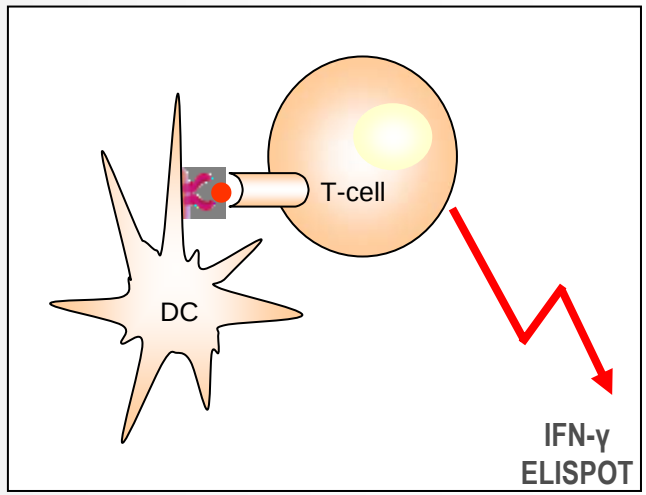
Human Cell-Based Guideline

- Objectives of the non-clinical studies are to
  - demonstrate proof-of-principle
  - define the pharmacological & toxicological effects predictive of the human response.
- The goal of non-clinical studies include:
  - to provide information on safe dose for clinical trials
  - to support the route of administration & application schedule
  - to support duration of exposure
  - to identify target organs for toxicity

In Vitro Preclinical Testing can Contribute to Proof of Concept

- Reasonable when using self antigens for tumor vaccination, e.g. peptides or mRNA
- Test for presence of antigen-specific T cells in peripheral blood of healthy donors
- Verify absence of central tolerance



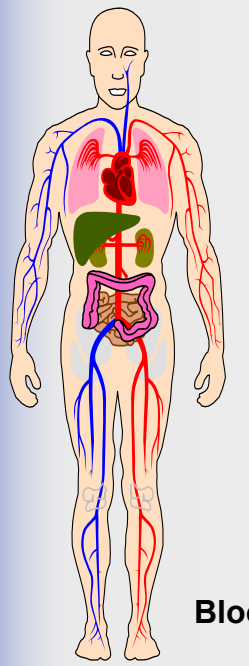


Animal Models

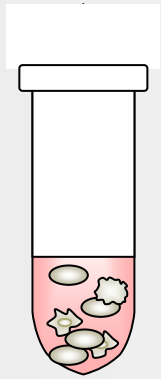
Human Cell-Based Guideline

- Relevant animal models should be used
- The chosen animal model may include immuno-compromised, knockout or transgenic animals
- Homologous models may be useful (mouse cells in mice)

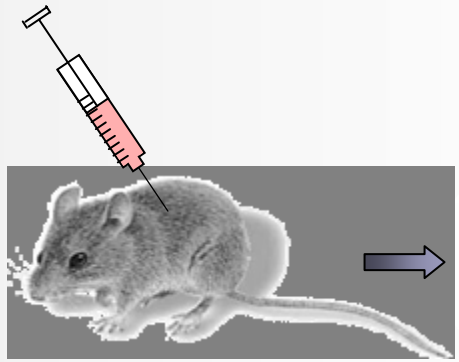
Several Preclinical Animal Models Could be Envisaged



