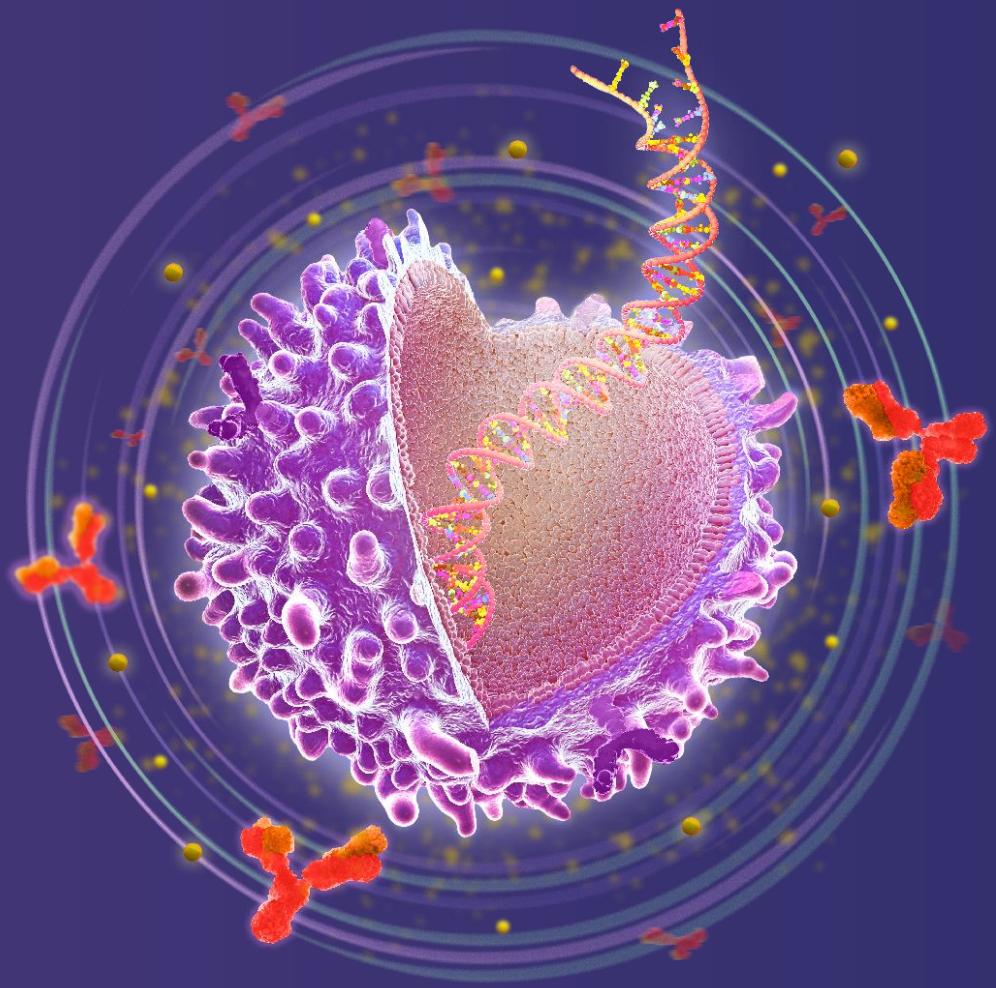
Answers to common challenges

The ins and outs of CAR T cells in the real world

Presented by: **Prof. Dr. Michael Hudecek**

Cellular Immunotherapy Program



LymphomaHub MultipleMyelomaHub

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Disclosures

The following declarations are made for the last 3 years and the following 12 months (where arrangements have already been made):

- Research grant(s)/in kind support: BMS
- Participation in accredited CME/CPD: BMS, Janssen, Novartis
- Consultant/strategic advisor: T-CURX
- Patents/shares or stocks related or unrelated to this presentation:
  - Inventor on patent applications and granted patents related to CAR technology and therapy
  - Co-founder and equity owner T-CURX (CAR-T Biotech, Würzburg, Germany)
- Non-financial interests: None

Main challenge:
How to improve patient access and scalability of CAR-T cell therapy?

- Fast CARs?
  - Experience so far with approved CAR T-cell therapies from an EU and US perspective

- How to manufacture CARs faster?
  - Virus-free genetic engineering
  - Automated multiplexed manufacturing
  - In vivo CAR production

CAR, chimeric antigen receptor; EU, European Union; US, United States.

Real-world evidence of CAR T-cell therapy

Although striking improvements for immunotherapy (e.g. immunomodulators, anti-CD38, and proteasome inhibitors) have been achieved in the past decade, a significant number of patients relapse[1-5]

The first CAR T-cell product was approved by the U.S. FDA and EMA in 2018, with four more approved since then[9-11]:

- Idecabtagene vicleucel
- Lisocabtagene maraleucel
- Ciltacabtagene autoleucel
- Tisagenlecleucel
- Brexucabtagene autoleucel
- Axicabtagene ciloleucel

Emerging CAR T-cell therapies are promising treatment options for refractory or relapsed patients

- Infusion success rates of 44–91% 24 months after treatment[6-8]
- Complete response rates of 28–68% 24 months after treatment[6-8]

Significant investments in clinic sites, expertise network, logistics, and education of MDTs

- Number of European CAR-T centers expanded from ~30 to ~85 in 2019 alone[12]
- New facilites in Switzerland, France, and Netherlands[12]
- Establishment of Education Guidelines of multidisciplinary care teams[13]

Adoption of EMA AMTP guidelines by EU countries

AMTP, advanced therapy medicinal products; CAR, chimeric antigen receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; MDT, multidisciplinary team.

