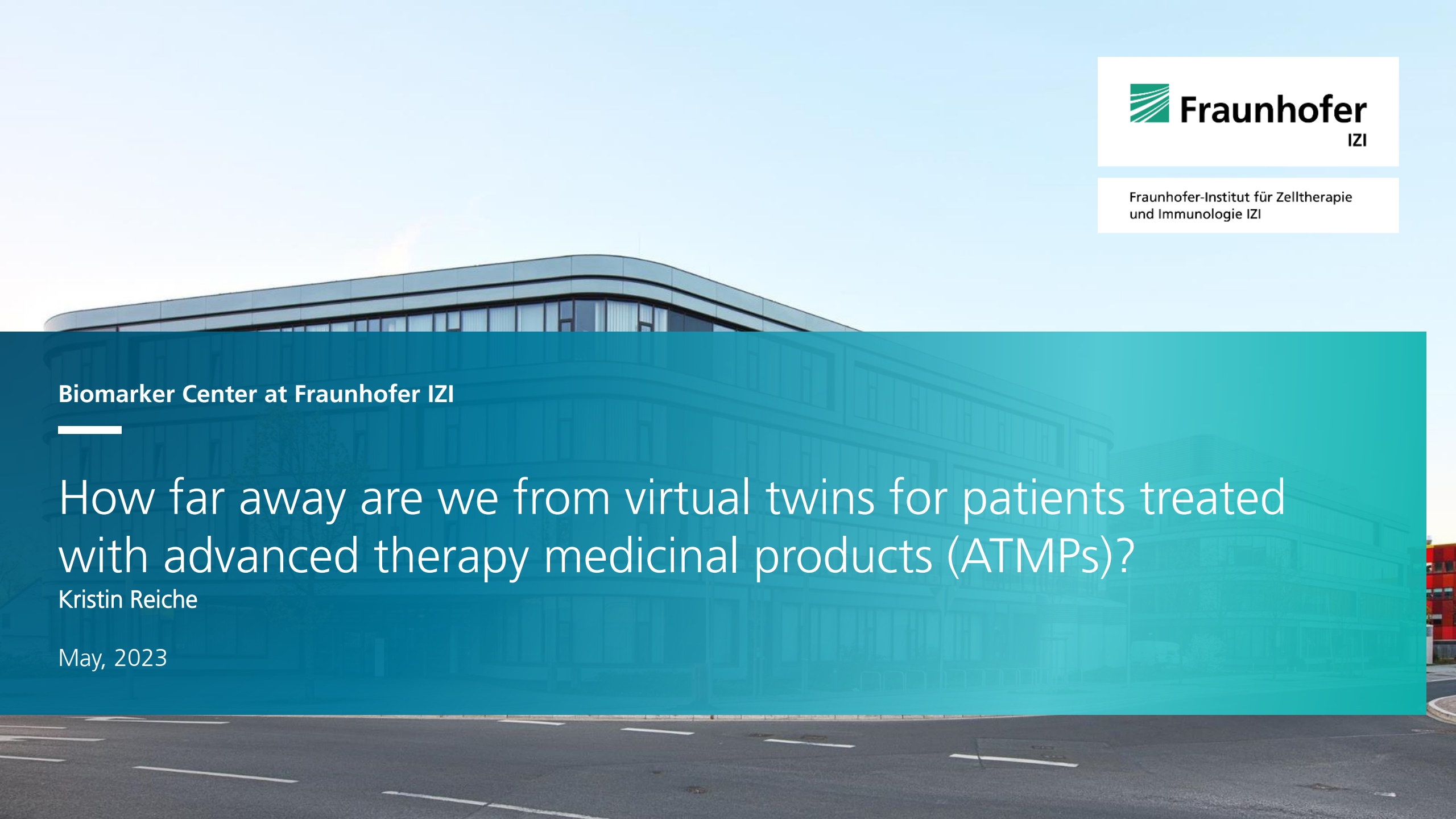

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Fraunhofer-Institut für Zelltherapie und Immunologie IZI

Biomarker Center at Fraunhofer IZI

How far away are we from virtual twins for patients treated with advanced therapy medicinal products (ATMPs)?

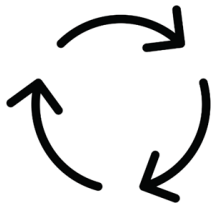
Kristin Reiche

May, 2023

Virtual Twins for patients receiving ATMPs as therapy

Components?

patient



periodic data analysis and feedback

Virtual twin

?

?

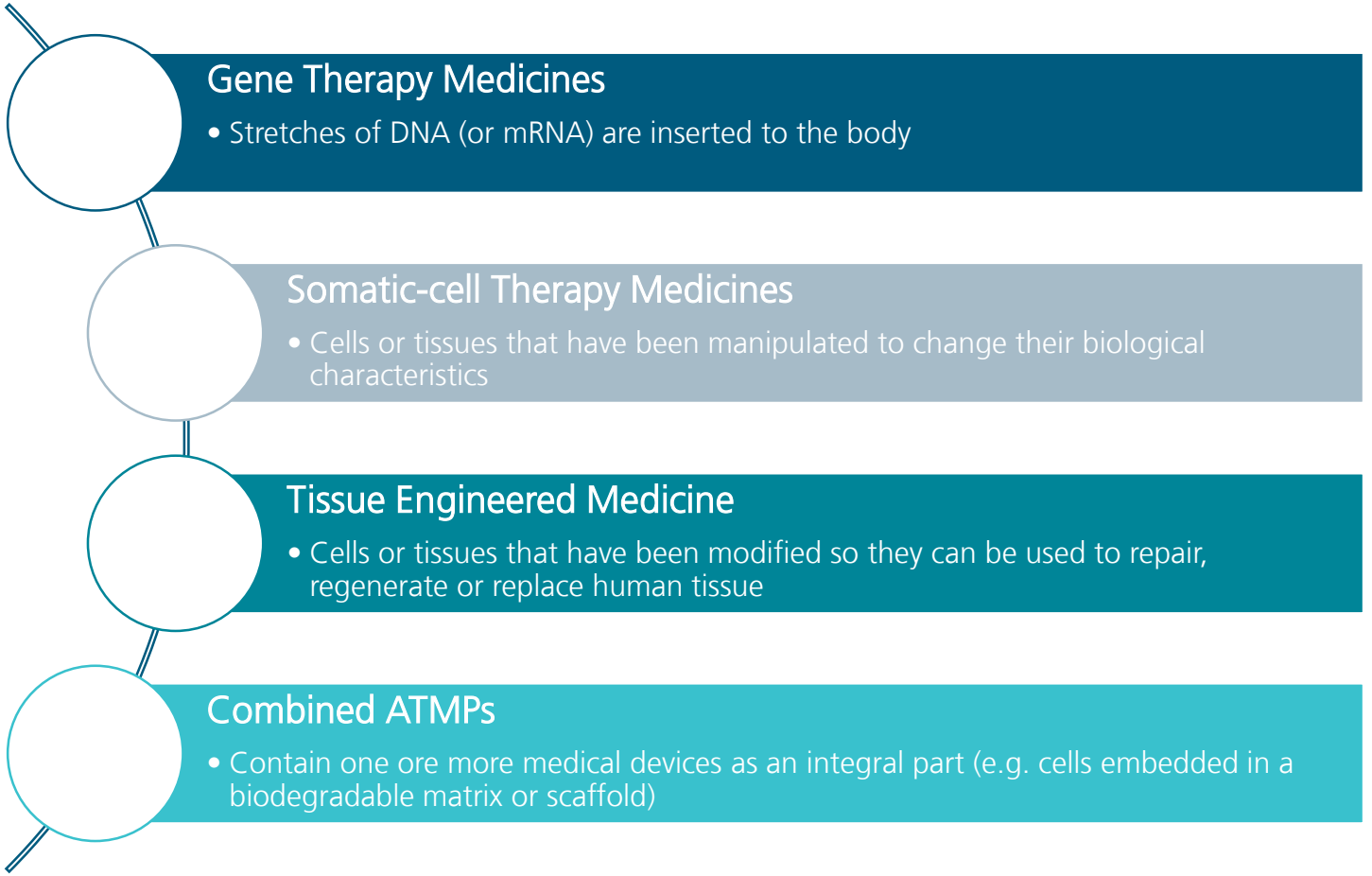
?

Advanced Therapy Medicinal Products (ATMPs)

Definition according to EMA

ATMPs are medicines for human use that are based on **genes, tissues or cells**.

They offer groundbreaking new opportunities for the treatment of diseases and injury

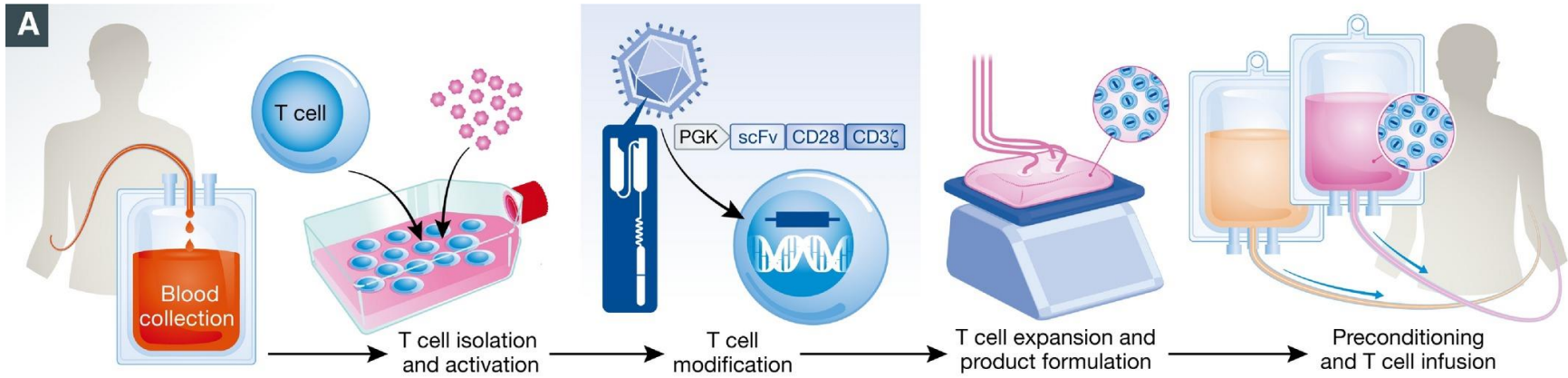


ATMP = advanced therapy medicinal products | EMA = European Medicines Agency

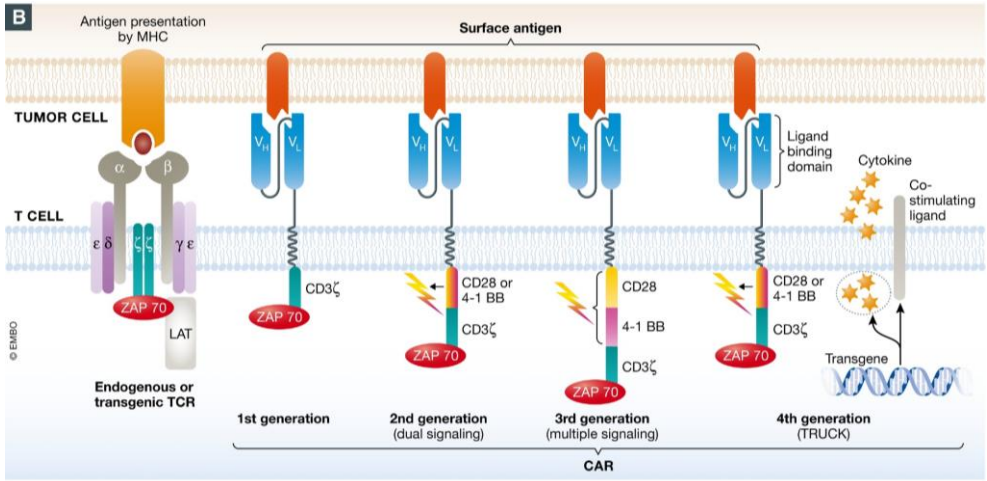
https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview

CAR T Cell Therapies – A new type of Immunotherapy

CAR T Cell Therapies are Gene Therapy Medicinal Products (GTMPs)



- Genetically modified T lymphocytes:
  - Autologous CAR T cells: patient's own T lymphocytes
  - Allogenic CAR T cells: cells from another (healthy) person
- Genetic modification: Expression of a chimeric antigen receptor (CAR) that is directed against surface components of tumour cells



EU Regulation 1394/2007 | McGrath E. & Machalik P. The Regulatory Framework for CAR-T Cells in Europe: Current Status and Foreseeable Changes and Centre Qualification by Competent Authorities and Manufacturers | Hartman et al. Clinical development of CAR T cells-challenges and opportunities in translating innovative treatment concepts. EMBO Mol Med. 2017 Sep;9(9):1183-1197

CAR T Cell Therapies

A hope for (some) cancer patients

First patient treated with CAR T-Cell Therapy

11 years cancer free

https://emilywhiteheadfoundation.org/10-years-of-car-t/

CAR T Cell Therapies

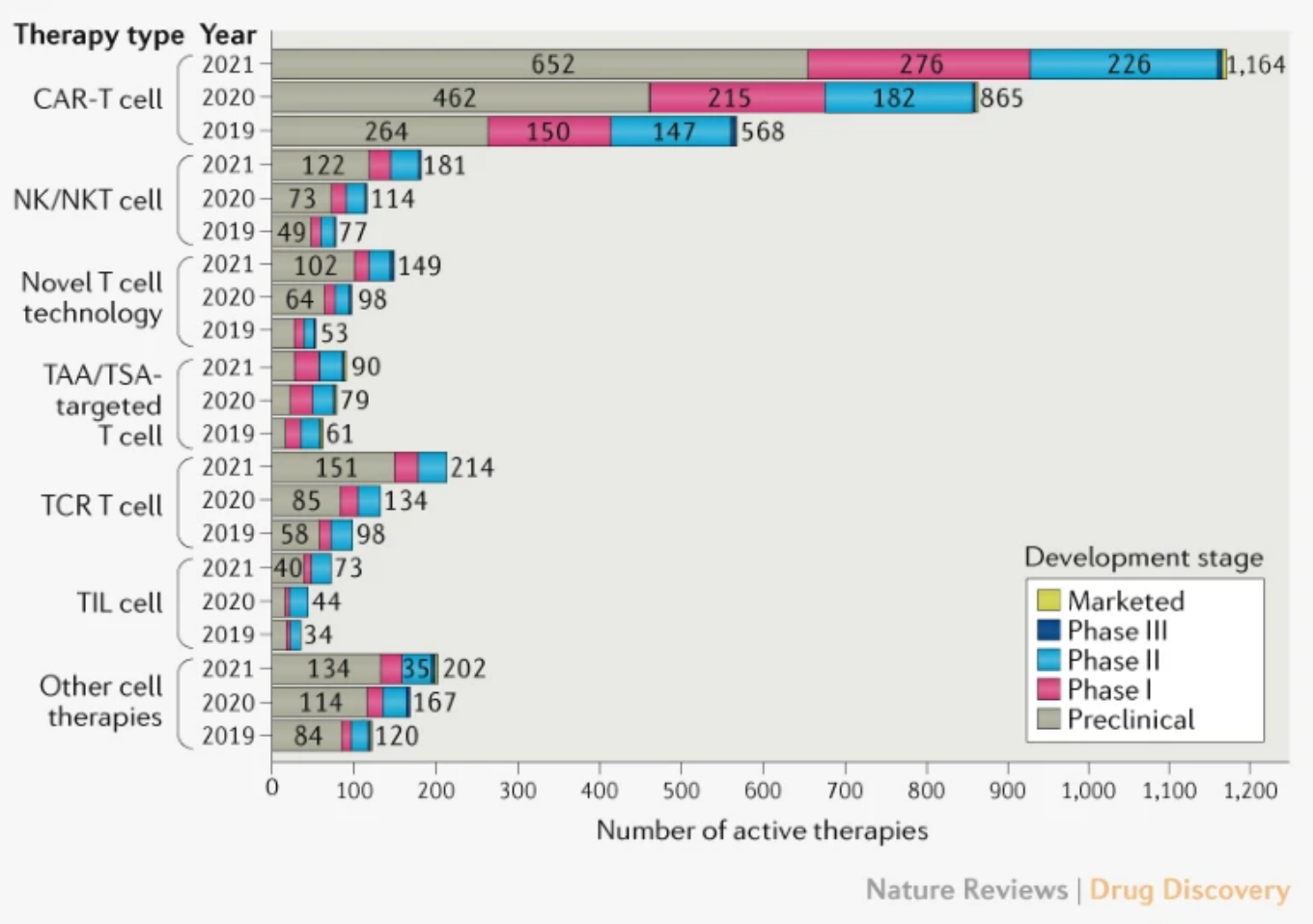
EMA approved products: 6

	Target antigen	Refractory or relapsed B-acute lymphocytic leukemia (<=25 years)	Refractory and relapsed B-acute lymphoblastic leukemia (> 26 years)	Follicular lymphoma	Aggressive B-cell lymphoma	Mantle cell lymphoma	Relapsed and refractory Multiple Myeloma	EMA approval in year	Company
Tisagenlecleucel (Kymriah®)	CD19	x		x	x			2018	Novartis
Axicabtagene (Yescarta®)	CD19			x	x			2018	Kite
Brexucabtagene autoleucel (Tecartus®)	CD19		x			x		2020	Kite
Idecabtagene vicleucel (Abecma®)	BCMA						x	2021	BMS
Lisocabtagene maraleucel (Breyanzi®)	CD19				x			2022	BMS
Ciltacabtagene autoleucel (Carvykti®)	BCMA						x	2022	Janssen

- Currently being developed primarily to treat refractory or relapsed leukaemia and lymphoma
- Likely to be also used to treat solid tumour

CAR T Cell Therapies

Number of active cancer cell therapies



- Among different types of cell therapy clinical trials, majority of trials cover CAR T cell therapies
- In 2021 more than 1000 CAR T cell clinical trials
- Most use autologous cells (twice as much as allogenic cells)
- CD19, CD22 and BCMA are the top targets for hematological malignancies
- For solid tumours: most TAAs are undisclosed, followed by HER2, EGFR, GPC2/3

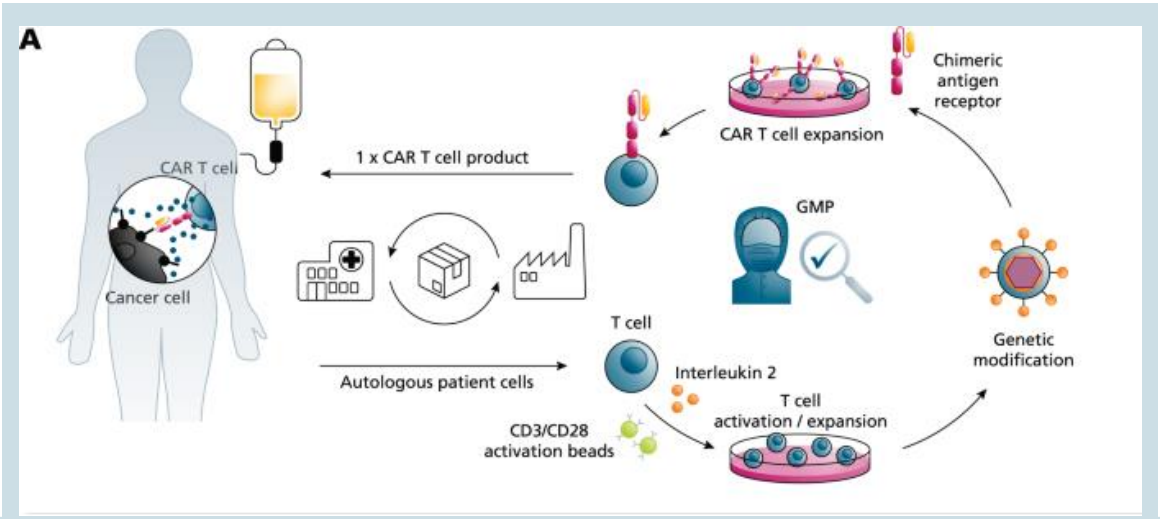
Upadhaya et al. 2021 The clinical pipeline for cancer cell therapies

TAA = tumor-associated antigen

CAR T Cell Therapies – Line of Therapy and Manufacturing

A hope for (some) cancer patients

Manufacturing of autologous CAR T cells



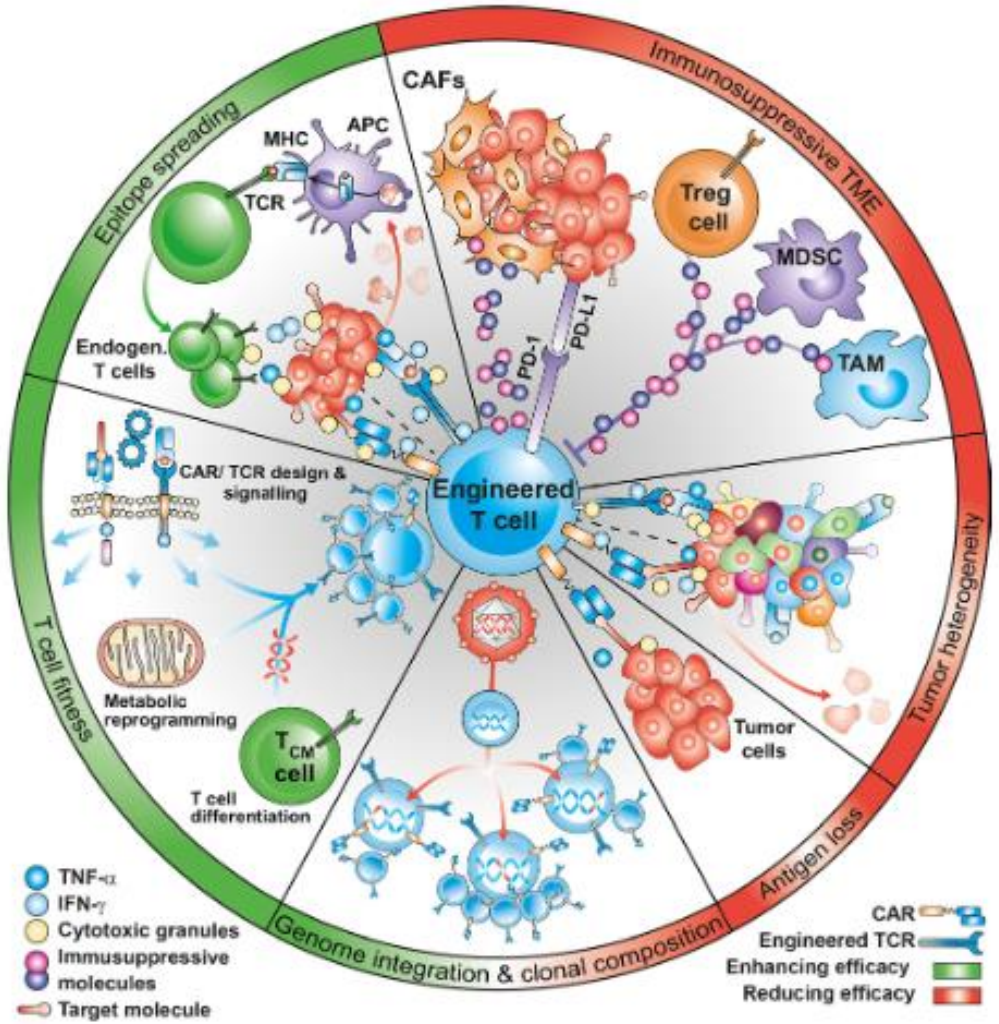
Diagnosis → Several lines of therapy → CAR T cell therapy → Patient monitoring (AEs, antigen loss, combination therapy)

