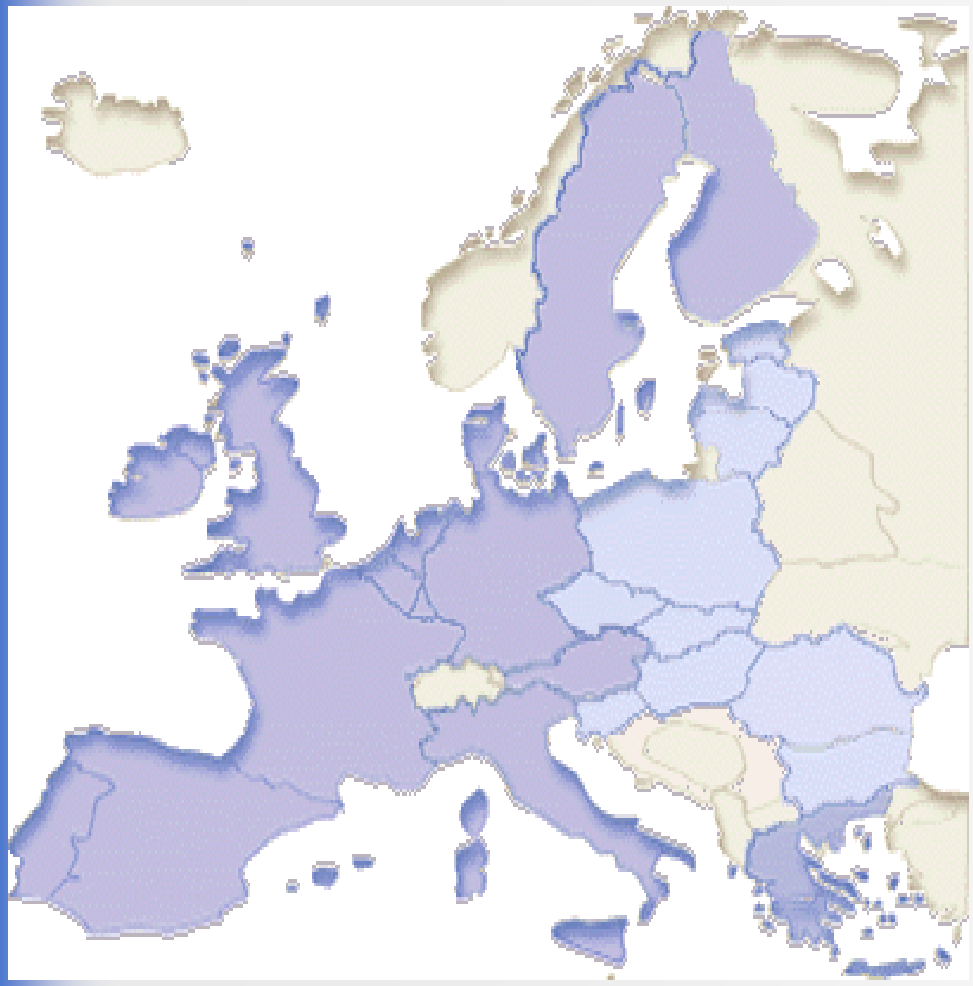
The Regulatory Environment for Therapeutic Vaccines

Thomas Hinz
Head, Section Therapeutic Vaccines
Paul Ehrlich Institute, Germany
hinth@pei.de

Topics Addressed

- Regulatory environment
  - EU
  - Germany
- Available EU Guidance for Therapeutic Vaccines
  - Guideline on human cell-based products
  - Guideline on potency assessment of cell-based immunotherapy products
- Preclinial and clinical issues

