HEIDELBERG
UNIVERSITY
HOSPITAL

ATMPs – Umsetzung und Regularien

Besonderheiten bei Herstellung -> Klinische Studien -> Zulassung

Und ihre Bedeutung für Long-term safety and efficiency

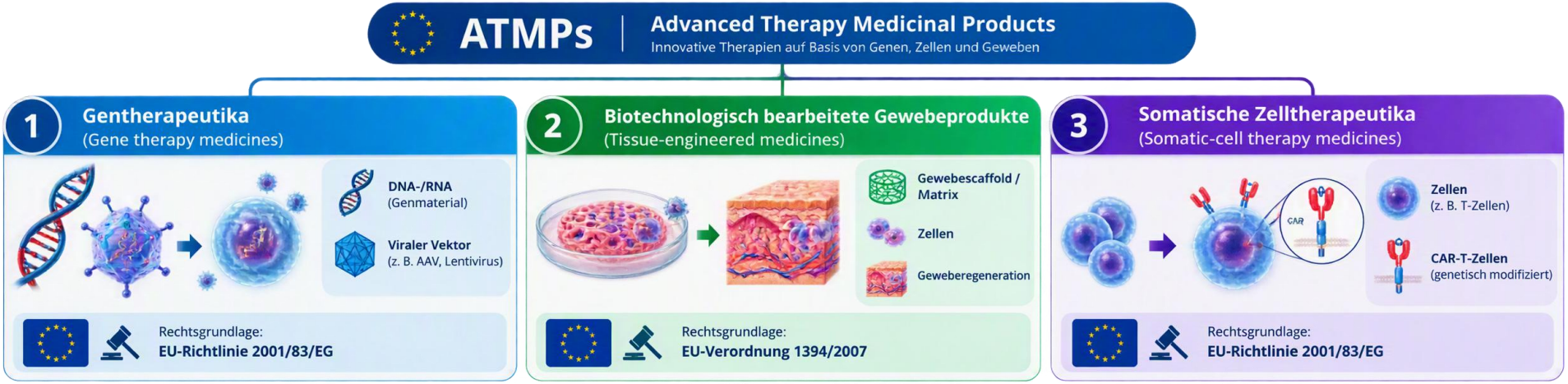






Department of Clinical Pharmacology and Pharmacoepidemiology
Prof. Dr. med. Julia Stingl

UK HD



Häufige Bezeichnung:

Zell- und Gentherapien (CGT)

Arzneimittelregulation







Accelerated market access

PRIME(Priority Medicines) program

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
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2-5 y

Zulassung:
Conditional Approval

Preclinical development:
In vitro models, in silico models, animal models (3R)

First in Human/Phase I +II

Phase III

Dose finding, PK, efficacy
20-30

Efficacy/safety
<100

PAES
(Post-Authorisation Effeety Study)