- Patients usually receive CAR T cells as late therapy (> 3rd line therapy) → immune system differs a lot from healthy status
- Complex and long manufacturing processes

Blache,…, Köhl, Fricke, Nat Commun, 2022

CAR T Cell Therapies

Factors effecting efficacy



- CAR-T or TCR-T efficacy are influenced by several factors, that can improve (in green) or worsen (in red) clinical outcomes.
- Treatment failure due to immunsuppressive TME, heterogeneity of antigen expression, loss of antigen expression
- Quality of infusion product influences optimal differentiation potential, metabolic profile, low expression of inhibitory molecules → key for mediate tumour control

Guedan S, Luu M#, … , Rade M#, Reiche K#, Rodriguez-Garcia A#, Rodriguez-Madoz JR#, Ruggiero E#, Themeli M#, Hudecek M, Marchiq I. Time 2EVOLVE: predicting efficacy of engineered T-cells - how far is the bench from the bedside? J Immunother Cancer. 2022 May;10(5):e003487.

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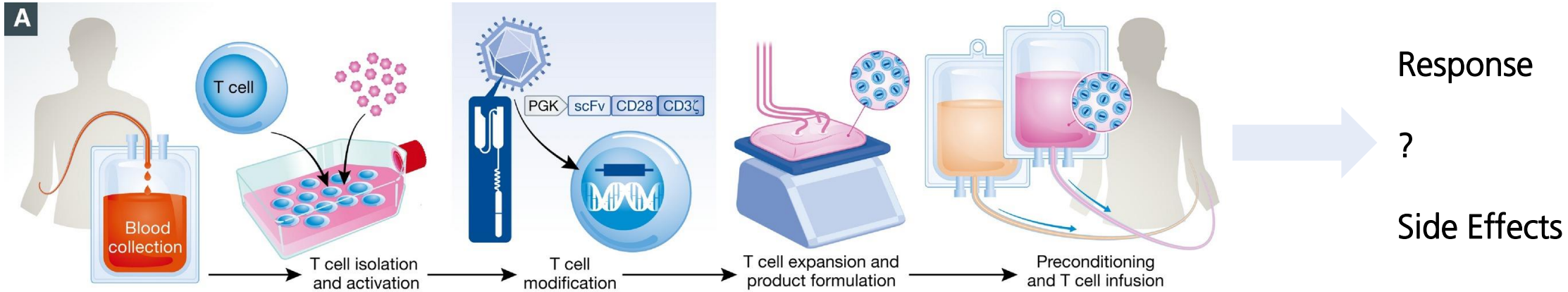
CAR T Cell Therapies

Factors effecting efficacy – CAR T cell phenotypes



Anti-CD19, B cell malignancy, n=71 (Chen et al. 2021)

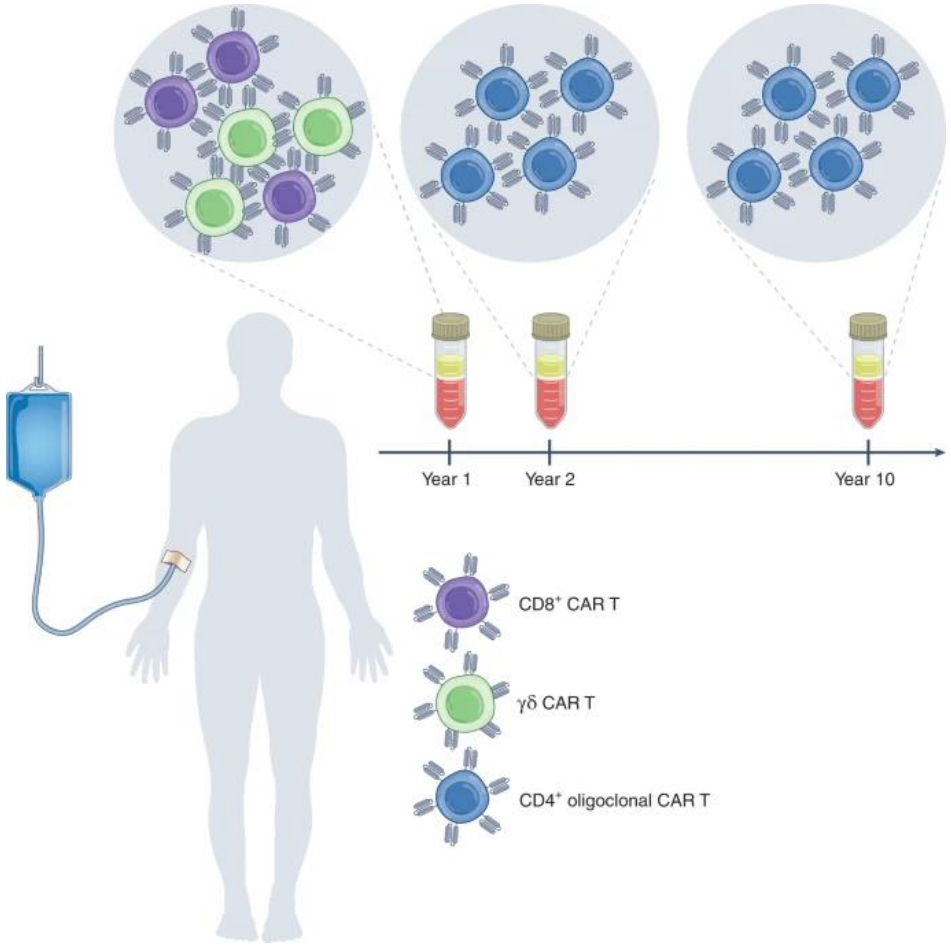
- ↑ proportion of naive and early memory CD8+ T cells ➔ longer CAR T cell persistence and greater efficacy

- ↑ proportion of memory phenotypes of CD8+ CAR T cells ➔ complete response (Fraietta 2018, Deng 2020, Bai 2022)
- ↑ proportion of exhausted CD8+ CAR T cells ➔ partial response or progressive disease (Fraietta 2018, Deng 2020)
- ↓ low levels of TCR clonotypic diversity ➔ partial response or progressive disease (Deng 2020)

Deng: n=24, Fraietta: n=41, Bai: n=12; (all anti-CD19 CAR T, different products)

CAR T Cell Therapies

Long term persistence of CD4+ CAR T cell clones



Anti-CD19, n=2, Melenhorst et al.

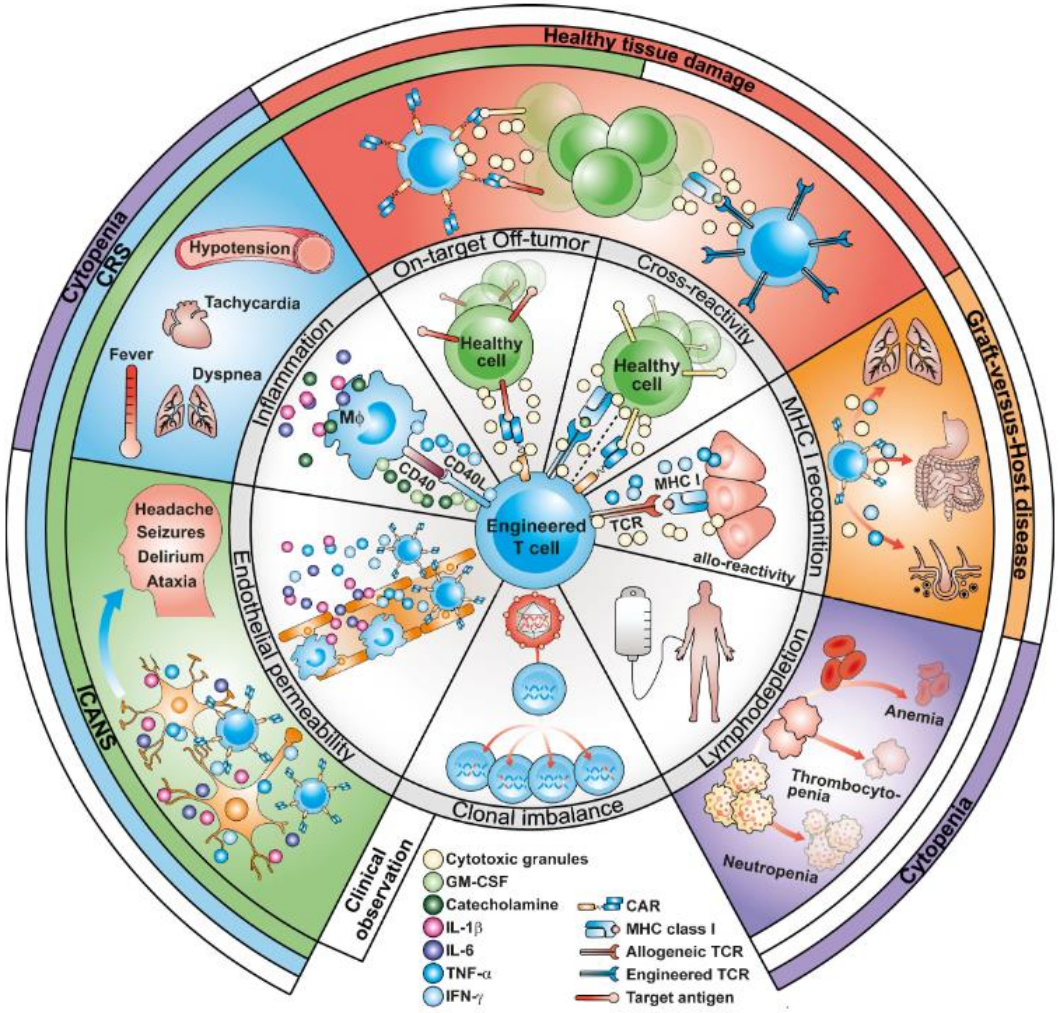
Decade long persistence of CD4+ CAR T cell clones with cytotoxic, proliferating and metabolically active phenotypes

→ Long term response **AND side effects?**

Maus. A decade of CAR T Cell evolution. Nature Cancer. Comment on Melenhorst et al. Decade-long leukaemia remissions with persistence of CD4+ CAR T cells. 2022

CAR T Cell Therapies

Factors effecting safety



- On-target off-tumor binding damages healthy tissue
- Cytopenia: Reduction in number of mature blood cells
- Cytokine Release Syndrome (CRS): Severe Inflammation
- Immune effector cell-associated neurotoxicity syndrome (ICANS): Affecting central nervous system

Donnadieu E, Luu M, Alb M#, …, Köhl U#, … , Rade M#, Reiche K#, …, Hudecek M, Casucci M. Time to Evolve: Predicting engineered-T cell-associated toxicity with next-generation models. J Immunother Cancer (JITC). J Immunother Cancer. 2022 May;10(5):e003486.

