



# Breakthroughs in biomedicines

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20th DGRA Annual Congress  
14th June 2018



*Das Paul-Ehrlich-Institut ist ein Bundesinstitut im Geschäftsbereich  
des Bundesministeriums für Gesundheit.*

*The Paul-Ehrlich-Institut is an Agency of the  
German Federal Ministry of Health.*

# Agenda

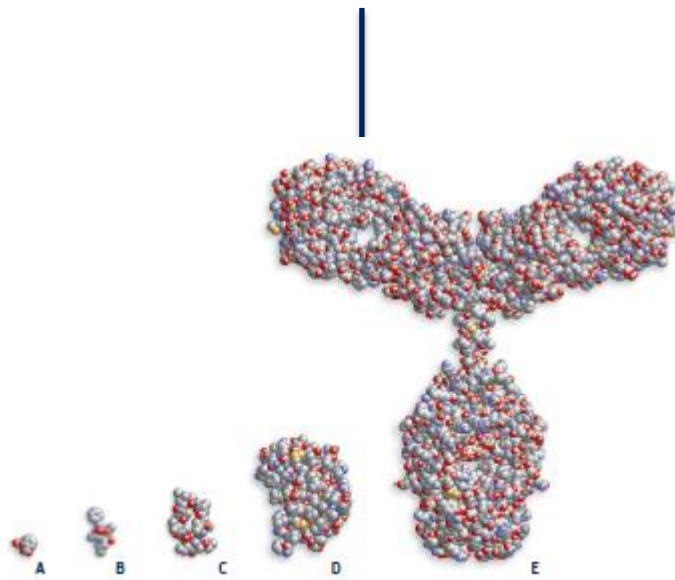


- Biomedicines regulation by Paul-Ehrlich-Institut
- Blockbuster antibody therapies and personalized medicines
- Rising star: cell and gene therapy a.k.a. ATMPs
- Support of innovation by regulators
- The future

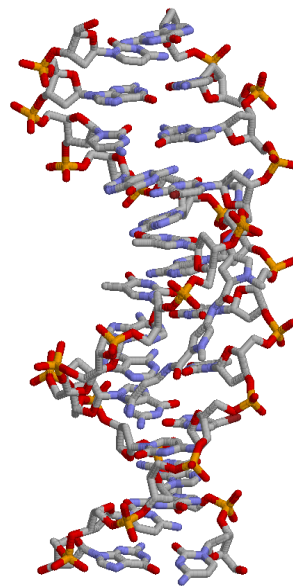




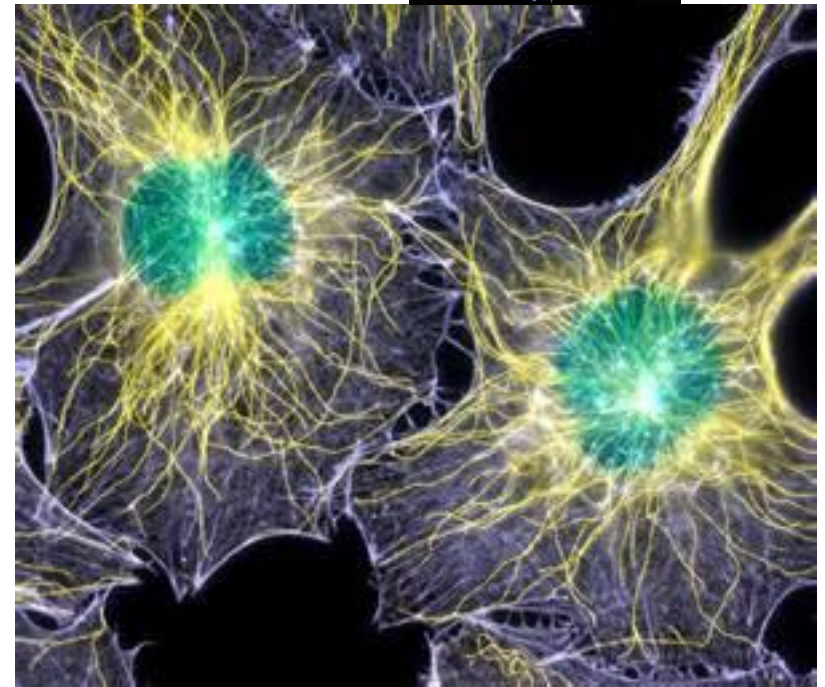
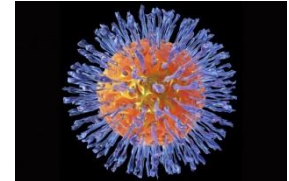
# Vaccines and biomedicines differ from chemical drugs in size and complexity



BfArM

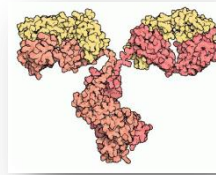


Paul-Ehrlich-Institut

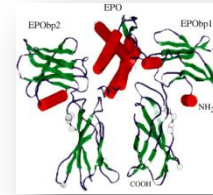




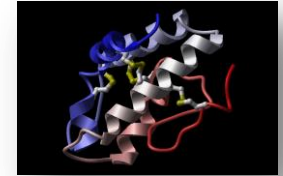
# active substances of biological and human origin (sub-cell)



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

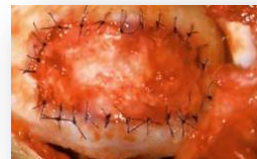


vector or  
nucleic acid vaccines

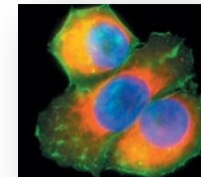
# human or animal cell-containing products, products derived from human tissues



cellular blood  
and  
transfusion products



tissue engineering  
MPs



somatic cell therapy  
gene therapy MPs  
xenogeneic cell therapy  
MPs



classical  
tissue preparations



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

assessment

official governmental batch release  
pharmacovigilance  
variations  
benefit/risk evaluation

inspection support (Länder, GMP, GFP)

inspection support (EMA, GCP)

