Development Stage of Therapeutic Vaccines: The Regulator’s View

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DISCLAIMER
This is the personal views of Thomas Hinz and does not necessarily reflect the official position of the Paul-Ehrlich-Institut
Topics Addressed

- Innovation Office at the PEI
- Levels of Regulation at PEI
- Nature of Therapeutic Vaccines
- Upcoming developments: combination therapies and personalized immunotherapies
Innovation Office
Role of the Innovation Office at PEI

- Central contact point for national scientific advice (quality & manufacture, nonclinical, clinical)
- Co-ordination of advice across various expert areas
- All-in-one service: bridge to EMA, IQWiG and G-BA and as far as possible to clinical trial centers and non-clinical facilities
<table>
<thead>
<tr>
<th>Target Groups</th>
<th>Products</th>
<th>Developmental Stages</th>
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<tbody>
<tr>
<td>• Academic institutions</td>
<td>• Gene Therapy Medicinal Products 1)</td>
<td>• Ahead &amp; during clinical studies</td>
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<td>(e.g. clinical research groups)</td>
<td>• Somatic Cell Therapy Medicinal Products 2)</td>
<td>• National authorization (hospital exemption)</td>
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<td>• Small and medium sized</td>
<td>• Tissue Engineered Products 3)</td>
<td>• Centralised marketing authorisation</td>
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<td>enterprises (SME)</td>
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1) e.g. genetically modified cells as therapeutic vaccines
2) e.g. autologous haematopoietic bone marrow stem cells for the treatment of myocardial infarction
3) e.g. autologous chondrocyte-transplants for the treatment of cartilage defects
Service and Information

- General information on the website of the PEI
- Request form available on PEI website
- Booklet on ATMP as guide to applicants
- Forms and further information related to national applications for ATMP (hospital exemption)
- Register of useful guidelines and links
- Selection of FAQs
Levels of Authorization
Levels of Authorization at PEI (Zulassung, Genehmigung)

- **Clinical trial authorization**: Currently the sole responsibility of National Authorities: PEI and Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM).

- **Hospital exemption**, for Advanced Therapies only, for national markets only, PEI is granting authorization in Germany
  - Prescribed individual preparation, prepared on non-routine basis, used in a specialized facility for health care.

- **National marketing authorization** (e.g. tissues, blood products, some vaccines)

- **EU Marketing authorization**: National Authorities are elected as Rapporteur or Co-Rapporteur by European Medicines Agency.
Approval of Clinical Trials

- Currently is the sole responsibility of the EU Member States where the trial is conducted
- Based on EU harmonized GCP legislation
Issues Currently Discussed to Revise GCP

- Single submission via EMA portal?
- Involve only EU Member States concerned? (Coordinated Assessment Procedure, CAP)
- CAP mandatory vs. optional?
- CAP for multinational trials only?
- Shortened timelines for approval of low risk trials?
- Content of documentation dependent on risk?
- Exclude academic trials from EU harmonized GCP?
Medicines Approved via EMA’s Centralized Procedure

- **Scope (mandatory)**
  - Biotechnology products / ATMP
  - Orphan drugs
  - Medicines for treatment of:
    - AIDS, Cancer, Neurdegenerative disorders, Diabetes, Auto-immune diseases/Immune dysfunctions, Viral diseases

- **Scope (optional)**
  - New chemical entity
  - Significant therapeutic, scientific or technical innovation
Regulation of Therapeutic Vaccines is Challenging

- No legal definition for therapeutic vaccines exists
- No specific EMA guidance possible, since there is no legal definition
- Use available guidance for chemicals, biologicals, cell-based products, ATMP
- One specific clinical FDA guidance exists (Clinical considerations for therapeutic cancer vaccines)
- Some guidance in EMA anticancer guideline (Guideline on the evaluation of anticancer medicinal products in man; currently under revision)
The Nature of Therapeutic Vaccines is Diverse
Dendritic Cells Are Often Used for Immunotherapy of Cancer

Sipuleucel-T/Provenge (Dendreon)

- Licensed by FDA in 2010
- Advanced, hormone-resistant prostate carcinoma
- Autologous dendritic cells loaded with PAP
- +4.1 months median survival
- Minimal adverse effects
Sipuleucel-T Uses Immature DC

Leukapheresis

Immature DC, other cells, PAP-GM-CSF

Tumor patient
In Vitro Transcribed RNA and RNA-Loaded DC Advanced Therapies?