1. Majithia N, et al. *Leukemia.* 2016;30(11):2208-2213. **2.** Childrens hospital of Philadelphia. https://www.chop.edu/conditions-diseases/relapsedrefractory-acute-lymphoblastic-leukemia-all. **3.** Koschade SE, et al. *Ann Hematol*. 2022;101(8):1703-1710. **4.** Kesireddy M, Lunning M. *Oncology (Williston Park)*. 2022;36(6):366-375. **5.** Sawalha Y. *J Pers Med*. 2021;11(12):1345. **6.** Capel KM, Kochenderfer JN. *Nat Rev Clin Oncol.* 2023. Online ahead of print. DOI: 10.1038/s41571-023-00754-1. **7.** Sengsayadeth S, et al. *EJHaem.* 2021;3(Suppl 1):6-10.. **8.** Qi, et al. *Nat Med*. 2022;28(6):1189-1198. **9.** OHSU Knight Cancer Institute. https://www.ohsu.edu/knight-cancer-institute/car-t-cell-therapy-cancer. **10.** UPMC Hillman Cancer Center. https://hillman.upmc.com/mario-lemieux-center/treatment/car-t-cell-therapy/fda-approved-therapies. **11.** Jommi C, et al. *Front Pharmacol.* Online ahead of print. DOI: 10.3389/fphar.2022.915342. **12.** LEK. https://www.lek.com/insights/ei/car-t-unlocking-barriers-adoption-Europe. Published Jun 23, 2020. **13.** Beaupierre A, et al. *J Adv Pract Oncol*. 2019;10(Suppl 3):29-40.

Real-world evidence of CAR T-cell therapy

Comparable challenges in EU and US regarding access, patient referral, and logistical challenges

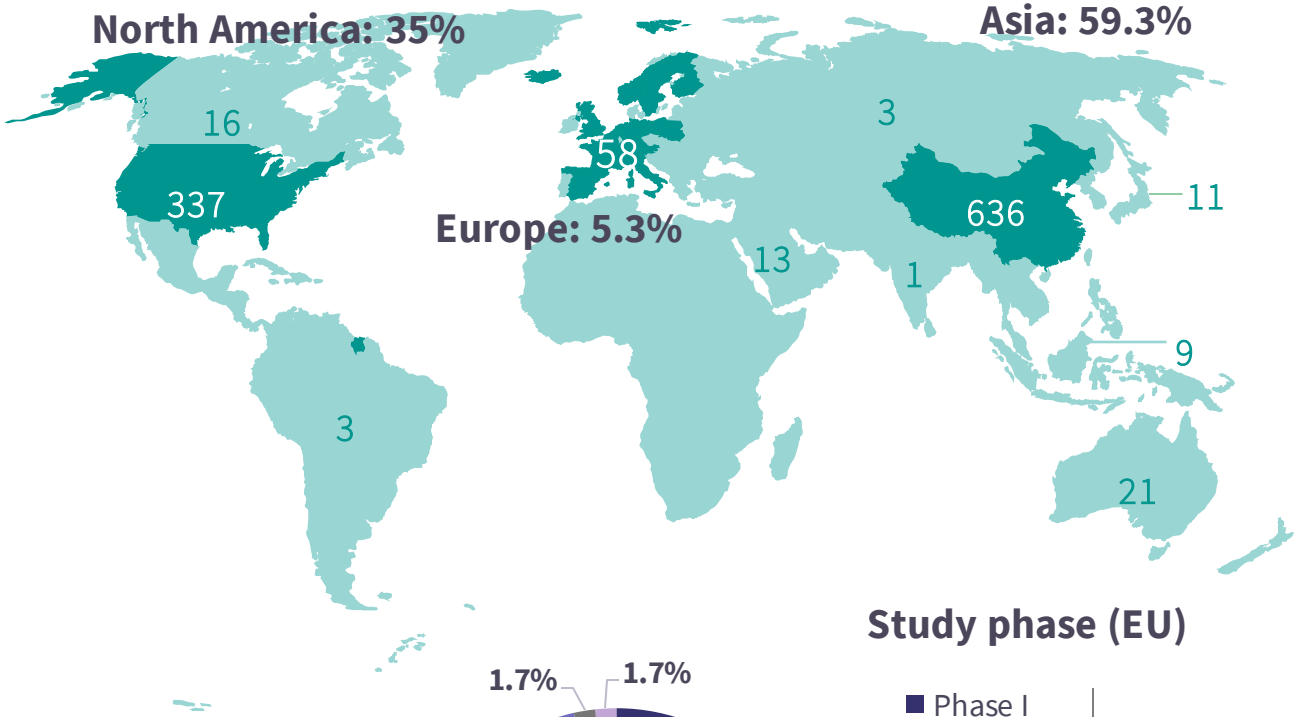
Considerable geographical disparities and variation in outcome[1,2]

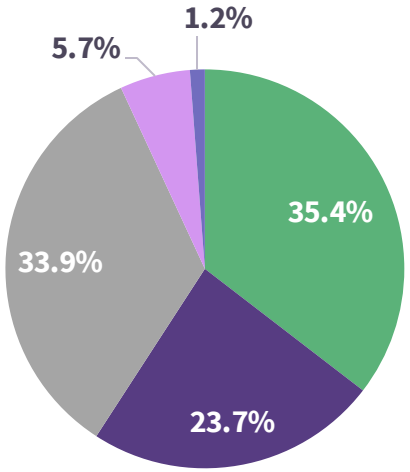
- Cost of therapy between 253,000 USD and 319,000 USD per QALY[6]
- Inadequate reimbursement policies for US and EU[3–5]
- Centralization of CAR-T treatment centers → Demand of mobility/caretaker[4,5]
- Bureaucratic burdens[4]
- Access inequality to education and hands-on practice between high-, middle-, and low-income countries[6]

CAR, chimeric antigen receptor; EU, European Union; US, United States; USD, United States Dollar.

1. Ludwig H, et al. *Oncologist*. 25(9):e1406-e1413. **2.** Gagelmann N, et al. *Lancet Haematol*. 2022;9(10):e786-e795. **3.** ASGCT. https://asgct.org/global/documents/patient-ed-infographics/asgct-car-t-access_one-pager_2-22-21.aspx. **4.** Jommi C, et al. *Front Pharmacol.* Online ahead of print. DOI: 10.3389/fphar.2022.915342. **5.** Hopfinger G, et al. *memo.* 2023;16:79-90. **6.** Cappell KM, et al. *Nat Rev Clin Oncol*. 2023;20:359-371.

