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Herausforderungen in der Regulation von CAR-T-Zellprodukten

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Paul-Ehrlich-Institut

Federal Institute for Vaccines and Biomedicals

- Marketing Authorisation
- Approval of Clinical Trials
- Pharmacovigilance
- Inspections
- Batch release
- Research in related areas




Advanced Therapy Medicinal Products (ATMP)

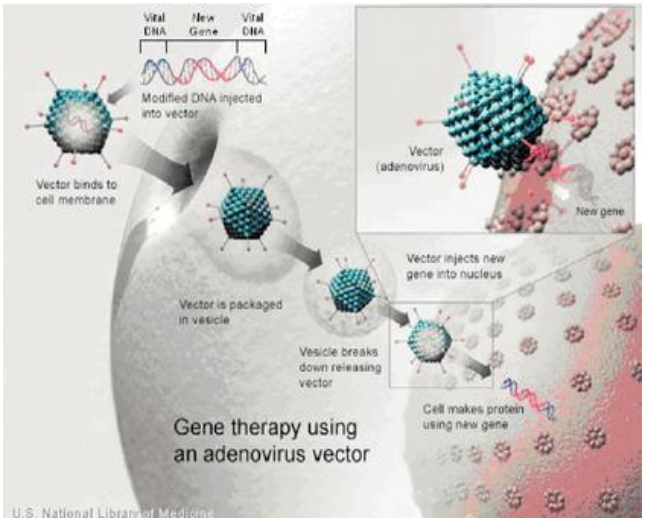
Regulation (EC) No 1394/2007

Gene therapy medicinal product GTMP

Somatic cell therapy

Tissue engineered product

Genetically modified cells



http://www.mta-dialog.de

http://www.biotechnologie.de

http://www.authormapper.com

➔ **Recombinant nucleic acid**

➔ **Pharmaco-immunological…**

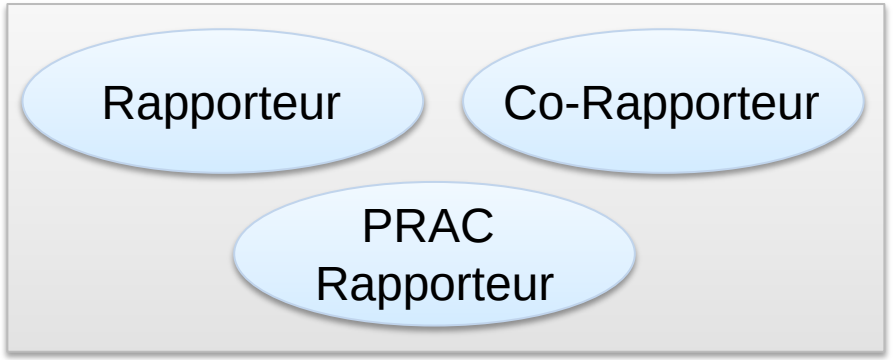
➔ **Regeneration, repair….**

Centralized Authorization Procedure of ATMPs

Assessment of MA application

Scientific assessment on quality, safety and efficacy

→ benefit-risk



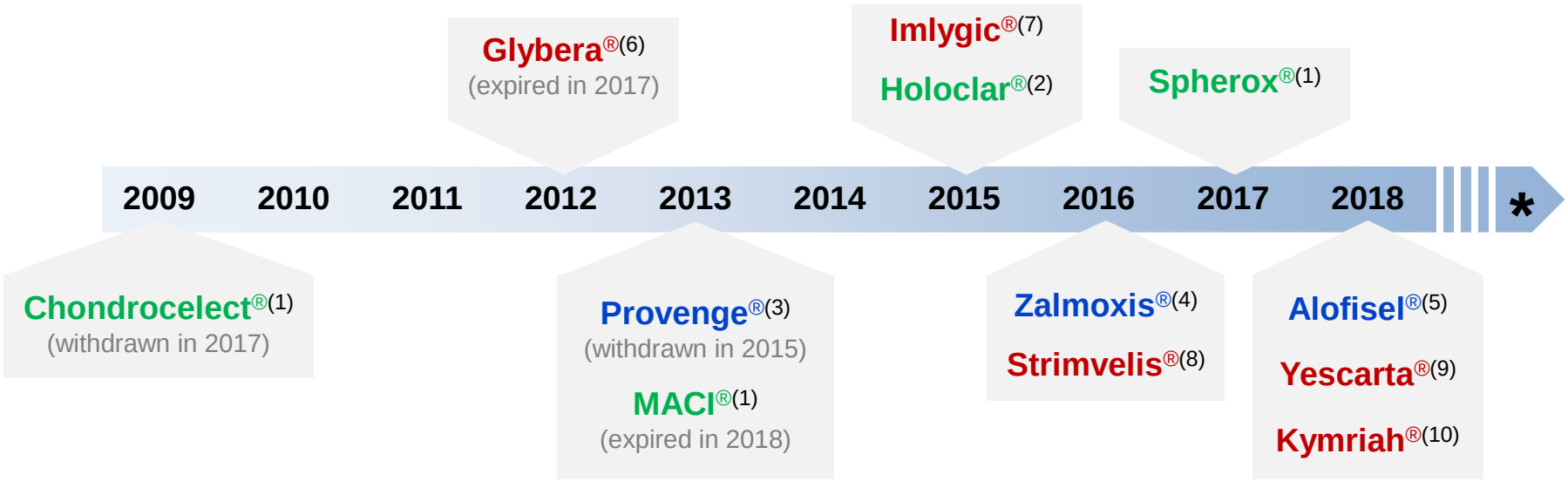
Draft opinion → Final opinion → **Authorization** for placing ATMPs on the market in the European Union

European Commission

5 „double members“
CHMP and CAT
(DE/PEI, Lithuania, Malta, Portugal, Spain)

MA = Marketing Authorization
CAT = Committee for Advanced Therapies
CHMP = Committee for Medicinal Products for Human Use
PRAC = Pharmacovigilance Risk Assessment Committee

Advanced Therapies – EU Marketing Authorisations



Tissue engineered products (TEPs)

(1) Autologous cartilage cells, expanded, knee cartilage defects
(2) Autologous human corneal epithelial cells containing stem cells, expanded, corneal lesions.

Somatic cell therapy medicinal products (STMPs)

(3) Autologous peripheral blood mononuclear cells, activated, metastatic prostate cancer
(4) Allogeneic T cells, genetically modified, adjunctive treatment in haploidentical HSCT
(5) Allogeneic mesenchymal adult stem cells from adipose tissues, expanded, treatment of complex perianal fistula (Mb. Crohn).

