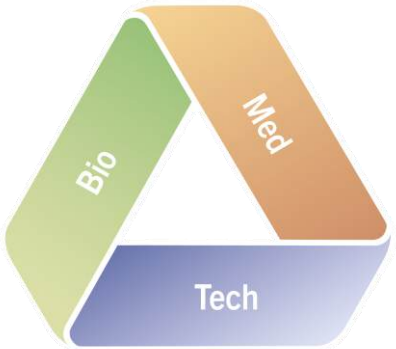


In-vivo CAR-T: Challenges and Opportunities

Dr. Lorenz Mayr
BioMedTech Consulting GmbH, Basel, Switzerland

SaxoCell Annual Conference 2026
Dresden, Germany
June 2-3, 2026

In-vivo Chimeric Antigen Receptor (CAR) T-cell Therapy

Does it work?

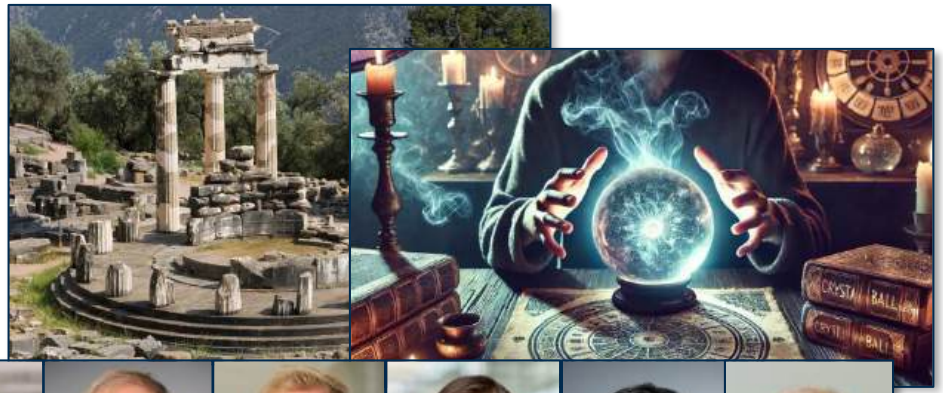
In-vivo Chimeric Antigen Receptor (CAR) T-cell Therapy

How do we answer that question?

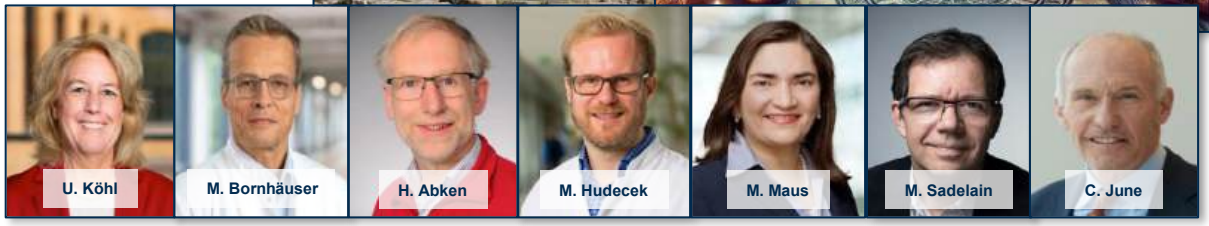
In-vivo Chimeric Antigen Receptor (CAR) T-cell Therapy ?

Sources of Information:

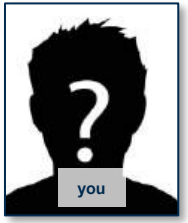
1. Oracle of Delphi



2. Crystall Ball



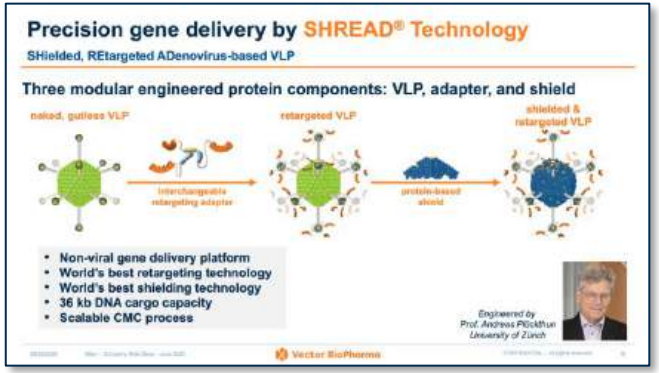
3. KOL/SME



4. Scientific Literature

In-vivo Chimeric Antigen Receptor (CAR) T-cell Therapy ?

My own in-vivo CAR-T journey started back in 2021: Vector BioPharma AG, Basel



In-Vivo Cell Therapy Conference, July 10-12, 2023, Boston/MA

Speakers:
Lorenz Mayr, CEO, Vector BioPharma AG
Sheena Smith, Head PM, Vector BioPharma AG

In-vivo CAR-T: The remarkable years 2023-2026

- Many companies ceased to exist, including Vector BioPharma AG, Basel
- Technology development for autologous ex-vivo CAR-T moved on (e.g. Fraunhofer IZI)
- Technology development for gene delivery moved on (e.g. LV, AAV, LNP/mRNA, EDV)
- Clinical use for autologous CAR-T provided additional proof (e.g. dual CD19/20 CAR-T)
- Clinical use for other areas (e.g. autoimmune) provided huge excitement (e.g. Uni Erlangen)
- China entered Pharma's main stage with massive investments in CGT (e.g. IIT)

By mid 2025, a new star was born:

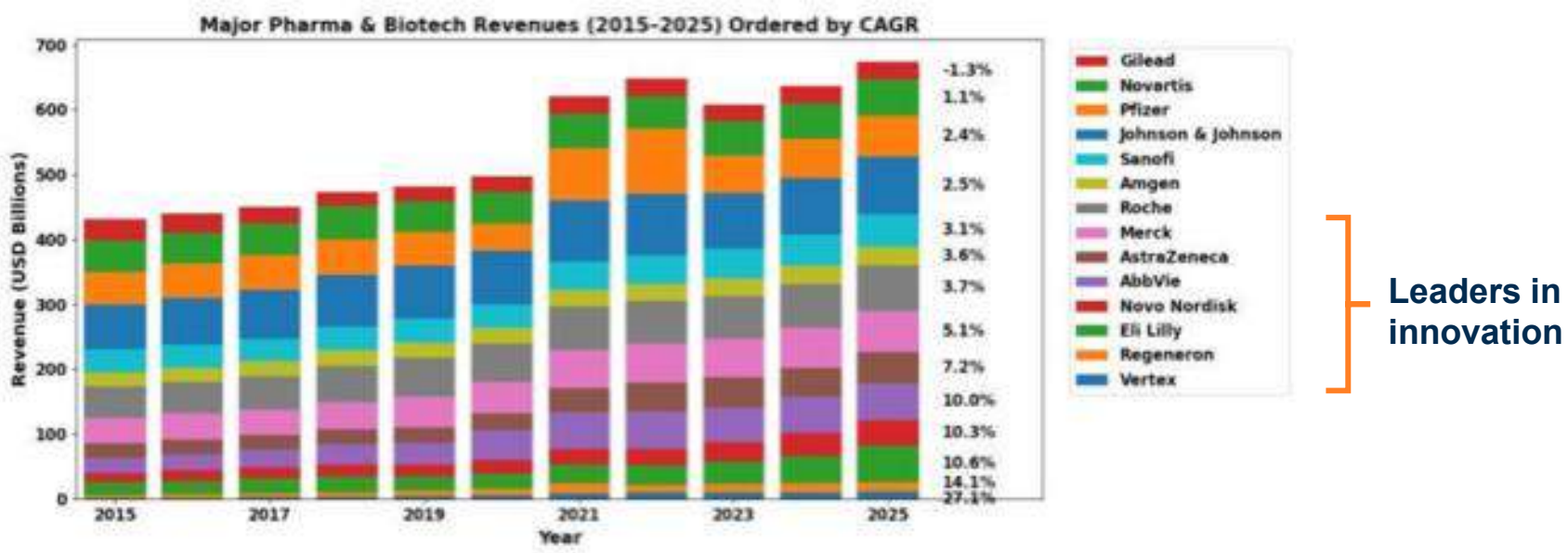
The expectations/claims of in-vivo CAR-T:

- Off-the shelf therapy (i.v. injection)
- Efficacious & safe treatment (good T.I.)
- Broad range of applications (hem/onc, autoimm)
- Affordable for everyone (10'000 EUR p.pt.)
- Scalable (to 10'000-100'000 pt per year)
- Simple logistics, easy access, every hospital
- Platform for more (NK, B, MP) cell therapies
- Better treatments, eventually also solid tumors

This has triggered a gold rush in Pharma !

BioPharma Industry: Moderate Growth, but some Outliers

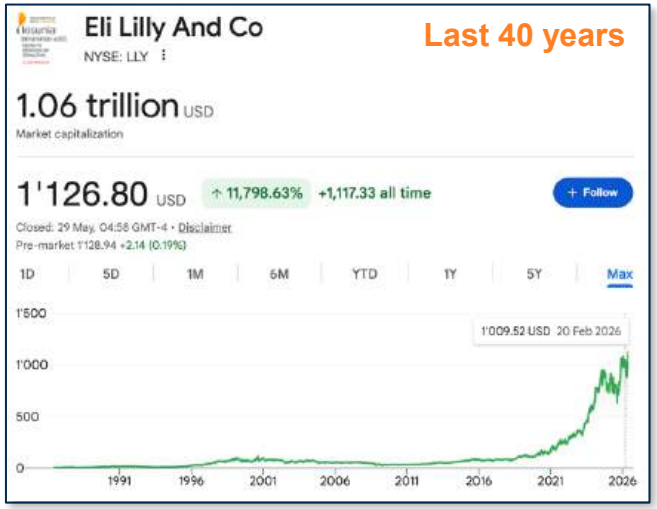
Revenue growth (CAGR, 2015-2025) of global BioPharma companies: mostly single digit growth rate
GDP growth (CAGR, 2015-2025) of selected countries: CN: 7.9%; US: 2.6% CH: 1.9%; EU: DE: 0.8%
Top 15 BioPharma account for approx. 45% ($ 638 billion) of the global Pharma market ($ 1.4 trillion)



BioPharma's: needs to move into fast growing and highly profitable markets

Biopharma Industry: The Lilly Success Story (& Challenge)

First global **BioPharma** with market cap **exceeding $ 1 Trillion** ($ 1'000'000 million)
Year 2025: revenue: $ 65.2 billion; net income: $ 20.64 billion
Year 2026e: revenue: $ 82-85 billion (Q1: +56%); net income (EPS): $ 35.5-37.0 (Q1: +170%)
Current dividend yield (May 27, 2026): **0.74%** (equals: $ 7.8 billion)



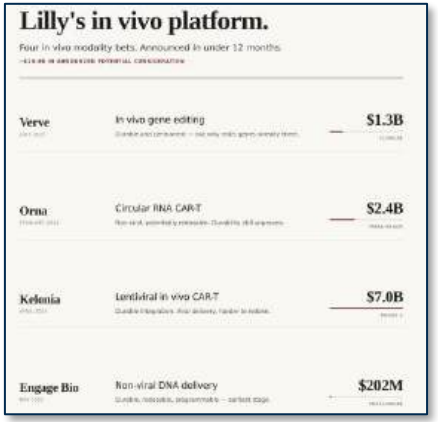
Current valuation requires massive investments into new markets

Combined market cap (June 2, 2026) of top 4 European BioPharma (Novartis, Roche, AstraZeneca, GSK): $1'05 T
Novartis: CHF 241.1 B; Roche: CHF 276.6 B; AstraZeneca: GBP 217.9 B; GSK: 75.7 B (cf. Bayer: EUR 38.3 B)

Biopharma Industry: The Lilly Strategy – in-vivo Delivery

Lilly is using **GLP-1 cash** to buy four different answers to **genetic medicine's** hardest problem: **delivery.**
Mounjaro and Zepbound generated $36.5 billion for Lilly in 2025 — about 56% of total revenue, at 83% gross margins. That cash is being deployed into one specific thesis: stop manufacturing therapies in clean rooms and start **manufacturing them inside the patient.**

In under a year, four acquisitions on delivery:
→ **Verve** ($ 1.3B) – in vivo gene editing
→ **Orna** ($ 2.4B) – circular RNA CAR-T
→ **Kelonia** ($ up to 7B) – lentiviral in vivo CAR-T
→ **Engage Bio** ($ 202M) – non-viral DNA delivery
→ **Seamless** ($ up to 1.12B) – genome editing
(*SaxoCell success story, F. Buchholz et al.*)



None of these technologies is fully proven, but it lays the foundation for future growth

In-Vivo CAR-T – Investment Activities (VC/Biopharma)

Total VC raised: ~$3.3 billion across private rounds, with an additional ~$6.6 billion in pharma acquisitions and option deals in roughly a 7-month window in 2025-2026 alone.