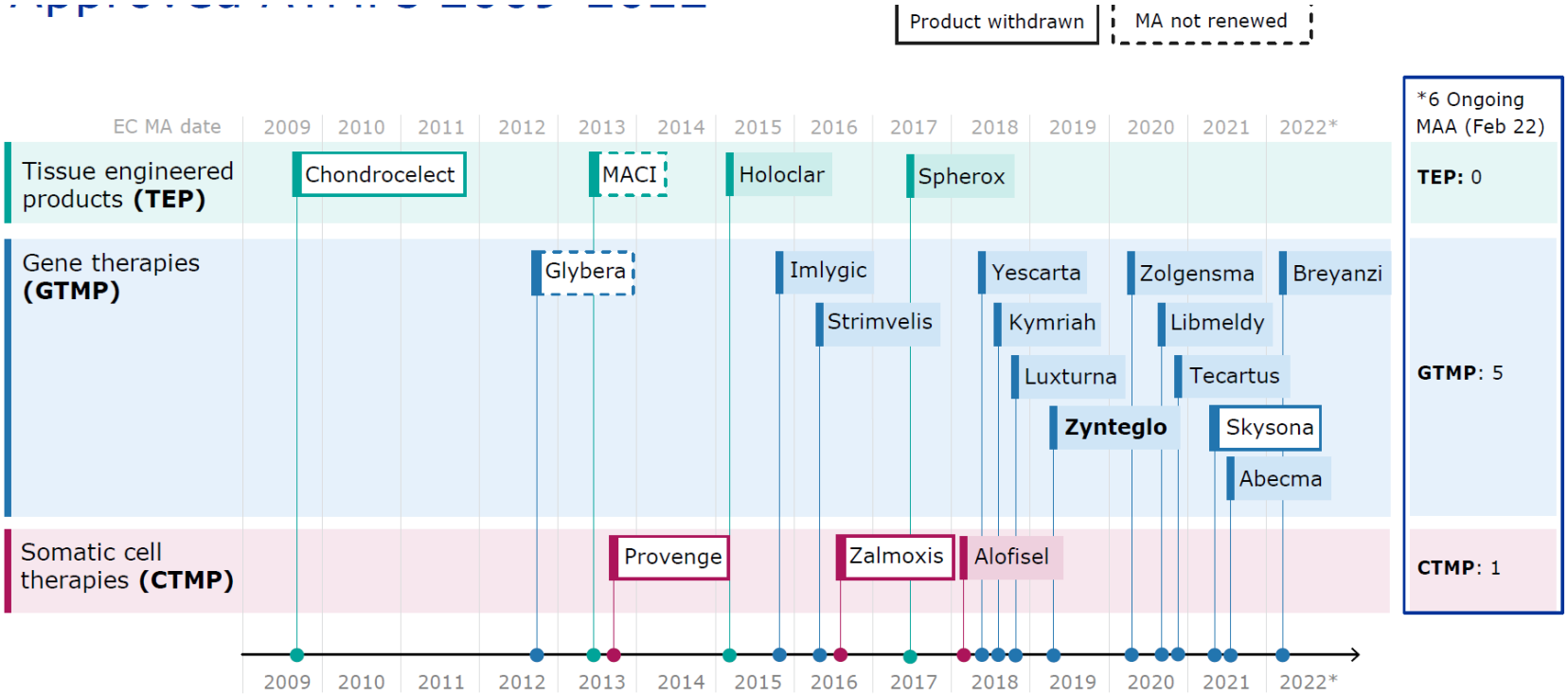
- Langzeitwirksamkeit
- Registerdaten
- Reale Versorgungsdaten (Real-World Evidence)

PASS
(Post-Authorisation Safety Study)

- Langzeitsicherheit
- Pharmakovigilanz
- Seltene & späte unerwünschte Ereignisse

Animal studies: genotoxicity, embryotoxicity

EMA Approved ATMPs 2009-2022



Neue Arzneimittel….
… haben keine Nebenwirkungen?

Häufigkeitsangaben in Fachinformation/ Packungsbeilage

Häufigkeitsangabe	Die Nebenwirkung betrifft
sehr häufig	mehr als 1 Behandelten von 10
häufig	1 bis 10 Behandelte von 100
gelegentlich	1 bis 10 Behandelte von 1.000
selten	1 bis 10 Behandelte von 10.000
sehr selten	weniger als 1 Behandelten von 10.000
nicht bekannt	Häufigkeit auf Grundlage der verfügbaren Daten nicht abschätzbar

Tabelle 1:
Studiengrößen zur Erfassung von UAW. Notwendige Studiengruppe, um einen zweifachen Anstieg einer UAW in der Verumgruppe bei einer kontrollierten oder Kohortenstudie erkennen zu können [1].

Häufigkeit der UAW in der Kontrollgruppe	Erforderliche Größe der mit dem Verum behandelten Gruppe
1/10	280
1/100	1.800
1/1.000	18.000
1/10.000	180.000
1/100.000	1,8 Mio

Neue Arzneimittel….
… haben keine Nebenwirkungen?