Gene therapy medicinal products (GTMPs)

(6) AAV1 vector containing human LPL gene, lipoprotein lipase deficiency
(7) HSV1 vector for oncolytic immunotherapy, injectable melanoma.
(8) Autologous CD34+ cells transduced with retroviral vector, ADA-SCID
(9) Autologous, CD19-CAR T cells transduced with retroviral vector, B-NHL
(10) Autologous, CD19-CAR T cells transduced with lentiviral vector, B-ALL, B-NHL

* **Under evaluation**
rAAV vector (Luxturna®) for treatment of inherited retinopathy

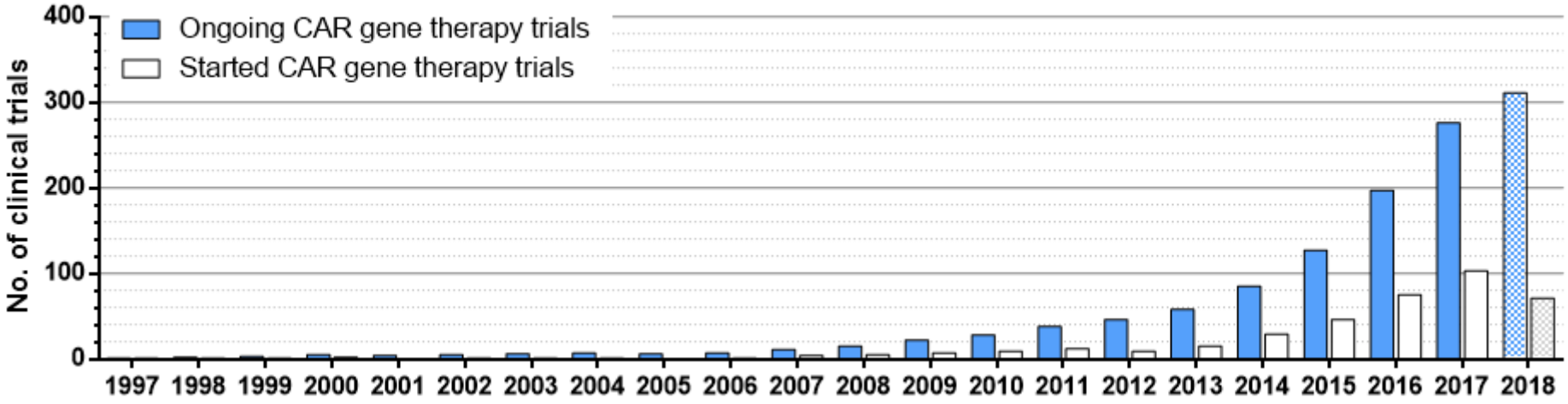
Two CD19-CAR T cell products approved in USA/EU

Yescarta™ (Axicabtagene ciloleucel)	Kymriah™ (Tisagenlecleucel)
γ-RV (scFv.CD28.CD3z)	LV (scFv.4-1BB.CD3z)
Refractory diffuse large B cell lymphoma (DLBCL)	B-ALL and refractory DLBCL
Study centers in US, Canada, EU, Israel	Study centers in US, Canada, Japan and EU
Commercial manufacturing in the US	Commercial manufacturing in the US
Approved 10/2017 by FDA	Approved 08/2017 and 05/2018 by FDA
Approved 08/2018 by EC	Approved 08/2018 by EC

Exponential Growth of CAR T cell trials

Number of clinical trials registered at *ClinicalTrials.gov* until 20.08.2018

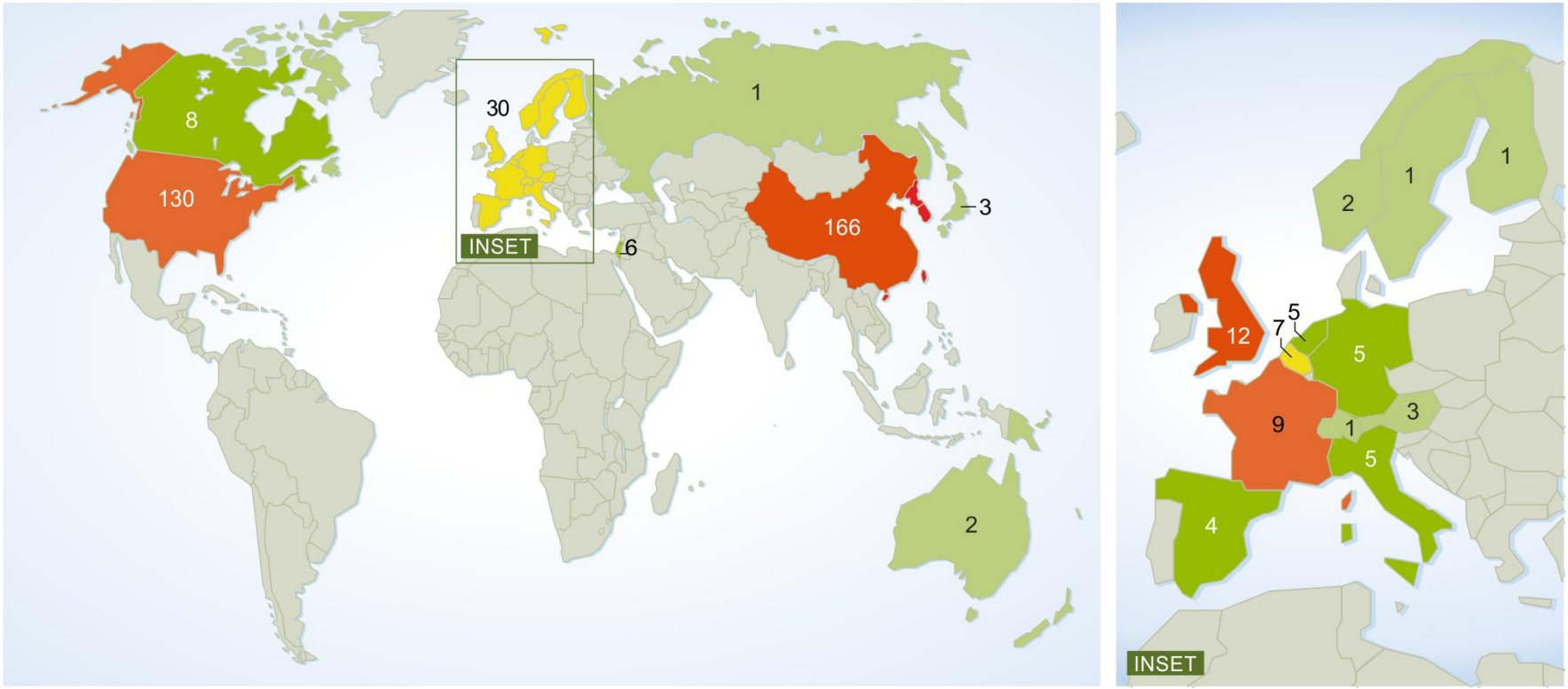
Registered CAR T cell trials:	415
Newly registered in 2017:	103
Already newly registered in 2018:	73
Ongoing trials:	343 (including 13 long-term follow-up studies)
Terminated, withdrawn suspended:	47
Unknown status:	27



* For some trials information on start date is not included in the database

Updated from:
Hartmann J, Schüßler-Lenz M, Bondanza A, Buchholz CJ, *EMBO Mol Med* , 8 2017.