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CAR T Cell Therapies

Factors effecting safety – ICANS

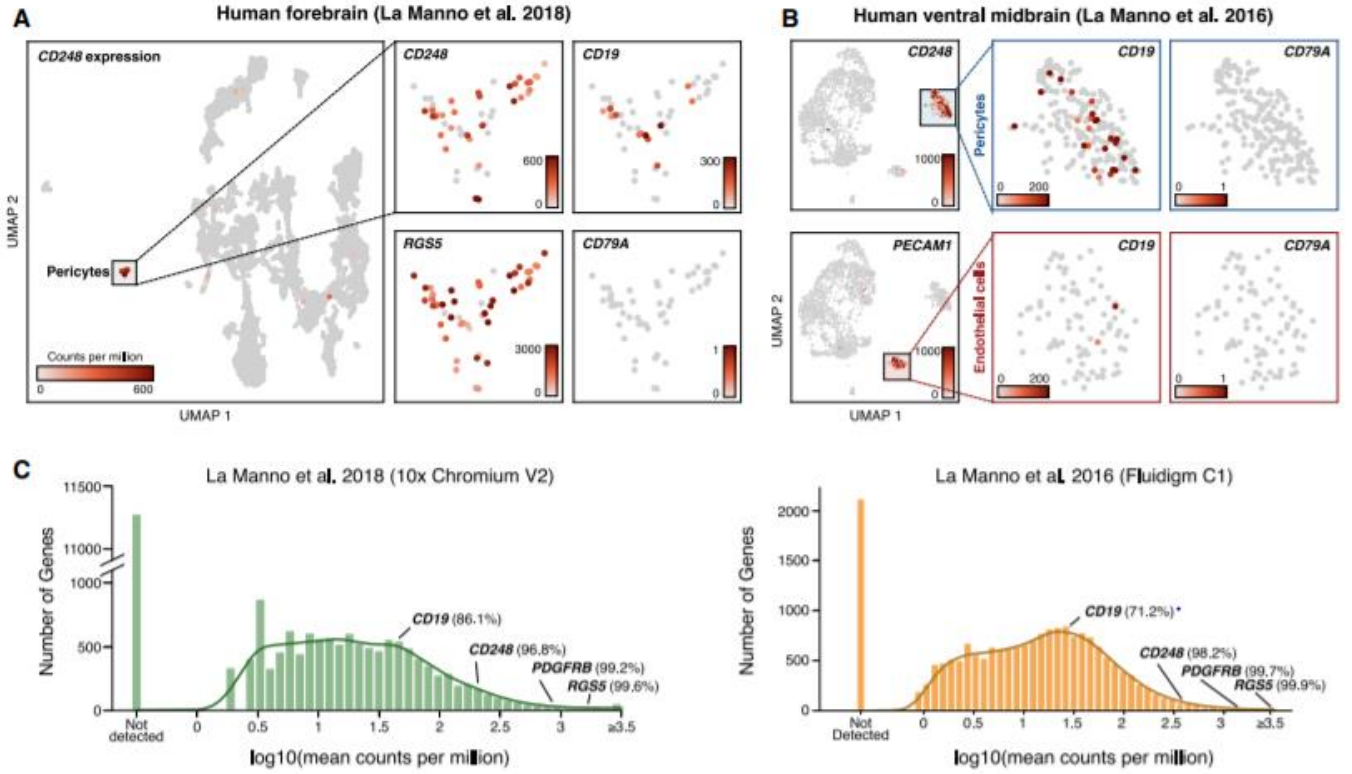

Figure 2. Confirmation of Mural Cell *CD19* Expression in Two Independent Datasets

(A and B) UMAP plots showing single-cell RNA-seq data from (A) human forebrain (La Manno et al., 2018) and (B) human ventral midbrain (La Manno et al., 2016), colored by gene-expression value, showing *CD19* expression in pericytes.

(C) Histogram of mean gene-expression values (log_{10} counts per million) in identified pericyte cells in La Manno et al. (2018) and La Manno et al. (2016). Relative gene-expression percentiles are shown for indicated genes.

- Single-cell RNA-Seq analyses revealed that mural cells surrounding the endothelium (that are critical for blood-brain-barrier integrity) express CD19

→ on-target off-tumor effect (Parker et al. 2020)

ICANS = Immune Effector Cell Associated Neurotoxicity

Parker et al. Single-Cell Analyses Identify Brain Mural Cells Expressing CD19 as Potential Off-Tumor Targets for CAR-T Immunotherapies. Cell. 2020

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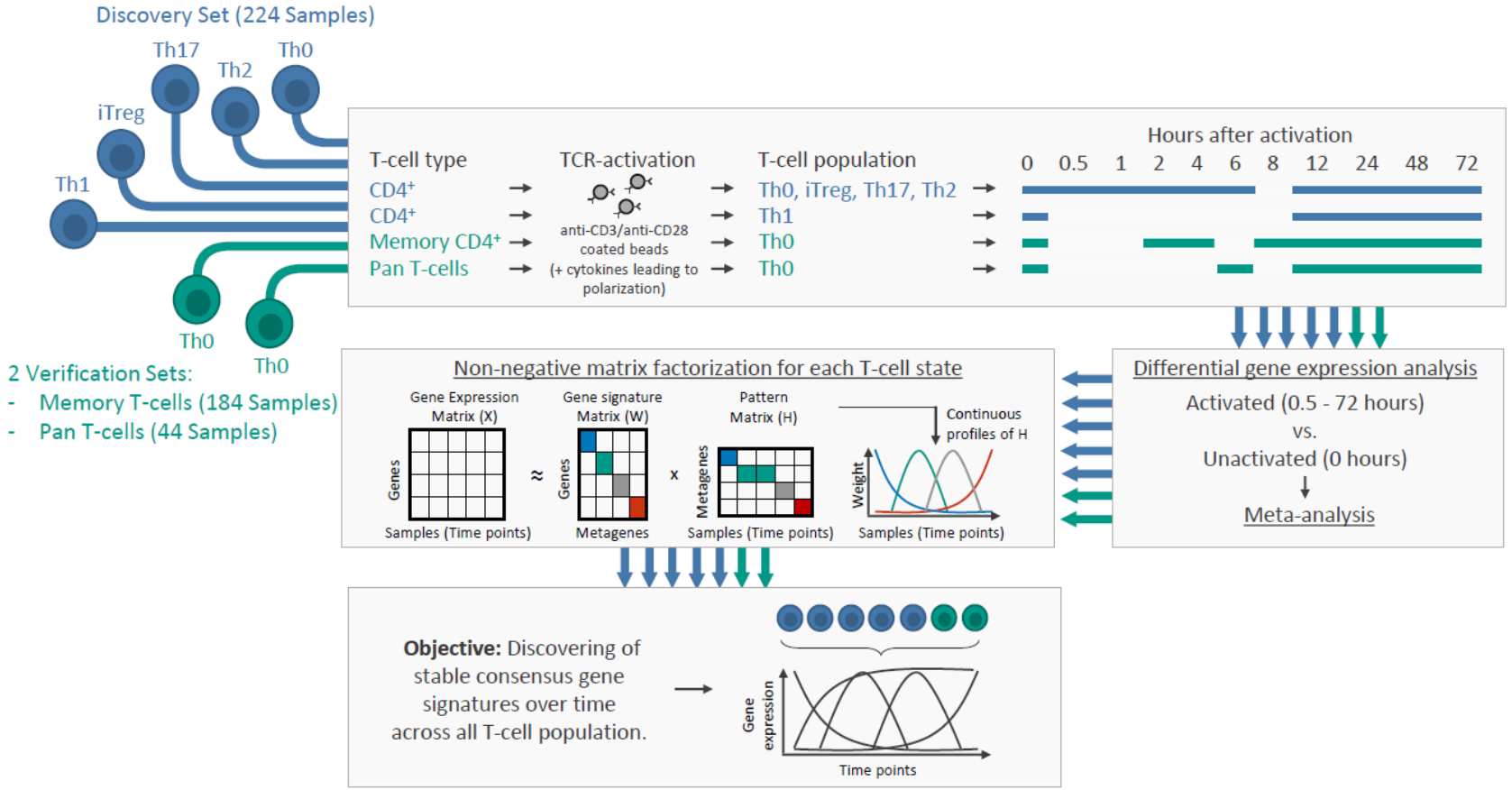
Re-analysis of data scRNA-Seq data of autologous anti-CD19 CAR T-cell infusion products from 24 patients with LBCL (Deng et al.)

A time-resolved meta-analysis of consensus gene expression profiles during human T-cell activation



Michael Rade et al. A time-resolved meta-analysis of consensus gene expression profiles during human T-cell activation. bioRxiv, 2023

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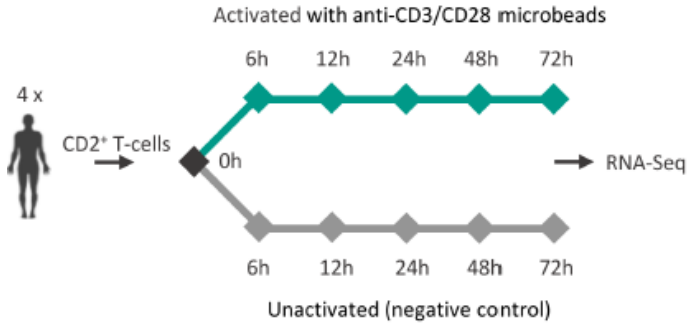
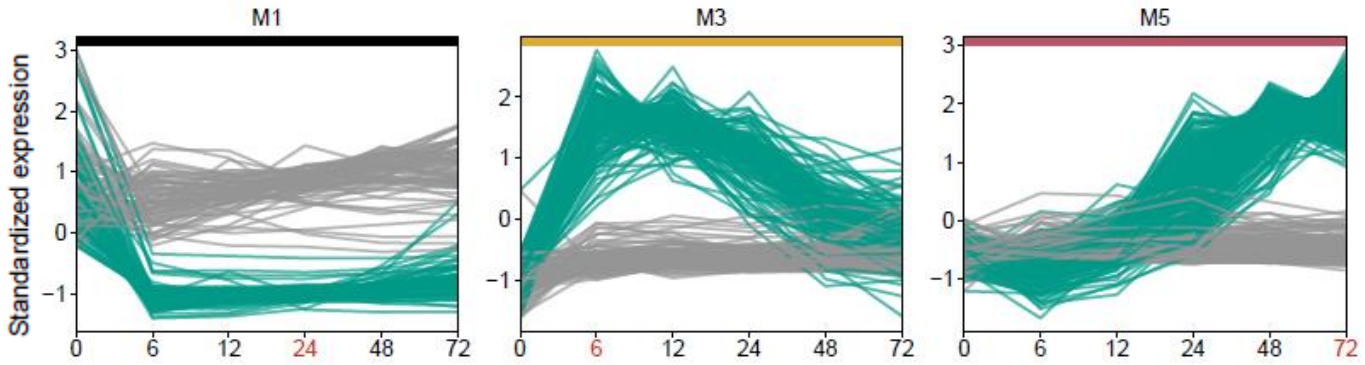
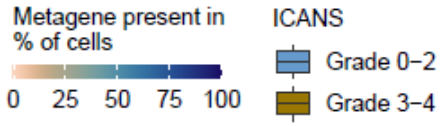
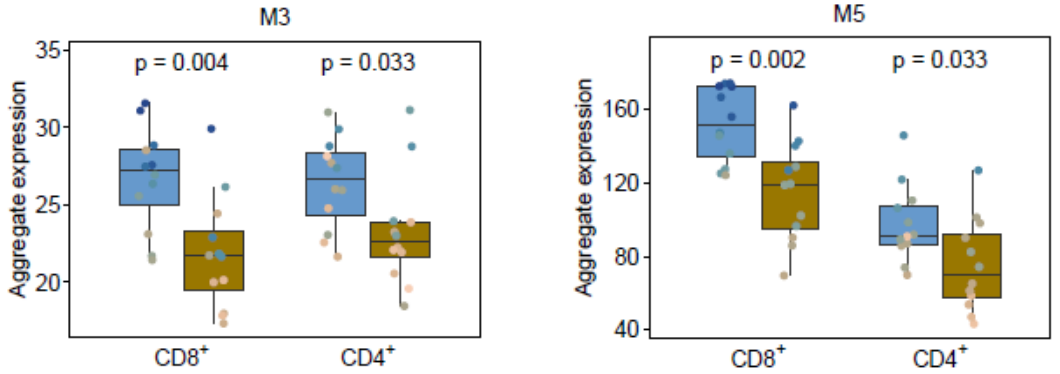