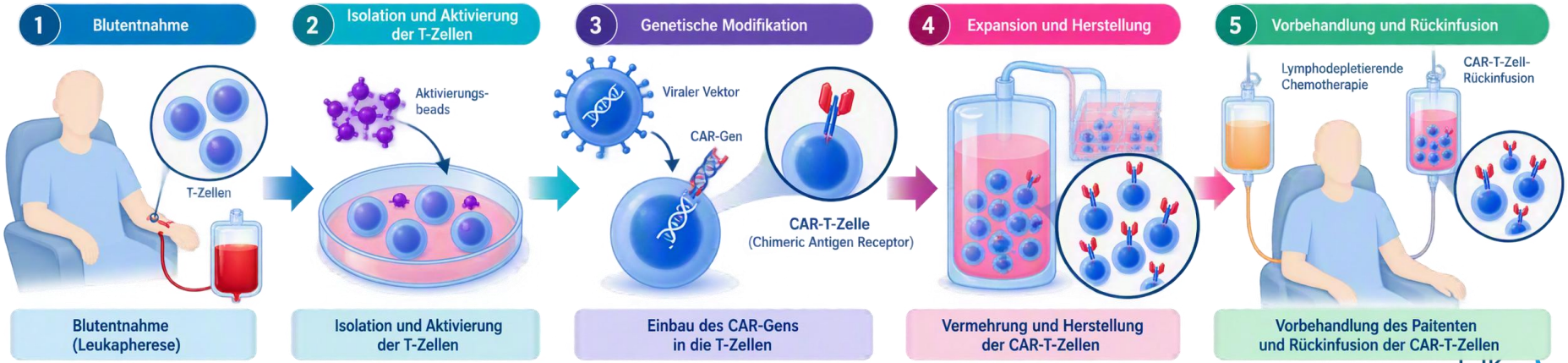
- Bsp.
- ➢ CAR-T-Zelltherapie Kymriah® (Tisagenlecleucel): Es wurden insgesamt etwa **291** Patienten in den klinischen Zulassungsstudien (Phase I-III) behandelt
- ➢ Spinraza® (Nusinersen): **173** Kinder bei Zulassung in 2017
- ➢ Zolgensma® (Onasemnogen abeparvovec) Gentherapie: **67** Kinder bei Zulassung in 2020
- ➢ BioNTech/Pfizer (Comirnaty®): **44.000** Teilnehmer bei Zulassung durch EMA im Dezember 2020

Die Bedeutung von Academia: Rolle der Universitätskliniken in ATMP-Entwicklung/Anwendung