Geographical Distribution of CAR T cell trials



326 ongoing trials world wide ←w/o LFU→

- including 12 multi-national trials (≥2 countries)
- Europe is counted as one country
- for 4 trials no information on trial sites

28 registered trials in Europe

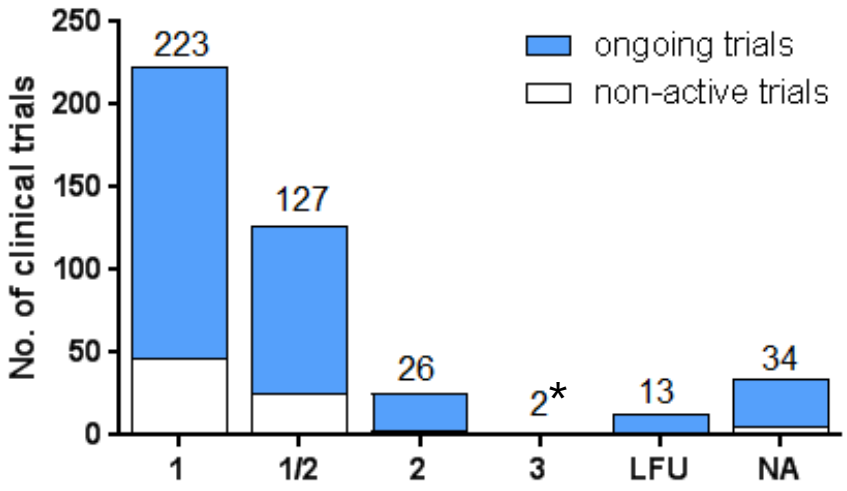
- including 9 multi-national trials (≥2 countries)
- 5 trials country not known
- at PEI 19 trials for DE are registered + 2 LFU

Updated from:
Hartmann J, Schüßler-Lenz M, Bondanza A, Buchholz CJ, *EMBO Mol Med* , 8 2017.

Statistical Analysis

Phase of CAR T cell trials

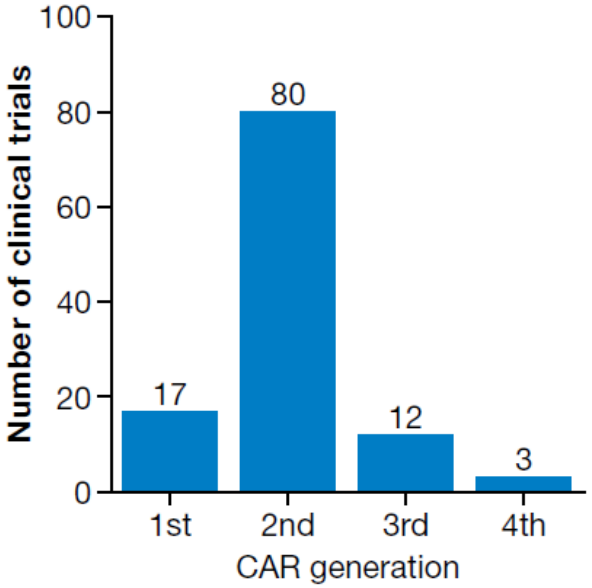
as entred in ClinicalTrials.gov
(20.08.2018)



* known from CTAs at PEI, not entered at ClinicalTirals.gov

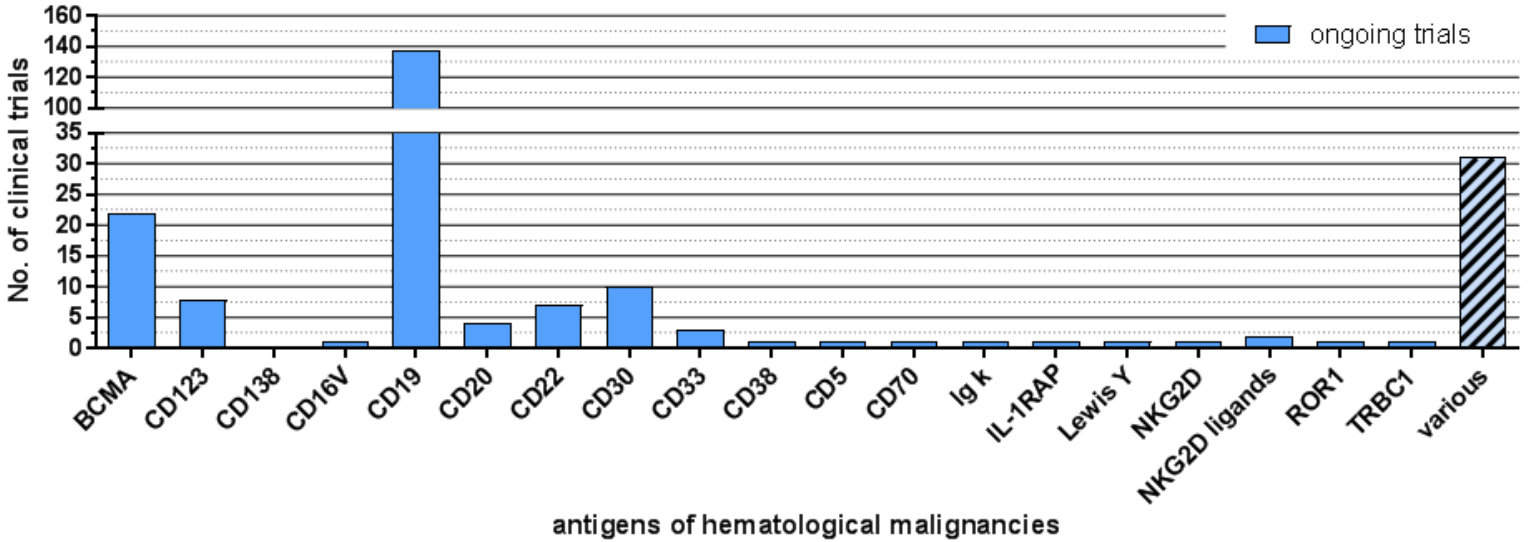
Generation of CAR T cell trials

as entred in ClinicalTrials.gov
(end of 2016)