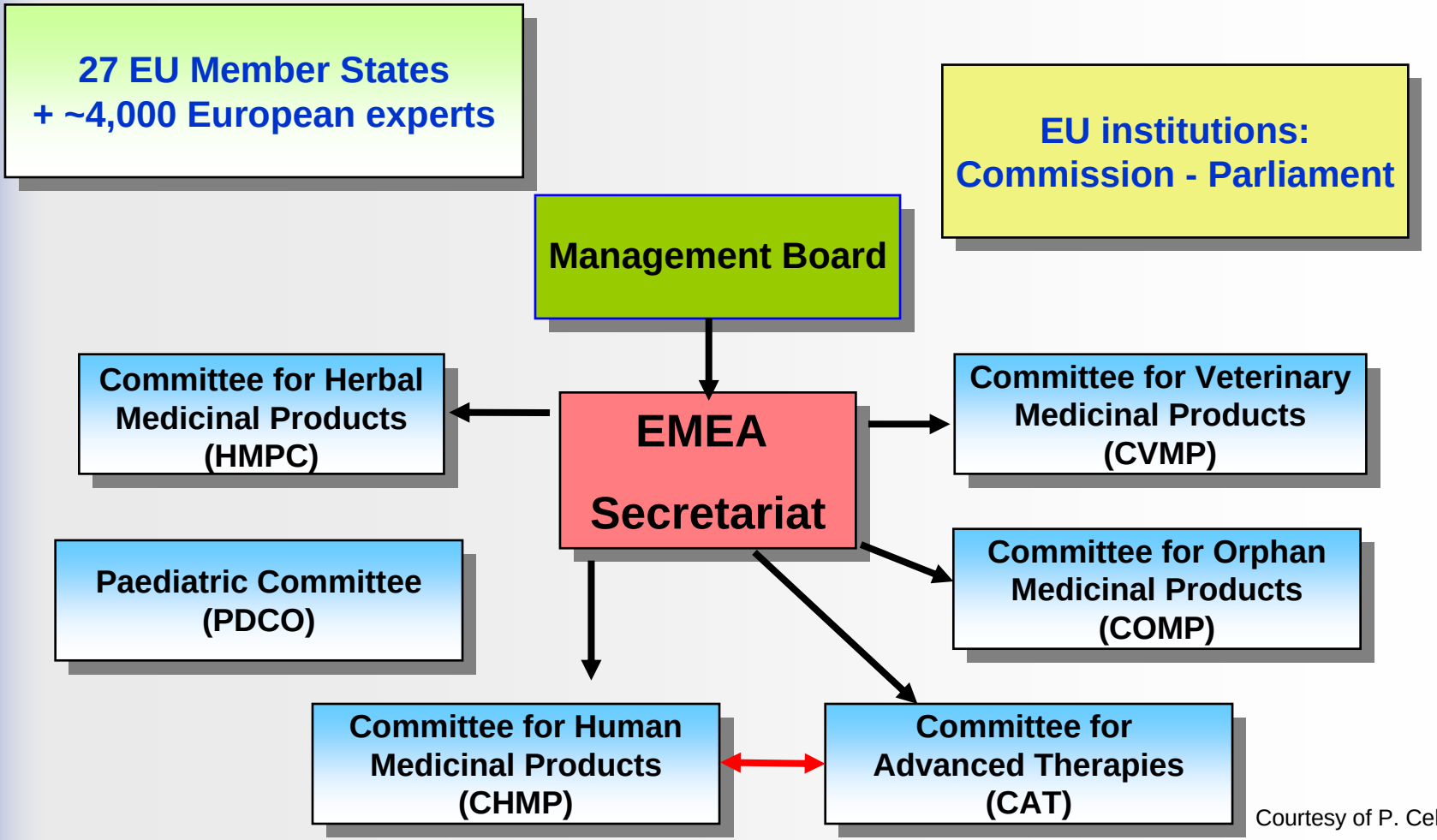
Network of EU Agencies



Courtesy of P. Celis, EMEA

Austria
Belgium
Bulgaria
Cyprus
Czech Republic
Denmark
Estonia
Finland
France
Germany
Greece
Hungary
Ireland
Italy
Latvia
Lithuania
Luxembourg
Netherlands
Malta
Poland
Portugal
Romania
Slovak Republic
Slovenia
Spain
Sweden
UK

European Medicines Agency (EMEA)