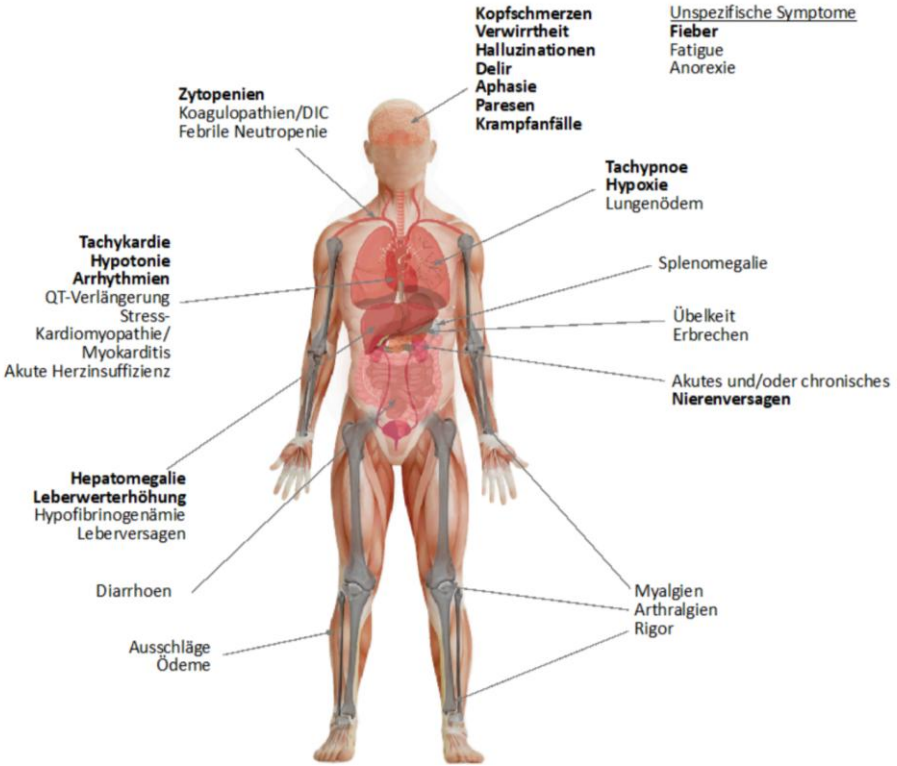
Beispiel: Car-T-Zelltherapie

- T-Lymphozyten werden gentechnisch mit einem Sensor für ein Oberflächenmolekül z.B.CD19, einem Chimären Antigen-Rezeptor: CAR ausgestattet.
- Aktivierung der CAR-T-Zelle mit dem anderen Teil des CAR, der Signaldomäne eines T-Zell-Rezeptors



Gefahren durch T-Zell-Aktivierung:

- Cytokine-Release-Syndrom



ATMP: **Key differences** from other medicines

- Novel safety concerns
- Need for long-term safety & efficacy follow-up after approval

ATMP key differences from other medicines

- Novel safety concerns
- Need for long-term safety & efficacy follow-up after approval



Pädiatrisches Klinisch-Pharmakologisches Studienzentrum (paedKliPS):

Gemeinsame Institution der Abteilung für Klinische Pharmakologie und Pharmakoepidemiologie und des Zentrums für Kinder- und Jugendmedizin

paedKliPS
UniversitätsklinikumHeidelberg

Medizinische Leitung:
Dr. Kristine Chobanyan-Jürgens
Dr. Andreas Ziegler

Studien-Therapeutika

- ✓ Small molecules
- ✓ Gentherapeutika
- ✓ Gen-editierende Therapeutika
- ✓ Biologika
- ✓ Anti-Sense Oligonukleotide (ASO)
- ✓ Enzymersatztherapie

2019 — Internationale multizentrische pädiatrische klinische Prüfungen seit 2019 bis 2026

„First patient in“
1. Sponsorstudie

Studien	Phase 1	Phase 2	Phase 3	Post-authorization	Total
Abgeschlossen	1	5	6	0	12
Laufend	1	3	7	2	12
Geplant	1	3	3	0	7
In Evaluation	1	1	1	0	3
Total	4	12	17	2	34

Rekrutierungs-quote ≥ 100 %

ATMP Safety risks: Beispiel Gentherapie

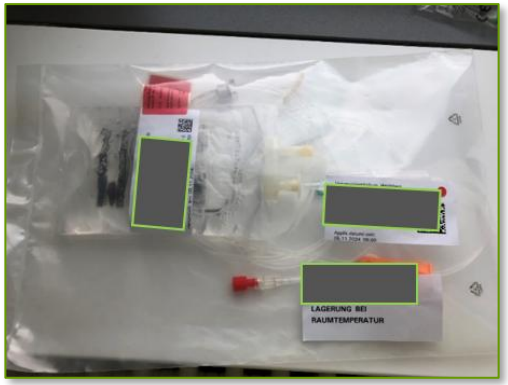
- Local and systemic immunological reaction against AAV8-Vector
  - Anaphylactic reaction/ acute infusion reaction
  - acute liver injury
  - autoimmune hepatitits

- AAV8-Antibodies from prior infections
  - Therapy failure

Vorsichtsmaßnahmen bei klinischer Studie

- Studie in jungen Erwachsenen statt in Kindern (=vulnerable Pat.)
- Prednisolon Einnahme, um immunologische Reaktionen zu vermeiden
- Genaues Screening bezüglich Risiken für Nebenwirkungen