Notable recent rounds:

Wugen – **$115M** (2025)
Umoja Biopharma – **$100M Series C** (2025)
Vyriad – **$85M Series B** (2026)
Azalea Therapeutics – **$82M Series A** (2026)
Vivacta Bio – **$50M+ Series A/A+** (2026)

Major acquisitions (2025/2026) driving the frenzy:

AbbVie → Capstan Therapeutics: **$2.1B**
BMS → Orbital Therapeutics: **$1.5B**
AstraZeneca → EsoBiotec: **$1.0B**
Lilly → Kelonia: **up to $7B**
Gilead/Kite → Interius: **$350M**

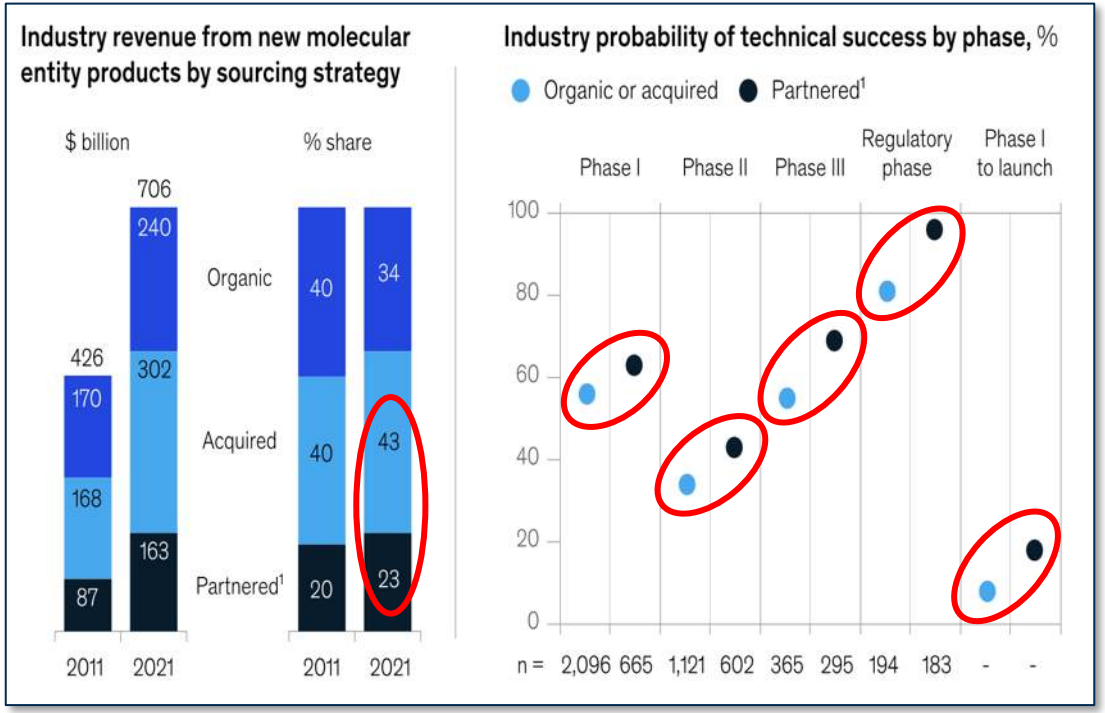
$ 10+ billion (more to come)

In-vivo Chimeric Antigen Receptor (CAR) T-cell Therapy

What should you know about BioPharma?

my favorite example:
Keytruda/Pembrolizumab
(anti-PD1 antibody)

Global Pharma – Sources of Innovation (McKinsey Study)



https://www.mckinsey.com/industries/life-sciences/our-insights/innovation-sourcing-in-biopharma-four-practices-to-maximize-success

Findings:

- In the year 2021, the **majority (66%)** of all products on the market originate from external sources
- The **technical probability of success** (tPoS) for molecules in development derived from external sources is **significantly higher**
- **AstraZeneca** and **Roche** insource **>80% of all assets** from external sources

Conclusion:

- **External sourcing** is a key success factor for sustainability and growth of Global Pharma
- **Future growth** depends on a vibrant biotech and startup community to provide new molecules for Pharma

Global Pharma and BioPharma Market – Last 30 years

Global Pharmaceutical Market Size, 1995–2025

Year	Estimated Global Sales (USD)	Key Context & Drivers
1995	~$390B	Dominated by small-molecule drugs; blockbuster era begins (e.g., statins, SSRIs)
2000	~$550B	Expansion of chronic disease treatments; rise of generics in mature markets
2005	~$650B	Biologics start gaining share; emerging markets grow faster than developed ones
2010	~$880B	Patent cliffs hit big brands; generics and biosimilars accelerate
2015	~$1.05T	Specialty drugs and oncology drive growth; biologics >20% of market
2020	~$1.27T	COVID-19 pandemic boosts vaccine and antiviral revenues
2023	~$1.60T [1]	mRNA vaccines, cell & gene therapies, and specialty drugs dominate pipelines
2025 (est.)	~$1.77T [2]	Continued growth in biologics, precision medicine, and emerging market demand

Total market (2025): **$1.77 trillion**
30-year CAGR: **~6–7%**
Regional dominance: **North America** (≈42% share in 2024)

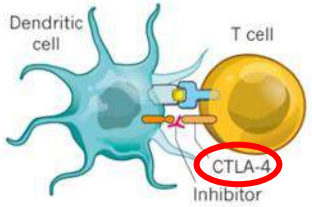
Global BioPharma Sales, 1995–2025

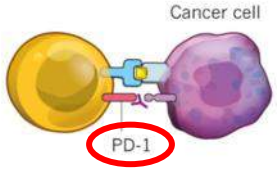
Year	Estimated Global Sales	Key Context & Drivers
1995	~$50B	Early biotech blockbusters (e.g., recombinant insulin, EPO) gain traction
2000	~$90B	Monoclonal antibodies (mAbs) like Rituxan & Herceptin enter market
2005	~$150B	Biologics surge; TNF inhibitors for autoimmune diseases boom
2010	~$220B	Oncology biologics expand; biosimilars emerge in EU
2015	~$300B	Immuno-oncology (e.g., Keytruda, Opdivo) reshape cancer care
2020	~$390B	COVID-19 accelerates mRNA vaccines & global biologics demand
2023	~$478B	Gene therapies, CAR-T, and rare disease biologics gain share
2025 (est.)	~$450–480B	Personalized medicine, AI-driven drug discovery, wider biosimilar uptake

Total market (2025): **$480 billion**
30-year CAGR: **~8–9%** (vs.global GDP **3.4%,** $39t->105$t)
Biologics: **>35%** of Pharma market (8 of top 10 blockbuster)

BioPharma Success Stories – Immuno-Oncology

‘Checkpoint’ proteins block T-cell activity. Inhibitor drugs can release the brakes on T-cells at different stages.





The **CTLA-4** checkpoint protein prevents dendritic cells from priming T-cells to recognize tumors. Inhibitor drugs block the checkpoint.

The **PD-1** checkpoint protein prevents T-cells from attacking cancer cells. The inhibitor drug allows T-cells to act.

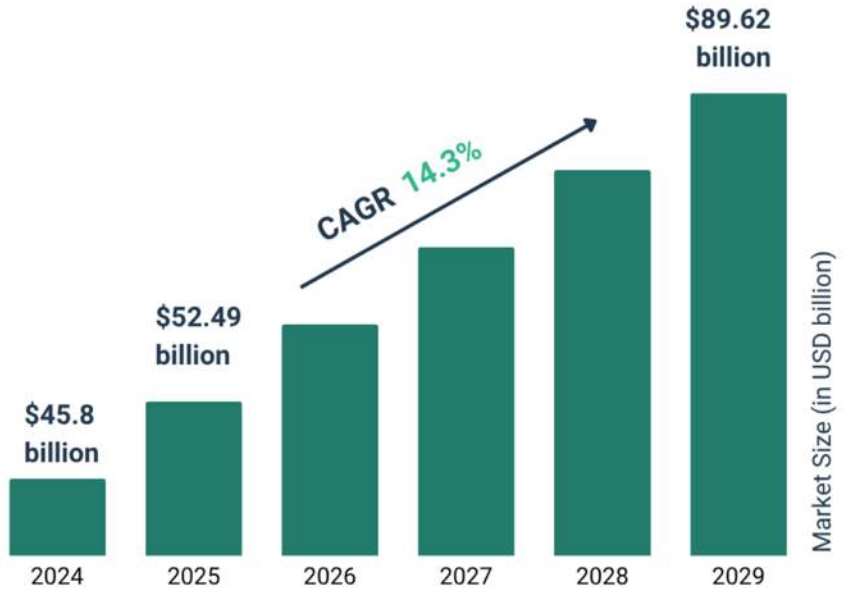
Keytruda (Merck)
Sales (2025): $31.7 bn
(CAGR: +7%)

Opdivo (BMS)
Sales (2025): $10.0 bn
(CAGR: +3.3%)

+4 more PD-1/PD-L1 drugs

PD-1/PD-L1 drugs:

A highly attractive and profitable market
CAGR: +14.3 % (cf. iPhone: 7.6%)



Case Study: Keytruda (Pembroluzimab)

What is the **clinical impact** of **Keytruda**? Across multiple large trials, Keytruda consistently reduces the risk of death and increases long-term survival compared to older treatments.

Non–Small Cell Lung Cancer (NSCLC)

In the KEYNOTE-189 trial for metastatic non-squamous NSCLC: 5-year survival:

- **Keytruda + chemo: 19.4%**
- **Chemo alone: 11.3%**

→ Nearly double the chance of being alive at 5 years.

In the KEYNOTE-407 trial for squamous NSCLC: 5-year survival:

- **Keytruda + chemo: 18.4%**
- **Chemo alone: 9.7%**

→ Again, almost double.

Melanoma

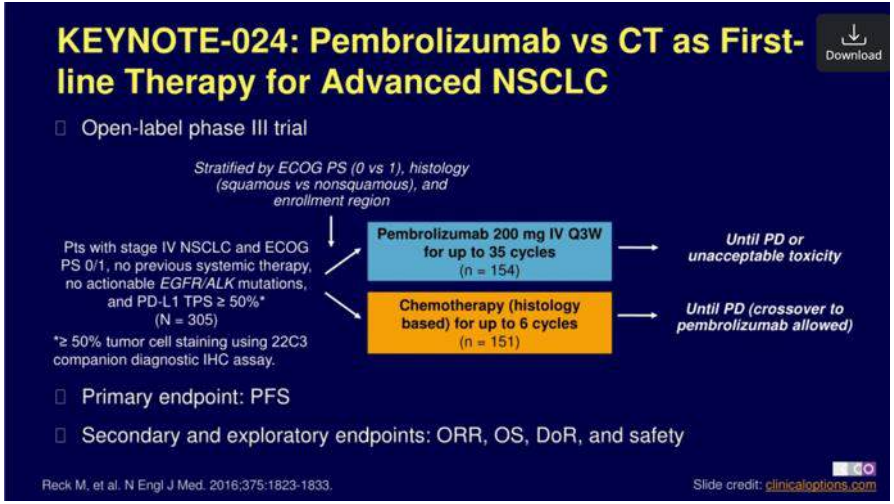
In the KEYNOTE-006 trial: 7-year survival:

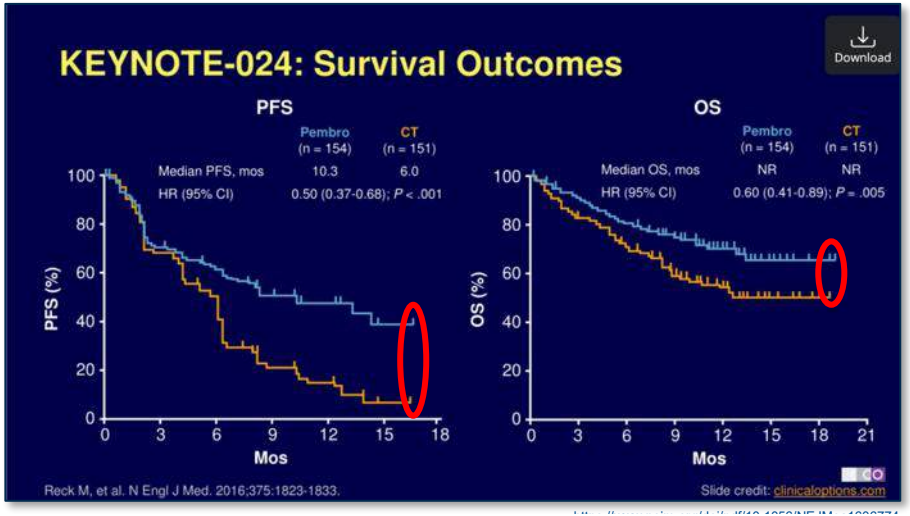
- **Keytruda: 37.8%**
- **Ipilimumab: 25.3%**

→ A major long-term survival improvement.

Huge progress has been seen over the last 2-3 decades, but can we make cancer therapy curative?

Case Study: Keytruda (Pembroluzimab) for NSCLC





How much does KEYTRUDA cost per treatment?
The list price for each indicated dose of **KEYTRUDA** when given **every 6 weeks** is **$23,590.88**. Most people will not pay the list price, although it may have an impact on your out-of-pocket costs. These costs may be reduced by supplemental insurance or manufacturer co-pay assistance programs.

How much does immunotherapy cost in the USA?
Immunotherapies often cost **more than $100,000 per patient**. For some of the newest immunotherapies, the price tag is even steeper: When including the value of the medical support necessary to deliver these treatments, a price tag of $850,000 per patient is not unheard of.

Why is immunotherapy so costly?
Producing immunotherapy drugs usually requires **years of cancer research, extensive clinical trials, and innovative technology**. The costs of advanced research, lab studies, and preclinical testing, along with multiphase human trials, add up effectively in the overall cost of the drugs.