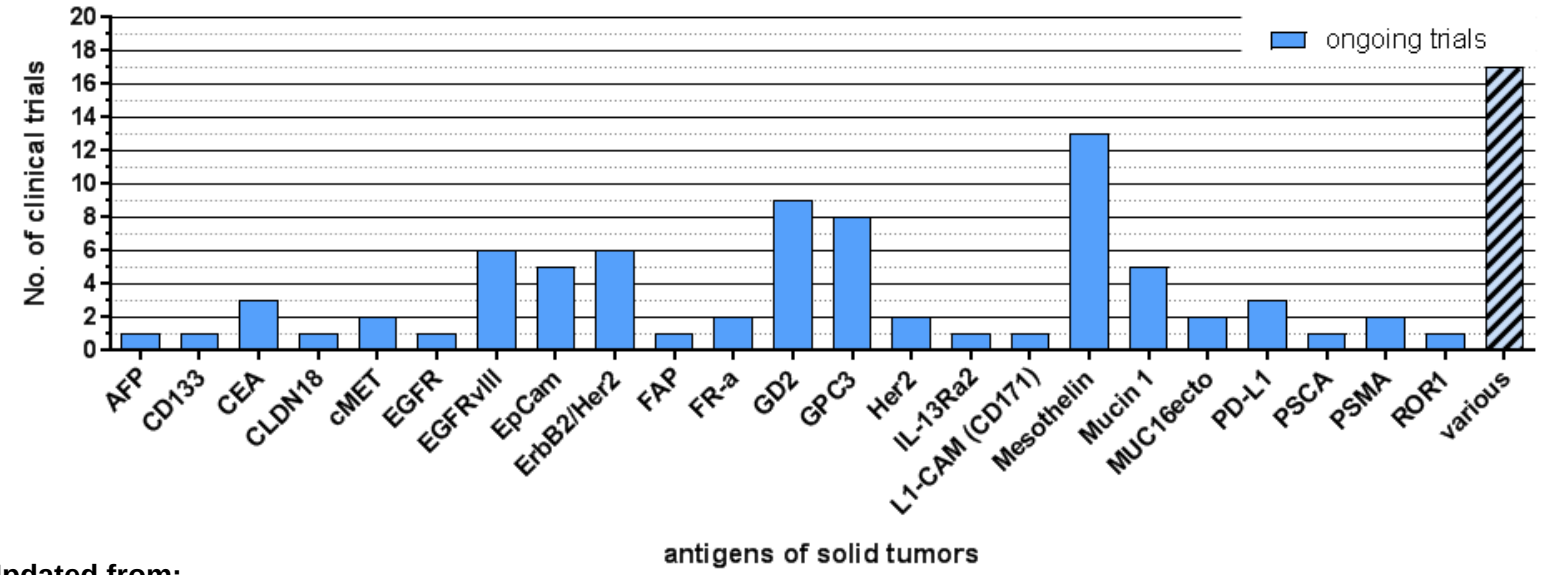


Updated or original from:
Hartmann J, Schüßler-Lenz M, Bondanza A, Buchholz CJ, *EMBO Mol Med* , 8 2017.

Various target antigens for CAR T cell therapy



n=19

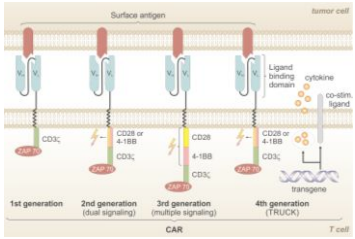


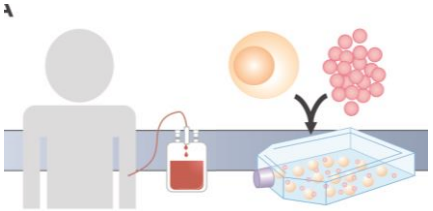
n=23

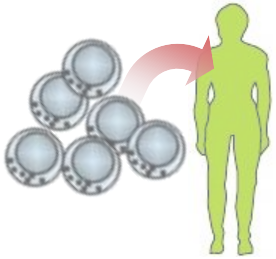
CAIX
EphA2
VEGFR-2

Updated from:
Hartmann J, Schüßler-Lenz M, Bondanza A, Buchholz CJ, *EMBO Mol Med* , 8 2017.

CAR T cell trials differ in various parameters







targeting domain
co-stimulatory domains
advanced features

autologous vs. allogenic
unselected vs. defined subset
culture conditions

dosing and schedule
- per kg or m^2 vs. flat
- single vs. split-dose
- based on tumor load

Target choice — tissue distribution, oncogene addiction, surface density

CAR construct

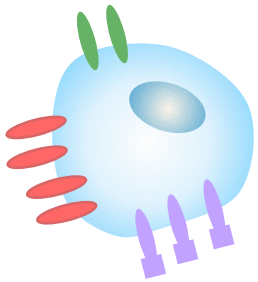
Vector choice — viral gene gene transfer, non-viral gene transfer, short vs. long term expression

T cell subset

LD regimien — host conditioning, mono- vs. combination therapy

Adminis-tration

Efficacy Toxicity — efficacy analysis, follow-up time, toxicity management



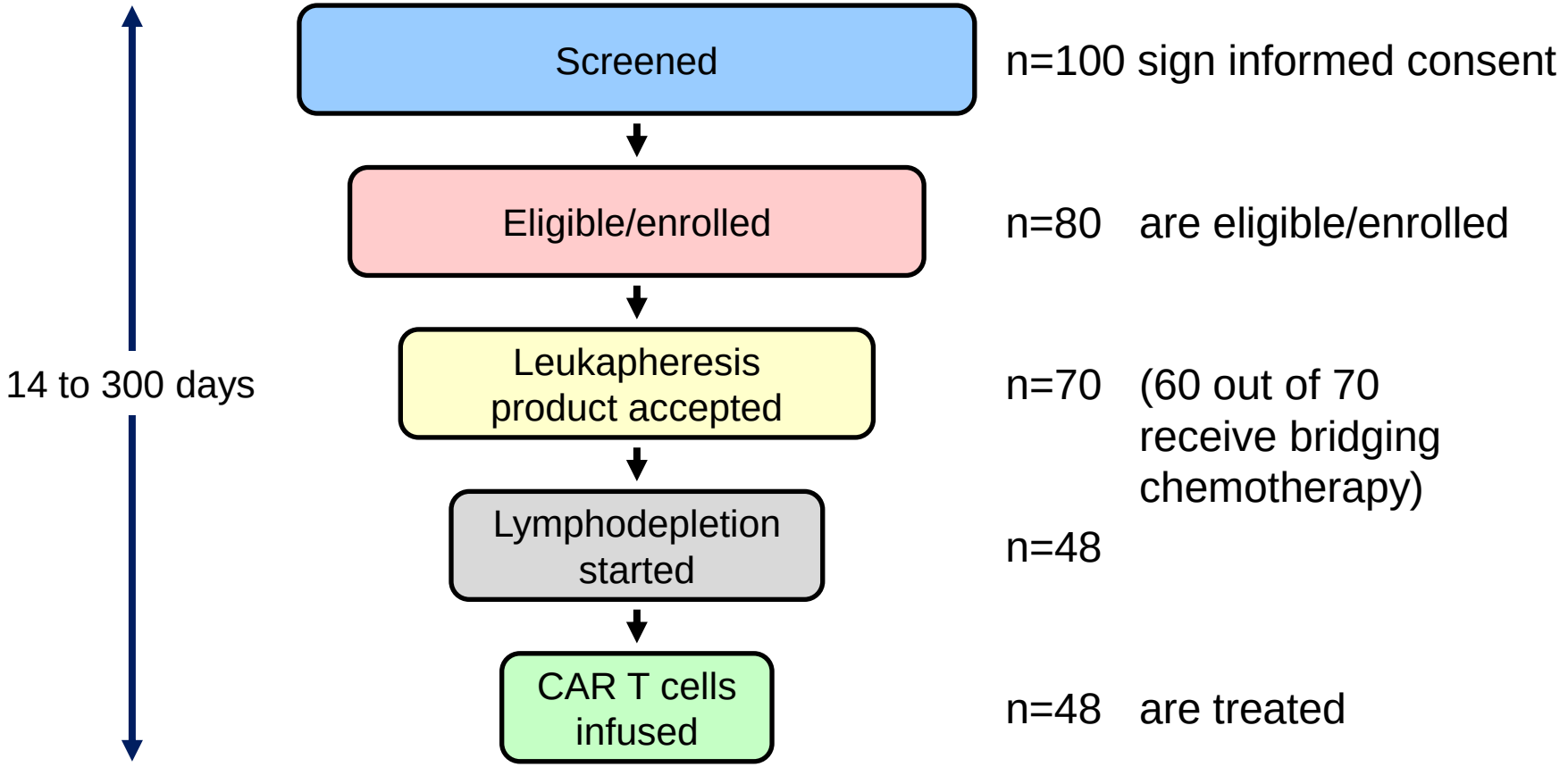
- Retrovirus
- Transposons
- RNA
- Lentivirus