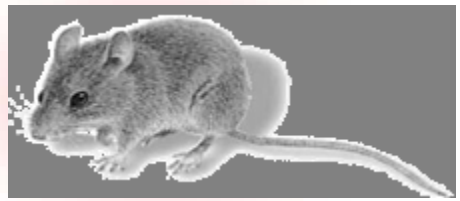
Blood donation



Isolation of human stem cells

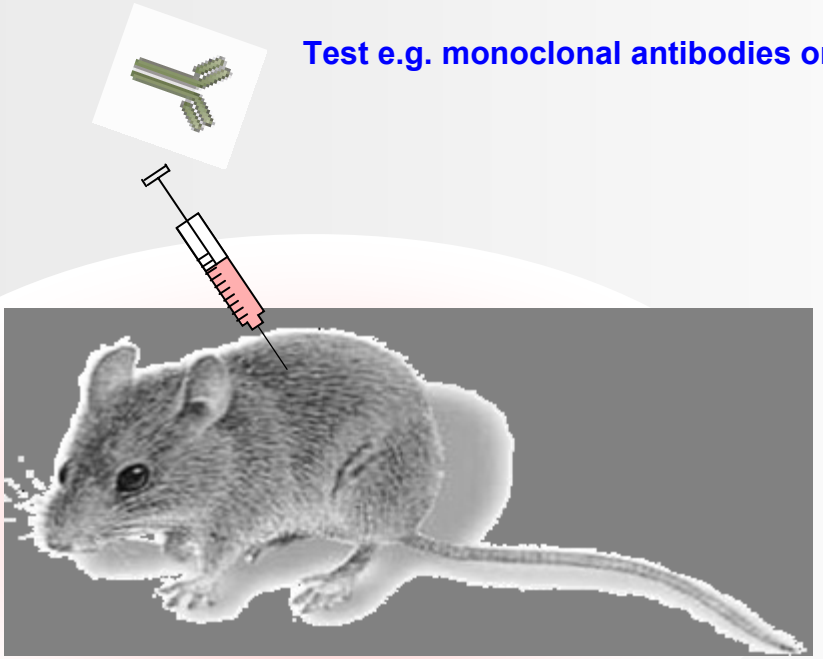


Transfer of human stem cells To e.g. RAG $^{-/-}\gamma c^{-/-}$



`Humanized´ mouse

Use of Humanized Mice for Preclinical Analyses



Test e.g. monoclonal antibodies or cells

Humanized mouse

- Cytokine storm?
- T cell proliferation?
- Depletion of cell subsets?

Toxicology
Human Cell-Based Guideline

Toxicity might emerge for example from

- Altered in vivo behaviour (proliferation, differentiation)
- Materials used during manufacturing
- Use of combination therapies (e.g. cell product plus adjuvants, cytokines etc.)
- **Auto immunity** especially in case of immune therapies

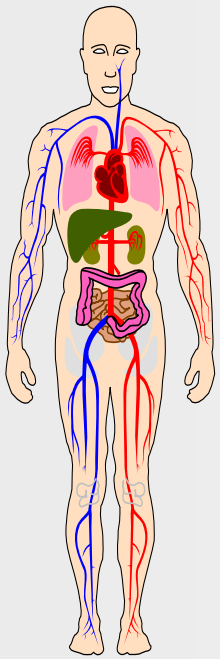
Local tolerance studies

- May be performed in single or repeated dose toxicity studies

Other toxicity studies

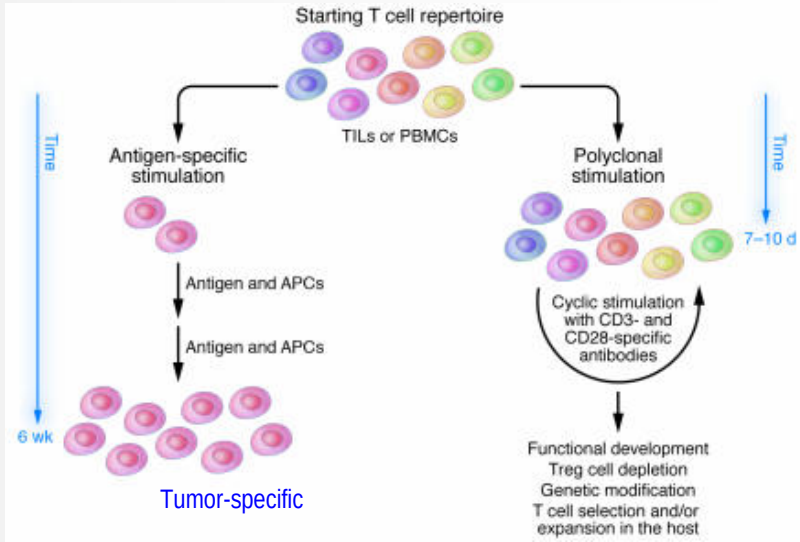
- Conventional carcinogenicity/genotoxicity normally not be required
- Tumourigenicity studies might be required (stem cells, tumour cells)

Risk for Auto Immunity after e.g. Adoptive Transfer of Tumor-Specific T Cells



Cancer patient

Isolate TILs from tumor tissue



Case of Autoimmunity After Adoptive T cell Transfer

- Carbonic Anhydrase IX (CAIX)-specific T cells expressing scFv adoptively transferred to treat renal cell carcinoma
- Stop of clinical trial due to grade 2-4 liver toxicities
- T cell infiltration around bile ducts
- CAIX expression found on bile duct epithelial cells
- Lamers, C.H. et al. (2006). Treatment of metastatic renal cell carcinoma with autologous T-lymphocytes genetically retargeted against Anhydrase IX: First clinical experience. J. Clin. Oncol. 24: e20

Estimate Risk Of Autoimmunity

- Tissue expression of some self antigens is well known, and sometimes restricted to only a few tissues, e.g. MAGE
  The risk for autoimmunity thus can be estimated and is probably low

- In case of new antigens their expression in tissues and organs should carefully be evaluated before going into clinical trials (in **vitro analyses**, such as RT-PCR, chip technology, histology etc.)

- Risk for autoimmunity is part of overall benefit/risk estimation

Thank you for your attention !