Courtesy of P. Celis, EMEA

Committee for Advanced Therapies (CAT)

- Evaluate & prepare draft opinions on Advanced Therapy Medicinal Products (ATMP)
  - Gene therapy, somatic cells, tissue engineered products
- Involvement in Scientific Advice on ATMP
- Additional tasks:
  - Certification of Quality / Non-clinical data (for SMEs)
  - Scientific recommendation on classification as ATMP
  - Evaluation of products already on the market

Products Licensed by EMEA via Centralized Procedure

- Scope (mandatory)
  - Biotechnology products / ATMP
  - Orphan drugs (rare diseases)
  - Medicines for treatment of:
    - AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune diseases/immune dysfunctions, viral diseases
- Scope (optional)
  - New chemical entity
  - Significant therapeutic, scientific or technical innovation

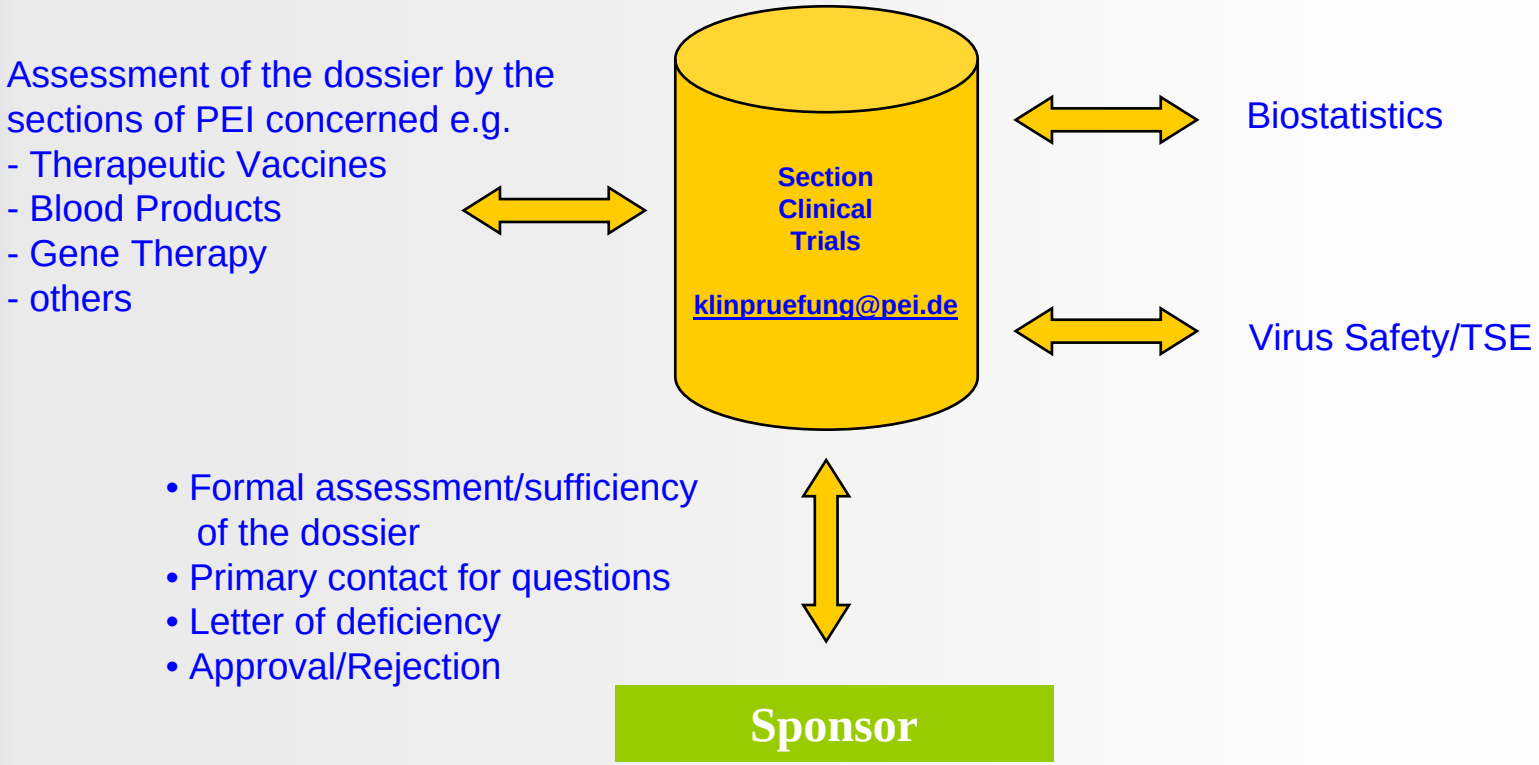
Paul-Ehrlich-Institut

- Marketing authorization of medicines in D or EU
  - 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
- Research in the fields of e.g. immunology, virology, hematology, allergology
- Batch control (licensed vaccines)
- Pharmacovigilance (safety. i.e. AE, SAE, SUSAR)
- National scientific advice
- Inspection (GCP, GMP)
- Clinical trial authorization

Approval of Clinical Trials

- Remains the responsibility of the member states where the trial is conducted
- Based on EU harmonized GCP legislation