Perspective on CAR-T studies[1]

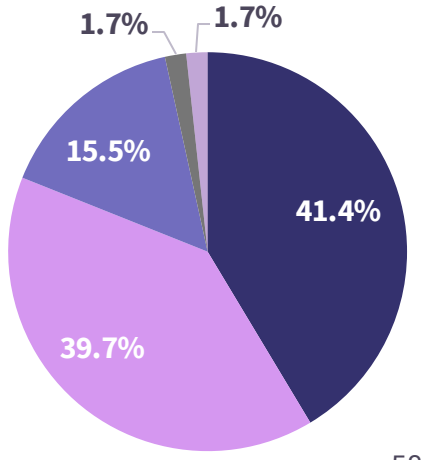




Funding type (worldwide)

- Academic
- Industrial
- Academic | Industry
- Academic | Government
- Academic | Industry | Government

n = 1,087

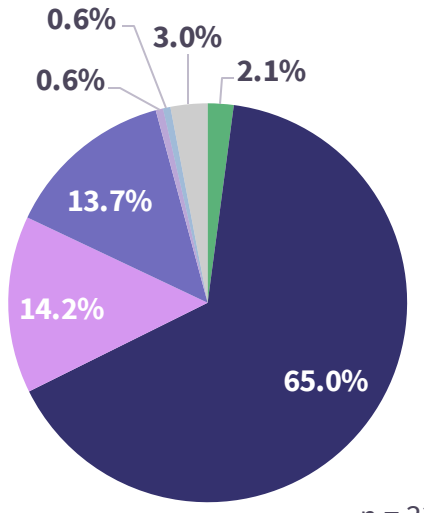


Study phase (EU)

- Phase I
- Phase I/II
- Phase II
- Phase II/III
- Phase III
- Phase IV (0)
- Not specified (0)

81.1%

n = 58



Study phase (USA)

- Early phase I
- Phase I
- Phase I/II
- Phase II
- Phase II/III
- Phase III
- Phase IV (0)
- Not specified

81.3%

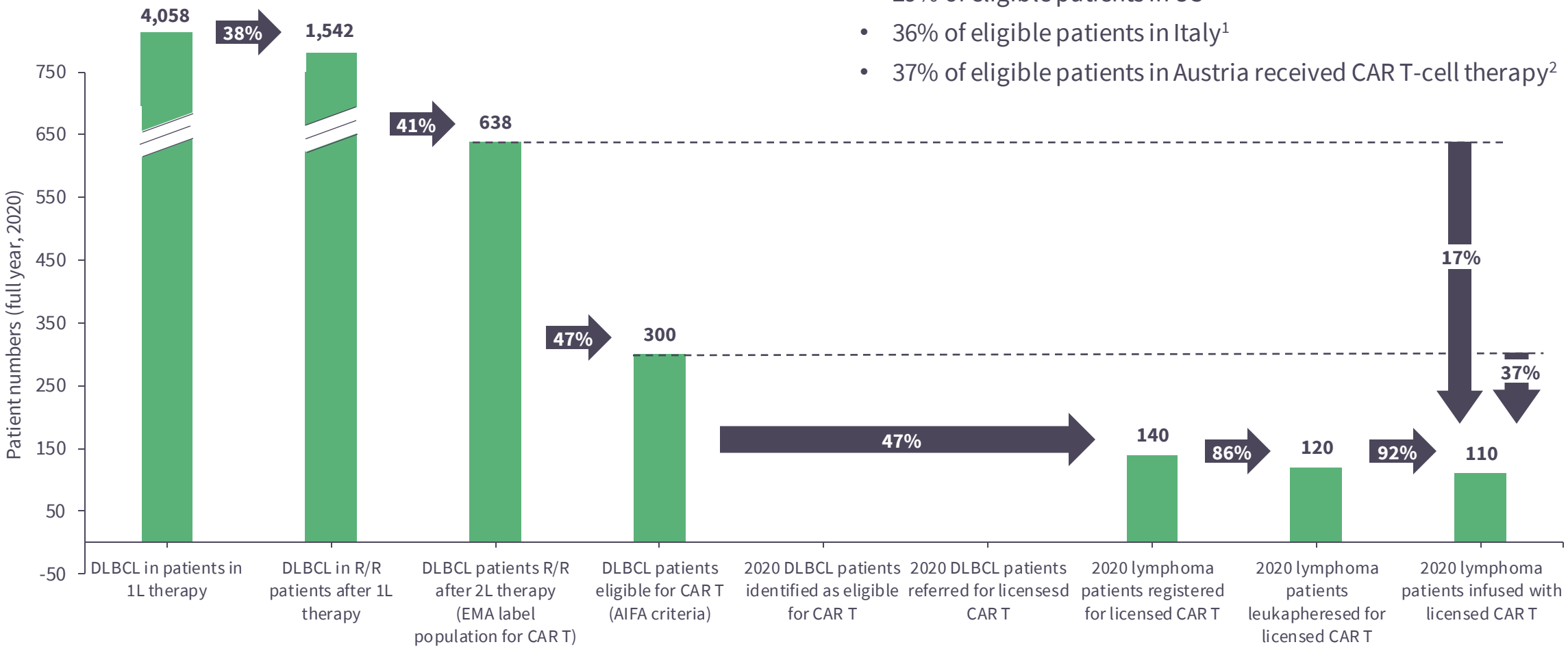
n = 337

CAR, chimeric antigen receptor; EU, European Union.