Metagenes M3 and M5 are associated with low-grade ICANS





Michael Rade et al. A time-resolved meta-analysis of consensus gene expression profiles during human T-cell activation. bioRxiv, 2023

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How is this all related to VTs for patients receiving ATMPs?

VT = Virtual Twin

CAR T cell therapies / cellular immunotherapies are „living drugs“

Compared to conventional therapies, cellular immunotherapies have the speciality that the treatment itself is a complex and stochastic “living” system.

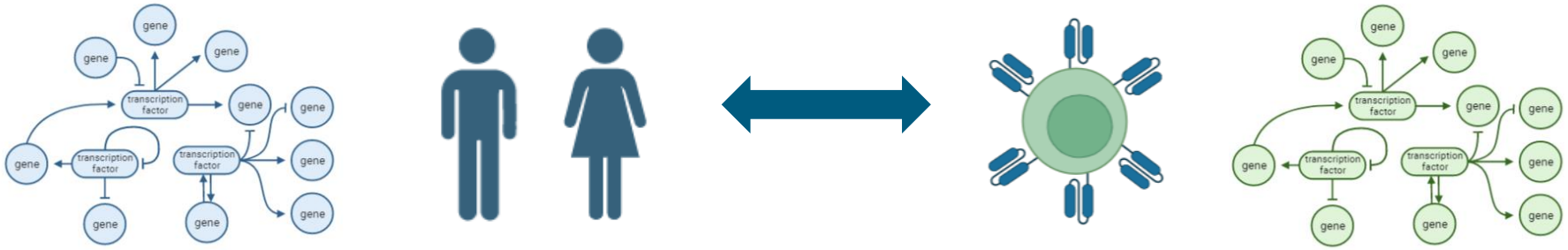
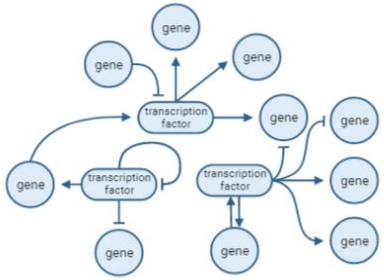
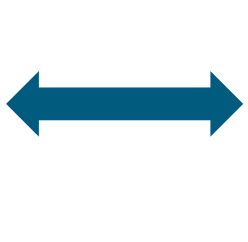
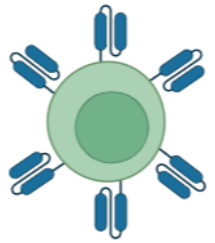


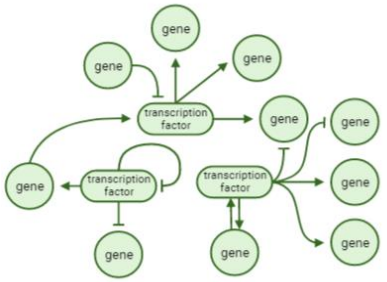
Figure created with Biorender.com

Towards Virtual Twins for patients receiving cellular immunotherapies









Description of Status & Response to Cell Therapy
Genetics (e.g. genotoxicity)
Intra-Cellular / Molecular / Surfaceome
Inter-Cellular / Cell-cell communication
Tissue
Organ
Body

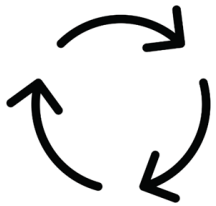
Description of Cell Product
Genetics
Molecular
Surfaceome
(Changes due to) Interaction with Host
Inter-Cellular / Cell-cell communication
Tissue
Organ

Figure created with Biorender.com

Virtual Twins for patients receiving cell-based ATMPs as therapy

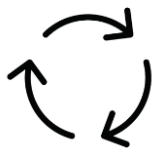
Components

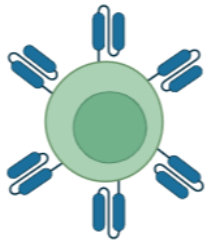
patient



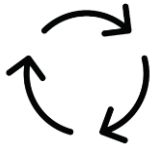
periodic data analysis and feedback

Virtual twin





Digital Twin(s) for modified immune cells



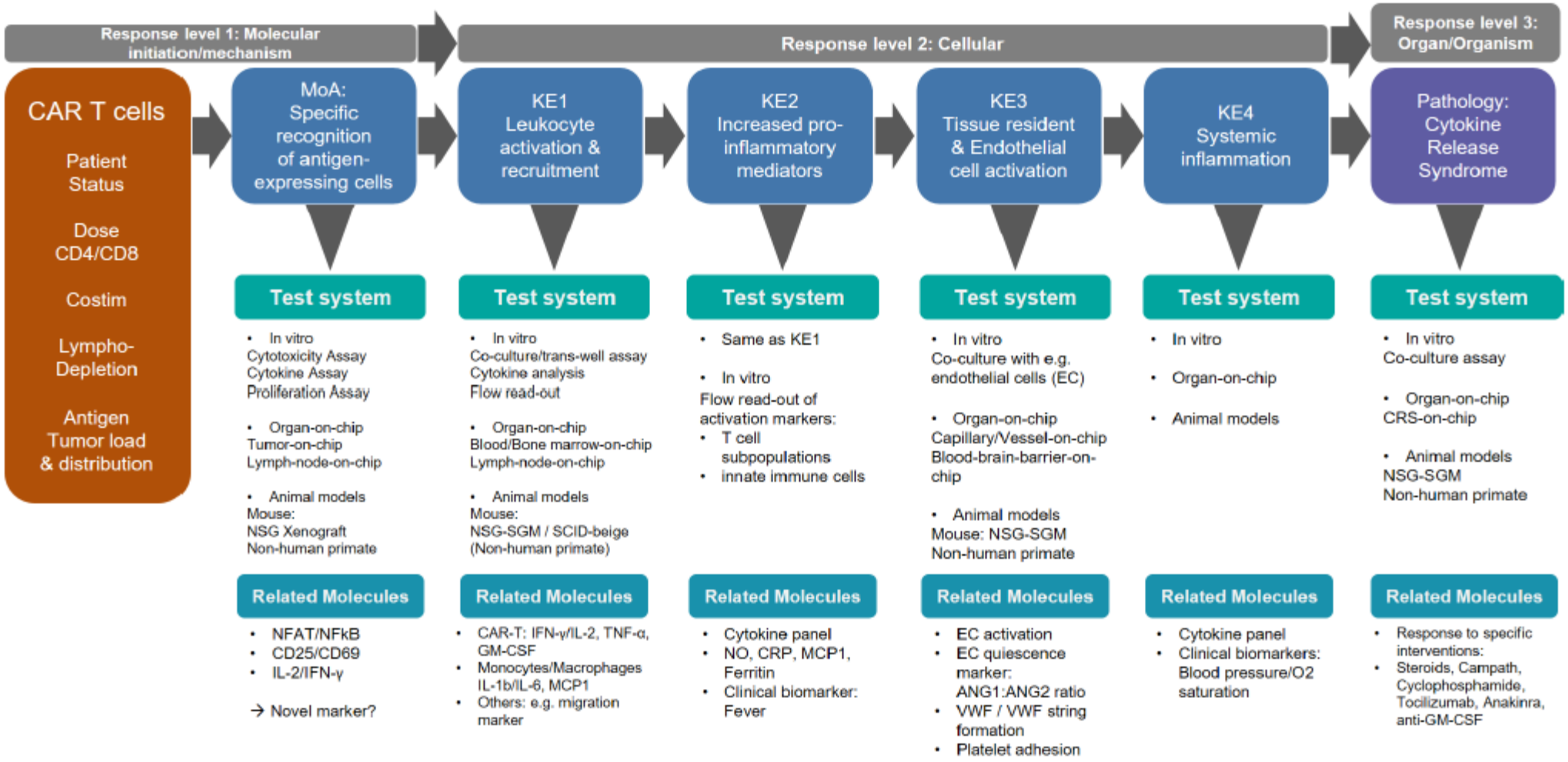
Digital Twins for organs of patient
(incl. immune system AND normal tissue)