- EMEA is hosting the 'Clinical trials facilitation group'
  - Voluntary Harmonized Procedure (VHP) might be possible for multinational, first-in-human, phase III trials. For more information see http://www.hma.eu/78.html

Approval of Clinical Trials at PEI



Regulation of Therapeutic Vaccines in the EU

Legal Basis for Therapeutic Vaccines

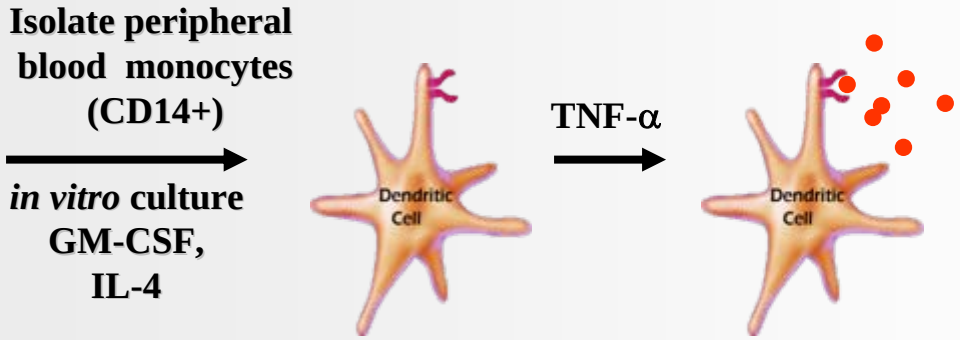
- No Pharm. Eur. definition for Therapeutic Vaccines available
  - specific and active immunity in man against an infecting agent (Ph. Eur. 5.05)
- No Definition of Therapeutic Vaccines in Community Code (Directive 2001/83/EC)
- No Definition in German Drug Law (Arzneimittelgesetz)
- Problem: The legal basis for EMEA guidelines addressing the manufacturing and quality control, preclinical and clinical requirements for Therapeutic Vaccines is missing.

Why No Legally Binding Definition for Therapeutic Vaccines?

- Political: Public might be confused since vaccination means the protection of healthy people, mainly children, against infectious diseases
  - Terminology like ‘immunotherapy medicinal product’ might be more appropriate
- Legal: Batch release might be required when classified as vaccine
- Development often complex, often different from classical (prophylactic) vaccines

Single Specific EMEA Guideline Available

- Potency testing of cell based immunotherapy medicinal products for the treatment of cancer. CHMP/BWP/271475/06