Approved indications:
Melanoma: For unresectable or metastatic cases and certain post-surgery stages.
Non-Small Cell Lung Cancer: For tumors expressing PD-L1 or other specific cases.
Head and Neck Squamous Cell Carcinoma: For recurrent or metastatic disease after chemotherapy.
Colorectal Cancer: For unresectable/metastatic MSI-High or dMMR cases.
Esophageal and Gastroesophageal Junction Carcinomas: For unresectable/metastatic PD-L1-positive cases.
Stomach and GEJ Adenocarcinoma: Combined with chemotherapy for HER2-positive advanced cases.
Kidney, Bladder, Cervical, Uterine Cancers: Approved for specific advanced or metastatic forms.
Other Cancers: Includes hepatocellular carcinoma, primary mediastinal large B-cell lymphoma, cutaneous SCC, and malignant pleural mesothelioma

Keytruda Sales Forecast (2025): $33-35 bn
Keytruda Sales Forecast (2028): $36.0 bn

Case Study: Keytruda (Pembroluzimab)

Keytruda has saved 100’000s of lives

However, anti-PD1 immunotherapy is not necessarily a curative treatment. What can we do better?

Case Study: Kymriah (tisagenlecleucel) (anti-CD19 CAR-T)

CAR-T (7 approved drugs) has saved 1’000s of lives

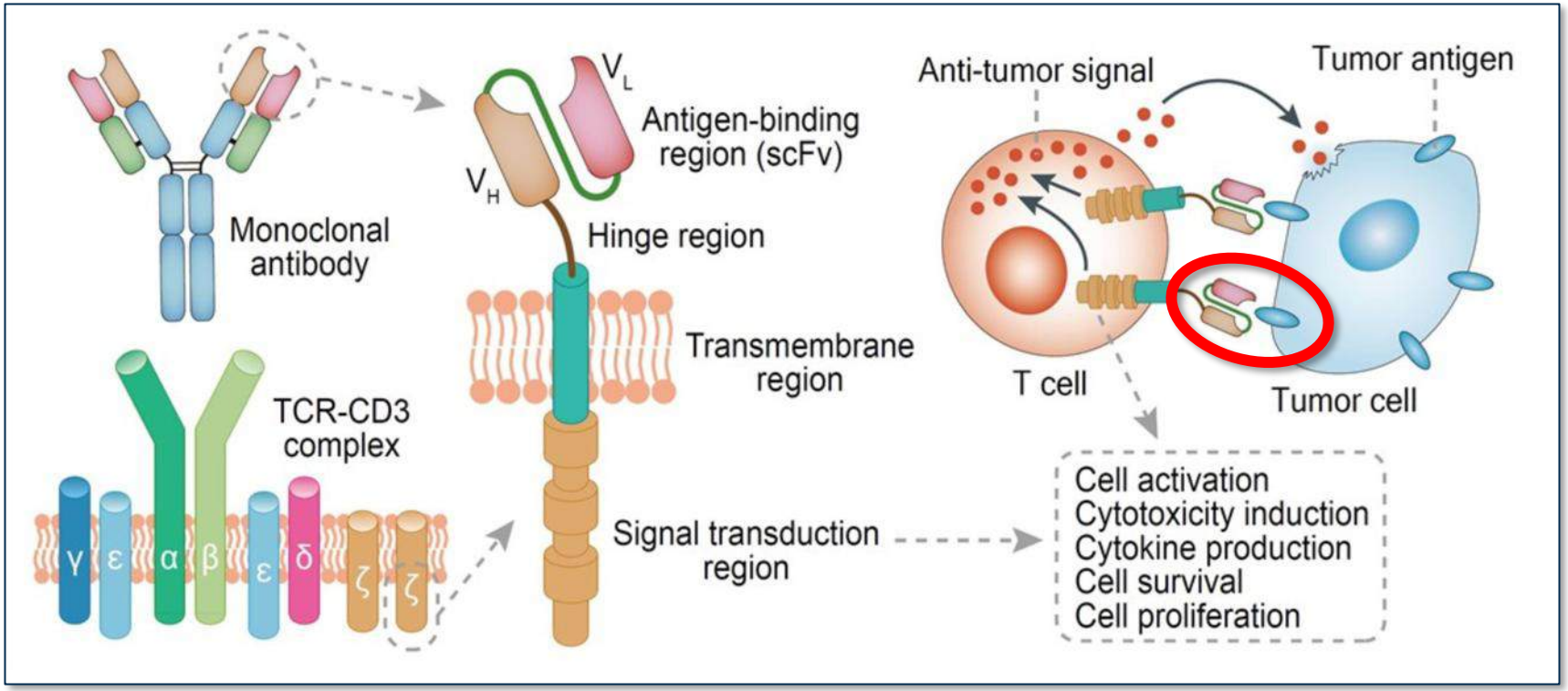
CAR-T therapy can be a curative treatment.
Expansion to more patients and more diseases?

Case Study: Kymriah (tisagenlecleucel) (anti-CD19 CAR-T)

What is CAR-T Therapy?

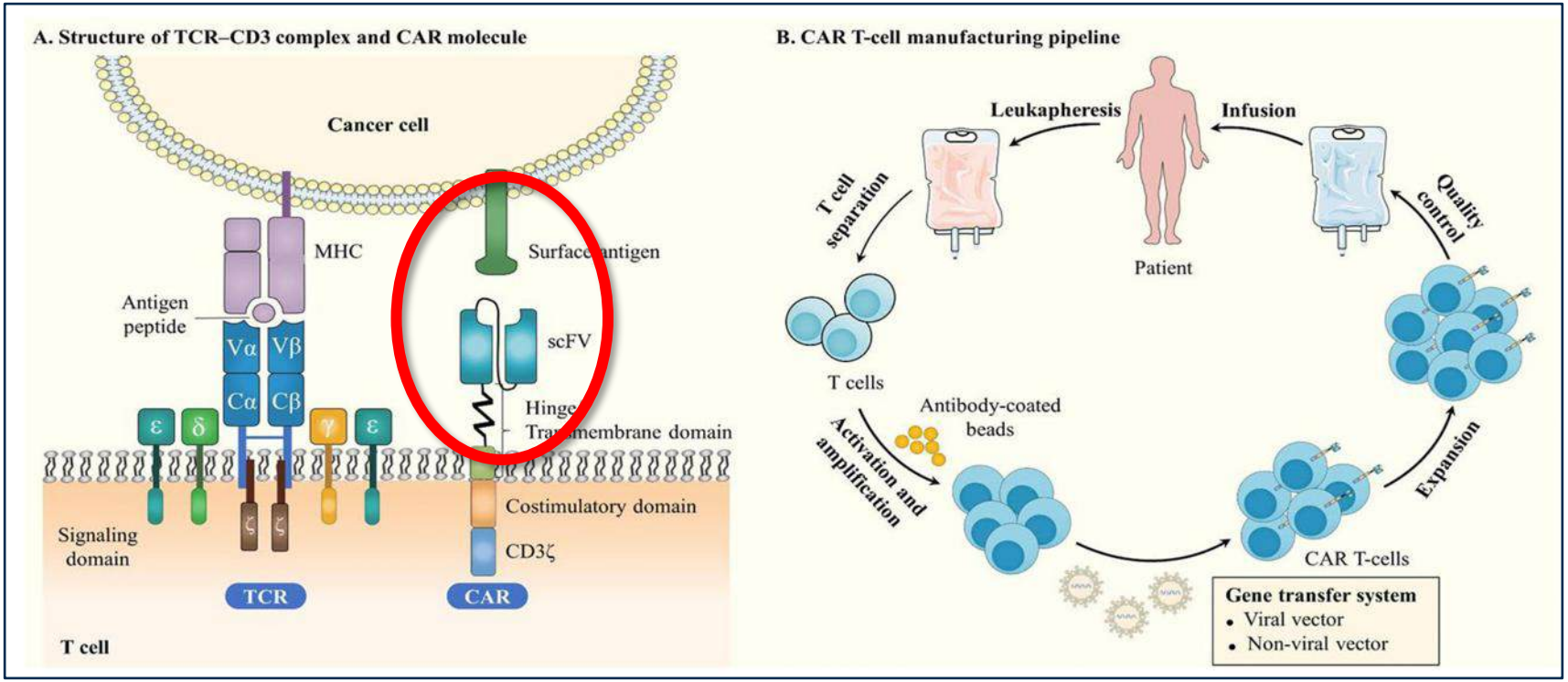
Chimeric Antigen Receptor T-cell Therapy

CAR-T: combination of mAb technology and TCR biology



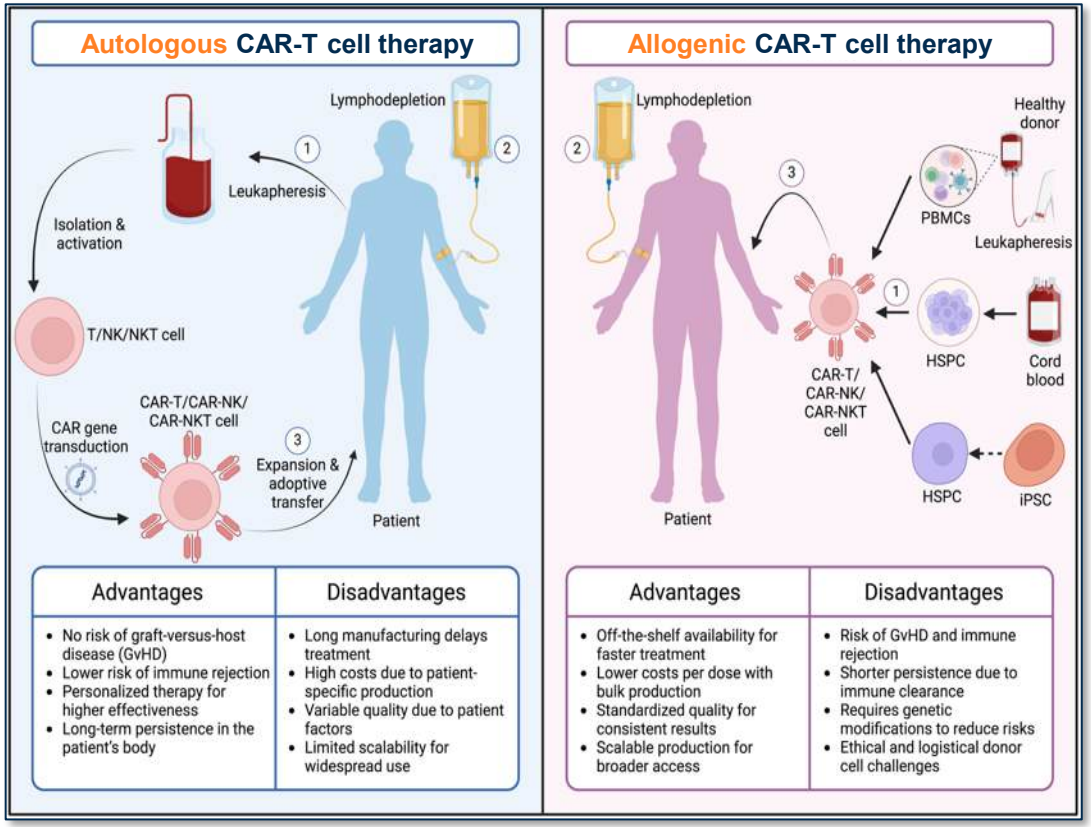
CAR construct engineered into T-cells mimics TCR-antigen recognition

Ex-vivo CAR-T: autologous process with engineered T-cells



CAR construct engineered into T-cells mimics TCR-antigen recognition

Ex-vivo CAR-T: autologous vs. allogeneic approach



Ex-vivo CAR-T technology:

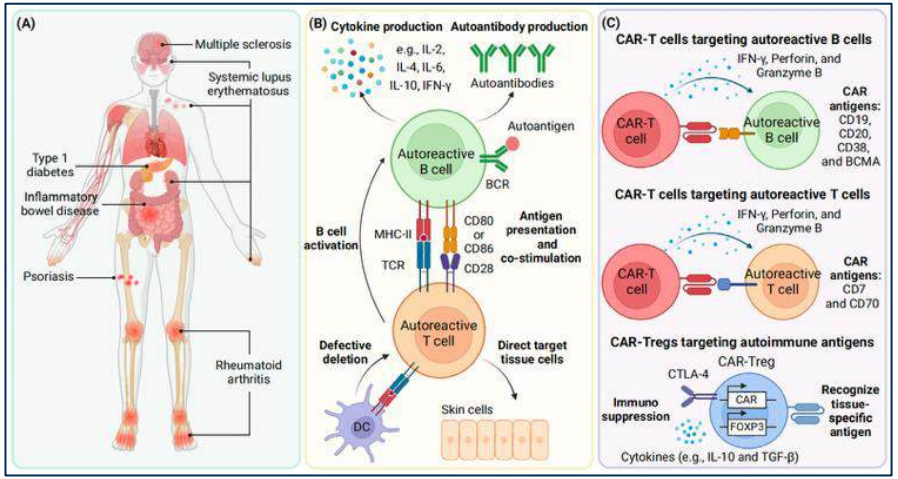
- Various products (7) approved
- **Very high response rate up to 70% (5 years) in haematological malignancies (recent data with dual CAR approach even 100%)**
- Proven clinical applications in haemato-oncology, autoimmune and other disease areas
- Research towards solid tumors
- Complex manufacturing and high cost of goods
- Limited success with allogeneic CAR-T cell therapy (no approvals)