Challenges for gene therapy with CAR/TCR-T cells

- Known side effects:
  - **“On target, off-tumor“-toxicity**
    (expression of Tumour antigens in healthy tissues, GvHD, B-cell aplasia)
    (mainly Tumour-**associated** antigens, only few tumour-**specific** antigens)
  - **“Off-target”-toxicity** (Minor problem in CAR T-cells)
  - **Cytokine release syndrome**, **Neurotoxicity** and **Tumor lysis syndrome**
  - **Anaphylaxis / allergy**
    (Immune responses to mouse-derived and/or rec. proteins)
- Possible side effects:
  - Side effects related to **product specificities** (Construct design, manufacturing)
    (Influence of co-stimulatory domains, spacer etc.)
    (expression of endogenous T-cell receptor, heterodimers with TCR modified T cells)
    (T cell phenotype or population, impurities etc.)
  - Side effects related to **patient**, **disease stage**
  - **Insertional mutagenesis** ??? (Minor problem in T-cells)
- **Dose finding** (persistence, expansion → living drug)
- **Surrogate end points**

➢ **Relevant animal models** (mode of action, toxicity)

Enrolled versus treated patients



- Product not manufactured
- Physician‘s decision
- Adverse events
- Patient died

→ Discrepancy in intention to treat (ITT; enrolled patients) vs. modified ITT (treated patients) analysis

Uncertainties at Marketing Authorization for CAR T

Marketing Authorization is granted based on positive Benefit-Risk Balance

Favorable effects

Efficacy

Medical need

Evidence

Unfavorable effects

Toxicity

Life threatening AEs

Supply

Available treatment options

Uncertainties

Uncertainties at Marketing Authorization for CAR T

- Efficacy assessment for CD19-CAR T cells
  - High overall remission rates ~ 80 %
  - High complete remission rates ~ 50-60% in
    - Pediatric and young adult patients with relapsed/refractory B-cell ALL
    - Adult patients with relapsed/refractory DLBCL
- Do the benefits of CAR T cells outweigh their risks?
  - Is the effect (ORR, CR rate) meaningful and relevant?
  - Are toxicities manageable under real world conditions?
- Uncertainties pertain to
  - Non-controlled, single arm studies (external controls)
  - Limited patient numbers
  - Patients dropping out between screening → enrolment → treatment
  - Limited follow-up time

Uncertainties at Marketing Authorization for CAR T

- Points which need to be considered:
  - CAR T cell production capacity and production time
  - Turn around time EU-US-EU, supply chain
  - Enrichment for patients with more favorable prognosis → bias

    → how representative are CAR T cell treated patients form claimed indication (“real-world-population”)?

- How can remaining uncertainties be addressed?

  → Post-approval commitments/obligations

  → Use of Registries as data sources for safety and efficacy follow-up?

Differential responsibilities CTA vs. MAA

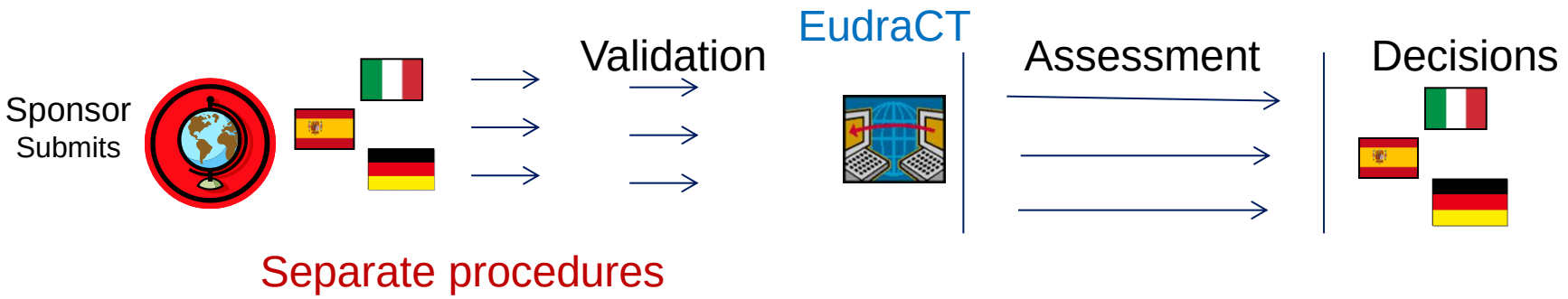
National vs. centralized

Clinical Trial Authorization	Marketing Authorization
Member states (national) - PEI, BfArM, AEMPS, ANSM…. - Ethics Committees - Competent authorities for Environmental Risk Assessment	**European Medicines Agency** - Committees - CHMP, CAT, PRAC, PDCO, COMP……

MA = Marketing Authorization Application
CTA = Clinical Trial Authorization

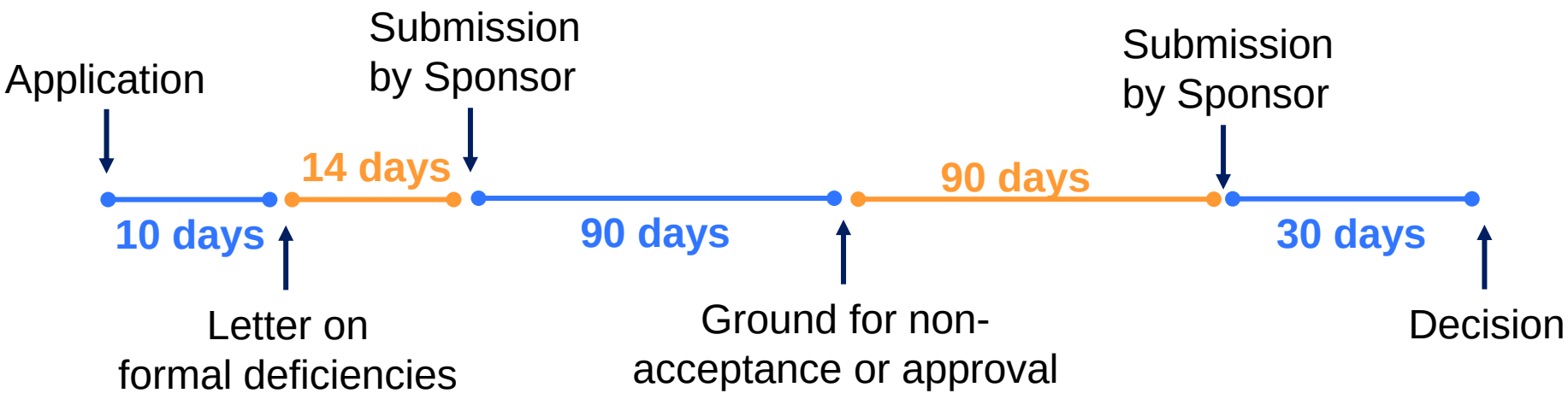
The Clinical Trial Authorization Process

The current process – multinational (Directive 2001/20/EC)