1. Wang V, et al. *Cancers (Basel)*. 2023;15(4):1003.

Real-world evidence of CAR T-cell therapy[1]

- "Loss" of patients



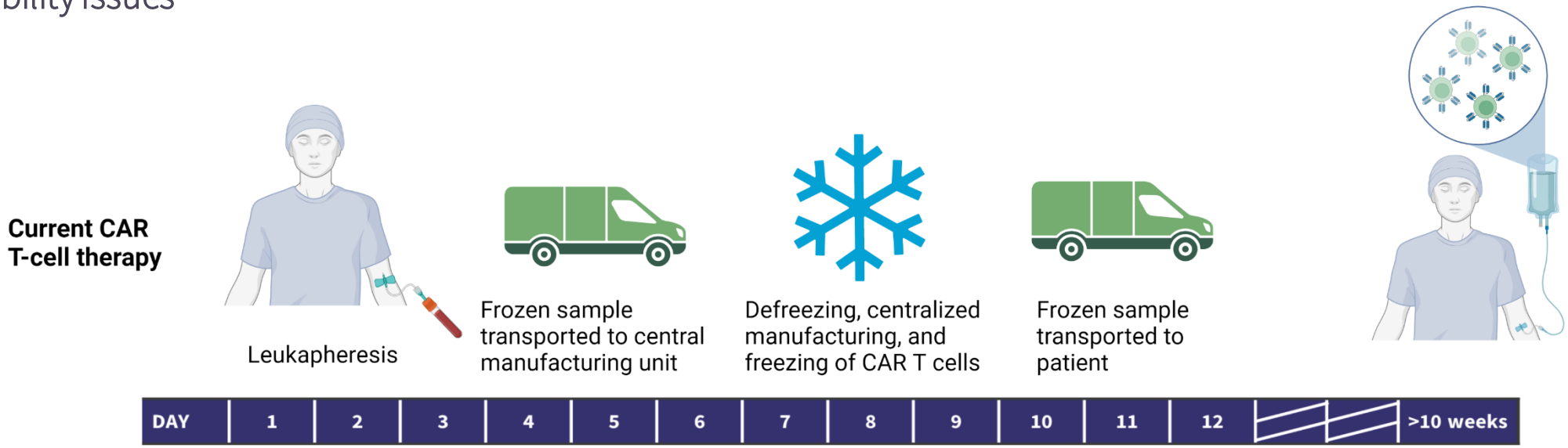
- ASH report 2022:
  - 29% of eligible patients in US
  - 36% of eligible patients in Italy[1]
  - 37% of eligible patients in Austria received CAR T-cell therapy[2]

ASH, American Society of Hematology; CAR T, chimeric antigen receptor T-cell therapy; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; R/R, relapsed/refractory; RWE, real-world evidence; 1L, first-line; 2L, second -ine.

1. Jommi C, et al. *Front Pharmacol.* Online ahead of print. DOI: 10.3389/fphar.2022.915342. **2.** Hopfinger G, et al. *memo.* 2023;16:79-90.

Logistical challenges

- CAR T-cell therapy only considered after several prior treatments, deteriorating effects on autologous cell generation[1]
- Time of referral until infusion 4–10 weeks→ reduces number of eligible patients[2,3]
- In 2021, roughly 4,000 CAR T-cell therapies were reimbursed worldwide
- Demand of concept needed to adress 100-fold more patients
- Scalability issues



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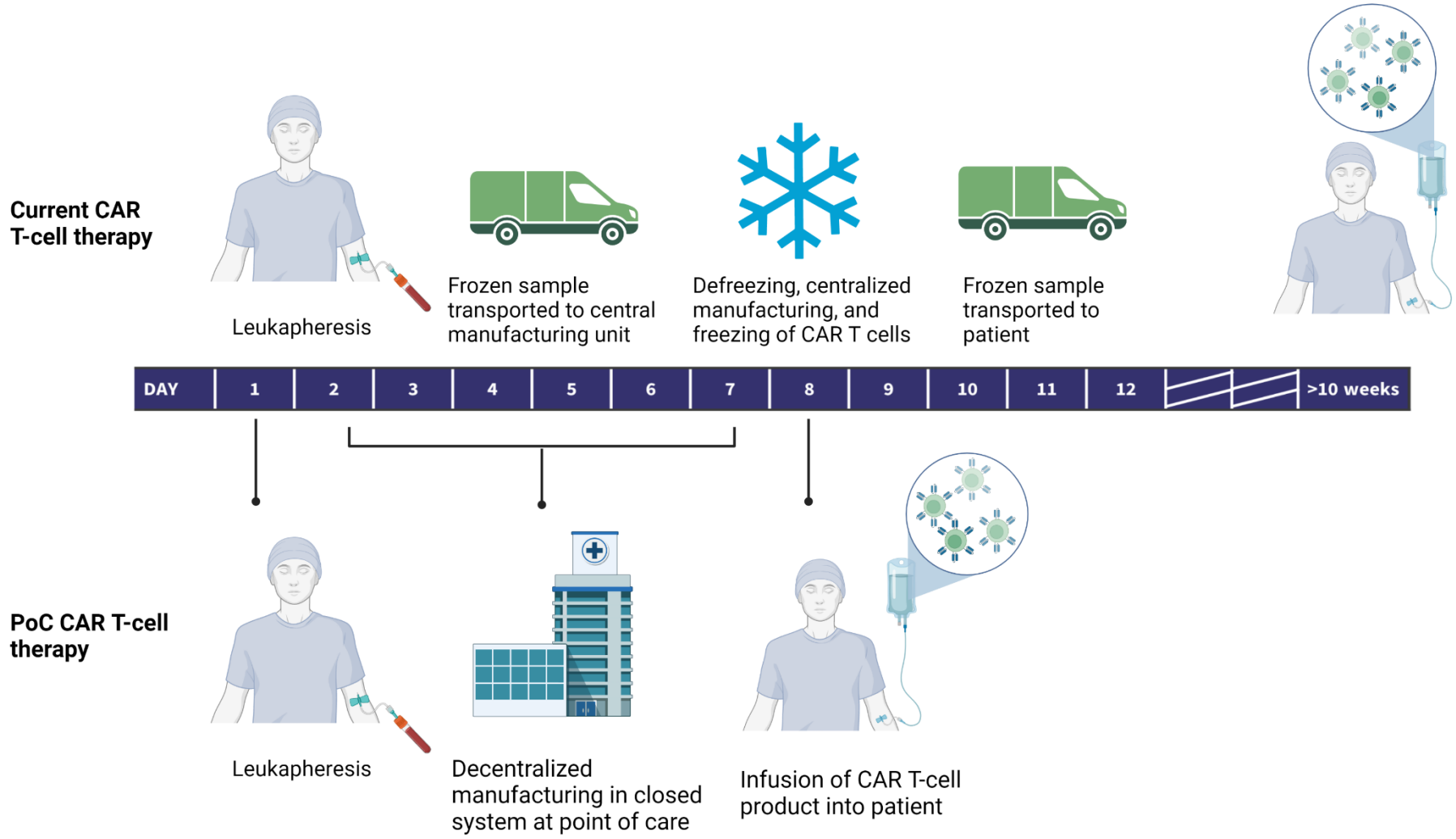
CAR, chimeric antigen receptor.