Ref: Li, Y.R. et al. (2025) Med 6, 100677; https://www.cell.com/action/showPdf?pii=S2666-6340%2825%2900104-7

Ex-vivo CAR-T: superb clinical data (haem/onc, autoimmune)

Haemato-Oncology:

Autoimmune (SLE, MS, RA, T1D, IBD, etc):



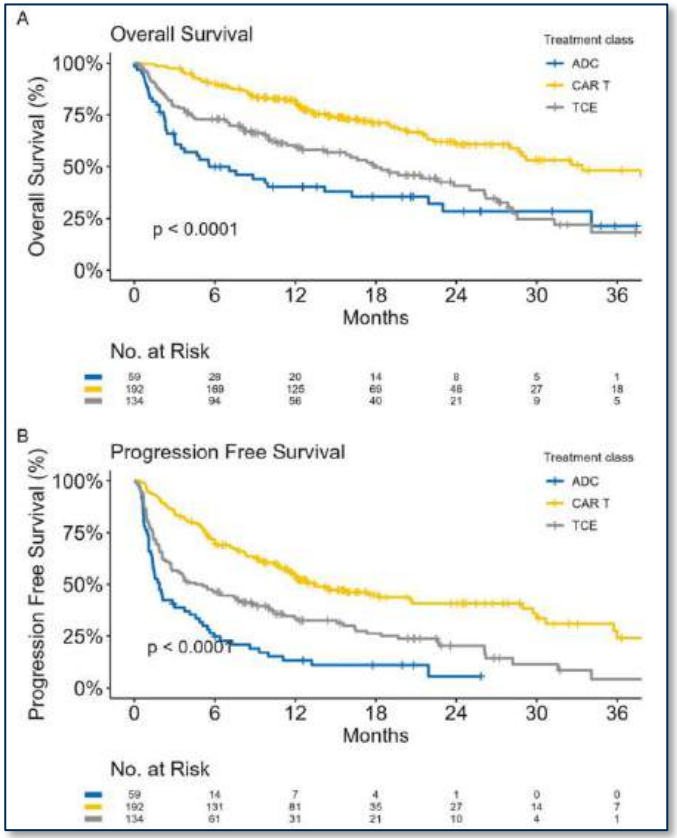
High response rate (ORR):

- **70-80%** (J&J: 100%: CD19/CD20 dual)
- **Potentially curative (50%)** for liquid tumors
- Promising first results with **solid tumors**
- SweCARnet: **268** patients (by Sep. 2, 2025)

High response rate (ORR):

- **up to 100% response** (16/16 SLE pts; once and done)
- **Potentially curative** for autoimmune disorders
- **Complete reset** to naïve immune state possible
- **Very Promising** results with **non-viral delivery**

Ex-vivo CAR-T: superb clinical data for MM (multiple myeloma)



Comparison of various modalities:

ADC: antibody drug conjugate (protein)
TCE: T-cell engager (protein)
CAR-T: chimeric antigen receptor (cell therapy)

Cumulative data (2018-2023) from Mayo Clinic with 338 individuals representing 385 B-cell directed therapies with commercially and clinically available treatments for MM seem to indicate that **CAR-T has the highest impact** on OS (overall survival) and PFS (progression free survival).

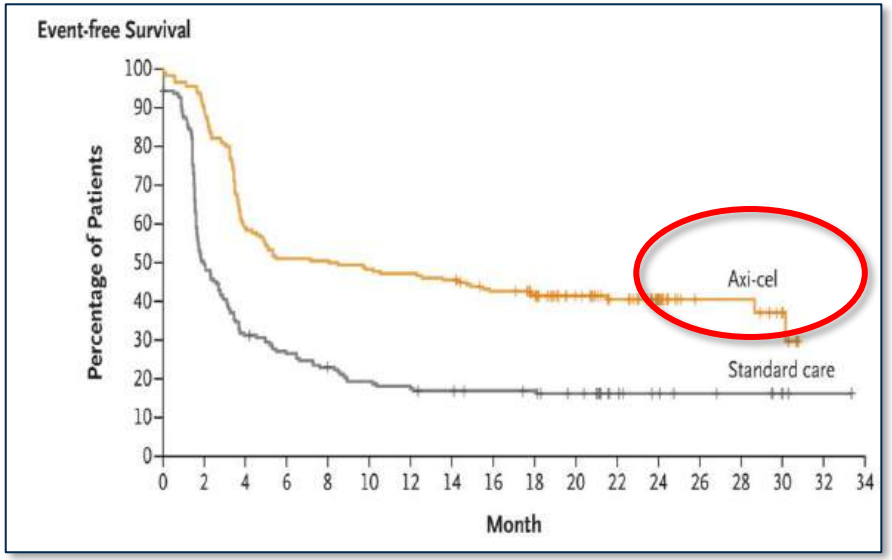
More comparative studies are needed not only in haemato-oncology but also in autoimmune disorders.

Ref: Rees, M.J. et al (2024) Blood Cancer Journal 14, 122; https://www.nature.com/articles/s41408-024-01081-z

Ex-vivo CAR-T: superb clinical data vs. standard-of-care

Large B-cell lymphoma:

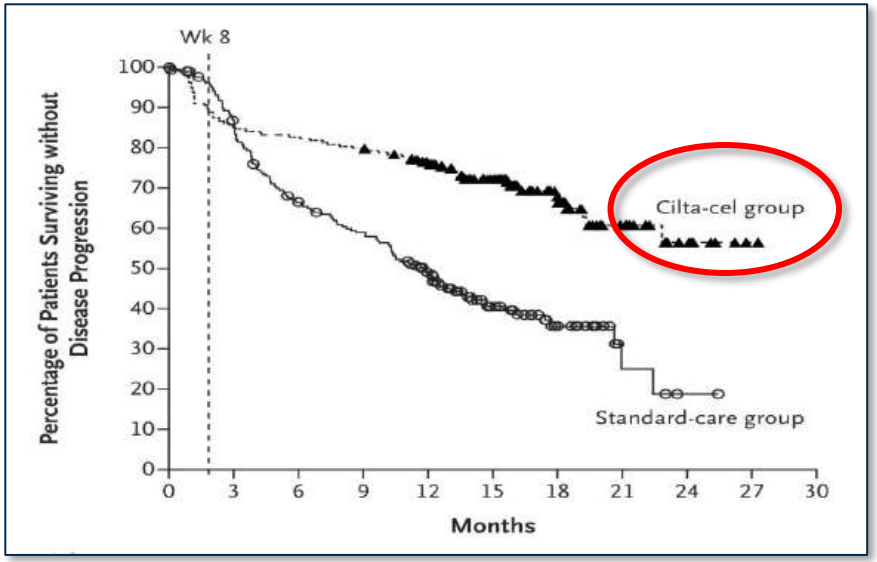
Treatment with **axicabtagene ciloleucel** (axi-cel, **Yescarta**), an autologous anti-CD19 chimeric antigen receptor T-cell therapy for patients with large B-cell lymphoma that were refractory to or had relapsed after first-line chemoimmunotherapy.



Ref: Locke, F.L. et al (2022) NEJM 386, 640-654; https://www.nejm.org/doi/full/10.1056/NEJMoa2116133

Multiple myeloma:

Treatment with **ciltacabtagene autoleucel** (cilta-cel, **Carvykti**), an autologous anti-B-cell maturation antigen (BCMA)–directed CAR T-cell therapy, is effective in heavily pretreated patients with relapsed or refractory multiple myeloma.



Ref: San Miguel, J. et al (2023) NEJM 389, 335-347; https://www.nejm.org/doi/full/10.1056/NEJMoa2303379

Ex-vivo CAR-T therapy: 7 approved products

Product name, target, disease, approval data, company, annual sales (2025)

- **Kymriah** (tisagen lecleucel): targets CD19, for B-cell ALL and DLBCL *(First FDA approval 2017) – Novartis*
  Annual sales (2025): $ 400 million
- **Yescarta** (axicabtagene ciloleucel): targets CD19 for large B-cell lymphoma *(FDA approval 2017) – Gilead/Kite*
  Annual sales (2025): $ 1.5 billion
- **Tecartus** (brexucabtagene autoleucel): targets CD19, for MCL and ALL *(FDA approval 2020) – Gilead/Kite*
  Annual sales (2025): $ 344 million
- **Abecma** (idecabtagene vicleucel): targets BCMA, for multiple myeloma *(FDA approval 2021) – BMS/bluebird*
  Annual sales (2025): $ 350 million
- **Breyanzi** (lisocabtagene maraleucel): targets CD19, for several R/R NHL (FDA approval 2021) – BMS/Juno
  Annual sales (2025): $ 1.36 billion
- **Carvykti** (ciltacabtagene autoleucel): targets BCMA, for multiple myeloma *(FDA approval 2022) – J&J/Legend*
  Annual sales (2025): $ 1.9 billion
- **Aucatzyl** *(*obecabtagene autoleucel): targets CD19, for R/R B-cell precursor ALL (FDA approval 2024) – *Autolus*
  Annual sales (2025): $ 74.3 million

Ex-vivo CAR-T/TIL therapy: number of patients treated

Annual Estimate of Patients Treated with Approved Cell Therapies										
Therapy Name	2017	2018	2019	2020	2021	2022	2023	2024	2025	Cumulative Patients Treated by Therapy
KYMRIAH®	13 (Aug 2017)	162	588	999	1,236	1,131	1,072	934	794	6,931
YESCARTA®	19 (Oct 2017)	711	1,225	1,511	1,864	3,111	4,018	3,707	3,530	19,697
TECARTUS®	-	-	-	119 (Jul 2020)	474	803	996	918	735	4,045
ABECMA®	-	-	-	-	393 (Mar 2021)	927	1,127	970	987	4,404
BREYANZI®	-	-	-	-	214 (Feb 2021)	447	815	1,534	2,788	5,798
CARVYKTI®	-	-	-	-	-	290 (Feb 2022)	1,076	2,073	3,400	6,839
AMTAGVI®	-	-	-	-	-	-	-	203 (Feb 2024)	411	614
AUCATZYL®	-	-	-	-	-	-	-	0 (Nov 2024)	145	145
Total Patients Treated per Year	32	873	1,813	2,629	4,184	6,709	9,104	10,341	12,790	48,473

Ref: OriBiotech Access Tracker; https://oribiotech.com/insight/patient-access-tracker

Last update: March 2026

Note: Amtagvi (lifileucel) was the first tumor-infiltrating lymphocyte (TIL) cellular therapy for advanced, unresectable or metastatic melanoma in adults.

Ex-vivo CAR-T cell therapy: autologous process

Limitations:

- Personalized autologous cell therapy (i.v. injection)
- Procedure requires isolation of T-cells (leukapheresis)
- Costs: CAR-T cells: $ 300’000-475’000, total costs: $ 500’000-1’000’000 per patient
- Complex manufacturing process under GMP-BSL2 conditions
- Limited scalability in production; unequal treatment access for patients
- Intense QC process during production and post treatment

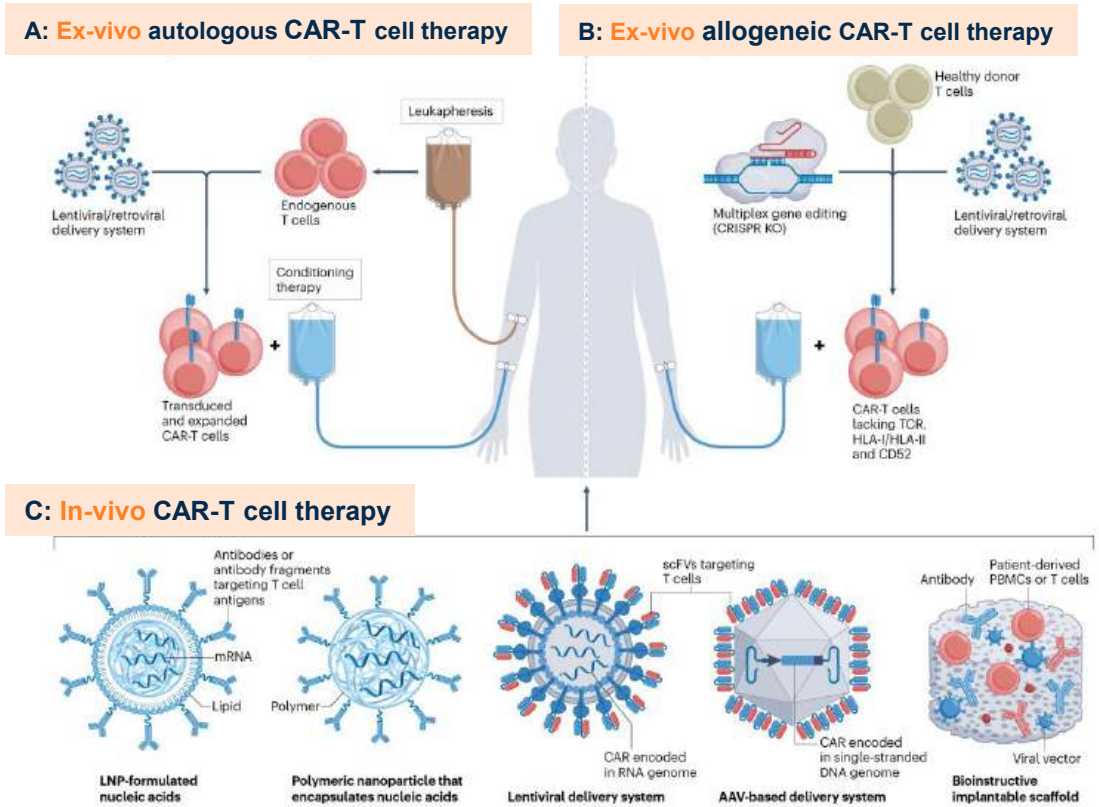
Ex-vivo CAR-T cell therapy

What if we wanted to treat 100’000 cancer and autoimmune patients p.a. in Germany?