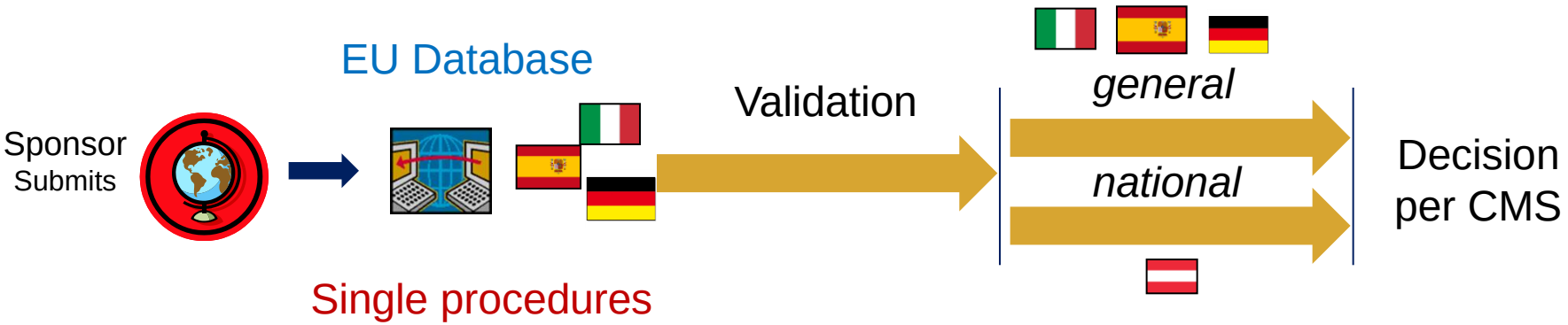
Time line for ATMP assessment in Germany (PEI)

NCA / Sponsor



The Clinical Trial Authorization Process

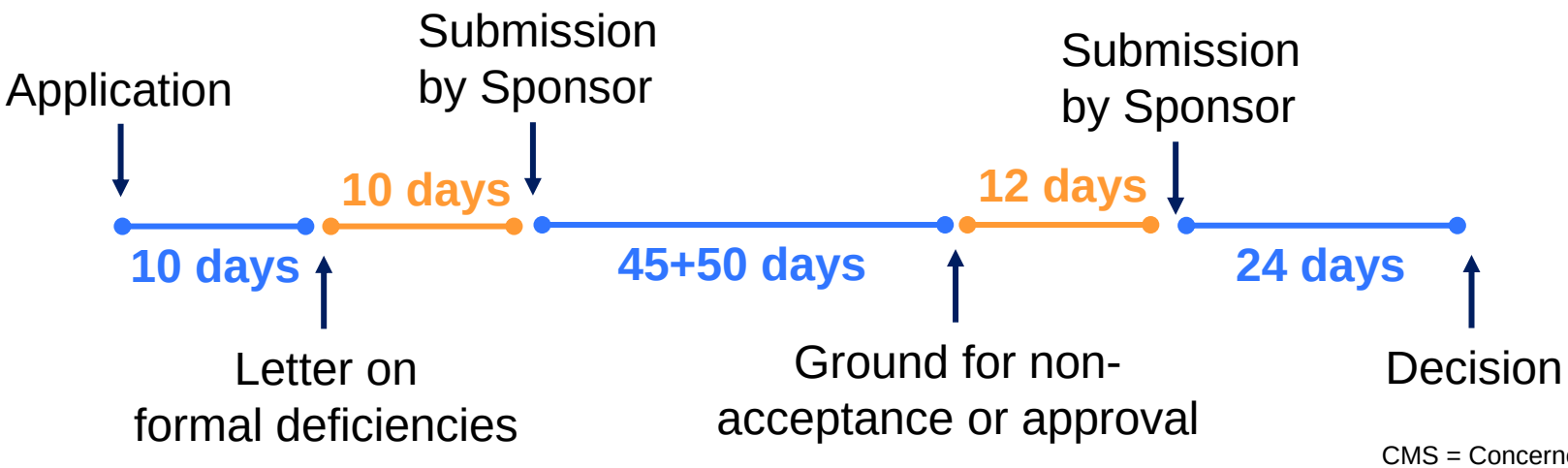
The future process – harmonized (Regulation 536/2014)



IMP containing GMO → **ERA on national level**

Time line for ATMP assessment

NCA / Sponsor



CMS = Concerned Member State

Environmental Risk Assessment for CTA

Dissimilarities between member States:

- Definition of GMO (plasmid GMO in e.g. in NL but not in DE)
- GMO within clinical trials
  - contained use (CU) (e.g. AU, PL, DK)
  - deliberate release (DR) (e.g. **DE**, NL, ES, SE, EL)
  - CU or DR
- Responsible Body for ERA evaluation
  - Ministries of Environment (e.g. Sweden, Spain, The Netherlands)
  - Ministries of Health (e.g. Finland, Austria)
  - Other external bodies (e.g. **Germany** (BVL), Belgium, France)
- Timings and procedures
  - **Single** portal and parallel assessment (e.g. SE, EL, **DE**)
  - **Parallel** application and assessment (e.g. NL, ES, IT, NO, UK, AT)
  - ERA approval **before** CTA (e.g. PL)
  - Not defined

BVL = Bundesamt für Verbraucherschutz und Lebensmittel
(Federal Office of Consumer Protection and Food Safety)

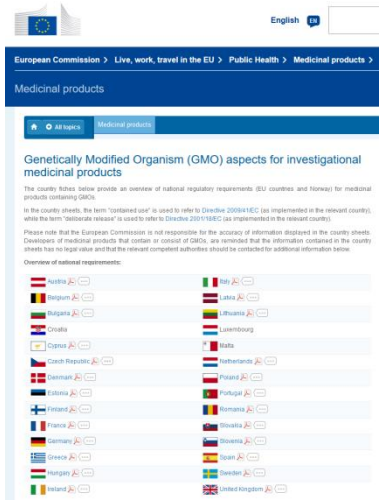
Environmental Risk Assessment

- Initiative of European Commission (EC) to reduce discrepancies across EU regarding application of GMO rules relevant for Gene Therapy Medicinal Products (EC-CAT-NCA joint initiative)
  - ➢ Ongoing - Q3 2018
  - **Good Practice Document**
  - **Common Application Form**

    (applicable for Austria, Belgium, Cyprus, Denmark, France, Germany, Greece, Hungary, Italy, Luxembourg, Malta, Portugal, Romania, Spain and Norway)

    https://ec.europa.eu/health/human-use/advanced-therapies_en#1

- Overview of national regulatory requirements for medicinal products containing GMOs
  - https://ec.europa.eu/health/human-use/advanced-therapies/gmo_investiganional_en
  - https://www.pei.de/EN/information/license-applicants/clinical-trial-authorisation/gmo/clinical-trial-gmo-node.html
    (PEI homepage)



Scientific Guidance on Advanced Therapies

- EC Guideline on **GMP specific to ATMPs** (22 May 2018)
  - Address novel scenarios such decentralized manufacturing, automated production and reconstitution of ATMPs
  - Risk-based approach to allow for some flexibility in manufacturing process

- Guideline on **genetically modified cells**
  - including guidance on CAR T cells
  - Revised guideline in public consultation (31/07/18-31/07/19)

- Guideline on **Safety and Efficacy and Risk Management Plans for ATMPs**.
  - Revised guideline in public consultation (01/02/18-30/04/18)

- Develop further guidance document to address
  - Investigational ATMPs / Clinical Trials
  - Comparability of ATMPs – quality/manufacturing

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000410.jsp&mid=WC0b01ac058002958d