Is mRNA-loaded DC gene therapy?
“...with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;”

Courtesy of Ugur Sahin
Further Active Immunotherapy Approaches Utilizing ATMPs

- Gene modified tumor cells (e.g. secreting cytokines, expressing co-stimulation)
- Naked DNA, Plasmid
- Recombinant virus vectors (e.g. MVA, AAV, retrovirus)
- Recombinant bacteria
- T cells expressing chimaeric T cell receptors
- Others
Some Promising Non-ATMP Immunotherapies
Synthetic Peptide-Based Immunotherapy

- Peptide mixtures are in Phase III
- Phase II data suggest correlation of immune response to clinical outcome
Randomized Phase 2 study Using Multi-Peptide Vaccination in Advanced Renal Cell Carcinoma (Biotech, now in Phase III)

Figure 5: Picture on the left shows an example for a patient with a systemically detectable anti-TUMAP response (“immune responder”, observed in 66% of vaccinated patients) as detected in a MHC multimer analysis (peptide-specific T cells are highlighted in the green circle). Kaplan-Meier curves show overall survival of immune responder versus non-responder in all immune-evaluable patients per-protocol (N=61, mid graph) and in patients thereof randomized to receive prior cyclophosphamide (N=30, right graph) confirming better survival in patients responding to vaccination with IMA901.
Further Example of a Non-ATMP

Liposomal formulations are currently in global phase III studies (Pharma)
Upcoming Immunotherapy Developments
Cancer Vaccine Combined to Other Compounds Like Cytotoxics

Ramakrishnan, Gabrilovich (2010). JCI 120: 1111
Personalized Immunotherapy

- **De novo manufacture of antigen cocktails**
  - Sequence tumor genome and identify tumor-specific mutations
  - Identify/predict MHC-restricted epitopes
  - Manufacture a patient-specific cocktail of tumor-specific antigens
  - Cocktail could be peptides or a poly-mRNA

- **Warehousing**
  - Mixture of personalized antigen cocktail from preexisting library of antigens, e.g. synthetic peptides
## Conventional/Finished Product vs. Personalized

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<thead>
<tr>
<th>Conventional Medicines</th>
<th>Warehousing &amp; de novo synthesis</th>
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<tr>
<td><strong>Quality</strong></td>
<td></td>
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<tr>
<td>• Consistent quality, every patient treated with identical medicine</td>
<td>• Not applicable. Identity changes from patient to patient</td>
</tr>
<tr>
<td>• Manufacturing up-scaling, further product characterization</td>
<td>• Not applicable</td>
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<tr>
<td><strong>Nonclinical</strong></td>
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<tr>
<td>• Primary pharmacology (immunity) in animals, or in vitro, or in homologous animal models if available</td>
<td>• Not feasible for every individual product</td>
</tr>
<tr>
<td>• Proof of principle normally done in animals (cancer therapy feasible)</td>
<td>• Not feasible for every individual product</td>
</tr>
<tr>
<td>• Toxicity studies, use homologous model if available</td>
<td>• Not feasible for every individual product</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
</tr>
<tr>
<td>• Collect safety data during phases I and III of the product</td>
<td>• Not applicable, every product has its own safety profile</td>
</tr>
<tr>
<td>• Show efficacy</td>
<td>• Show efficacy</td>
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Summary and Outlook

- No comprehensive guidance available for therapeutic vaccines
- Use available guidance for chemicals, biologicals, cells
- First break through is there (Provenge)
- Further promising products are clinically far developed
- Future personalized approaches will challenge the existing regulatory system