Breakthroughs in biomedicines

Klaus Cichutek, Egbert Flory, Martina Schüßler-Lenz, Matthias Renner, Christian Buchholz
Agenda

- Biomedicines regulation by Paul-Ehrlich-Institut
- Blockbuster antibody therapies and personalized medicines
- Rising star: cell and gene therapy a.k.a. ATMPs
- Support of innovation by regulators
- The future
Vaccines and biomedicines differ from chemical drugs in size and complexity.
active substances of biological and human origin (sub-cell)

- monoclonal antibodies
- sera, Igs, mAb-fusion proteins
- rec. clotting factors
- plasma-derived products
- hu. and vet. allergens (therapy, *in vivo* diagnosis)

...derived from or produced using micro-organisms or viruses

- hu. and vet. vaccines
- vet. immunomodulators

human or animal cell-containing products, products derived from human tissues

- cellular blood and transfusion products
- tissue engineering MPs
- somatic cell therapy MPs
- xenogeneic cell therapy MPs
- classical tissue preparations
- vector or nucleic acid vaccines
PEI’s tasks in support of EMA

**MA by European Commission/PEI**

- EMA scientific advice (SAWP)
- EMA certification (CAT)

**PEI’s tasks as a Member State Medicines Agency**

- Clinical trial authorization
- Official governmental batch release
- Pharmacovigilance
- Variations
- Benefit/risk evaluation

**PEI inspections**
- (GCP, pharmakovig., assessment-driven)

**Inspection support**
- (Länder, GMP, GFP)

**Inspection support**
- (EMEA, GCP)

**Innovation office**
**Scientific advice**
**Joint advice HTA/PEI**
Philosophy of the Paul-Ehrlich-Institut since 1896: medicines regulation & top-level research

Staining methods:
- Idea of an organ-specific therapy => medicines as Magic Bullets

Basics of nowadays immunology:
- Father of modern immunology => side chain theory -> antibodies

Biomedicines development:
- Chemotherapy of infectious disease (Syphilis, Malaria, sleeping sickness) => Salvarsan

Experimental testing of biomedicines:
- Active substance of anti-diphtheria serum => potency assay
EU No. 1 in CHMP (Co-)Rapportages for vaccines and biomedicines

25% of all exp. product testing in European OMCL network

40% of current clinical trial authorizations in DE for vaccines and biomedicines

no. CTAs

reg. research supporting translation

DZIF, DKTK, Loewe, DFG, EC, BMG

PEI

Pathogen-Host & Biomedicine-O rganism Interactions

Experimental Vaccines, Therapies & Diagnostics

Regulatory Research & Innovative Medicinal Product Testing

small molecules/cytokines

vaccines & biomedicines
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Evolution and humanization of monoclonal antibodies (mAbs)

New constructs
- bispecific antibodies
- diabodies
- single chain fragments
- engineered Fc mAbs
- conjugated mAbs
- ...

Murine mAb
„-omab“
Arcitumomab (CEA-Scan®) (1996)

Chimaeric mAb
„-iximab“
Infliximab (Remicade®) (1999)

Humanized mAb
„-zumab“
Trastuzumab (Herceptin®) (2000)

Fully Human mAb
„-umab“
Adalimumab (Humira®) (2003)

Immunogenicity
New constructs – antibody derivatives

- Bi-specific mAb
- DVD Ab (dual variable domain Ab)
- Nanobodies (derived from $V_H$ of camelid Ab)
- BITE (bi-specific T cell engager) = (2x scFv)
- Immune cytokine
- ADC (ab-drug-conjugate)
Clinical use of mAbs

- Cardio-vascular diseases
- Eye & neurological disease
- Infectious diseases
- Osteoporosis
- Crohn’s disease
- Colitis ulcerosa
- Rheumatoid arthritis
- Psoriasis
- Cancer
“Added benefit” is a rare result of the HTA evaluation for monoclonal antibodies

- not quantifiable (orphan drugs)
- not proven
- small
- considerable
Severe side effects of antibody TGN1412 for rheumatoid arthritis in a UK trial – PEI explores suitable animal model for cytokine storm testing

PBMCs → NOD RAG⁻/⁻γc⁻/⁻ → humanised mouse → TGN1412 administration

![Graph showing survival rate](www.newstmp.bbc.co.uk)
Paradigm shift in immuno-oncology: from extended life span to long-term survival with checkpoint inhibitor antibodies

What are the existing classes of personalised medicines?