Receptor targeted CAR delivery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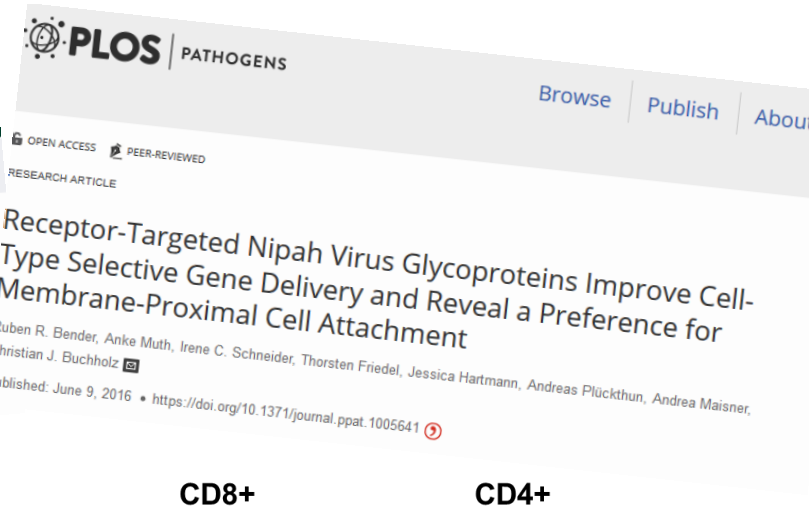
ORIGINAL ARTICLE

A library-based screening strategy for the identification of DARPins as ligands for receptor-targeted AAV and lentiviral vectors

Jessica Hartmann, Robert C. Münch, Ruth-Therese Freiling, Irene C. Schneider, Birgit Dreier, Washington Samukange, Joachim Koch, Markus A. Seeger, Andreas Plückthun, Christian J. Buchholz

Published Online: July 05, 2018

Publication stage: In Press Accepted Manuscript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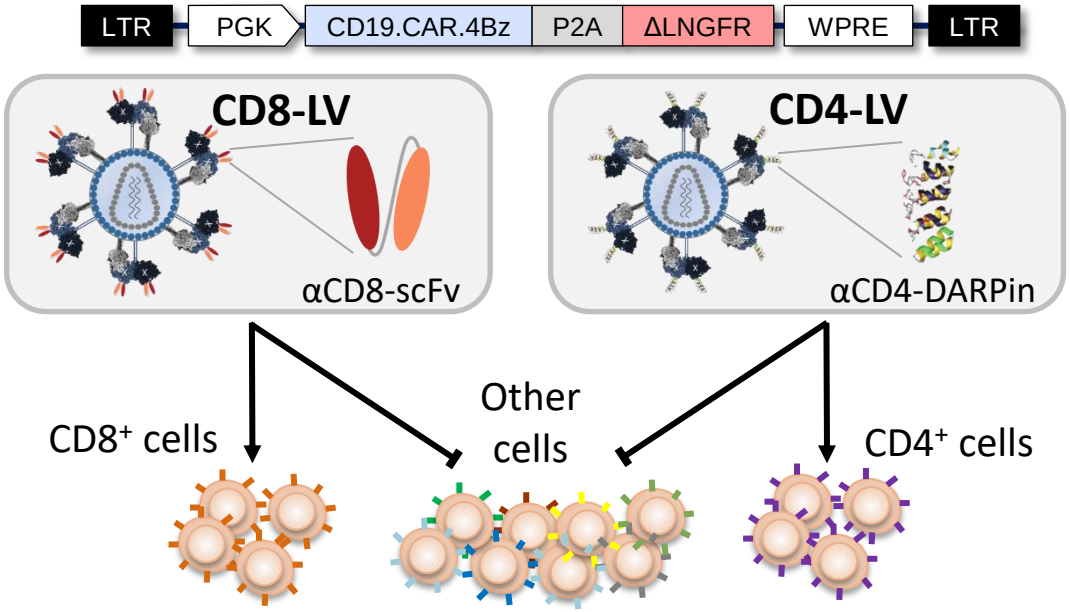
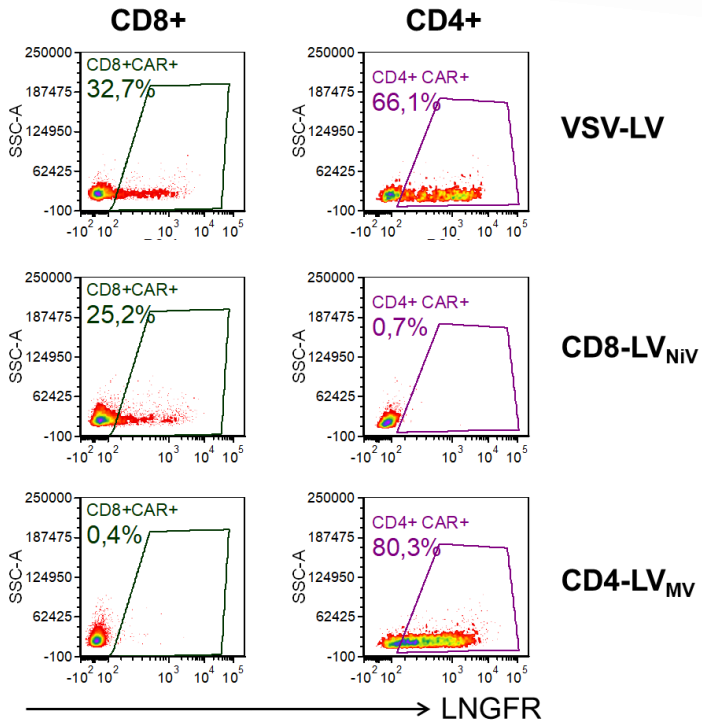
RESEARCH ARTICLE

Receptor-Targeted Nipah Virus Glycoproteins Improve Cell-Type Selective Gene Delivery and Reveal a Preference for Membrane-Proximal Cell Attachment

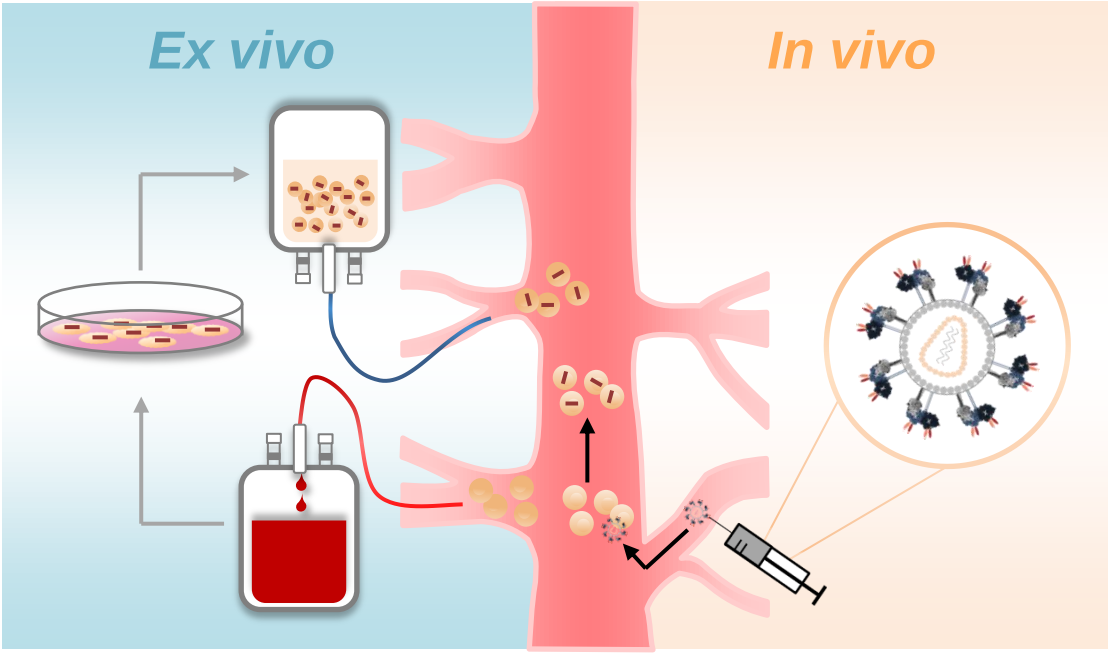
Ruben R. Bender, Anke Muth, Irene C. Schneider, Thorsten Friedel, Jessica Hartmann, Andreas Plückthun, Andrea Maisner, Christian J. Buchholz