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

innovation office      scientific advice      Joint advice HTA/PEI

# Philosophy of the Paul-Ehrlich-Institut since 1896: medicines regulation & top-level research



## Founding Director Nobel prize winner Paul Ehrlich



Nobel prize in Physiology & Medicine 1908

### 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

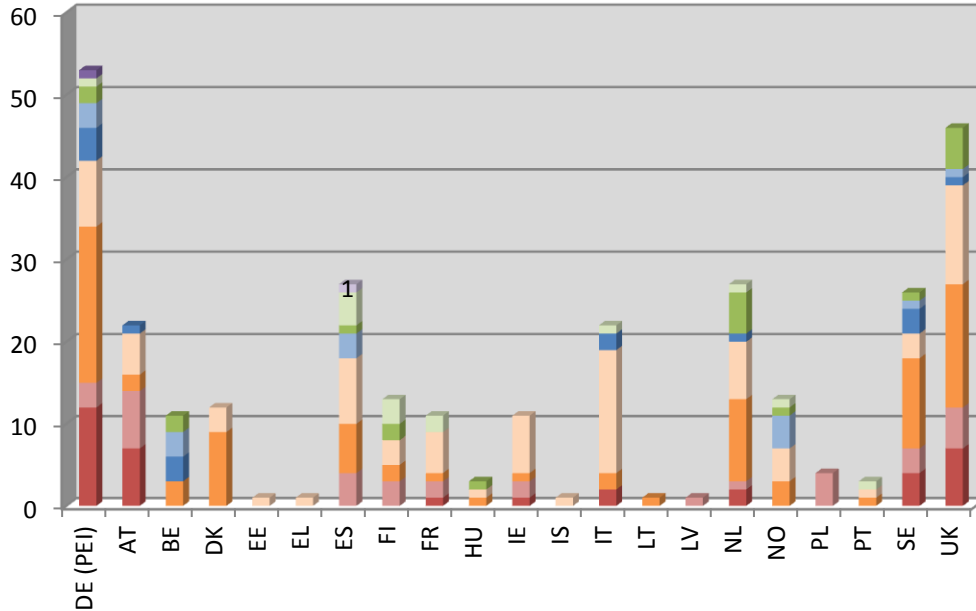
### Experimental testing of biomedicines:

- **Active substance** of anti-diphtheria serum  
=> potency assay

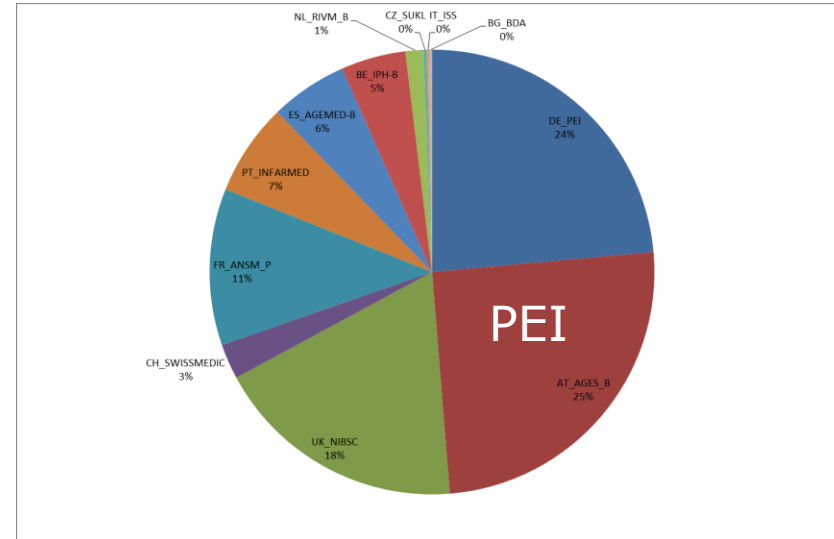


Recovery of anti-diphtheria serum

## EU No. 1 in CHMP (Co-)Rapportages for vaccines and biomedicines

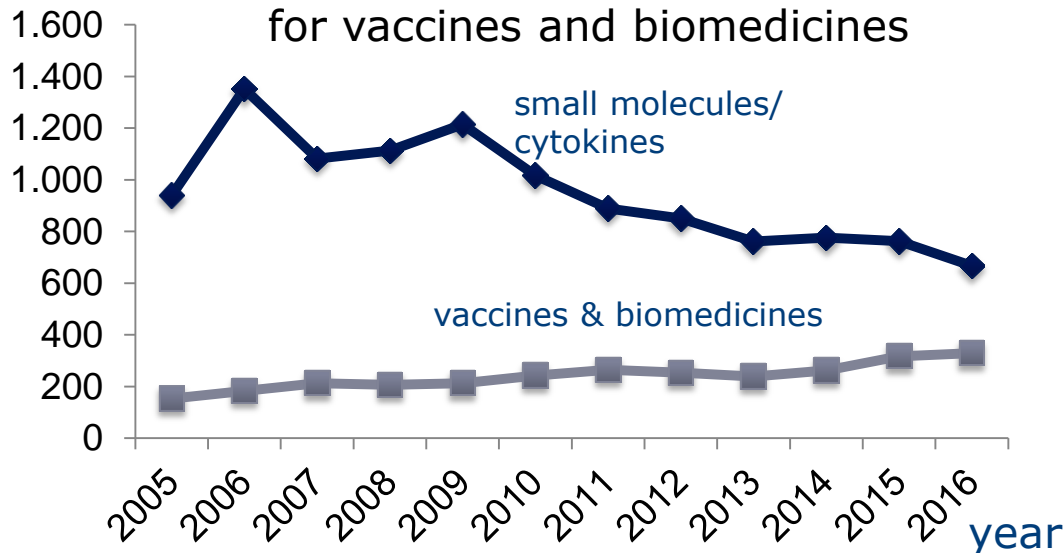


## 25% of all exp. product testing in European OMCL network



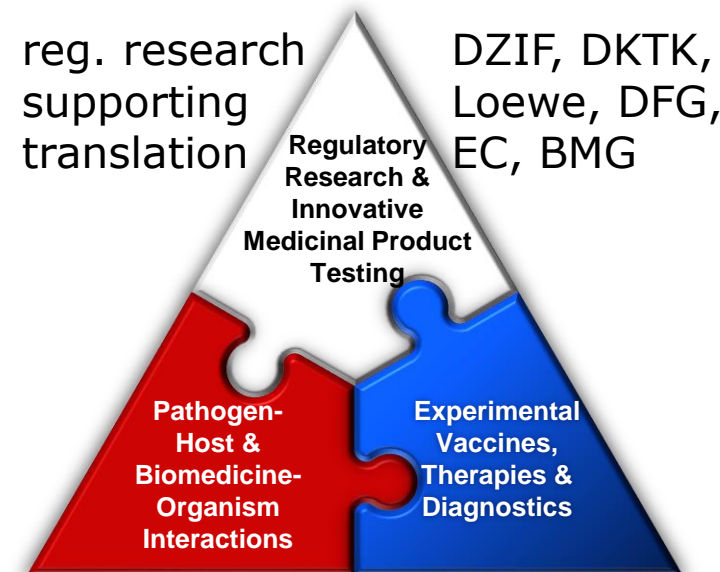
## no. CTAs

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



reg. research supporting translation

DZIF, DKTK, Loewe, DFG, EC, BMG



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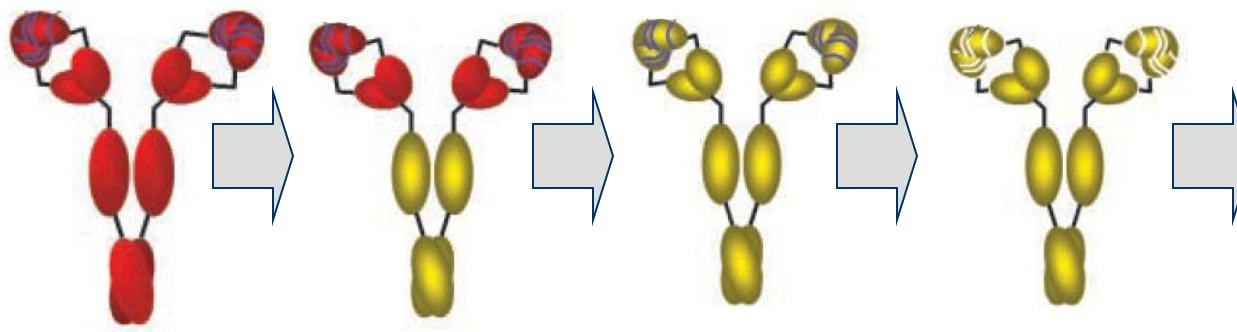
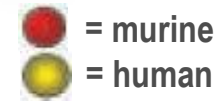


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# Evolution and humanization of monoclonal antibodies (mAbs)



## New constructs

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

Murine mAb

Chimaeric mAb

Humanized mAb

Fully Human mAb

„-omab“

„-iximab“

„-zumab“

„-umab“

Arcitumomab  
(CEA-Scan®)  
(1996)

Infliximab  
(Remicade®)  
(1999)

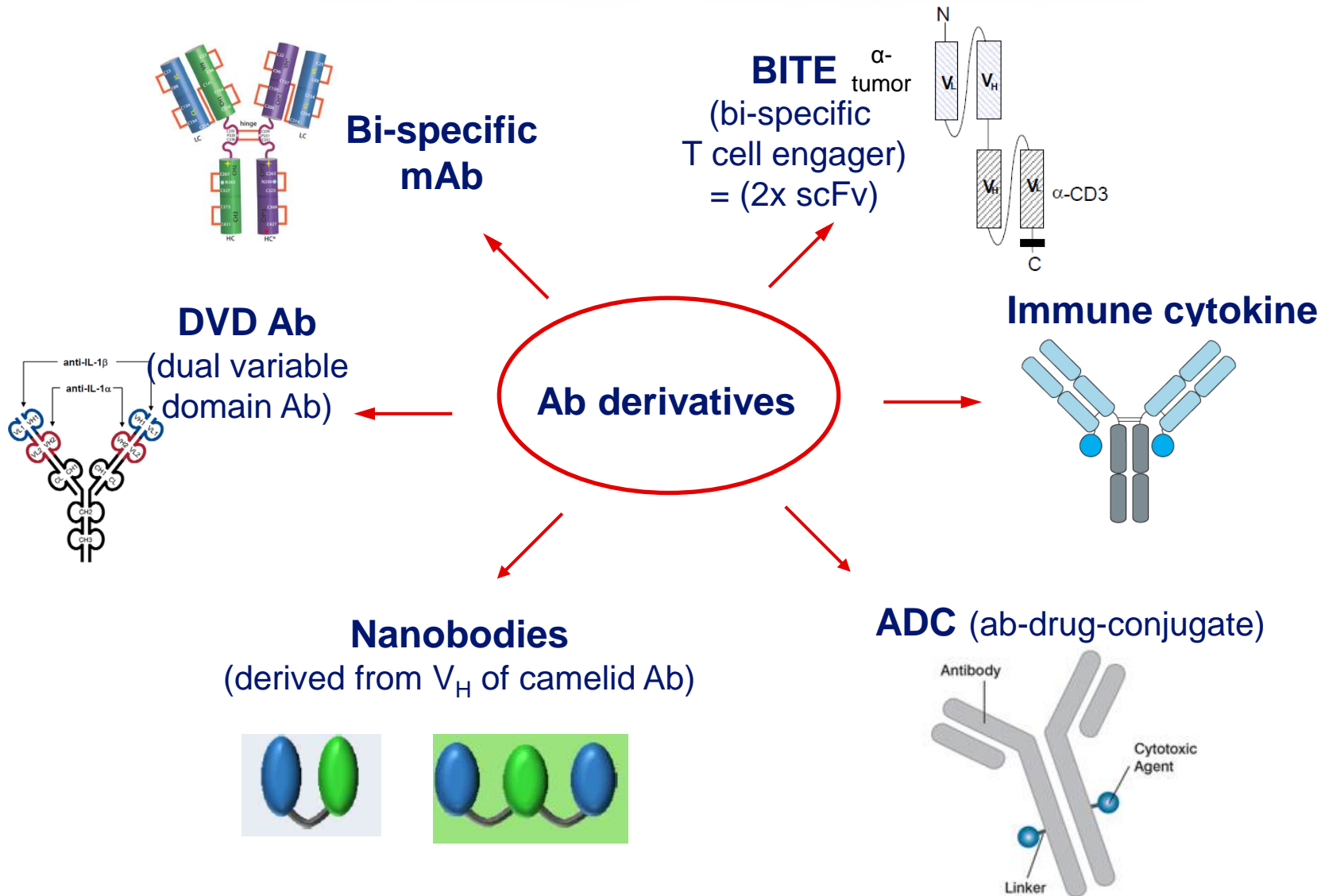
Trastuzumab  
(Herceptin®)  
(2000)

Adalimumab  
(Humira®)  
(2003)