1. McClanahan A, et al. *J Adv Pract Oncol*. 2022;13(3):328-332. **2.** Wang V, et al. *Cancers (Basel)*. 2023;15(4):1003. **3.** Chen AJ, et al. *Value Health*. 2022;25(8):1344-1351.

Point-of-care versus centralized CAR T-cell manufacturing



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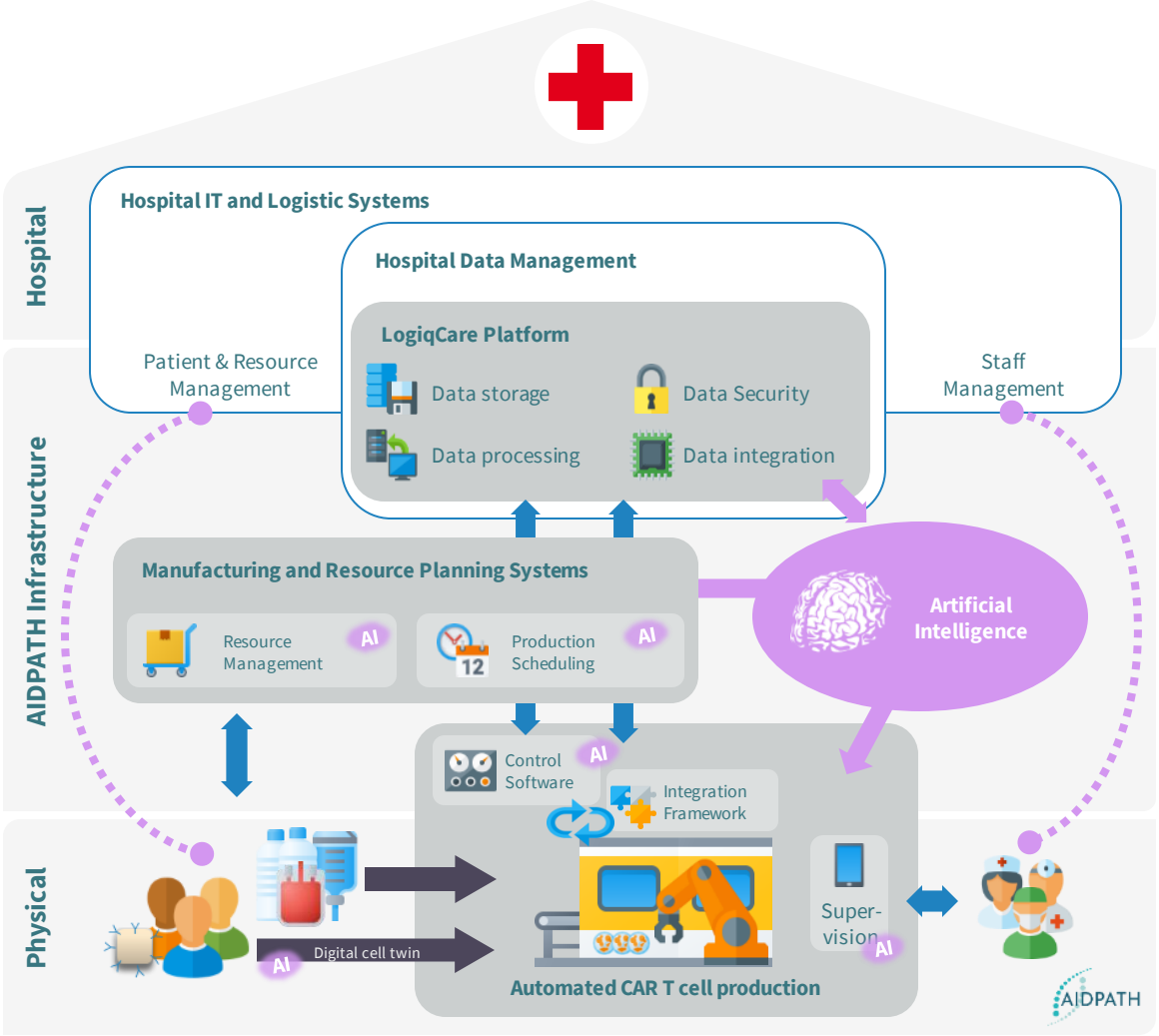
CAR, chimeric antigen receptor; PoC, point of care.

The Smart Manufacturing Hospital - Data management and decision support[1]

- Close Integration in the hospital IT infrastructure
  - Data management platform establishes patient and manufacturing data availability to AI
  - Storage platform stores batch data and historical data sets
- Decision support and process insight intensification through integration of five distinct artificial intelligences:
  - Reactive Bioreactor Control Strategy
  - CAR-T Digital Twin
  - Clinical Decision Support
  - Production Scheduling
  - Resource Management



This work has been performed in the framework of the H2020 project AIDPATH co-funded by the EU under grant agreement number 101016909.

AI, artificial intelligence.