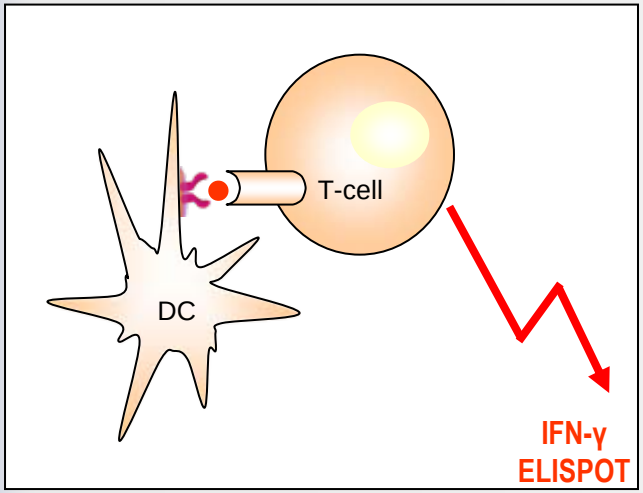


Dendritic cells for cancer vaccination is classified as `Somatic Cell Therapy Product´ by EMEA

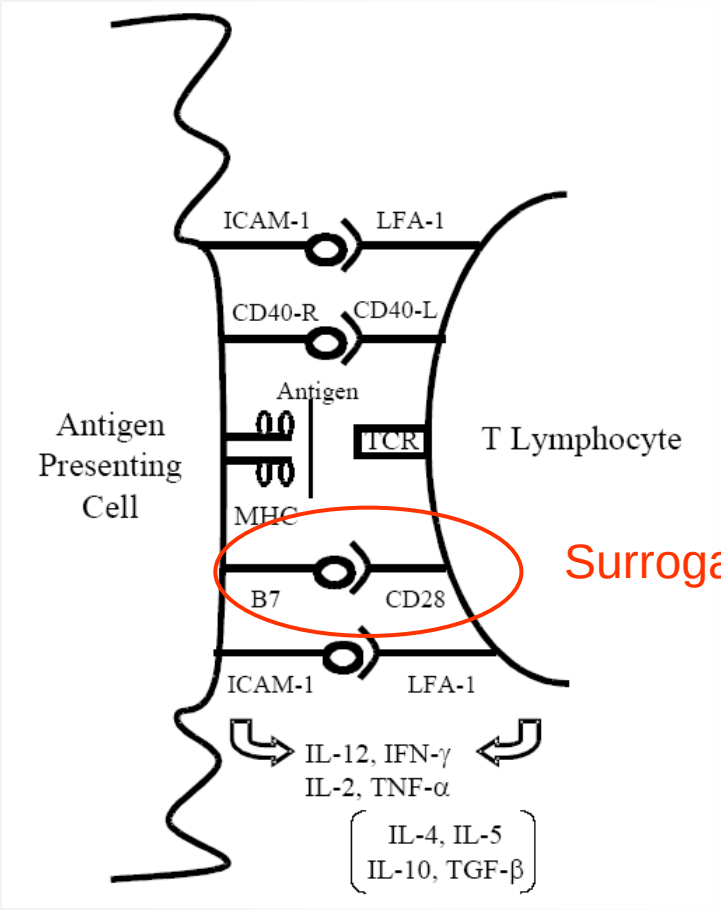
EMEA Potency Guideline

- 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 should be shown

Example of Potency Testing for Dendritic Cells



Potency



Surrogate

Further EMEA Guideline Important for Cell-Based Therapeutic Vaccines

- Guideline on Human Cell-Based Medicinal Products, CHMP/410869/06
  - Quality & manufacturing, preclinical, and clinical aspects are covered
  - Introduces a risk-based approach for the development of cell-based products

Risk-Based Approach for Cell-Based Products

- The results of the risk analysis should be used to
  - identify risk factors associated with the quality and safety of the product
  - to determine the extent and focus of the data required during non-clinical and clinical development
  - establish the need for risk minimisation activities
  - determine the post marketing risk management activities to be specified in the pharmacovigilance plan

Risk-Based Approach for Cell-Based Products

- Risk criteria to be considered are e.g.
  - Origin (autologous or allogeneic)
  - Ability to proliferate and differentiate
  - Level of cell manipulation (in vitro/ex vivo expansion/activation genetic manipulation)
  - Mode of administration (ex vivo perfusion, local, systemic)

    .