**Immunogenicity**



# New constructs – antibody derivatives



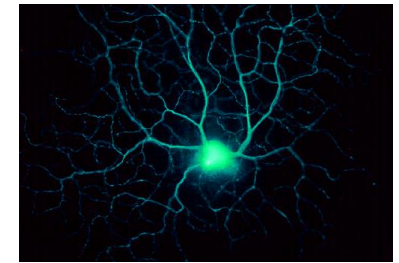
# Clinical use of mAbs



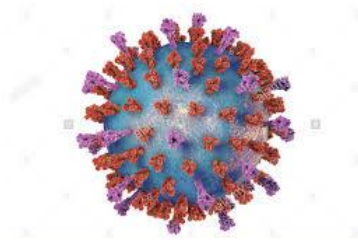
Osteoporosis



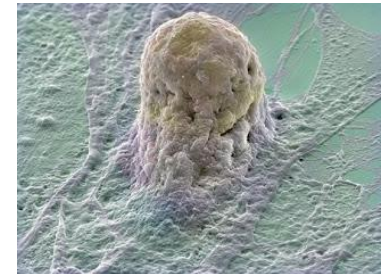
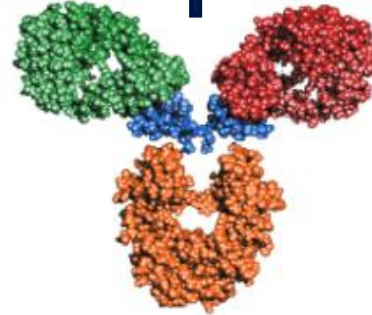
cardio-vascular diseases



eye & neurological disease



Infectious diseases



cancer



Crohn's disease  
Colitis ulcerosa



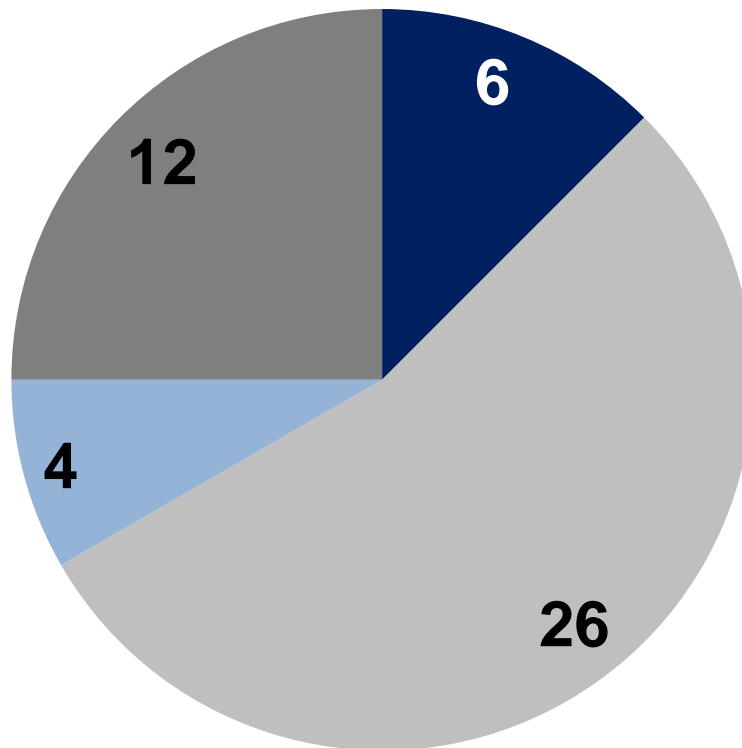
Rheumatoid arthritis



Psoriasis



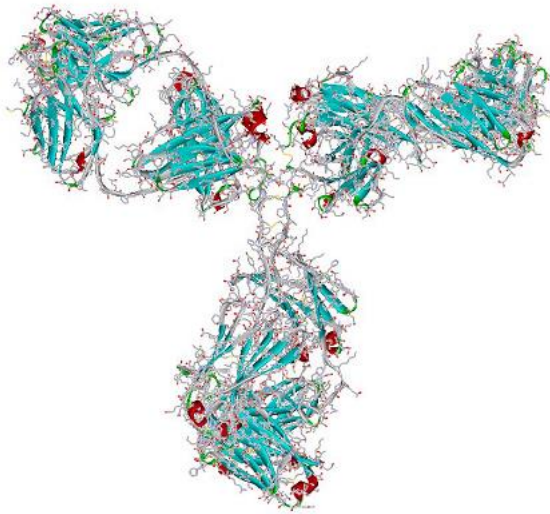
# „Added benefit“ is a rare result of the HTA evaluation for monoclonal antibodies



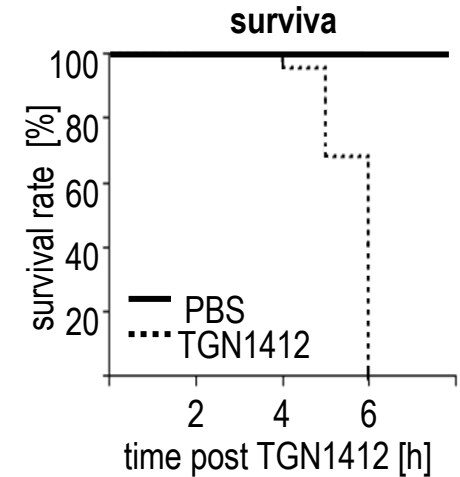
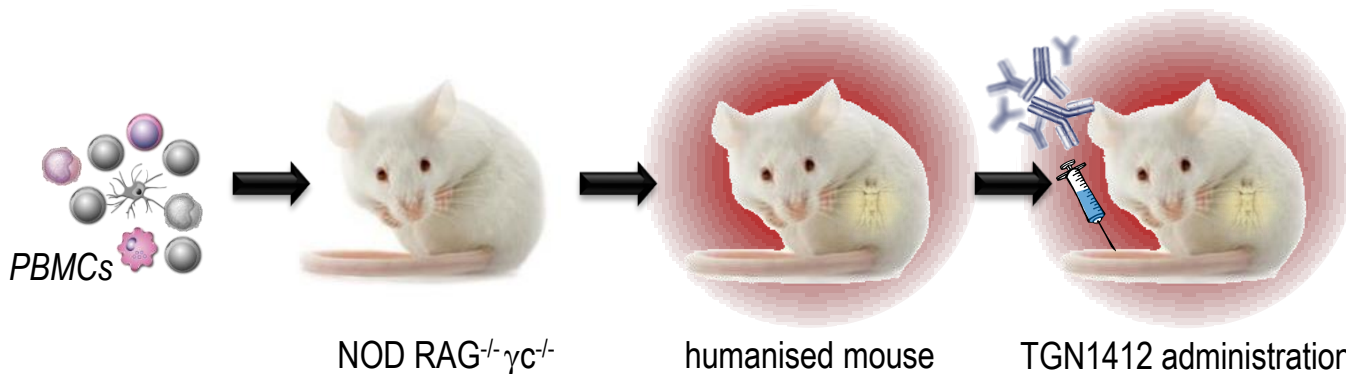
- not quantifiable (orphan drugs)
- not proven
- small
- considerable



# Severe side effects of antibody TGN1412 for rheumatoid arthritis in a UK trial – PEI explores suitable animal model for cytokine storm testing