1. Hort S, et al. Front. *Med.* 2022;9:913287.

Use cases of AI in CAR-T manufacturing[1]

	CAR -T Digital Twin	Reactive Bioreactor Control	Clinical Decision Support	Production Scheduling	Hospital Resource Management
Challenge	CAR-T cell culture progress prediction	Biological variability of patient Material	Patient reaction to treatment dependent on treatment history	Production scheduling are complex optimization problems	Hospital resource allocation is non-optimal for manufacturing
Utilized data sources	Experimental batch and continuous cell culture data	In-line Bioreactor data Platform QC	Patient treatment history Platform QC	Live process data Resource availability Digital twin predictions	Hospital resource allocation Patient occurrence
AI Use Case	**On-line modeling of cell response to manufacturing conditions**	**Prediction of cell quality parameters to optimize process conditions**	**Optimizing treatment procedure**	**Efficient production scheduling with a focus on patient parallelization**	**Optimize hospital resource allocation**

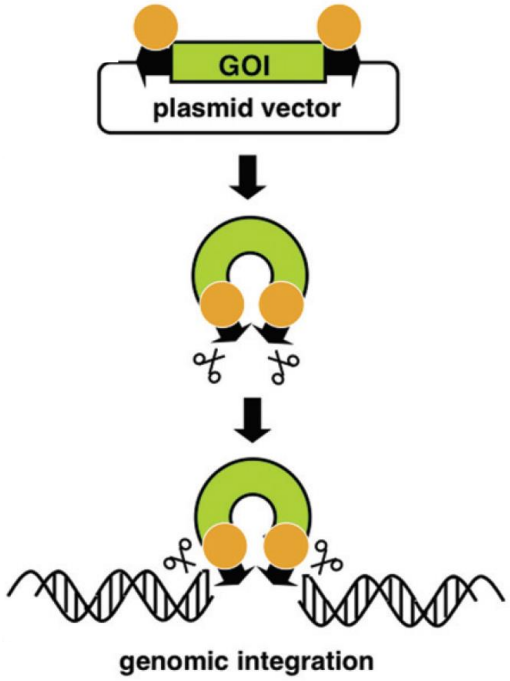
QC, quality control.

1. Hort S, et al. Front. *Med.* 2022;9:913287.

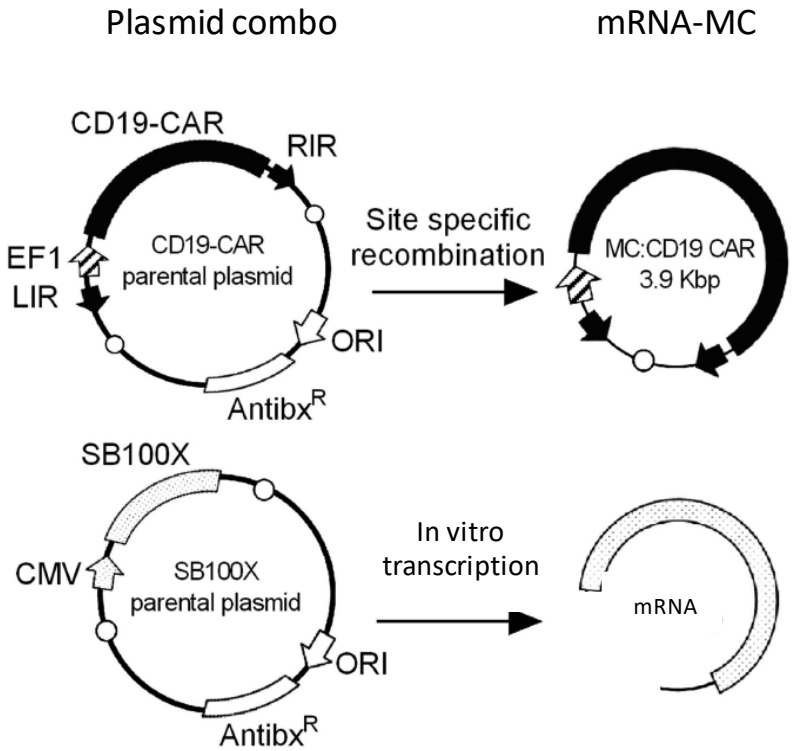
This work has been performed in the framework of the H2020 project AIDPATH co-funded by the EU under grant agreement number 101016909.

Next-gen CAR-T manufacturing: scalable, exportable, affordable[1,2,3]

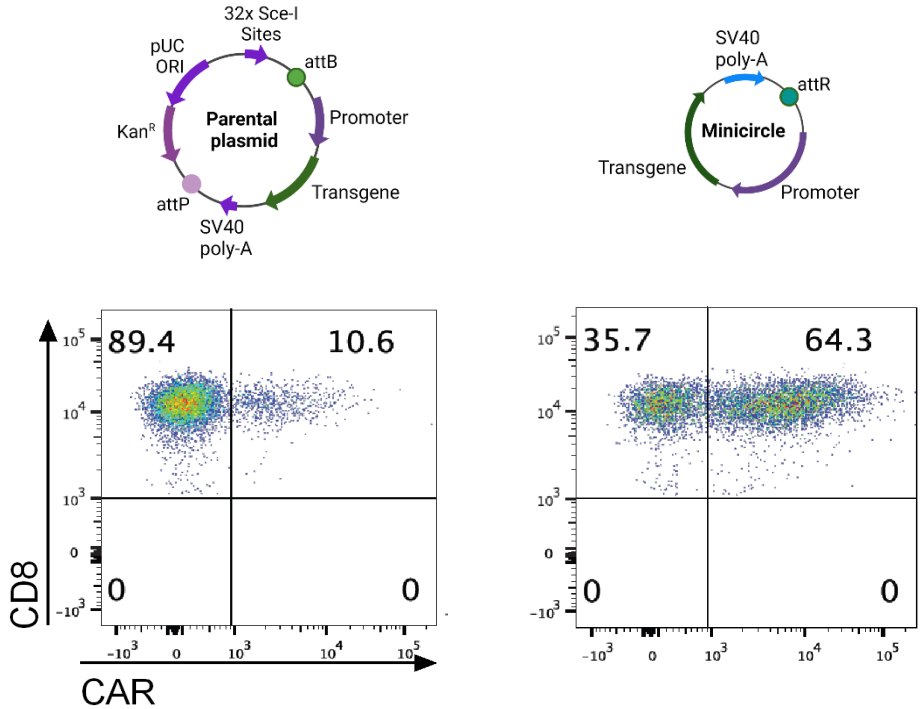
Sleeping Beauty transposition: mRNA & minicircle DNA to deliver transposase & transposon



Hudecek M, Ivics Z. *Curr Opin Genet Dev*. 2018;52:100-108.