Very first steps towards modules for VTs for patients receiving ATMPs

VT = Virtual Twin

Modelling side effects using irAOPs

imSAVAR



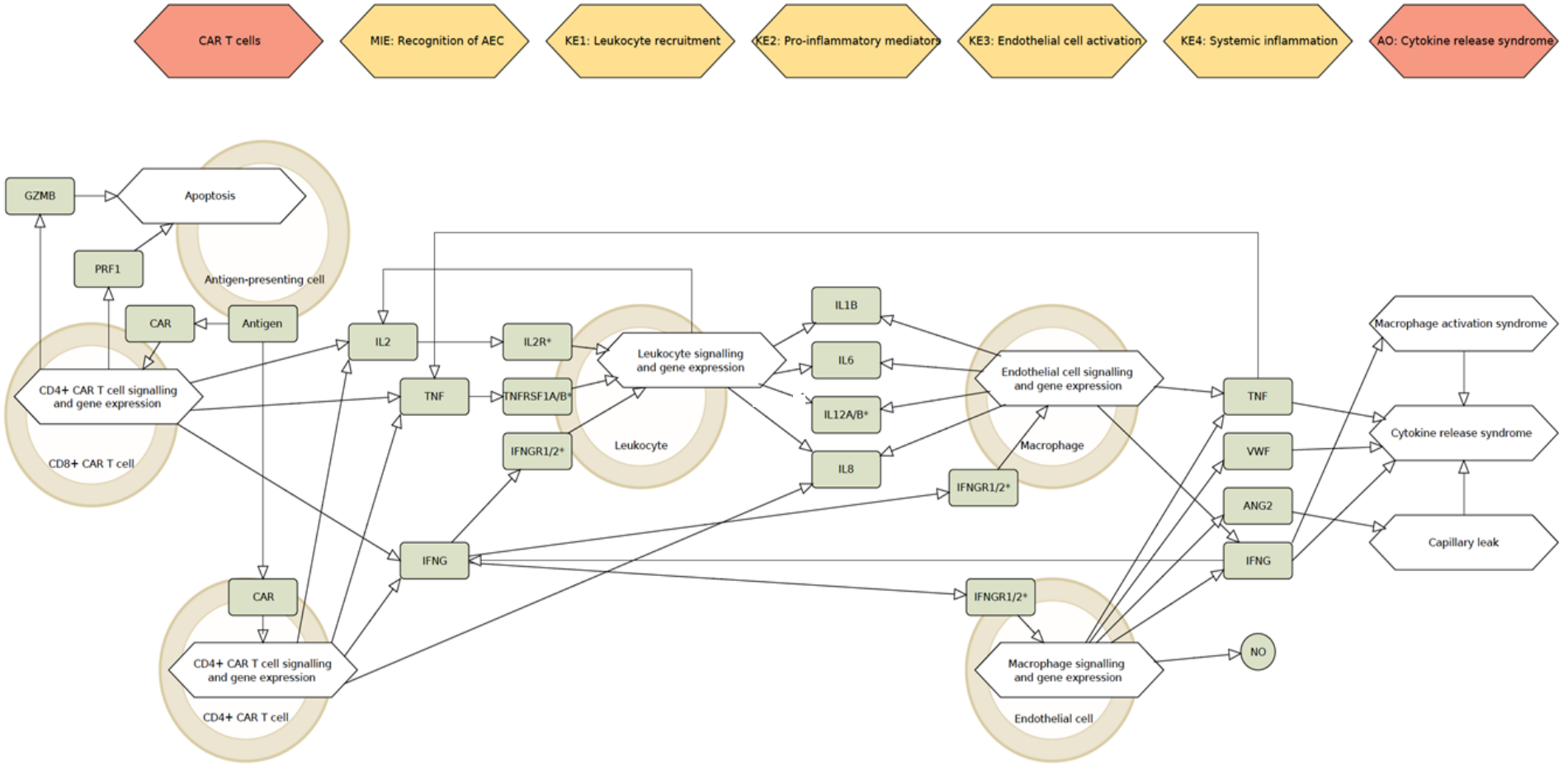
irAOP = immune-related adverse outcome pathway

Alb et al. The imSAVAR consortium

Fraunhofer IZI

Modelling side effects using irAOPs

imSAVAR



Alexander Mazein et al. Using interactive platforms to encode, manage and explore immune-related adverse outcome pathways. bioRxiv, 2023

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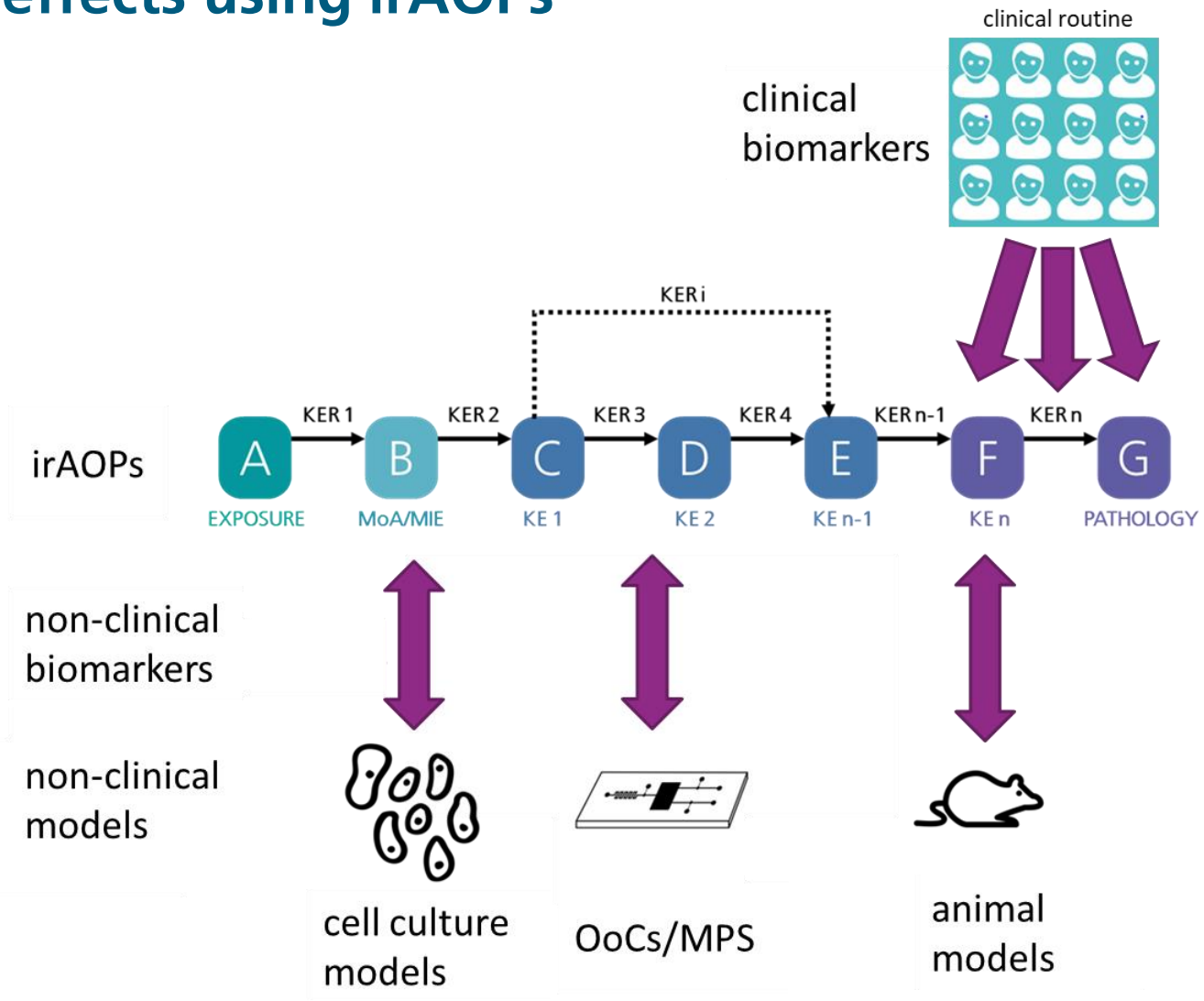
Modelling side effects using irAOPs

imSAVAR



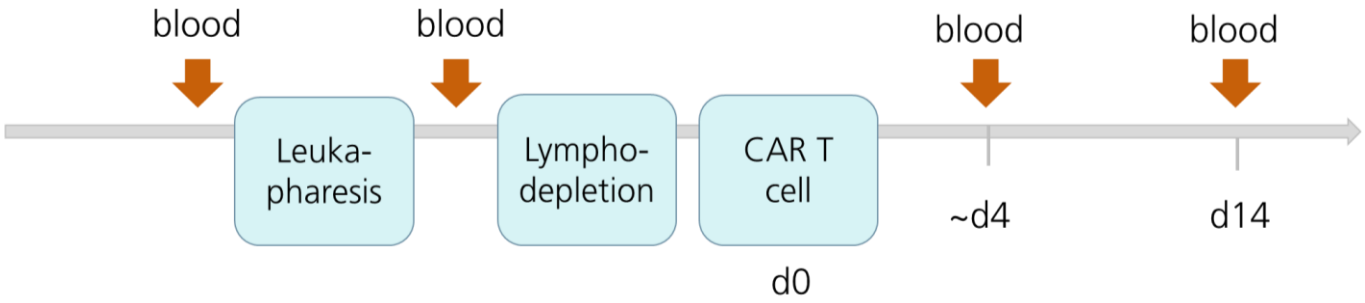
OoCs = organ-on-a-chip | MPS = microphysiological system

In-depth characterization of the immune microenvironment of patients undergoing CAR T cell therapy

Q: Which patients are at risk to develop CRS?

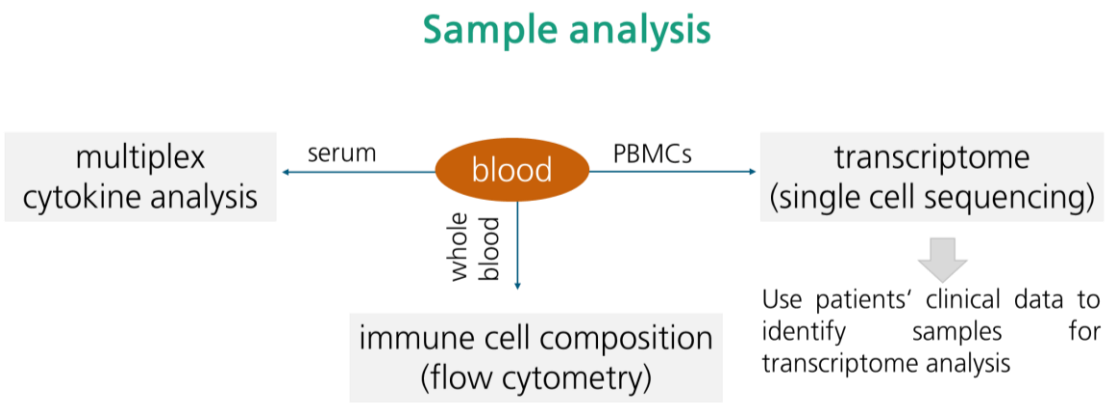
Q: How do cellular and molecular signatures differ between patients that develop irAEs and those that don't?

→Longitudinal molecular and cellular phenotyping of patients undergoing CAR T cell therapy
→Thorough characterization of microenvironment and immune cell populations before and after application of CAR T cells
→Correlate with occurence of adverse events



Weirauch et al.