Germany: population – 84 mio people (GDP: €4.47 T / $5.05 T; global #3 economy)
Germany: cancer – 550’000 new cases per year (95% solid, 5% liquid tumors)
Germany: autoimmune diseases – 6-8’000’000 (7-10% prevalence)
Germany: current (year 2026) CAR-T therapies: ca. 1’500-2’000 patients (€ 350-500k p.p.)
Germany: healthcare costs: € 5’832 per capita ($ 9’365 ppp adjusted) (11.7-12.8% of GDP)

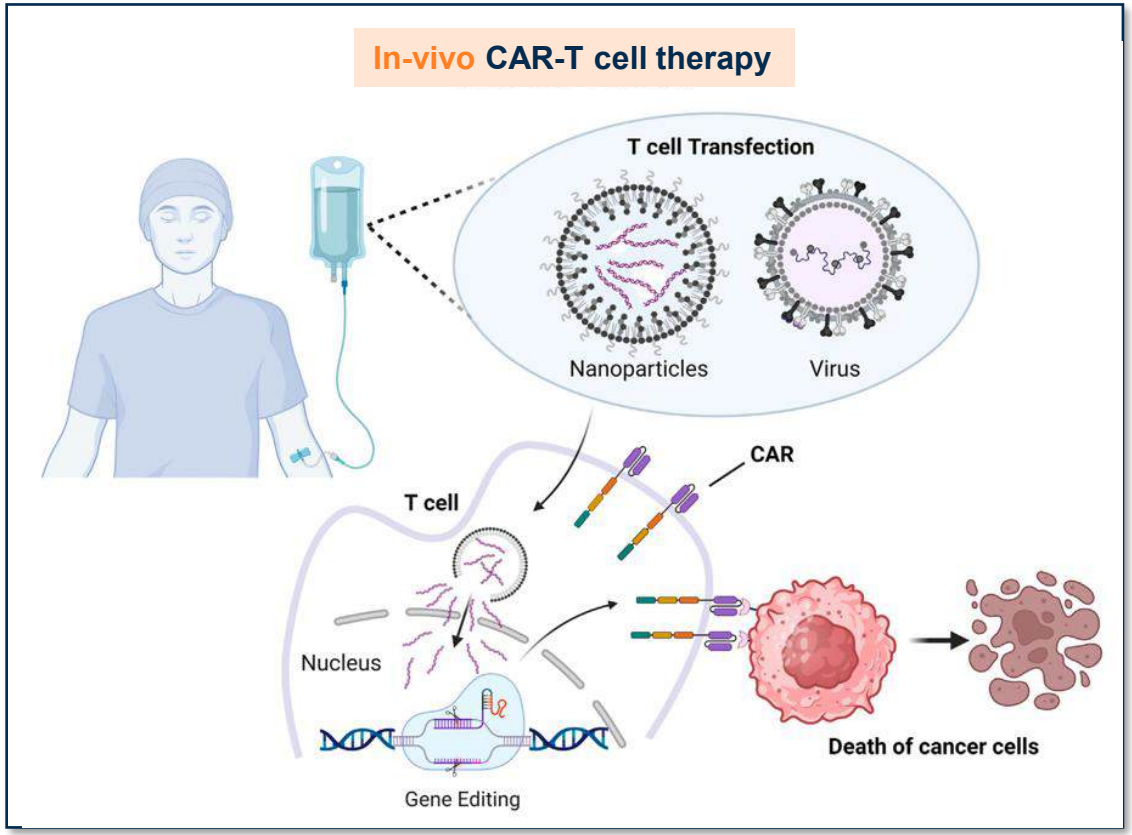
There is absolutely NO WAY to cope with expected FUTURE DEMAND!

CAR-T cell therapy: different production processes



Ref: Li, Y-R et al. (2025) Nature Reviews Immunology 25, 725-744; https://www.nature.com/articles/s41577-025-01174-1

CAR-T cell therapy: in-vivo (viral/non-viral) delivery



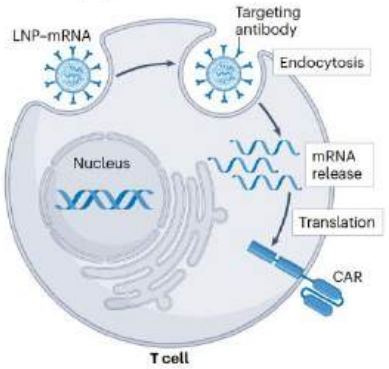
Ref: Bui, T.A. et al. (2024) eBioMedicine 106, 105266; https://www.thelancet.com/action/showPdf?pii=S2352-3964%2824%2900302-5

In vivo CAR-T technology:

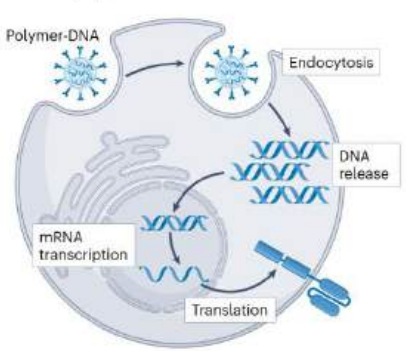
- **Huge potential for oncology and autoimmune diseases**
- Need for better gene delivery technologies (viral/non-viral)
- Safety/efficacy challenges, such as genotoxicity, tissue specificity, epitope masking, persistence, CMC
- **Very active field of M&A for Biopharma** (AbbVie, AstraZeneca, Bristol Myers Squibb, Gilead, Lilly, etc.)

CAR-T cell therapy: in-vivo engineering of T-cells

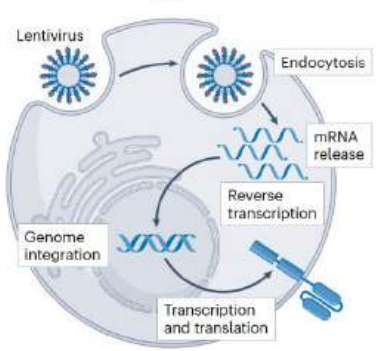
A: LNP or polymer-formulated mRNAs



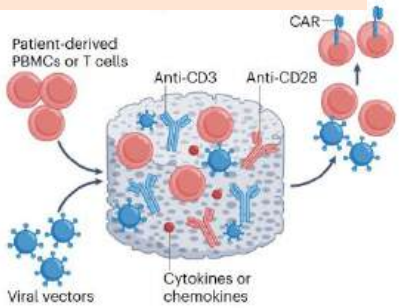
B: LNP or polymer-formulated DNAs



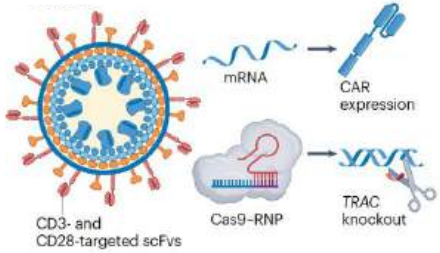
C: Lentiviral delivery system with DNA



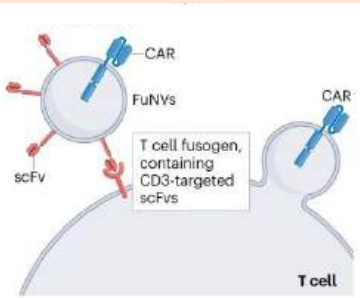
D: Bioinstructive implantable scaffold



E: Cas9-packaging EDVs



F: Virus-mimetic fusogenic nanovesicles



Ref: Li, Y-R et al. (2025) Nature Reviews Immunology 25, 725-744; https://www.nature.com/articles/s41577-025-01174-1

In-vivo CAR-T cell therapy: CMC* requirements

Table 1. Comparison of CMC information for ex vivo versus in vivo CAR-T therapy medicinal products

CMC information		Ex-vivo CAR-T (Lentiviral vector)	In-vivo CAR-T (Lentiviral vector)	In-vivo CAR-T (LNP-mRNA)
Design of delivery system		• Self-inactivation • Non-replicating • Pseudotyping	• Self-inactivation • Non-replicating • Envelope engineering or antibody conjugation	• Lipid composition optimization • Surface modifications • Antibody conjugation
Scalability		• Scale out strategy • Decentralized or point-of-care manufacturing • Validation of production capacity	• Scale up strategy • Centralized manufacturing • Standardized and suitable for scaled production	• Scale [illegible] strategy • Cen[illegible]d manufacturing • [illegible]rdized and suitable for scaled [illegible]ion
Manufacturing of active substance	Starting materials and raw materials	• Donor-derived live cells • Human serum (if applicable) • Magnetic beads • Cytokines and antibodies	• Plasmids and packag[illegible] banks • Fetal bovine se[illegible] applicable)	• Plasm[illegible], transcriptase and nucleotides • Lipids • Serum free
	Manufacturing process	• Cell processing procedures • Extended, and labor-intensive • Complex supply chain with process-the-product model	• [illegible] processes and shorter [illegible] timelines • Higher batch-to-batch consistency • Rapid production with optional antibody conjugation	• Efficient mRNA transcription and LNP production • Rapid production with optional targeted LNP conjugation
Quality Control		• Viral vector: p[illegible]sical titer, [illegible]fectious titer, purity, impuri[illegible], [illegible]ency, sterility, mycoplasma, RCL • CAR-T cell product: T-cell viability, quantity, CAR$^+$ cell percentage, immunophenotype, VCN, RCL, sterility and mycoplasma	• Viral vector: physical titer, infectious titer, purity, impurities, potency, sterility, mycoplasma, RCL • Conjugated product: Antibody density and conjugation sites (if applicable)	• mRNA: purity, integrity, capping efficiency, polyA tail, impurities, potency • LNP: size, PDI, EE, potency, impurities • Conjugated LNP: antibody density and sites; physicochemical properties, purities and impurities (if applicable)

CMC chemistry, manufacturing and control; *EE* encapsulation efficiency; *LNP* lipid nanoparticle; *PDI* polydispersity index; *VCN* vector copy number; *RCL* replication-competent lentivirus

Challenging!

*CMC: In the pharmaceutical industry, **CMC** stands for **Chemistry, Manufacturing, and Controls**. It refers to the technical and regulatory framework that details the chemical makeup of a drug, how it is produced, and how its quality is consistently tested and controlled

Ref: Lu, J et al. (2026) Signal Transduction and Targeted Therapy, in press; https://www.nature.com/articles/s41392-026-02633-4

In-Vivo CAR T-cell Therapy: Regulatory considerations

Table 2. Challenges for in vivo CAR-T therapy medicinal products, examples of mitigation strategies and regulatory considerations

Challenges	Mitigation Strategies	Regulatory considerations
Targeting specificity	• Viral vector engineering • Improve targeting ligand affinity and stability • Develop site-specific, stable conjugation methods • Optimize cationic lipids	• Quality control of viral vector and targeting ligand • Characterization of conjugation sites and density • Process validation • Evaluation of off-target effects
CAR expression durability	• Sustained-release systems • Self- and trans-amplifying RNA • Circular RNA	• Assessment of mRNA sequence design, translational fidelity and immunogenicity • Risk mitigation strategies
Scalable manufacturing process	• Quality by design • Definition of critical process parameters • Establish comparability study protocols	• Standardized comparability studies • Risk-based approach • Non-inferiority clinical bridging studies when needed
New testing methods	• Method development and validation • Compliance with ICH Q14 and Q2(R2) guidelines	• Multi-dimensional quality characterization • Standardize sample handling and analytical procedures
Off-target effects, insertional mutagenesis, immunogenicity, and biodistribution issues	• Engineer viral capsids • Develop sensitive detection methods with bioinformatics tools • Conduct long-term follow-up studies	• End-to-end safety optimization • Prioritize rational animal models • Assay validation
Ethical	• Compliance with applicable regulations • Thorough risk-benefit assessments	• Assembly of expert panels • Evaluation of gene therapy-related ethical issues
Biosafety	• Compliance with applicable biosafety regulations • Enhance personnel protection during viral handling	• Conduct comprehensive biosafety assessments • Differentiated biosafety standards based on viral vector classification

Challenging!

Ref: Lu, J et al. (2026) Signal Transduction and Targeted Therapy, in press; https://www.nature.com/articles/s41392-026-02633-4

In-vivo Chimeric Antigen Receptor (CAR)-T cell therapy

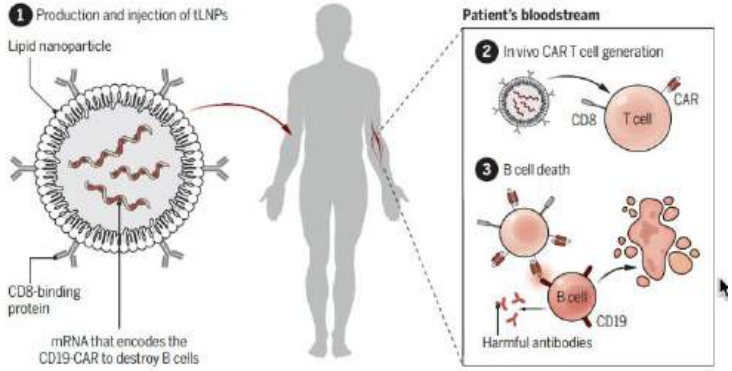
Late-Breaking News - ASCO:
(Chicago, May 31, 2026)
18/18 multiple myeloma patients treated with Kelonia's KLN-1010 (in-vivo LV with BCMA-CAR-T) had no detectable cancer (MRD) in bone marrow at 4 weeks post end of treatment.