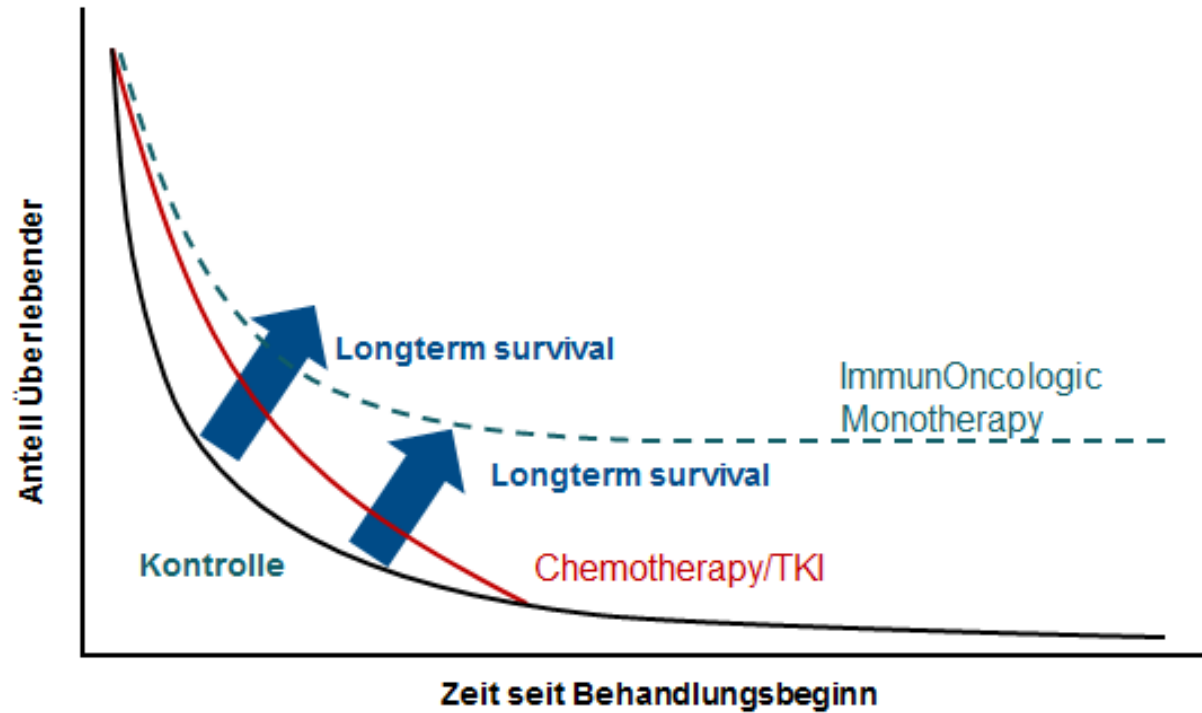
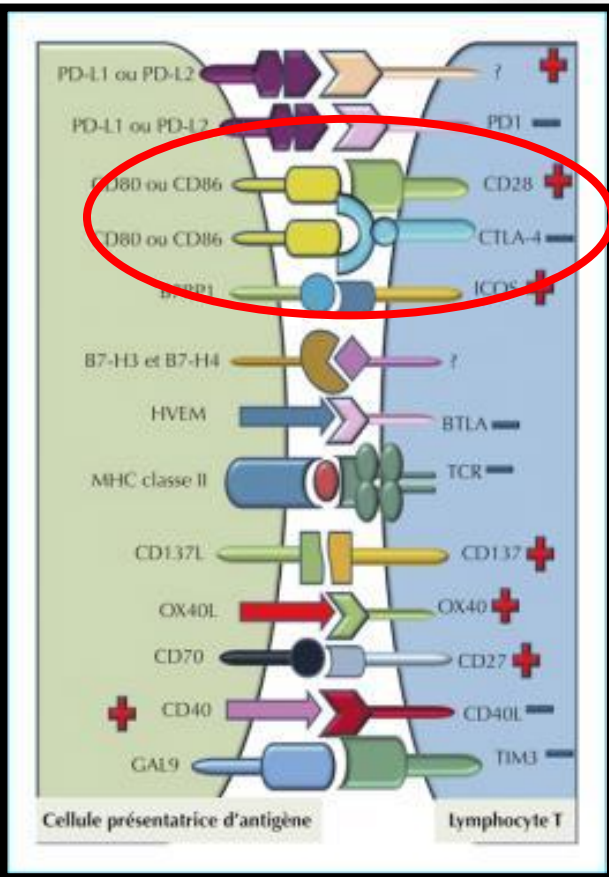


[www.newsimg.bbc.co.uk](http://www.newsimg.bbc.co.uk)





# Paradigm shift in immuno-oncology: from extended life span to long-term survival with checkpoint inhibitor antibodies



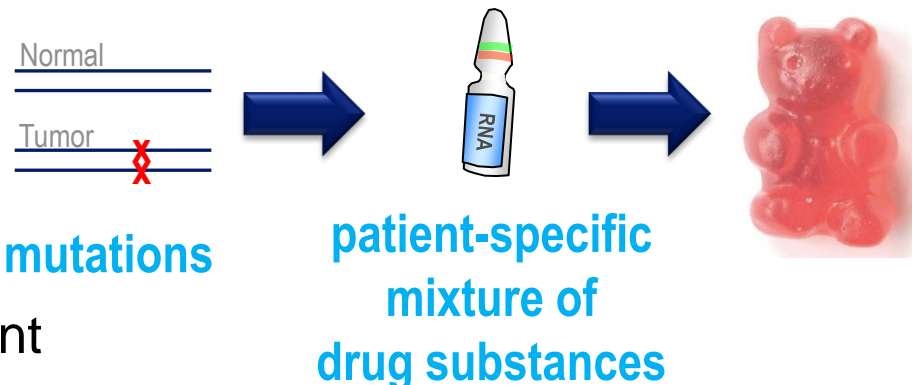
[Nat Rev Cancer. 2012 Mar 22;12\(4\):252-64.](#)



# 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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# Advanced Therapy Medicinal Products (ATMPs)