Final Study-Wide Enrollment

Subjects Screened	Subjects Dosed	Screen Failed	Crossover Completed
64	37	27	19

Reasons for Screen Failures:

- Medical conditions that affected participation or eligibility
- Positive for AAV Antibodies
- Withdrew Consent

2 Screen failure in HD:
4 Pat.screened: 2 positive for AAV8 antibodies

Research issues for Post Approval Safety Studies (PASS), Post Approval Efficacy Studies (PAES)

SAFETY

- Long-term safety (e.g., tumor risk, insertional mutagenesis for gene therapies)
- Immunological reactions (antibodies, graft-vs-host)
- Adverse events in real-world use
- Special populations

EFFICACY

- Real-world effectiveness (survival, disease progression, function)
- Long-term durability of effect
- Comparisons with standard therapies or historical controls

Aber - das ist nicht Alles!

Impact of manufacturing process on cells: e.g. on tumorigenicity profile

Regulatory Toxicology and Pharmacology 156 (2025) 105769

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Global regulatory considerations and practices for tumorigenicity evaluation of cell-based therapy

Dehu Dou [a,b,*], Jing Lu [a], Jinhui Dou [a], Yan Huo [a], Xinjiang Gong [a], Xuefeng Zhang [a], Xijing Chen [b]

[a] TriApex Laboratories Co., Ltd. Nanjing, Jiangsu, China
[b] China Pharmaceutical University, Nanjing, Jiangsu, China

Table 2
Case study on tumorigenicity evaluation of stem cell products (Partial) that have been marketed in the United States and Europe (FDA, 2022–02).

Product	cells/bracket	Indication	Tumorigenicity			karyotyping	Other animal model	Considerations of product
			In vivo	Soft AGAR cloning test	Cell proliferation			
Provenge	Autologous DC cell	Metastatic prostate cancer	/	/	/	/	/	A*
laViv	Autofibroblasts	Nasolabial fold	/	/	/	/	/	B*
HemaCord	Allogeneic hematopoietic progenitor cells	Hematopoietic progenitor cell transplantation	/	/	Yes	/	/	N/A
Epicel	Autologous keratinocytes	burn	Nude rat	Yes	/	Yes	Nude rat	N/A
Apligraf	Allogeneic keratinocytes and fibroblasts/bovine collagen	skin ulcer	Nude rat	/	/	Yes	Hu-scid mice	N/A
Gintuit	Allogeneic keratinocytes and fibroblasts/bovine collagen	new gum tissue	Nude rat	/	/	/	/	N/A
TransCyte	Allofibroblast/knitted nylon	burn	/	Yes	/	/	Nude rat	N/A
Dermagraft	Allofibroblast/polymer net	skin ulcer	Nude rat	/	/	Yes	Nude rat	N/A
OrCel	Allogeneic keratinocytes/ fibroblasts	Burns/epidermolysis	/	/	/	/	Nude rat/ scid mice	N/A
ChondroCelect	Autologous chondrocyte	cartilage injury	/	/	/	Yes	Nude rat	N/A

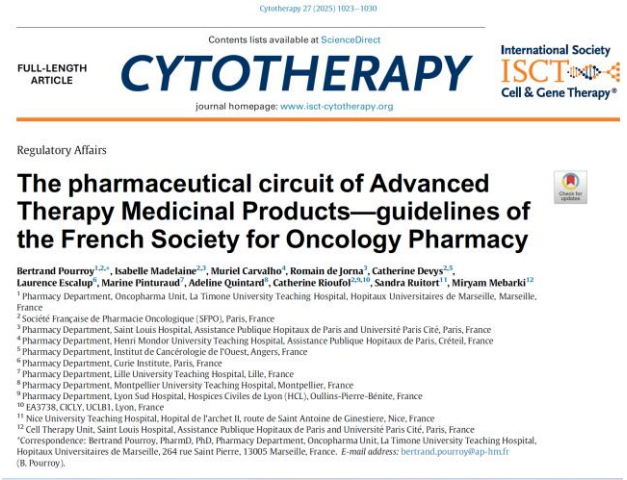
Note: "/" means not carried out; N/A indicates not applicable. A: Autologous products not evaluated. B:No preclinical evaluation based extensive clinical experience.