It works !

In-vivo CAR-T therapy has been shown to work with LNP-RNA (non-integrating) for autoimmune and with Lentivirus (integrating) for hemato-oncology

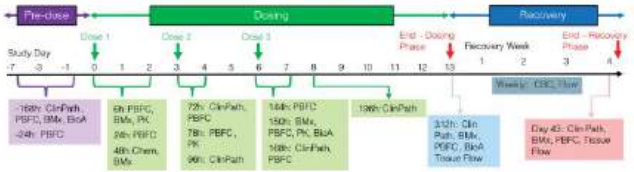
In-vivo CAR-T cell therapy: LNP/mRNA technology

Capstan/AbbVie - Idea: CD19 CAR-T

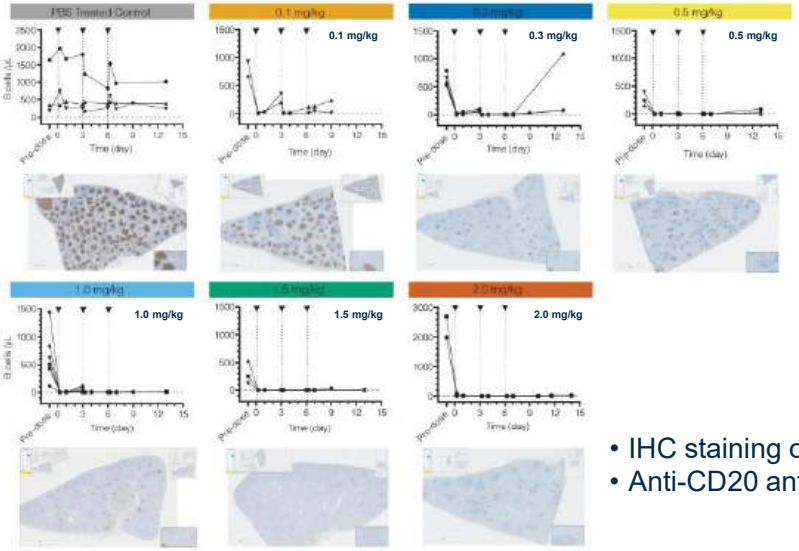


- No prior lymphodepletion needed
- Use of **targeted (scFv)-LNP-mRNA**
- **Transient expression, no stable integration**
- Possibly, a 'once-and-done' treatment
- Possibly, an 'affordable' treatment
- Possibly, redosing feasible, if needed

NHP: CD20 CAR-T (CD8-L829-tLNP-CD20)



- 3 doses (0.1-2.0 mg/kg)
- 3 weeks treatment
- depletion of B-cells

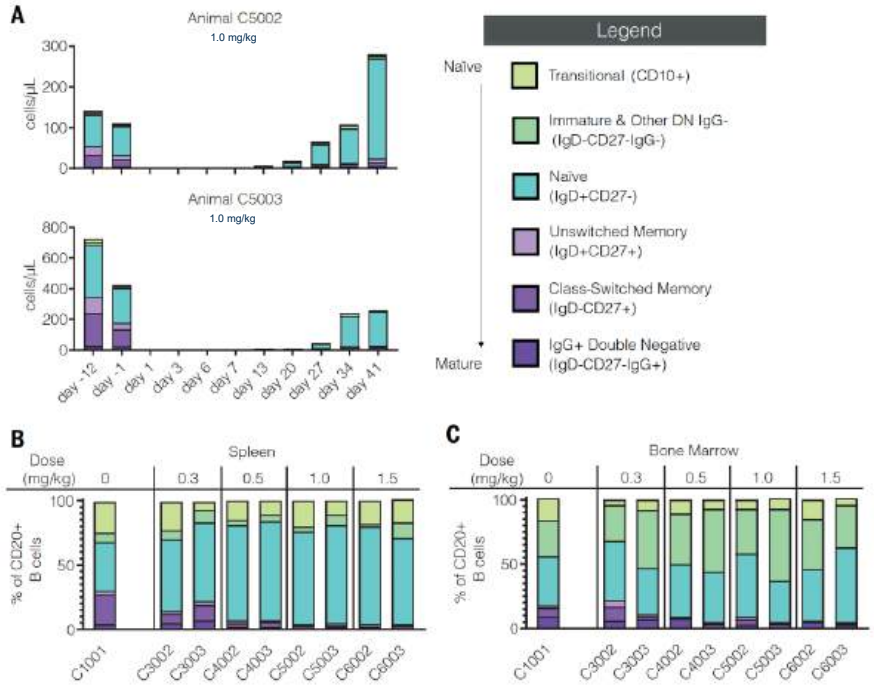


- IHC staining of spleen
- Anti-CD20 antibody

Ref: Hunter, T.L. et al. (2025) Science 388,1311-1317; https://www.science.org/doi/10.1126/science.ads8473

In-vivo CAR-T cell therapy: LNP/mRNA technology

Capstan (NHP): Reoccurence of naïve B-cells



Ref: Hunter, T.L. et al. (2025) Science 388,1311-1317; https://www.science.org/doi/10.1126/science.ads8473

Results (cynomolgus):

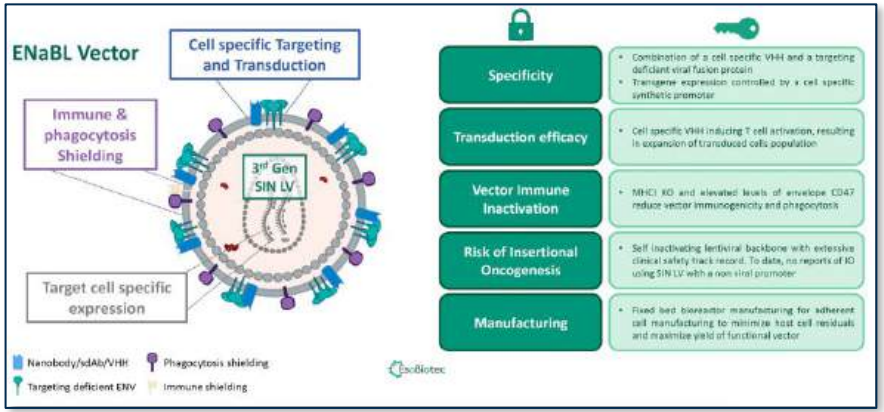
Highly efficacious depletion of B-cells with tLNP-mRNA therapy. Replenishment with naïve B-cells.

Open questions:

- **Dosing (e.g. 1mg/kg)**
  - Capstan: 80 kg x 3 x 1mg/kg = 240 mg mRNA
  - SARS-CoV-2: 30 ug (Pfizer) / 50 ug (Moderna) mRNA
  - in-vivo mRNA dose would be approx. 2'400-8'000x higher!
- **Immunogenicity (anti-PEG Ab, dsRNA response)**
  - Anti-PEG antibodies?
  - TLR3 (dsRNA) response?
- **COGS (mRNA, GMP grade):**
  - 100 mg: $ 20'000 - 30'000? (own research)
  - 100 mg mRNA: $ 50'000-250'000 (META AI search)
  - 1 gram: $ 1.0 - 1.5 mio? (own research)
- **CMC (GMP conditions):**
  - Scalability & consistency of production?
  - Formulation of drug product (proteins & chemicals)?
- **Durability of clinical response:**
  - Duration of clinical benefit?
  - Frequency of redosing?
  - Desensitization of patients?

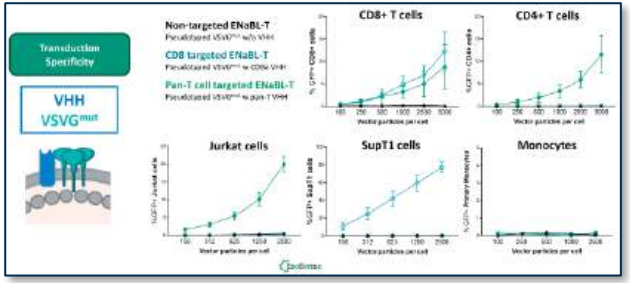
In-vivo CAR-T cell therapy: Lentivirus technology

EsoBiotec (AZ) - Idea: BCMA CAR-T

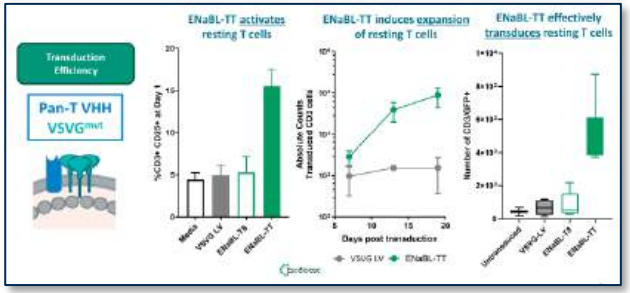


- No prior lymphodepletion needed
- Use of **targeted** (VHH) Lentivirus
- Use of **shielded** (MHC-I ko, CD47 up) Lentivirus
- Use of **T-cell specific synthetic** promoter
- Use of **SI-LV** for stable insertion & permanent expression
- Possibly, a 'once-and-done' treatment
- Possibly, an 'affordable' treatment
- Possibly, redosing feasible, if needed

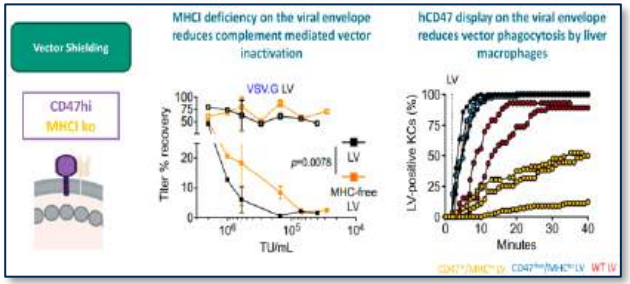
Transduction Specificity



Transduction Specificity



Vector Shielding



Ref: Parone, presentation at ESGCT 2025, Sevilla/Spain (personal communication)
Ref: Xu, J. et al. (2025) Lancet 406, 228-231; https://www.thelancet.com/action/showPdf?pii=S0140-6736%2825%2901030-X
Ref: An, N. et al. (2026) Nature Medicine 32, 1257–1266; https://www.nature.com/articles/s41591-026-04244-6

In-vivo CAR-T cell therapy: Lentivirus technology

IIT: investigator-initiated trial (China)

		Patient 1	Patient 2	Patient 3	Patient 4
Baseline	Serum M protein (g/L)	1,0	0,5	3,3	75,3
	Involved serum free light chain (mg/L)	2058,57	9,66	2492,45	99,3 (IgG, g/L)
	MM cells in BM by FCM (%)	0,03	-	17,71	92,5
	MM cells in CNS by FCM (%)	51,1	0	23,50	97,28
Month 1	Serum M protein (g/L)	0,0	0,0	0,8	15,5
	Involved serum free light chain (mg/L)	WNL	<LLN	75,9	22,3
	MM cells in BM by FCM (%)	0	0	0	0
	MM cells in CNS by FCM (%)	0	-	0	19,92
Month 2	Serum M protein (g/L)	0,0	0,0	0,8	15,5
	Involved serum free light chain (mg/L)	WNL	<LLN	75,9	22,3
	MM cells in BM by FCM (%)	0	0	0	0
	MM cells in CNS by FCM (%)	0	-	0	19,92
Month 3	Serum M protein (g/L)	0,0	0,0		
	Involved serum free light chain (mg/L)	WNL	<LLN		
	MM cells in BM by FCM (%)	0	0		
	MM cells in CNS by FCM (%)	0	-		
	Clinical Response	sCR	sCR	PR	PR

- Efficacy of in-vivo anti-BCMA CAR-T (ESO-T01) shown
- Single infusion of 2.5e8 TU/pt, absence of lymphodepletion
- ”Acceptable” safety profile (t.b.d.), see second publication
- “Manufacturability” with COGS per dose of € 11’000 p.p.
- Short turnaround time (patient inclusion – infusion): 7 days

Results:

- **Highly efficacious depletion** of B-cells in patients
- **No signs of disease** (MM) in 4/4 patients.
- **Possibly curative treatment** with very high overall response rate (ORR).
- **All patients experienced Grade3 adverse effects**:
  - Cytokine release syndrome occurred in 4/4 patients
  - Transient cytopenias and rev. hepatic enzyme elevations
  - 3/4patients experienced grade 2 infections.