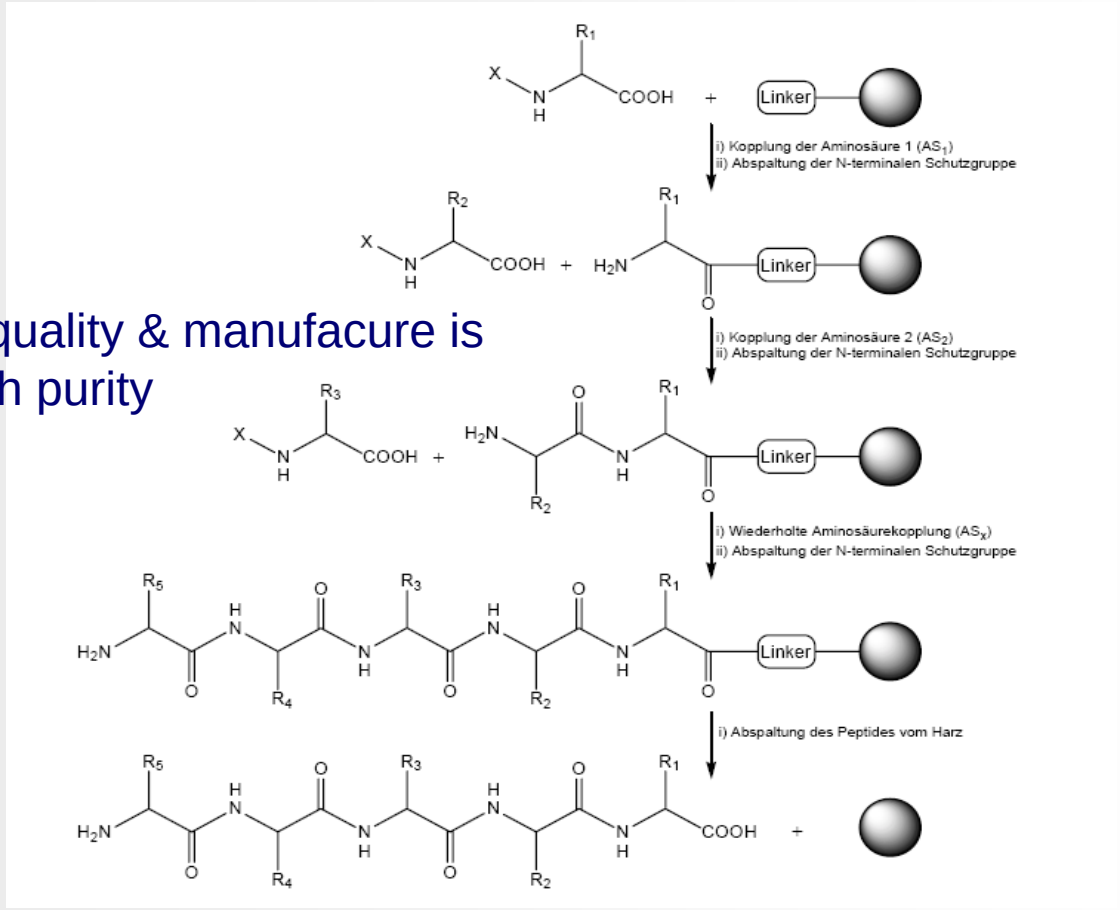
    .

    .
  - Availability of clinical data

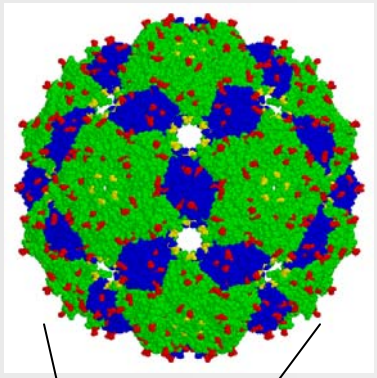
Other Types of Therapeutic Vaccines, Besides Cells