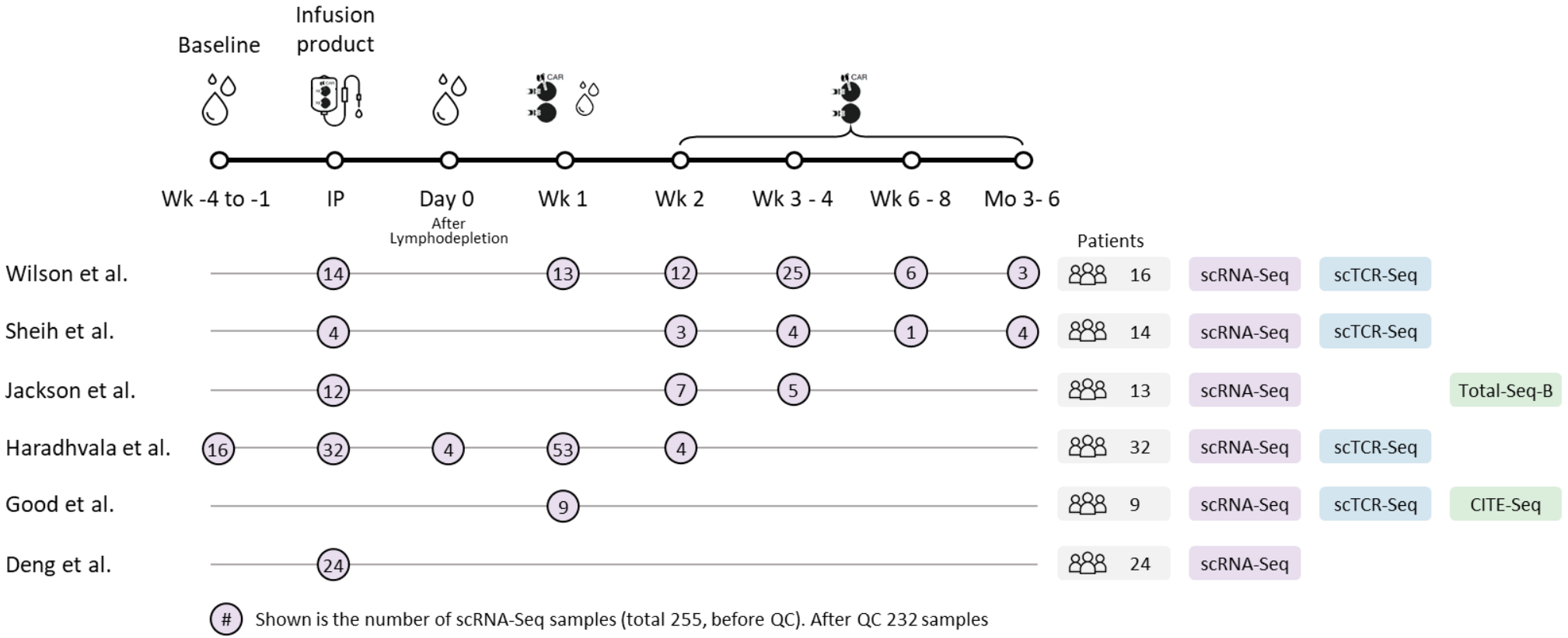
In-depth characterization of the immune microenvironment of patients undergoing CAR T cell therapy



	Center 1		Center 2		
Pat. enrolled (N)	26	%	Pat. enrolled (N)	65	%
male	18	69.2	male	41	63.1
female	8	30.8	female	19	29.2
age (mean)	63	(25-79)	age (mean)	60	(22-79)
CAR T Products/Infusions			CAR T Products/Infusions	46	
Abecma	12	46	Abecma	26	63.0
Yescarta	4	15	Yescarta	16	34.8
Tecartus	5	19	Tecartus	4	8.7
Kymriah	3	11			
Breyanzi	2	7	Tumor entity	60	
			Multiple Myeloma	34	56.7
			DLBCL	21	35.0
			MCL	4	6.7
			High Grade BNHL NOS	1	1.7

Towards a (CAR) T single Cell Atlas

Is there a significant correlation between T cell fates and clinical outcome and adverse events?



Towards a (CAR) T single Cell Atlas

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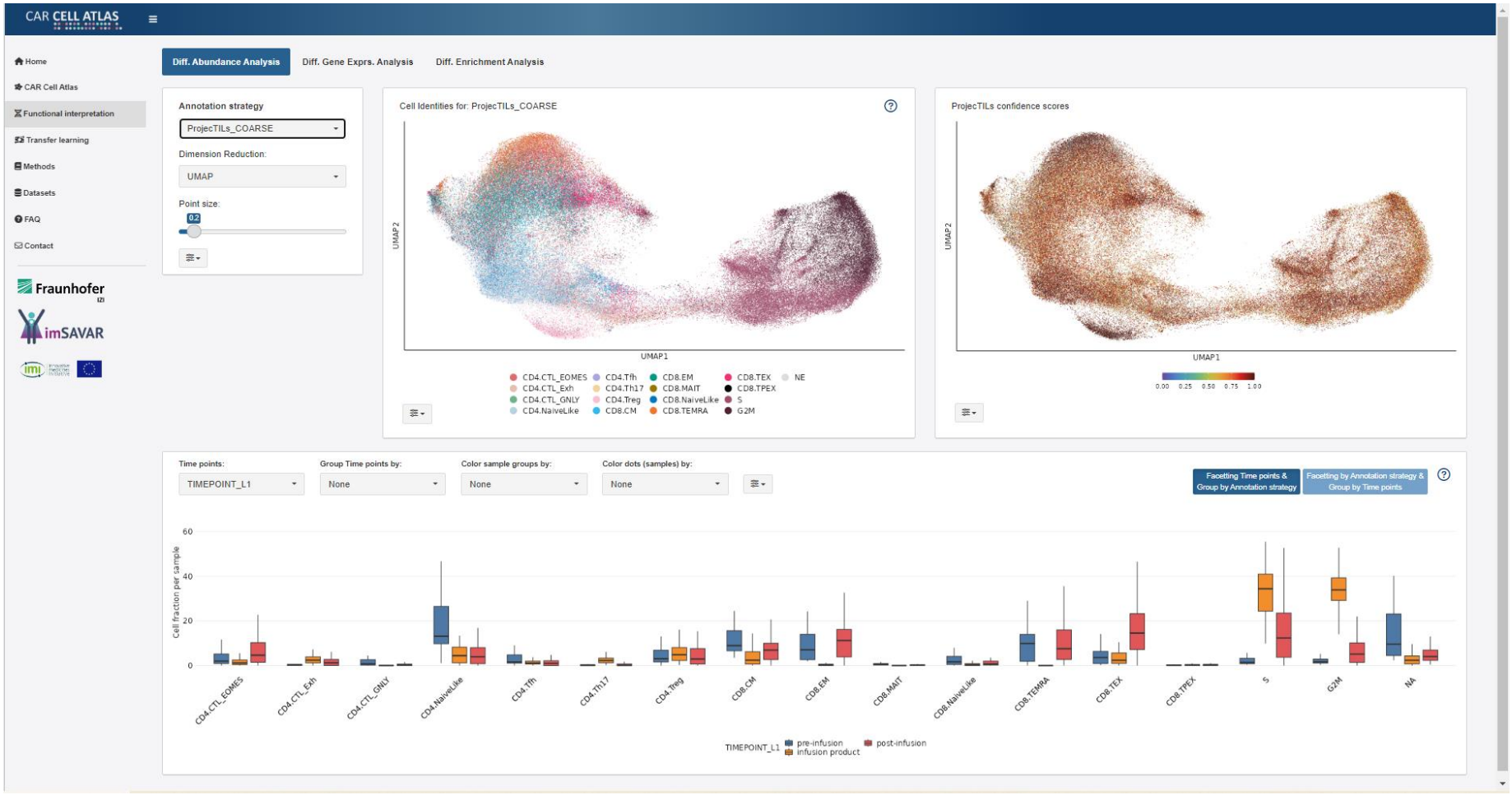
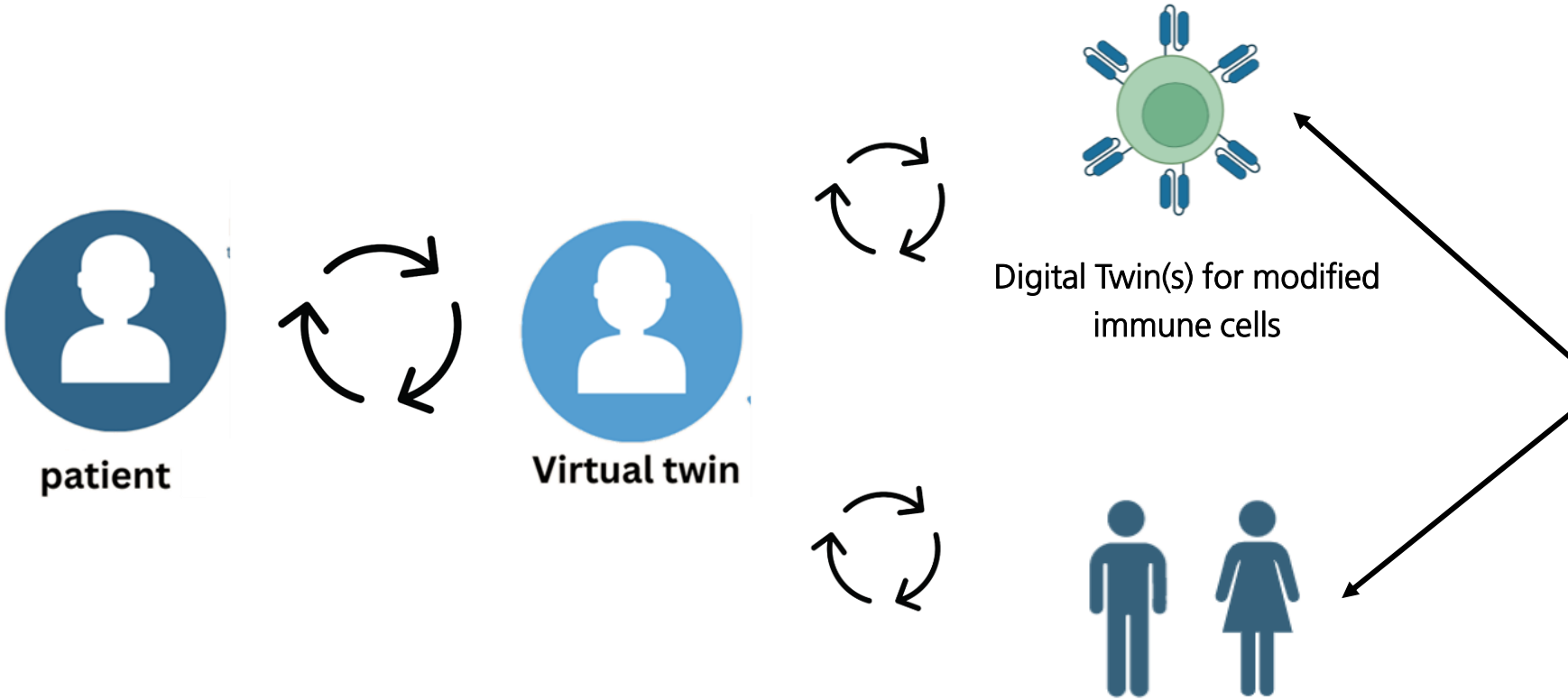
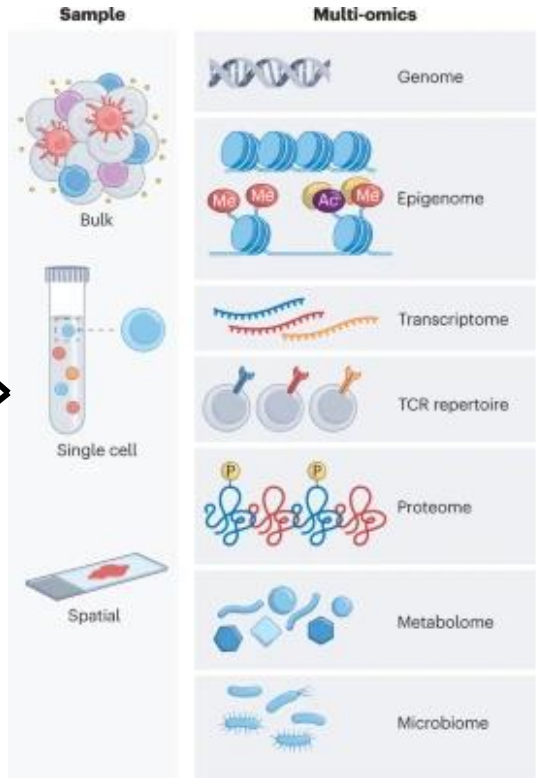