Hudecek M, et al. Crit Rev Biochem Mol Bio. 2017;52(4):355-380.



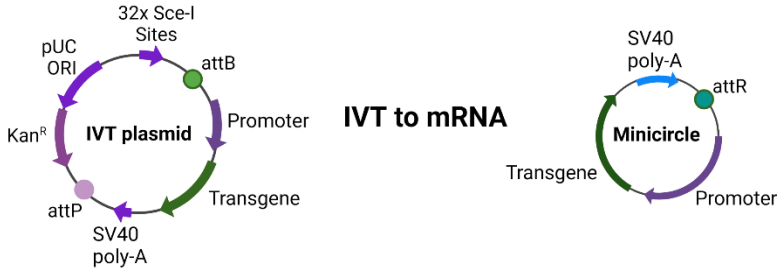
Monjezi R, et al. Leukemia. 2017;31(1)186-194.

- High gene-transfer rate & stable CAR expression
- High frequency of genomic safe habour insertions

Sleeping Beauty transposon technology enables scalable CAR T-cell production[1]

Vector	Transposase mRNA and transposon minicircle DNA	Lentivirus
Cost	Cost of gene-transfer vector **<$1.000 per dose**[1]	Cost of gene-transfer vector **~$20.000 per dose**[1]
Complexity	Established production processes for mRNA and DNA **Easy** to standardize, scale-up and export	Highly complex process (adherent producer cell lines) **Difficult** to standardize, scale-up and export
Batch size	Scalable to **>10,000 products per batch** **High consistency** between batches	Scale of **<1,000 (<100) products per batch** **High variability** between batches
Safety	Safety level class 1 (**low risk** and standard in all labs)	Safety level class 2 (**higher risk** and not standard)
Capacity	**High existing capacity**, easy to scale-up and expand Produced in large quantities in microbial fermentation	**Low existing capacity**, difficult to scale-up and expand Produced in small quantities with adherent producer cell lines
Regulatory effort	**Low regulatory effort**; mRNA and plasmid production is a regulatory standard for various therapeutics	**High regulatory effort;** only regulatory guidance available—no standard process yet—very elaborate

Making transposon vectors

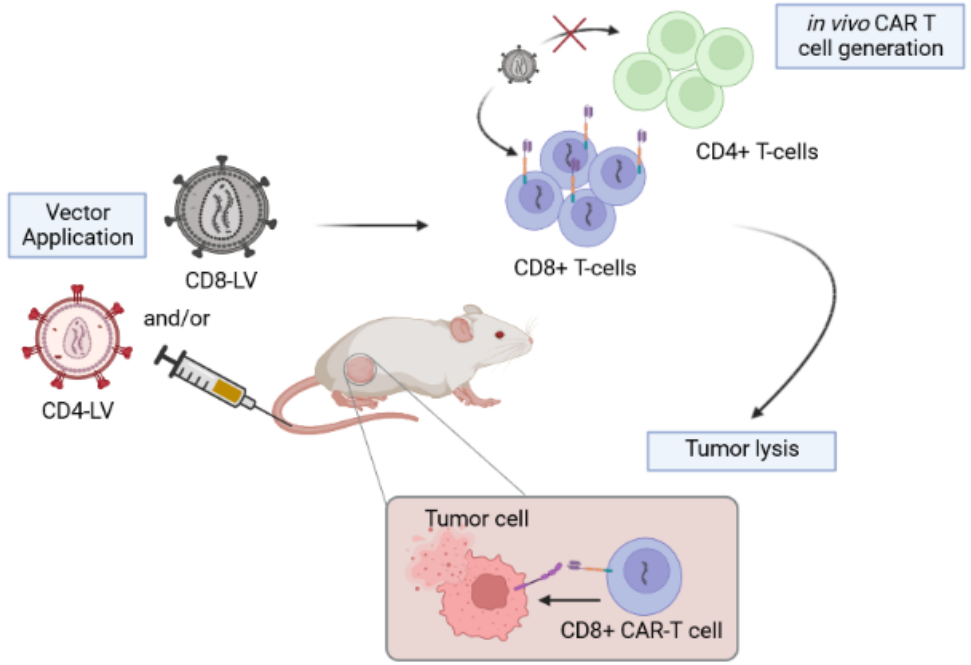


CAR, chimeric antigen receptor; IVT, *in vitro*-transcribed; mRNA, messenger RNA.

1. Monjezi R, et al. *Leukemia*. 2017;31(1)186-194.

In vivo gene transfer for CAR T-cell Generation[1,2]

- CD4/8-LV injection yields 40–60% CD19 CAR T cells in **NSG mice** transplaned with hPBMCs
- Effective CD19⁺ B cell elimination within 2–3 weeks post-injection
- CD4-LV injected mice display superior tumor cell killing capability compared to CD-8 LV or mixture injection
- αCD5 LNP enable **mRNA delivery** *in vivo* to CD5⁺ lymphocytes
- Formation of **transient** CAR T cells
- Significant improvement of cardiac function in heart failure mouse model



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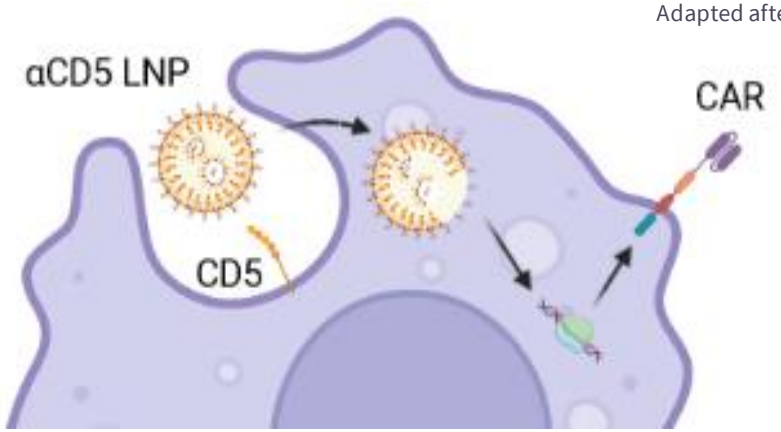
Adapted after Agarwal, et al.