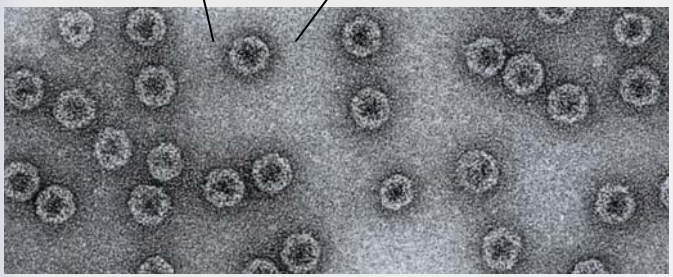
Synthetic Peptides

Low complexity, quality & manufacure is standardized, high purity



Virus-Like Particles

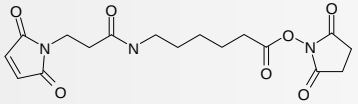




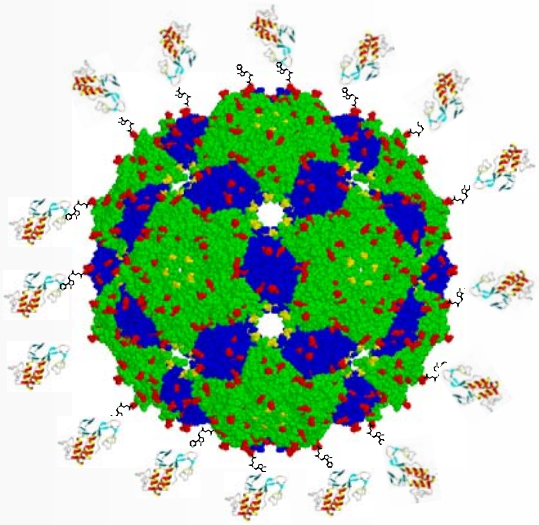
diameter = 30 nm

antigen

Cys



SMPH chemical linker



Courtesy of M. Bachmann

High complexity, CMC guidance for recombinant proteins available

Even More…

- In vitro transcribed mRNA
- Bacteria expressing tumor antigens
- Anti idiotypic antibodies
- Recombinant proteins
- Gene Therapy Approaches
  - Naked DNA
  - Retroviruses
  - Adenoviruses
  - Genetically modified cells

Guidance is available regarding manufacturing and quality control for most of these product classes

(http://www.emea.europa.eu/htms/human/humanguidelines/backgroun.htm)

Preclinical Issues for Human-Specific Products (I)

- Homologous models may be useful (e.g. mouse cells in mice) for proof of concept and toxicity (see e.g. Human Cell-Based Guideline)
- The chosen animal model may include immuno-compromised, knockout or transgenic animals (see e.g. Human Cell-based Guideline)
- Always use relevant animal models where the medicinal product is pharmacologically active (see e.g. ICH S6)

Preclinical Issues for Human-Specific Products (II)

- Autoimmunity: Carefully study human tissue expression pattern
- There are examples of severe autoimmunity after cancer vaccination:
  - 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: e20-2
  - Antigen expression in bile duct epithelial cells
  - Stop of clinical trial due to grade 2-4 liver toxicities

Clinical Issues

- Clinical development of cancer vaccines is clearly different from cytotoxic compounds (see Guideline on the evaluation of anticancer products for human use, CPMP/EWP/205/95/Rev.3)
- MTD normally not applicable in Phase I
- Pharmakocinetics often not relevant for cancer vaccines
- Tumor response normally measured in Phase II might be less relevant than stabilization of disease
- Efficacy in `last-line patients´ not probable
- Find window of opportunity in patients with less advanced disease, e.g. adjuvant therapy

Regulatory Environment Sufficient?

- In principle yes, but more scientific knowledge is required
  - Use of pharmacologically active adjuvants (e.g. TLR ligands)
  - Optimal use of cytokines
  - Use of stimulating mAb (e.g. anti CTLA-4)
  - Suppress Treg
  - Combination with chemicals or other biologicals
  - Optimal administration (local vs. systemic)
  - Nature of antigen: mRNA, protein, peptide
  - Optimally matured dendritic cells