Rade et al.
Fraunhofer IZI

Virtual Twins for patients receiving cell-based ATMPs as therapy

Components





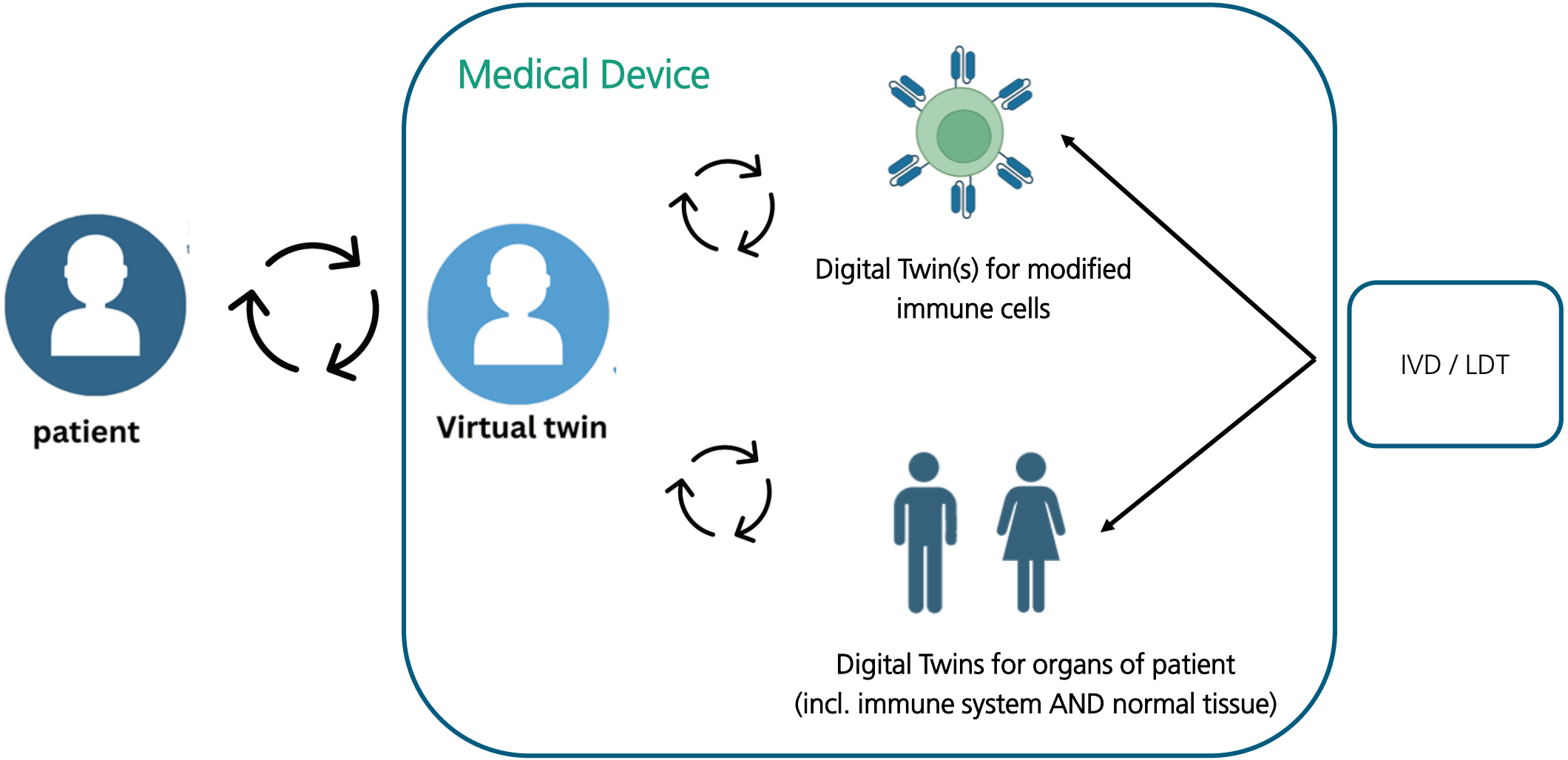
Yang et al. Advancing CAR T cell therapy through the use of multidimensional omics data. Nat. Rev. Clin. Oncol, 2023.

Software Engineering for VTs used in clinical decision making

VT = Virtual Twin

Virtual Twins for patients receiving cell-based ATMPs as therapy

VTs = Software as Medical Devices

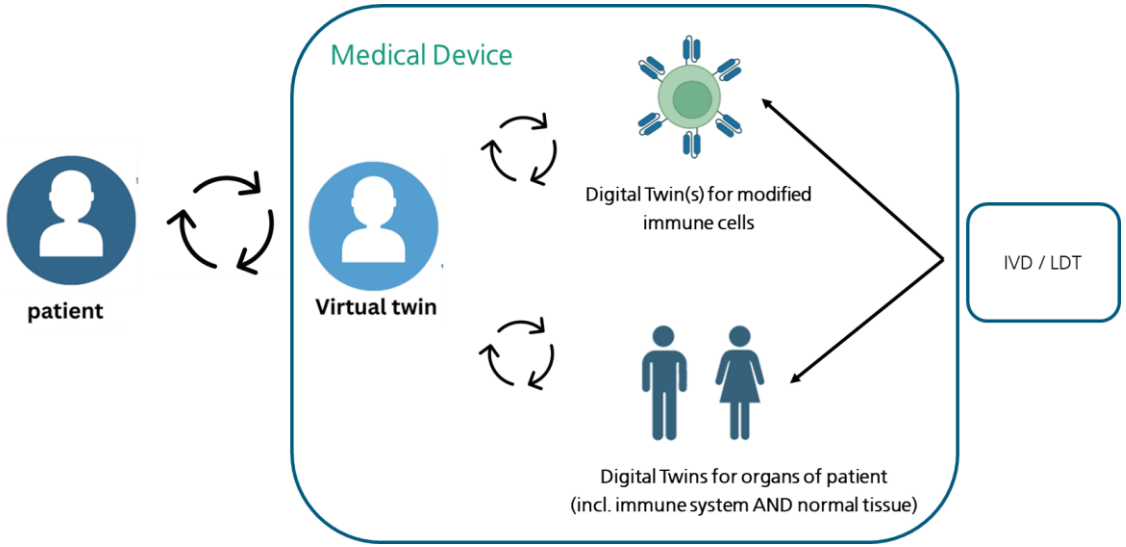


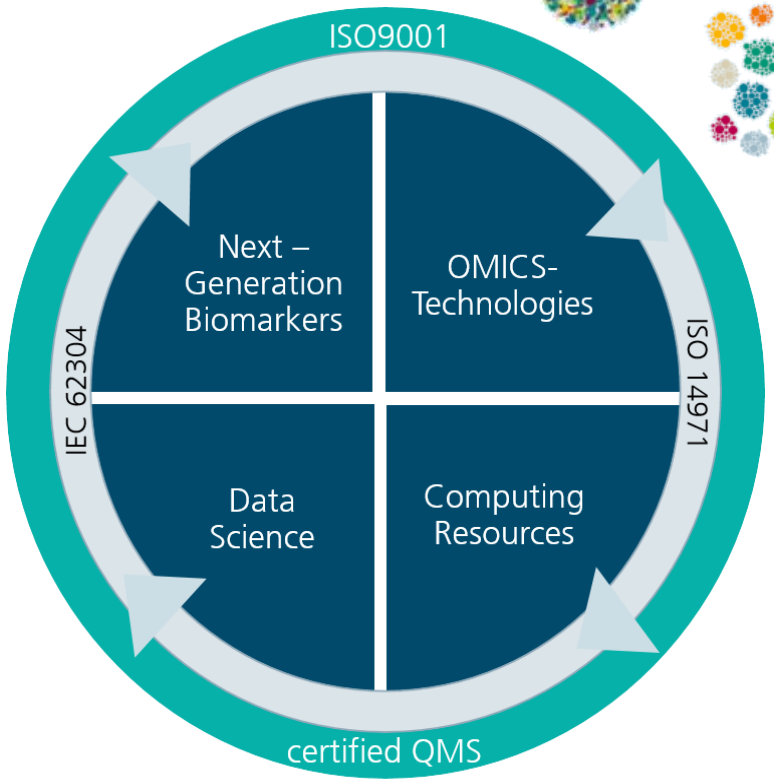
IVD = in-vitro diagnostics | LDT = lab developed test | VT = Virtual Twin

Fraunhofer IZI

Virtual Twins for patients receiving cell-based ATMPs as therapy

VTs = Software as Medical Devices





bulk/sorted cells

single cells

spatial resolution

IVD = in-vitro diagnostics | LDT = lab developed test | VT = Virtual Twin

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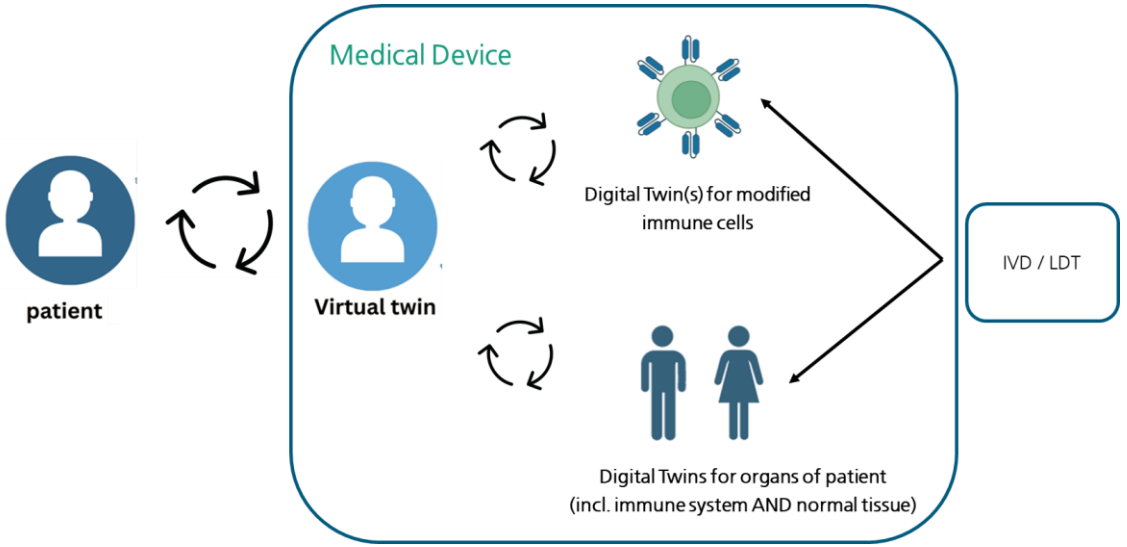
Summary – CAR T cell therapies as an example for ATMPs

- New type of cancer immunotherapy
- Mainly for haematological malignancies, but first results for solid tumours
- Limited availability: Complex and expensive manufacturing
- Efficacy and side effects depend from multiple factors
- It is a „living drug“ → Increased complexity for VTs



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- IZI: 1st European manufacturer for CAR Ts (Kymriah)
- Uni Leipzig: In 01/2023 1st clinical center providing all approved CAR T cells products to patients
- Comprehensive biobanking of longitudinal samples
- IVD and Software as Medical Device

VT = Virtual Twin

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Thank you for your attention

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