Research issues in ATMP development:

Impact of storage, distribution, site reconstitution on safety/efficacy

Minor deviations during **storage, distribution, and site reconstitution** directly dictate the product's safety profile and clinical efficacy

- Breach in the cold chain
- A mix-up in autologous or allogeneic products
- Container Integrity: Mishandling cryovials during transit
- Temperature change during thawing
- Short life span of cells



Cytotherapy 27 (2025) 1023–1030

Contents lists available at ScienceDirect

FULL-LENGTH ARTICLE

CYTOTHERAPY

International Society ISCT Cell & Gene Therapy®

journal homepage: www.isct-cytotherapy.org

Regulatory Affairs

The pharmaceutical circuit of Advanced Therapy Medicinal Products—guidelines of the French Society for Oncology Pharmacy

Bertrand Pourroy[1,2,*], Isabelle Madelaine[2,3], Muriel Carvalho[4], Romain de Jorna[5], Catherine Devys[2,5], Laurence Escalup[6], Marine Pinturaud[7], Adeline Quintard[8], Catherine Rioufol[2,9,10], Sandra Ruitort[11], Miryam Mebarki[12]

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[4] Pharmacy Department, Henri Mondor University Teaching Hospital, Assistance Publique Hopitaux de Paris, Créteil, France
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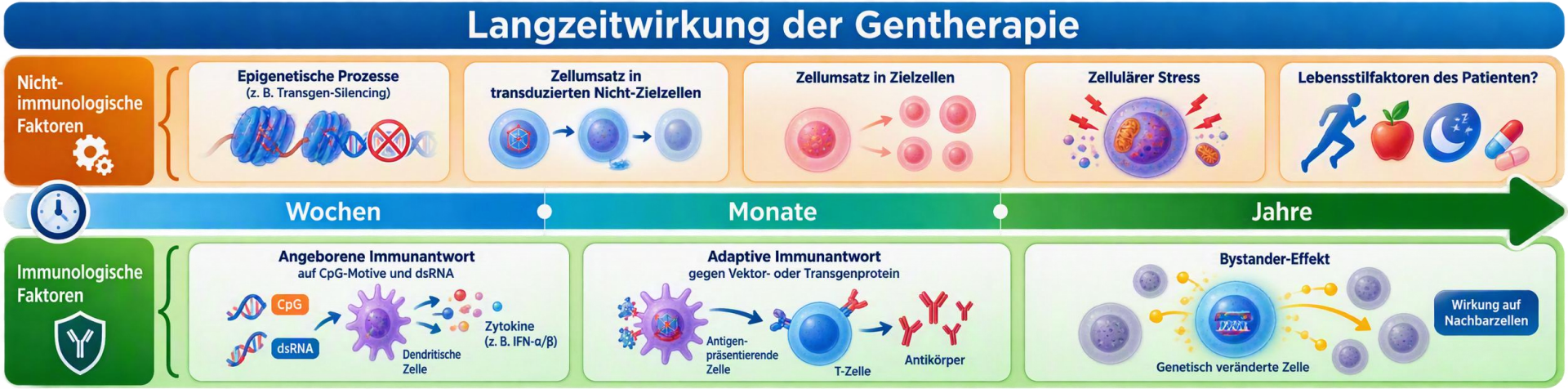
Research issues in ATMP development