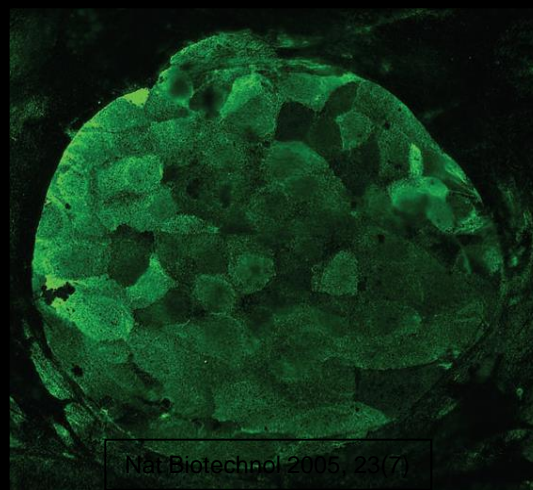
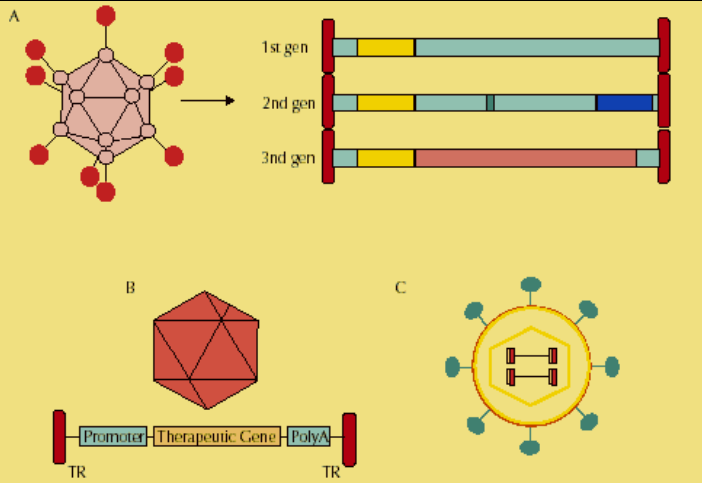


Gene therapy medicinal products

Somatic cell therapy medicinal products

Tissue engineered products

Cell-based medicinal products



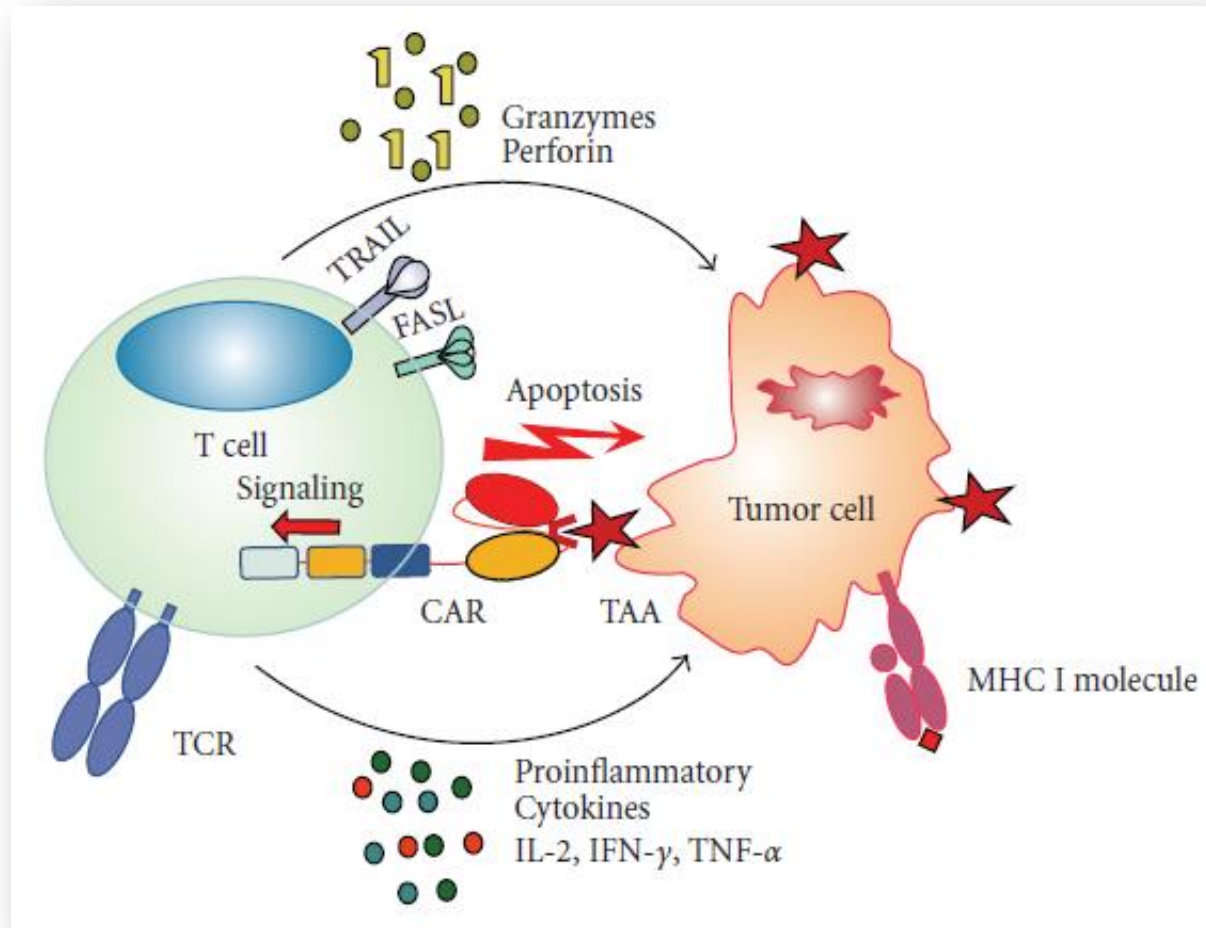
[www.biomed.brown.edu](http://www.biomed.brown.edu)

# ATMPs licensed in EU/EEA



|                      |                                  |             |   |   |
|----------------------|----------------------------------|-------------|---|---|
| <b>ChondroSelect</b> | <b>2009</b><br>withdrawn<br>2016 | <b>TEP</b>  | Ex vivo expanded autologous chondrocytes for cartilage repair of single symptomatic defects of the femoral condyle of the knee (ICRS grade III or IV) in adults   |   |
| <b>Glybera</b>       | <b>2012</b><br>Withdrawn<br>2017 | <b>GTMP</b> | AAV-1 vector transferring LPL gene for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions                      | <b>Orphan</b><br><b>Exeptional</b>  |
| <b>MACI</b>          | <b>2013</b><br>suspended<br>2014 | <b>TEP</b>  | Ex vivo expanded autologous chondrocytes for cartilage Repair of full-thickness defects with area 3 -20 cm2 in adults   |   |
| <b>Provenge</b>      | <b>2013</b><br>withdrawn<br>2016 | <b>CTMP</b> | autologous PBMC including CD54+ cells activated with PAP-GMSF colony-stimulating factor<br>Advanced Prostate Cancer   |   |
| <b>Holoclar</b>      | <b>2014</b>                      | <b>TEP</b>  | Ex vivo expanded autologous corneal epithelial cells containing stem cells for patients with limbal stem-cell deficiency caused by burns  | <b>Orphan</b><br><b>Conditional</b>   |
| <b>Imlygic</b>       | <b>2015</b>                      | <b>GTMP</b> | Oncolytic attenuated HSV 1 transferring GM-CSF gene for treatment of adults with unresectable melanoma regionally or distantly metastatic with no bone, brain, lung or other visceral disease                                       |   |
| <b>Strimvelis</b>    | <b>2016</b>                      | <b>GTMP</b> | Autol. CD34+ cells transduced with retroviral vector encoding the human adenosine deaminase (ADA) cDNA sequence for treatment of patients with ADA-SCID, for whom no suitable (HLA)-matched related stem cell donor is available    | <b>Orphan</b><br><b>administration</b><br><b>only in specialist</b><br><b>TX centre</b> |
| <b>Zalmoxis</b>      | <b>2016</b>                      | <b>CTMP</b> | Allog. T modified with replication-defective $\gamma$ -retroviral vector encoding for $\Delta$ NGFR and HSV-TK Mut2 for adjunctive treatment in haplo-identical HSC-TX of adult patients with high-risk haematological malignancies | <b>Conditional</b>  |
| <b>Spherox</b>       | <b>2017</b>                      | <b>TEP</b>  | Spheroids of human autol. matrix-associated chondrocytes for repair of symptomatic articular cartilage defects of the femoral condyle and patella of the knee with defect sizes up to 10 cm2  |   |
| <b>Alofisel</b>      | <b>2018</b>                      | <b>CTMP</b> | Alofisel is an allogeneic somatic cell therapy medicinal product for the treatment of complex perianal fistula(s) in adult patients with Crohn's disease  | <b>Orphan</b><br><b>Conditional</b>   |