Published: June 9, 2016 • https://doi.org/10.1371/journal.ppat.1005641





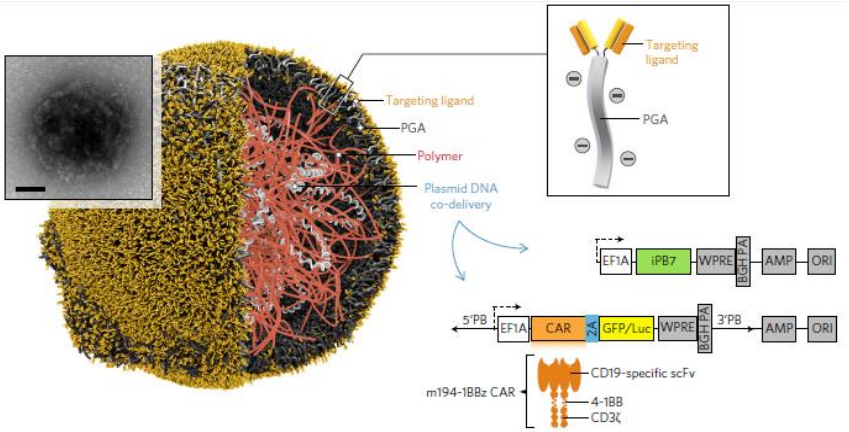
In vivo CAR T cell generation

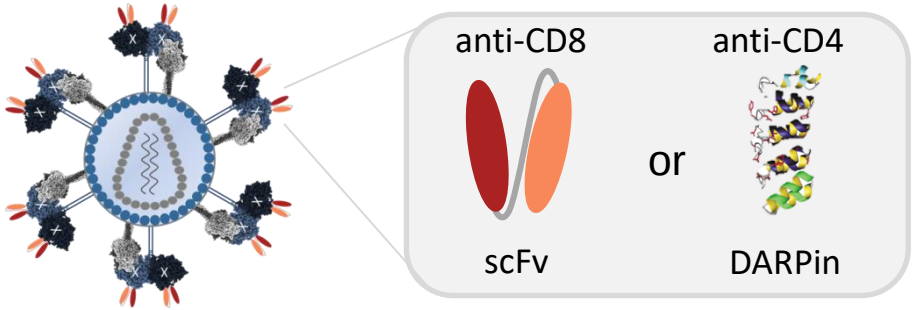


***In situ* programming of leukaemia-specific T cells using synthetic DNA nanocarriers**

Tyrel T. Smith[1], Sirkka B. Stephan[1], Howell F. Moffett[1], Laura E. McKnight[1], Weihang Ji[1], Diana Reiman[2], Emmy Bonagofski[2], Martin E. Wohlfahrt[1], Smitha P. S. Pillai[3] and Matthias T. Stephan[1,2,4,5]*

Nat. Nanotechnology 2017

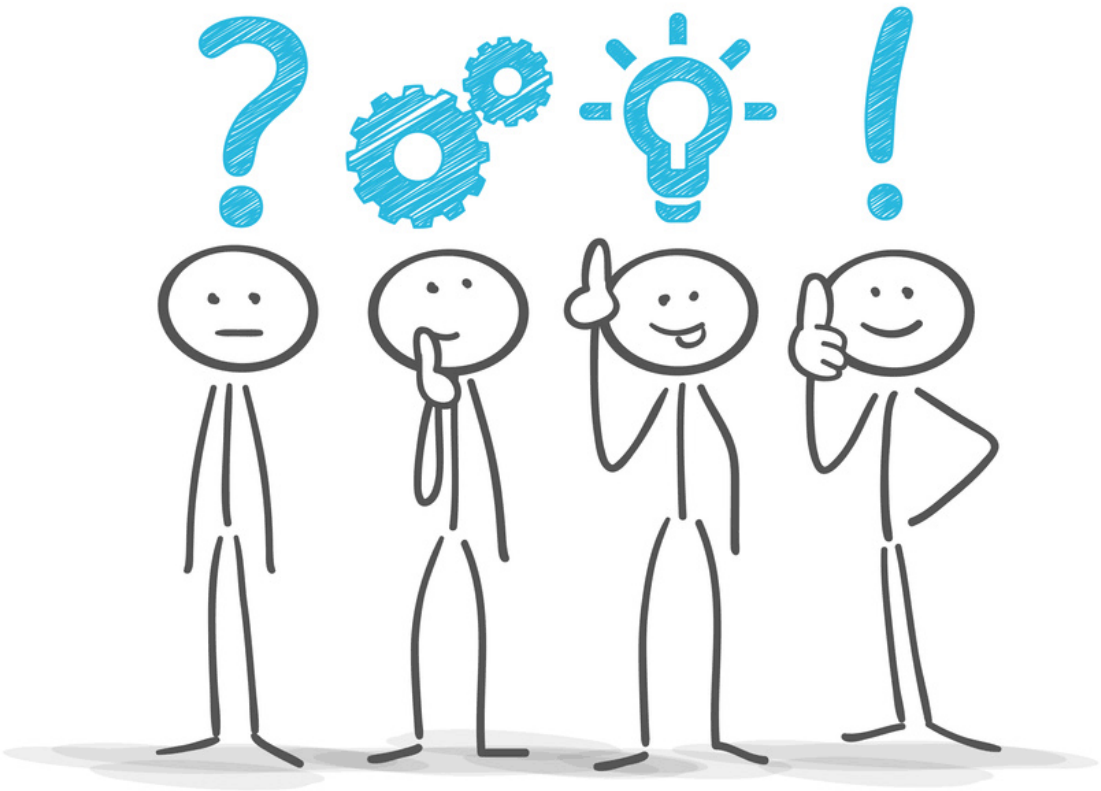




***In vivo* generation of human CD19-CAR T cells results in B cell depletion and signs of cytokine release syndrome**

A. Pfeiffer, F.B. Thalheimer, S. Hartmann, A.M. Frank, R.R. Bender, S. Danisch, C. Costa, W.S. Wels, U. Modlich, R. Stripecke, E. Verhoeyen, C.J. Buchholz

EMBO Mol Med, 2018 in press



Thank you for your attention