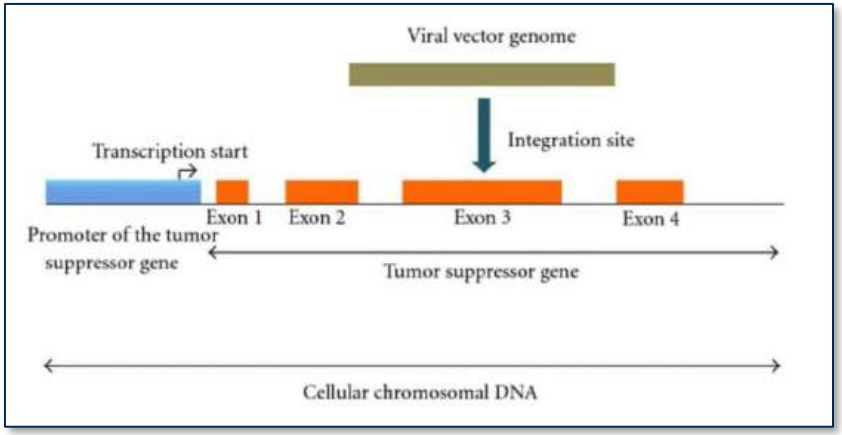
Open questions:

- **Insertional mutagenesis (e.g. oncogenes)?**
- **Epitope masking problem (increase in mortality)?**
- **Immunogenicity (strong acute antiviral response)?**
- **COGS/manufacturability (engineered LV)?**
- **Long-term: clinical benefit or even cause of mortality?**

Ref: Parone, presentation at ESGCT 2025, Sevilla/Spain (personal communication)
Ref: Xu, J. et al. (2025) Lancet 406, 228-231; https://www.thelancet.com/action/showPdf?pii=S0140-6736%2825%2901030-X
Ref: An, N. et al. (2026) Nature Medicine 32, 1257–1266; https://www.nature.com/articles/s41591-026-04244-6

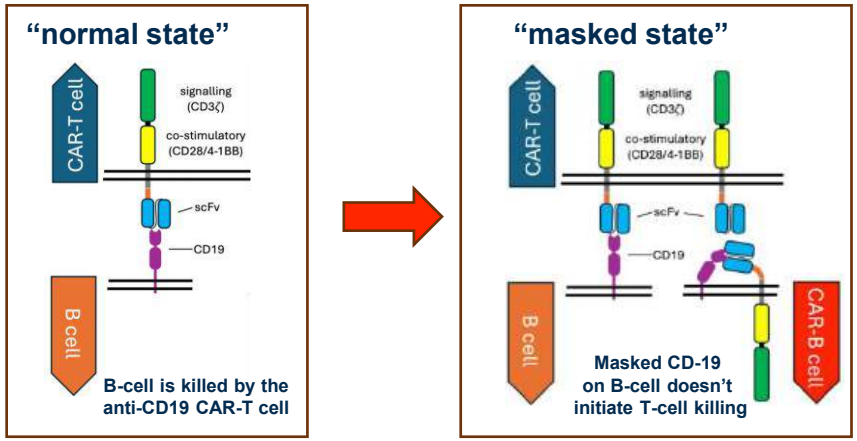
In-vivo CAR-T cell therapy: Risks of Lentivirus technology

Insertional mutagenesis:



- Humans have **73-260 different tumor suppressor** genes (UTexas), others define up to 1'000 coding and non-coding sequences as tumor suppressors
- **Viral genome insertion** occurs preferentially at transcriptionally active regions of the genome
- If possible, avoid integration into these sites by the use of **site-specific integration technologies**

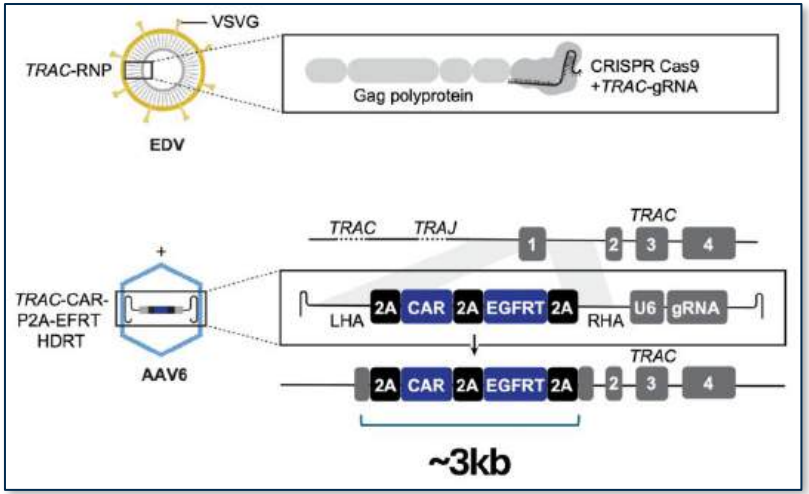
Epitope (e.g. CD19) masking:



- (Erroneous) infection of B-cells with CAR-constructs can cause expression of CAR construct in B-cells and cause **"epitope masking"** on the **"target organ" (B-cell)**
- (Erroneous) infection can be caused due to **non-perfect selectivity** (biodistribution, tissue specificity) of lentiviral vectors upon in-vivo infection (no issue for autologous)
- Epitope loss can cause **fatal outcomes** for B-cell lymphoma patients (will be visible only in long-term Ph2/3 studies)

In-vivo CAR-T cell therapy: TRAC insertion technology

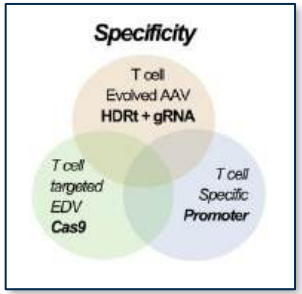
J. Eyquem / M. Sadelain / W.Nyberg Idea:



- Use of a **promoter-less CAR-construct** to avoid “epitope masking”
- Insertion into **highly regulated T-cell receptor** (TRAC) locus
- Insertion by **genome editing** (HDR-homology directed repair)
- 2 component delivery: **EDV** (Cas9 RNP), **AAVe** (DNA template)
- Generation of a **“native-like” engineered T-cell** in-vivo

Results:

- **Ultra-high specificity of in-vivo engineering**
- **(Possibly) better fitness of engineered T-cells**



3 separate layers of selectivity:

- Specificity of AAV (for T-cells)
- Specificity of EDV (for T-cells)
- Specificity of T-cell specific promoter

Open questions:

- **Efficiency of in-vivo engineering?**
- **COGS/manufacturability/scalability?**
- **Pre-existing immunogenicity (anti-AAV antibodies)?**
- **Safety/immunogenicity of 2 viral delivery systems?**

Ref: Eyquem, J. et al. (2017) Nature 543, 113-117; https://www.nature.com/articles/nature21405
Ref: Nyberg, W. et al (2026) Nature 652, 712-721; https://www.nature.com/articles/s41586-026-10235-x

In-vivo CAR-T cell therapy

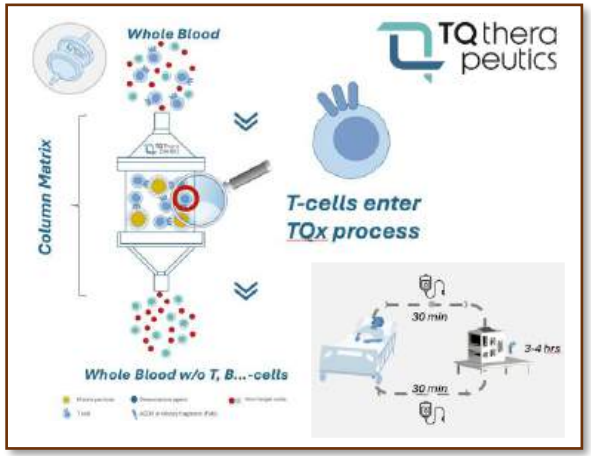
Can we make this better?

Can we develop an extra-corporeal in-vivo CAR-T process, working in a closed system (like dialysis) at the bed-side?

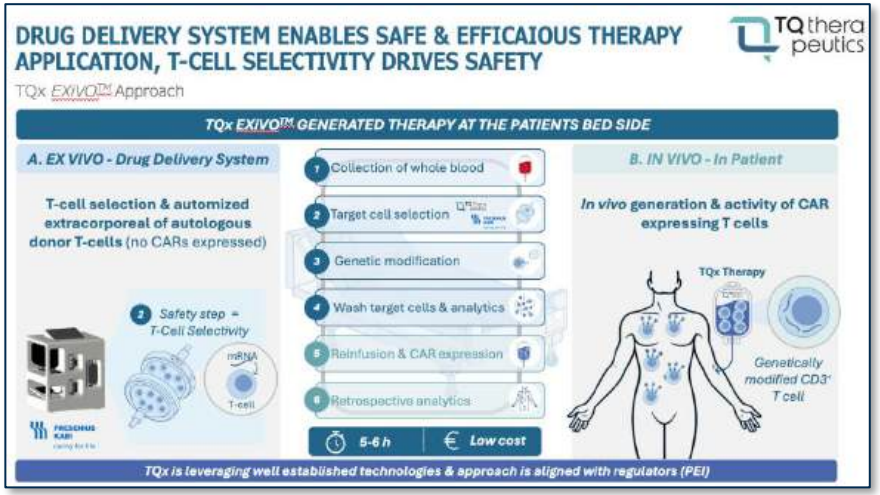
What can we learn from the well-established dialysis market (e.g. Fresenius)?
Germany: 80’000 dialysis patients, 740-760 dialysis centers
USA: 517’000 dialysis patients, 7’556 dialysis centers

In-vivo CAR-T therapy: Extra-corporeal (“hybrid”) Technology

TQ Therapeutics (Munich/DE):



- **Whole blood** as starting material (at the bedside)
- Flow through of non-target cells and contaminants
- **Affinity based enrichment** of target cells (T-cells)
- **Scalable and fast operation times** (<40 minutes)
- Cartridge manufactured in a sterilized format
- Compatible with **all methods of gene transfer**



Benefits:

- **Closed-loop system at the bedside, scalable process**
- **Significantly lower COGS, less material, faster**
- **Significantly lower risk profile**
- **Readily deployable in many hospitals (dialysis centers)**

In-vivo CAR-T cell therapy: Summary

The expectations/claims of in-vivo CAR-T:

- Off-the shelf therapy (i.v. or e.c. injection)
- Efficacious & safe treatment (good T.I.)
- Broad range of applications (hem/onc, autoimm)
- Affordable for everyone (10’000 EUR p.pt.)
- Scalable (to 10’000-100’000 pt per year)
- Simple logistics, easy access, every hospital
- Platform for more (NK, B, MP) cell therapies
- Better treatments, eventually also solid tumors

A new star is born – in-vivo CAR-T

SAXOCELL Annual Conference, June 2-3, 2026

A clear message coming from Dresden/Germany:

This bronze lion sculpture is one of two figures created in 1910 by sculptor Georg Wrba. It stands guard at the Goldene Pforte (Golden Gate) entrance of the New City Hall in Dresden, Germany.

German:

“Willst Du was schaffen, tu es nicht ohne Rat, doch vorwärts bringt Dich nur die frische Tat”

English:

“If you wish to achieve something, do not undertake it without counsel; yet only bold action will carry you forward”

In-vivo CAR-T cell therapy

Thank you

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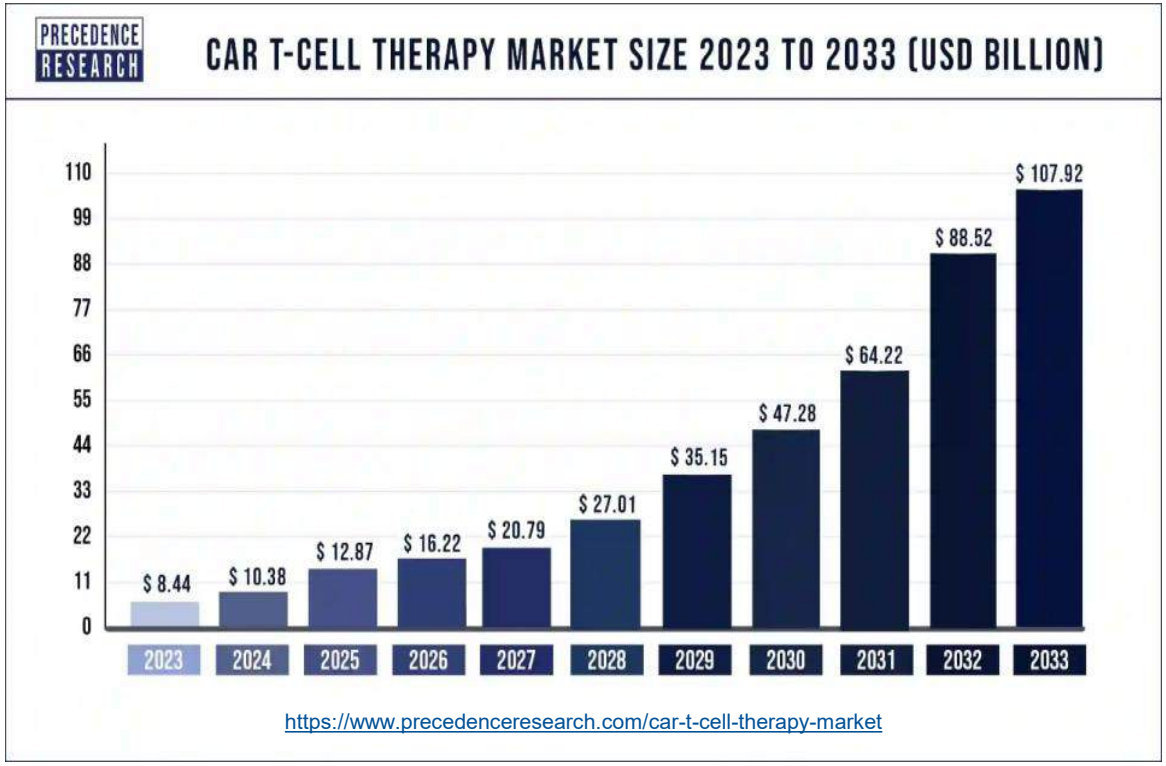
In-vivo CAR-T cell therapy