# CAR T cell therapy is immunotherapy



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

# 26 scientific advices on AAV in vivo gene therapy



| INDICATION                        | rAAV Serotype | GENE         |
|-----------------------------------|---------------|--------------|
| LPL deficiency                    | 1             | LPL          |
| Alpha-1 antitrypsin deficiency    | 1             | AAT          |
| Duchenne muscular dystrophy       | 6             | U1           |
| MPS IIIA                          | 9             | Sulfamidase  |
| Leber's congenital amaurosis      | 2             | RPE65        |
| Systolic heart failure            | 1             | SERCA2a      |
| MPS IIIA                          | 10            | SGSH / SUMF1 |
| Leber Hereditary Optic Neuropathy | 2             | ND4          |
| Systolic heart failure            | 1             | SERCA2a      |
| Crigler-Najjar syndrome           | 8             | UGT1A1       |
| Duchenne muscular dystrophy       | 8             | MD1          |
| MPS VI                            | 8             | ARSB         |

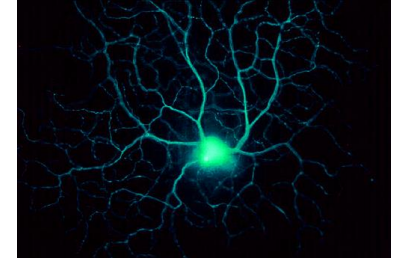
# Stem cell treatments in a variety of indications



bone fracture



cardio-vascular diseases



eye & neurological disease



GvHD



plastic surgery



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



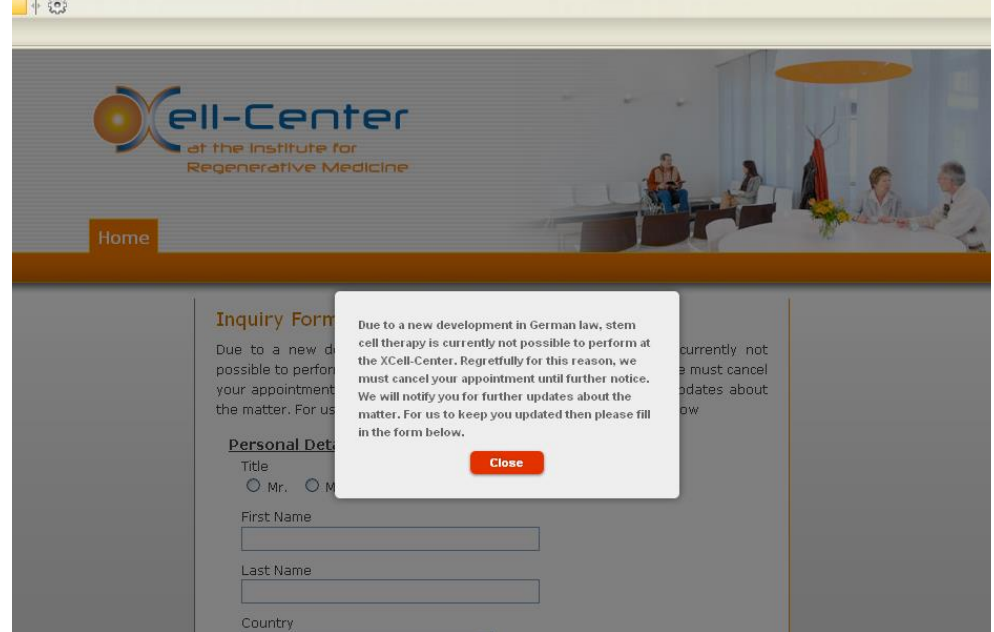
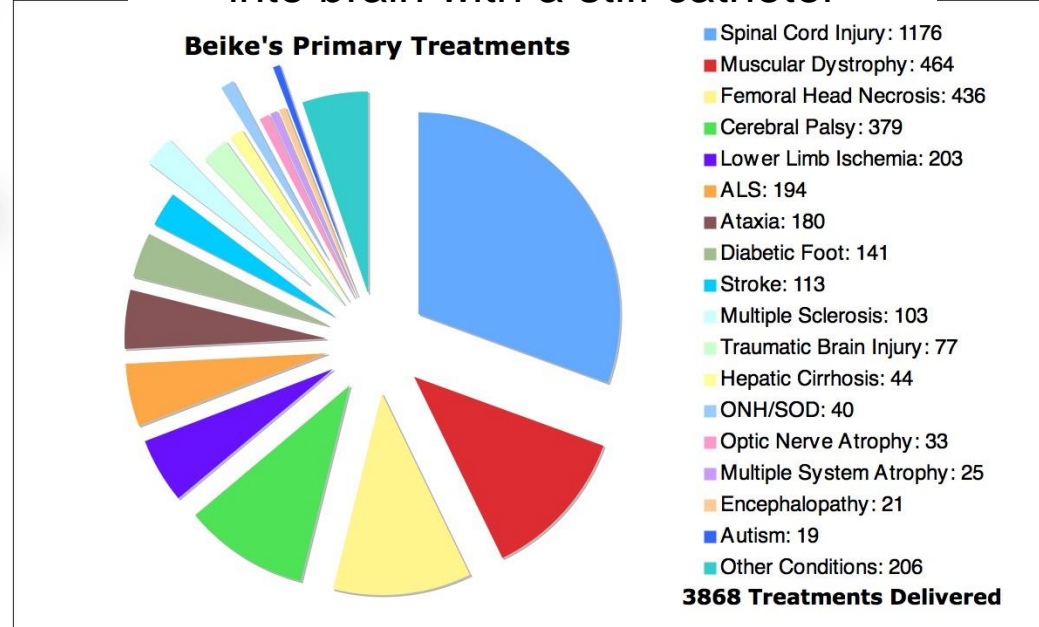
16 April 2010  
EMA/763463/2009