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Adapted after Rurik, et al.

CAR, chimeric antigen receptor; hPBMC, human peripheral blood mononuclear cells; mRNA, messenger RNA.

1. Agarwal S, et al. *Mol Ther*. 2020;28(8):1783-1794 **2.** Rurik JG, et al. *Science*. 2022;375(6576):91-96.

T²EVOLVE

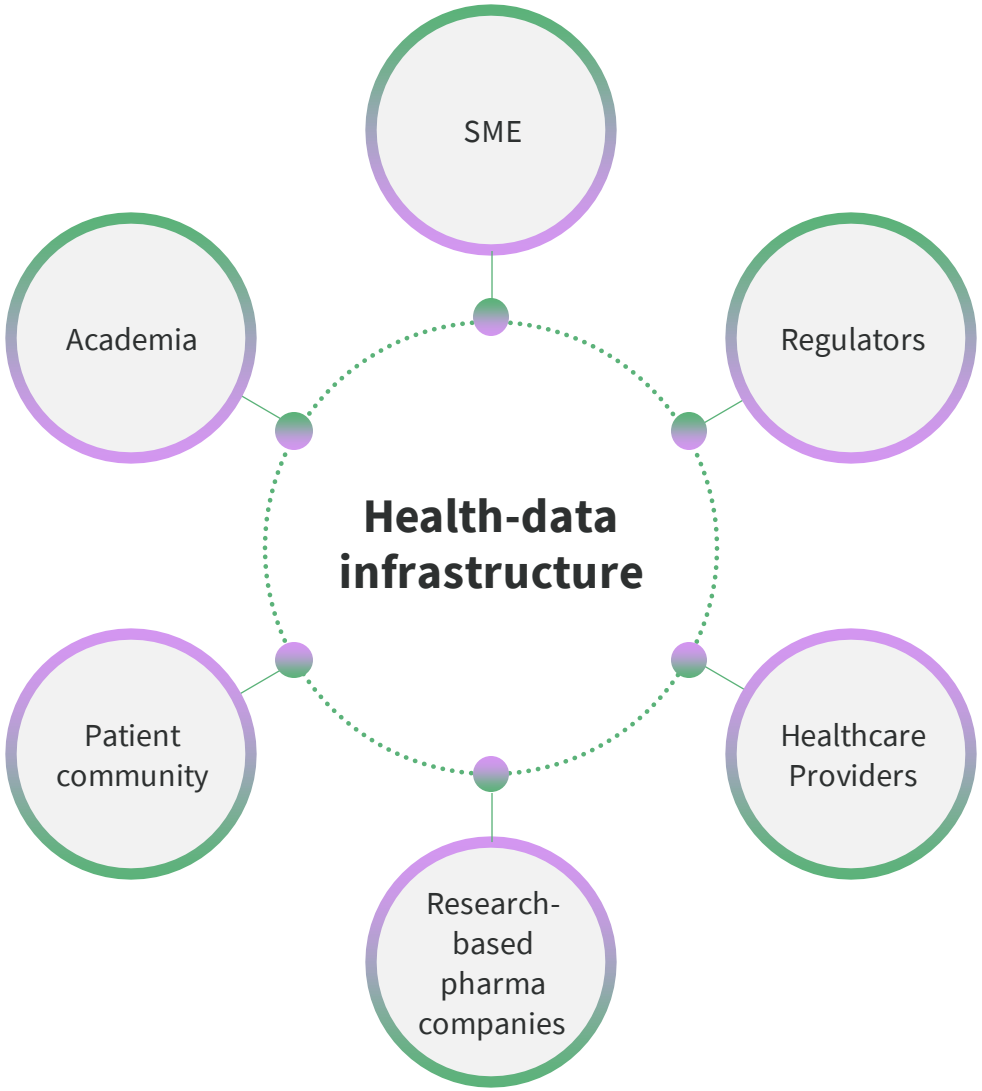
Accelerating the development and increasing access to CAR and TCR-engineered T-cell therapy

Ground-breaking alliance boosting Europe to the forefront of cancer immunotherapy

Coordinators: Michael Hudecek, Universitätsklinikum Würzburg
Hélène Negré, Servier

This project received funding from the innovative Medicines initiative 2 Joint Undertaking (JU) under grant agreement No 945393. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programe and EFPIA. More information can be found at: https://www.imi.europa.eu/

Innovation ecosystem in T2EVOLVE



SME, small and medium-sized enterprises.

Patient and caregiver involvement and education

WP2

Educational material hub
for patients and HCPs

Constantly improving communication between HCP and patients

✓ Successful workshops with patients, patient associations, and HCPs

Survey on
- ✓ Available information material
- ✓ Informed consent
- ✓ Quality of life

Improving patient care

HCP, healthcare provider; WP, work package.

Patient and caregiver involvement and education: Survey

WP2

- A survey for **European adult patients (≥ 18 years) who received CAR T-cell therapy for a hematologic malignancy**.
- This survey will help to understand **patients' experience** with CAR T-cell therapy, evaluate the **impact** of this treatment on **quality of life**, and identify **unmet needs.**

- The survey is available online in **7 languages**:

Password: **t2evolve**

t2evolve.fyi/patientsurvey

English **French** **Dutch** **Spanish** **Italian** **German** **Portuguese**

CAR, chimeric antigen receptor.

Gold standard analytical methods in manufacture and monitoring

WP5

Challenge: Heterogeneity in release and monitoring of engineered T-cell products

Difficulty to perform intra- and inter-trial comparisons

Survey

of current analytical practices

Set of standards

merging survey results and expert feedback from **STC committee**

Validation and dissemination

with **CENET** support

Harmonized evaluation of product and patient monitoring

What is your experience administering an out-of-specification product?

What is your assessment of the potential role of AI in CAR T-cell therapy?

Is your treatment center open to hosting point-of-care CAR T-cell manufacturing?

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Thank you!

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This activity was supported through an educational grant from Bristol Myers Squibb.