- **Passively stratified medicines (group)**
  - Selection of optimal patient target group via stratification
  - Stratification based on biomarker selection

- **Passively personalised medicines (individual)**
  - „autologous medicines“:
    substances taken from and administered to same patient
  - „directional medicines“:
    substances taken from on individual and given to another individual

- **Actively personalised med. (individual)**
  - individual medicine for each individual patient

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Normal  
Tumor

mutations

patient-specific mixture of drug substances
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Advanced Therapy Medicinal Products (ATMPs)

- Gene therapy medicinal products
- Somatic cell therapy medicinal products
- Tissue engineered products
- Cell-based medicinal products
<table>
<thead>
<tr>
<th>ATMPs licensed in EU/EEA</th>
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</thead>
<tbody>
<tr>
<td><strong>ChondroCelect</strong></td>
</tr>
<tr>
<td><strong>Glybera</strong></td>
</tr>
<tr>
<td><strong>MACI</strong></td>
</tr>
<tr>
<td><strong>Provenge</strong></td>
</tr>
<tr>
<td><strong>Holoclar</strong></td>
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<tr>
<td><strong>Imlygic</strong></td>
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<tr>
<td><strong>Strimvelis</strong></td>
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<tr>
<td><strong>Zalmoxis</strong></td>
</tr>
<tr>
<td><strong>Spherox</strong></td>
</tr>
<tr>
<td><strong>Alofisel</strong></td>
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</tbody>
</table>
CAR T cell therapy is immunotherapy

- **CAR** = chimeric antigen receptor, targets tumour cells which activates cell killing mechanism of CAR-modified cells

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>rAAV Serotype</th>
<th>GENE</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL deficiency</td>
<td>1</td>
<td>LPL</td>
</tr>
<tr>
<td>Alpha-1 antitrypsin deficiency</td>
<td>1</td>
<td>AAT</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>6</td>
<td>U1</td>
</tr>
<tr>
<td>MPS IIIA</td>
<td>9</td>
<td>Sulfamidase</td>
</tr>
<tr>
<td>Leber's congenital amaurosis</td>
<td>2</td>
<td>RPE65</td>
</tr>
<tr>
<td>Systolic heart failure</td>
<td>1</td>
<td>SERCA2a</td>
</tr>
<tr>
<td>MPS IIIA</td>
<td>10</td>
<td>SGSH / SUMF1</td>
</tr>
<tr>
<td>Leber Hereditary Optic Neuropathy</td>
<td>2</td>
<td>ND4</td>
</tr>
<tr>
<td>Systolic heart failure</td>
<td>1</td>
<td>SERCA2a</td>
</tr>
<tr>
<td>Crigler-Najjar syndrome</td>
<td>8</td>
<td>UGT1A1</td>
</tr>
<tr>
<td>Duchenne muscular dystrophy</td>
<td>8</td>
<td>MD1</td>
</tr>
<tr>
<td>MPS VI</td>
<td>8</td>
<td>ARSB</td>
</tr>
</tbody>
</table>
Stem cell treatments in a variety of indications

- cardio-vascular diseases
- bone fracture
- eye & neurological disease
- plastic surgery
- GvHD
- Krohn´s disease, anal fistulas
- joint degeneration, arthritis
- wound healing, diabetes
Unsafe stem cell treatments in Xcell clinic in Cologne: termination by PEI and competent authority of the German Land

Dubious Xcell promises to patients: cure by administration of stem cells into brain with a stiff catheter

Concerns over unregulated medicinal products containing stem cells
The Agency highlights that access to stem-cell medicinal products should only be under certain controlled conditions
§4b authorization used to lead ATMPs to the licensing state

**Hospital Exemption**


<table>
<thead>
<tr>
<th>Advanced Therapy Medicinal Product</th>
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<tbody>
<tr>
<td>individual medical prescription</td>
</tr>
<tr>
<td>+  custom-made product for an individual patient</td>
</tr>
<tr>
<td>+  prepared on a non-routine basis according to specific quality standards</td>
</tr>
<tr>
<td>+  Used in a hospital under the exclusive professional responsibility of a medical practitioner</td>
</tr>
<tr>
<td>+  prescribed, prepared and used within the same Member State</td>
</tr>
</tbody>
</table>

Manufacturing authorization by the competent authority of the Land.

DE-PEI ensures
- traceability
- pharmacovigilance
- specific quality standards

DE-PEI supports parallel clinical trials
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• Training in operational and regulatory aspects
• Assist with FlexFunds
• Organize structured dialogue researchers and regulatory bodies
• Guide product development
• Contracts, licenses, IP / Technology Transfer Consortium
• Scouting of novel technologies
Agenda

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CRISPR/Cas-based targeted gene modification

EMA expert meeting on genome editing technologies used in medicinal product developments

Programme
18 October 2017
European Medicines Agency, London, United Kingdom
Meeting room 3E

CRISPR/Cas-basierte Arzneimittel: Herausforderungen in der Regulation
CRISPR/Cas-based medicinal products: regulatory framework

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Summary

- Paul-Ehrlich-Institut benefits from research, experimental product testing and benefit-risk assessment under one roof.

- Monoclonal antibodies allow successful treatments in a number of clinical indications, but carry risks due to targets and triggered mechanisms.

- Regenerative medicine provides cell therapy of a variety of diseases.

- Personalized medicines encompass groups stratified and autologous passive personalization as well as actively personalized medicines.

- CAR T-cell therapy is a successful leukemia treatment.

- PEI regulators support translational science and product development.
The real heroes of biomedicines regulation: PEI experts in medicines committees at EMA, EDQM and WHO

CTFG

(28 EU MSs + 2 (Iceland, Norway))
Our Focus is on Health