### Public statement

### 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

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



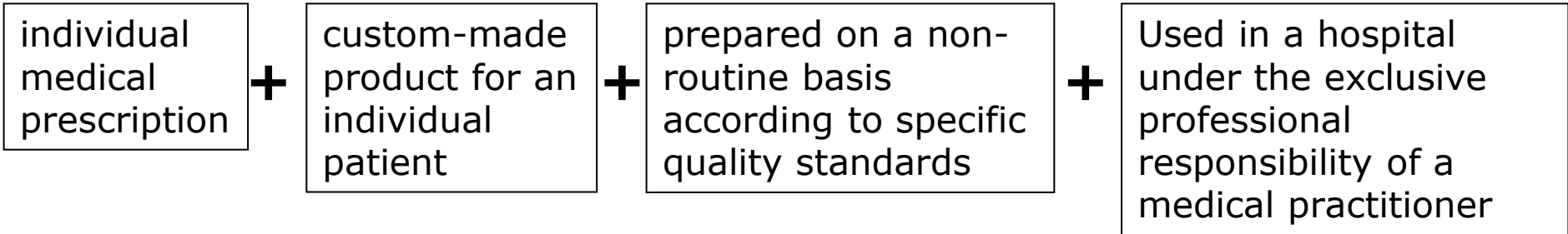


# §4b authorization used to lead ATMPs to the licensing state

## **Hospital Exemption**

Article 28 Regulation (EC) No. 1394/2007

Advanced Therapy Medicinal Product



+ prescribed, prepared and used within the **same** Member State

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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**PDU**  
Representative



**OSRA at PEI/BfArM**



**TPMO at HZI**

**local  
TT offices**



- 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

- Advice in commercial product development
- Elaborate corresponding plans
- Support the product development process

- Advise on regulatory aspects
- Provides link to BfArM, EMA, WHO
- Critical path definition via regulatory research
- Educates on regulatory topics

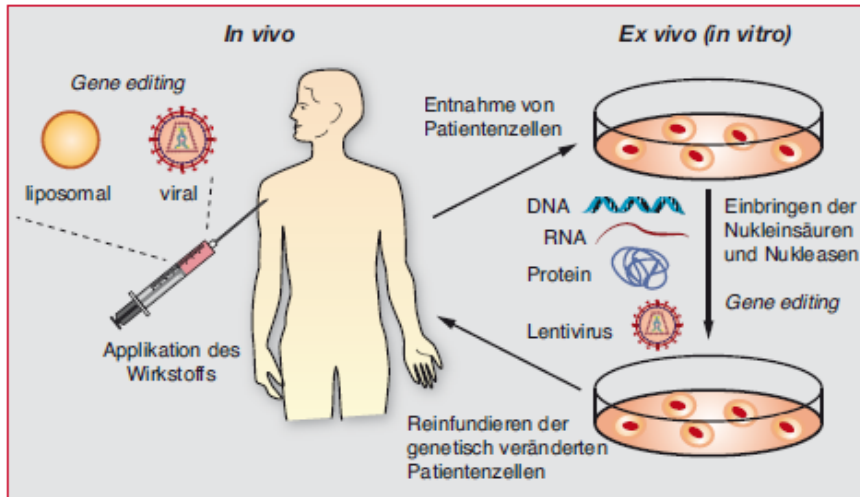
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# CRISPR/Cas-based targeted gene modification



**Abb. 2** Mögliche Therapie von Erkrankungen. Bei der In-vivo-Methode wird dem Patienten das CRISPR/Cas-System in Form von Vektoren direkt appliziert. Diese Strategie setzt voraus, dass der Vektor mit den Komponenten des CRISPR/Cas-Systems die Zielzellen im Körper mit ausreichender Effektivität erreicht. Bei der Ex-vivo-Methode werden Zellen des Patienten isoliert und kurzzeitig in Kultur genommen. Dann werden die Zellen mit dem CRISPR/Cas-System genetisch modifiziert und dem Patienten re-infundiert.

## CRISPR/Cas-basierte Arzneimittel: Herausforderungen in der Regulation

CRISPR/Cas-based medicinal products: regulatory framework

Matthias Renner, Katrin Féchir, Juliane Rau, Silke Schüle, Martina Schüssler-Lenz, Zoltán Ivics

Abteilung Medizinische Biotechnologie, Paul-Ehrlich-Institut, Langen

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





# Summary

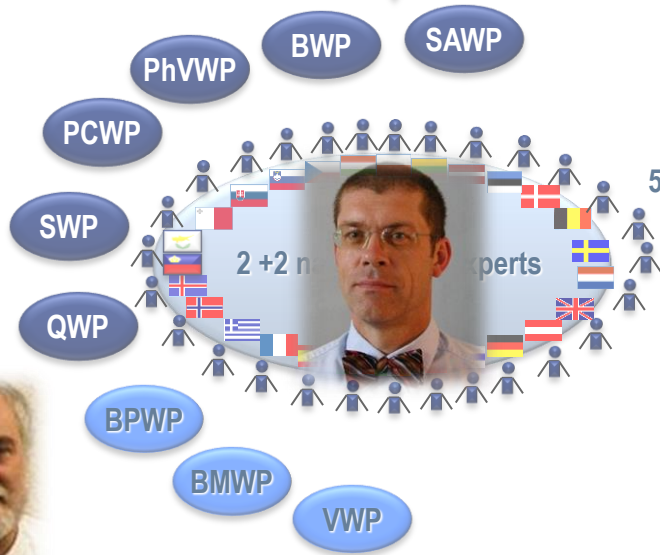


- Paul-Ehrlich-Institut benefits from research, experimental product testing and benefit-risk assessment under one roof
- Monoclonal antibodies allow successful treatments in a number of clinical indications, but carry risks due to targets and triggered mechanisms
- Regenerative medicine provides cell 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



5 „double members“



5 „double members“



2+2 representatives of patient organisations and physicians



**CTFG**

(28 EU MSs + 2 (Iceland, Norway))



# Im Mittelpunkt steht die Gesundheit Our Focus is on Health innovation@pei.de