Backup Slides

Gene Delivery Technologies

Market forecast:



*The global CAR T-cell therapy market size is calculated at **USD 10.38 billion in 2024** and is expected to reach around **USD 107.92 billion by 2033**, registering a solid **CAGR of 30%** between 2024 and 2033.*

BioPharma Market – Trends & Future Growth

Key Shifts Over the Decades:

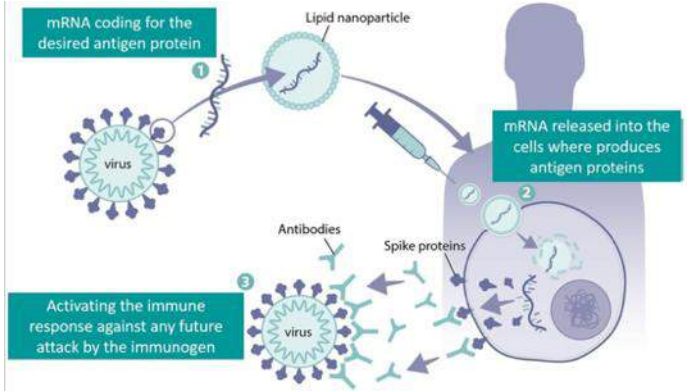
- **1990s:** Proof-of-concept era for biotech drugs
- **2000s:** Monoclonal antibodies & protein therapeutics go mainstream
- **2010s:** Immuno-oncology and targeted therapies explode
- **2020s:** mRNA, cell & gene therapies, and biosimilars reshape the market (and GLP-1)

Obvious Questions:

- What are the future trends?
- How long is(are) the(se) trend(s) going to last?
- How big is(are) the(se) trend(s) going to be?
- How to pick the winners?
- How to maximise RoI (return on investment) for investors/patients/society?

BioPharma Success Stories – mRNA Vaccines

mRNA vaccines use messenger RNA (mRNA) encoding a virus-specific antigen to produce an **adaptive immune response**. The mRNA is delivered by encapsulation in **lipid nanoparticles (LNPs)** that protect the RNA strands and help their absorption into the cells.



Comirnaty (Pfizer/BioNTech): sales (2022): **$55.9 bn**
Spikevax (Moderna): sales (2022): **18.4bn**

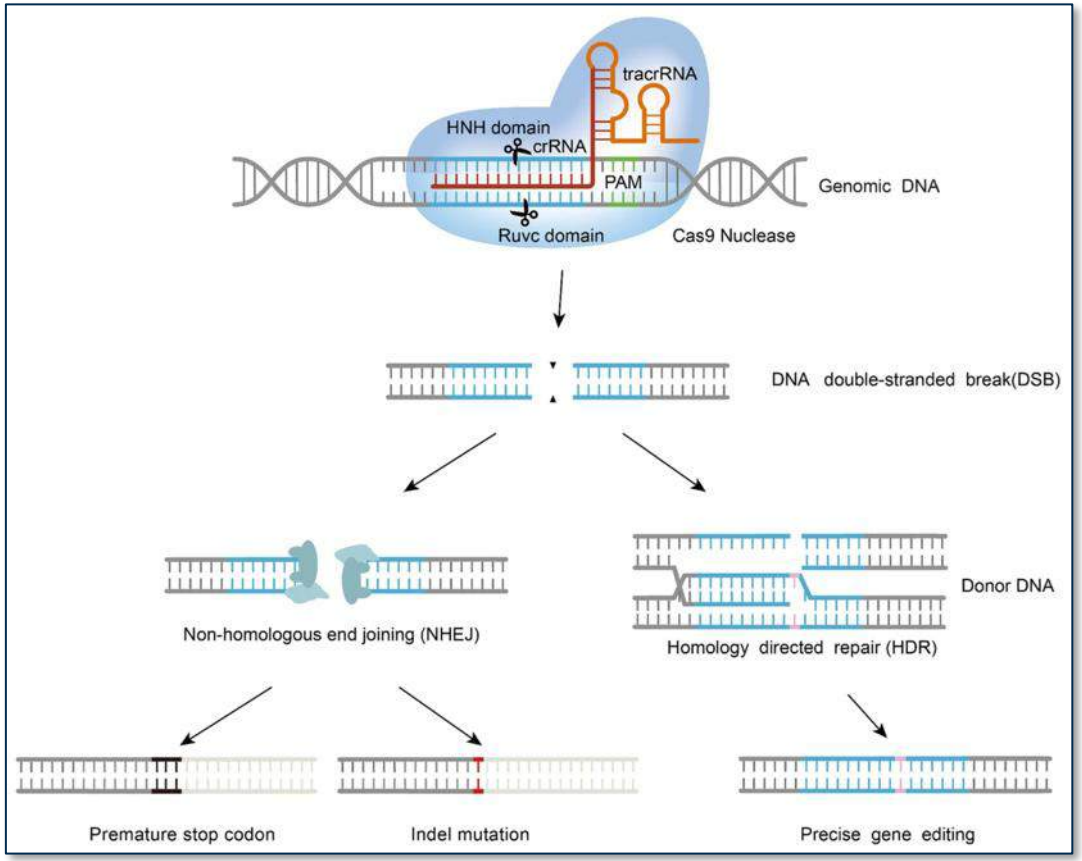
Total mRNA Sales in 2024: $8.9 bn

mRNA vaccines against COVID-19(*):
13.53 billion COVID-19 vaccine doses have been administered worldwide, with 70.6 percent of the global population having received at least one dose.

Global population (people, total): **8.2 bn**
Global population (vaccinated people): **5.88 bn**

*https://en.wikipedia.org/wiki/COVID-19_vaccine

BioPharma Success Stories – Genome Editing

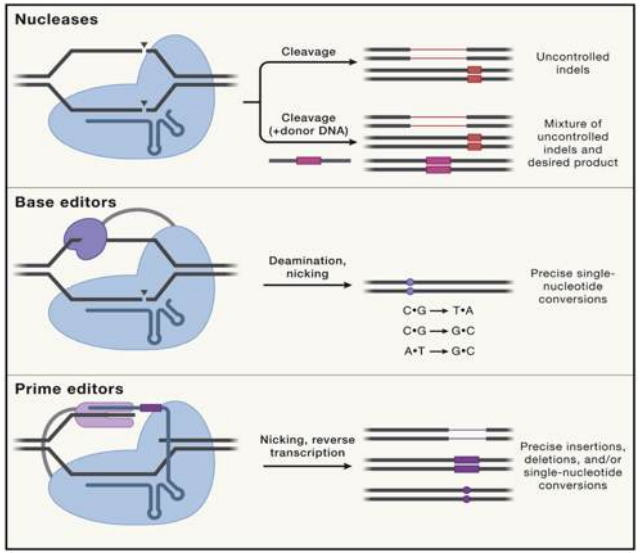


RNA-guided Cas9 Nuclease:

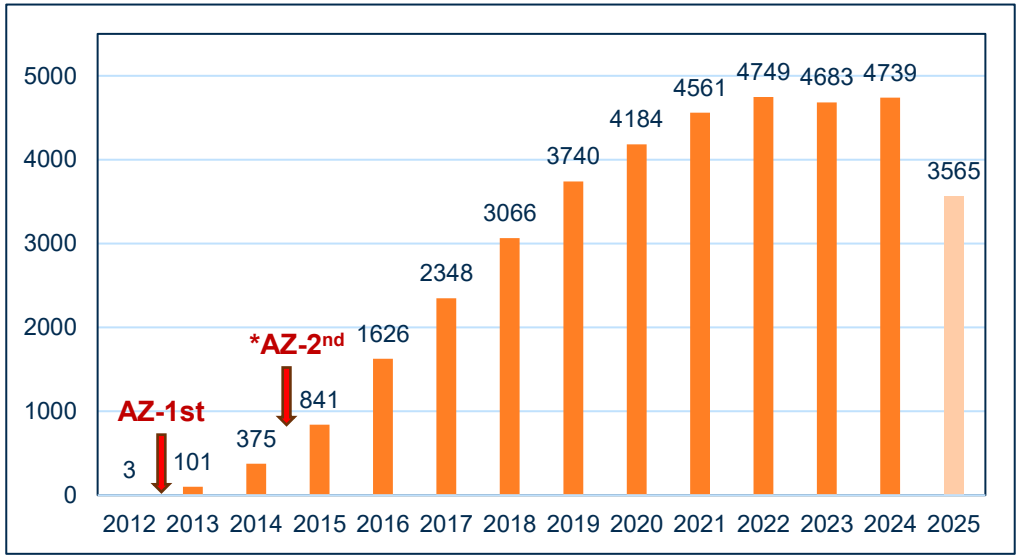
- Discovery in 2012 by Jennifer Douda, Emmanuel Charpentier and others
- Easy to program sequence specificity by endogenous gRNA (guide RNA)
- Wide range of applications for target discovery, target validation, GEMMs, therapeutic applications in cell & gene therapy, regenerative medicine, etc.
- Various modifications and further developments since 2012
- Foundation of Synthetic Biology, Genomic Medicine and other areas
- Approved drugs (Casgevy) on the market for use in humans (ex-vivo)

BioPharma Success Stories – Genome Editing

Nuclease, Base/Prime Editing:



PubMed Entries ("CRISPR"):



Genome Editing Technologies:

- Inactivation (InDel formation)
- Nucleobase editing (Base Editing)
- Short insertions (Prime Editing)

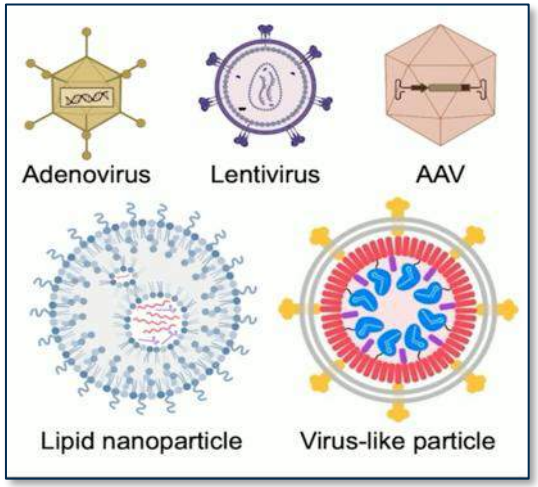
CRISPR- Publications:

- 2012: 3 papers (per year)
- 2025e: >4'800 papers (per year)

*AZ Global CRISPR collaboration announcement (BBC report, 29.Jan 2015)

BioPharma Success Stories – Gene Delivery Technologies

Gene Delivery:



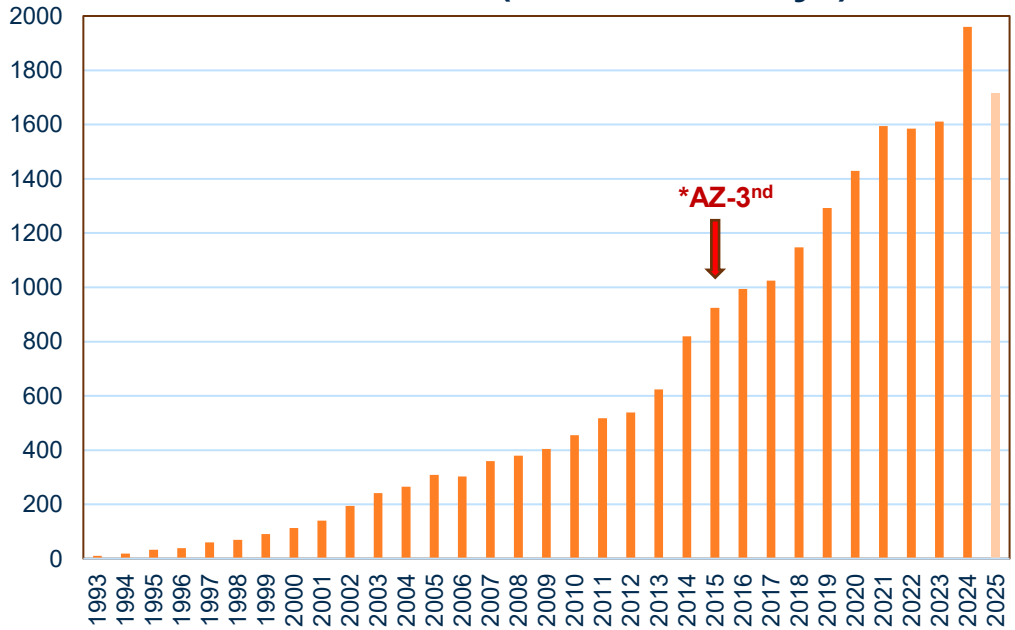
Technologies:

- Viral delivery (AdV, LV, AAV)
- Non-viral delivery (LNP, VLP, ECV)

Challenges:

- Immunogenicity, toxicity
- Scalability, CMC, costs, QC/QA

PubMed Entries ("Gene Delivery"):



Constant rise:>1'500 papers (per year)
One of the **most intense R&D** areas today

***AZ investment decision: Exosome (ECV) group in UK & Sweden, July 2015**