Impact of administration procedure

Delivery Method	Efficacy Vulnerabilities	Safety Vulnerabilities
Surgical Implantation (e.g., Tissue patches, Scaffolds)	**Poor host-tissue integration**; Lack of vascularization causing graft death.	**Structural tissue damage**; Structural failure of the scaffold; Post-operative infection.
Local / Image-Guided Injection (e.g., Subretinal, Intracerebral)	**Product leakage** from target niche; Low cellular retention; Loss of potency.	**Mechanical trauma to vital organs**; Accidental intravascular injection causing embolisms.
Systemic / Catheter Infusion (e.g., CAR-T cell therapies	**Cell death via shear stress** in the catheter line; Inefficient homing to target tumors.	**Anaphylaxis / Cytokine Release Syndrome (CRS)**; Microvascular occlusions.

Masson-Meyers DS, Tayebi L. Vascularization strategies in tissue engineering approaches for soft tissue repair. J Tissue Eng Regen Med. 2021 Sep;15(9):747-762. doi: 10.1002/term.3225. Epub 2021 May 31. PMID: 34058083; PMCID: PMC8419139.
Wahlberg, Brendon & Ghuman, Harman & Liu, Jessie. (2018). Ex vivo biomechanical characterization of syringe-needle ejections for intracerebral cell delivery. Scientific Reports. 8. 10.1038/s41598-018-27568-x.

ATMP: Langzeit-Wirkungen - Variabilität in Off-Target Wirkungen
Bsp. AAV-vektorbasierte Gentherapie

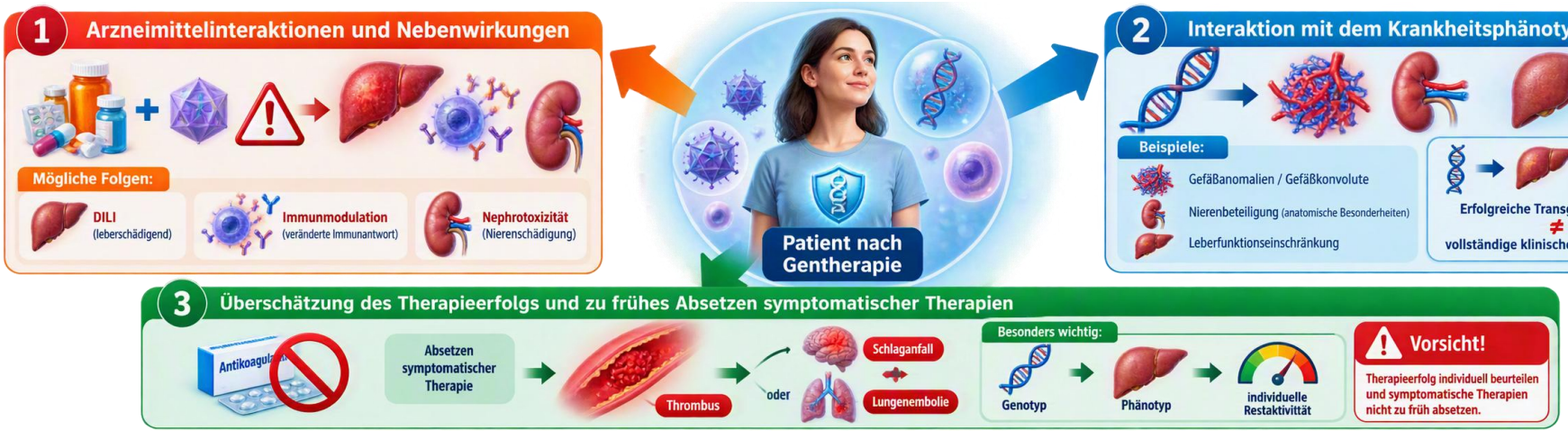


Adapted from: Muhuri et al. Molecular Therapy; 2022, Vol 30, Pages 1364-1380

Langzeit-Monitoring und individuelle Arzneimitteltherapie



Langzeit-Monitoring und individuelle Arzneimitteltherapie



Take Home Messages:
ATMPs: Besondere Anforderungen an Academia

