Health Technology at Fraunhofer with a special view to Living Medicine

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Institute of Clinical Immunology, University & Univ. Hospital Leipzig (UL/UKL)

Disclosure

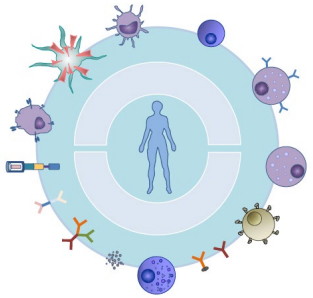
In relation to this presentation, I declare that there are no conflicts of interest

- Cooperation:
  Miltenyi Biotec (CD20-CAR-Time)
  Novartis (CTL019 European study trial & Kymriah®)
  Bristol-Myers Squibb (CAR T clinical investigational medicinal products)
  T cell Tolerance

- Consulting:
  AstraZeneca, Affimed, ATMPS, Glycostem, Zelluna, NovoNordisk

Overview

- Health Technology at Fraunhofer
- Living Drugs in Cell and Gene Therapy



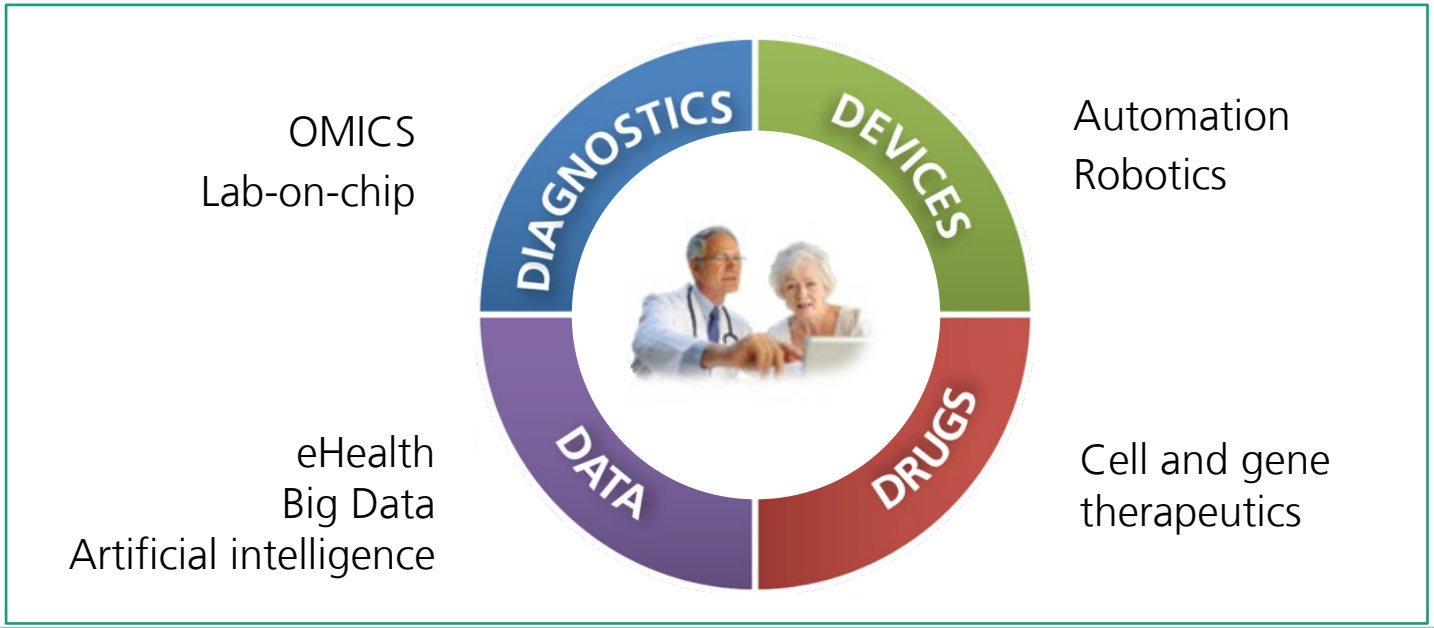
Mission – Vision – Strategy: „4D Concept“

> 45 Fraunhofer Institutes (>60%) are involved in health research (annual > 450 Mio €)

- **Mission** Translation & transfer into medical practice
- **Vision** Cost-intelligent precision medicine for affordable healthcare
- **Strategy** Transdisciplinary networking of the 4Ds - Drugs / Devices / Diagnostics / Data

Scientists

Computer scientists



Engineers

Physicians

Fraunhofer IZI

Fraunhofer „4D Concept“

Interdisciplinarity

The 4D of health research

Fraunhofer is the sole research organization capable of uniting all the essential expertise across the 4D spectrum!

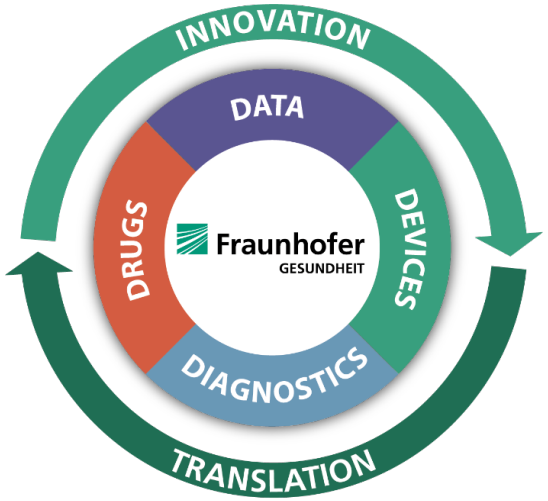
Interactions between the 4 important areas must be expanded

Fraunhofer Health Research

Individualized therapy

Transdisciplinary research:
Drugs, Devices, Diagnostics, Data

Networking at Fh Health



Medical technology

- ✓ Health
- ✓ Production
- ✓ Innovation research
- ✓ Information and communi-cations technologies (ICT)
- ✓ Sensor Technology
- ✓ Microelectronics
- ✓ Resource technologies and bioeconomy
- ✓ Materials
- ✓ Light & Surface (L&S)

Automated pharma production

- ✓ Health
- ✓ Production
- ✓ Innovation research and ICT
- ✓ Sensor Technology
- ✓ Microelectronics
- ✓ Resource technologies and bioeconomy
- ✓ Materials

Clinical research for drugs and medical devices

- ✓ Health
- ✓ ICT
- ✓ L&S
- ✓ Microelectronics

- **New drug classes /CIMD**
- **Center for Digital Diagnostics**

- ✓ Health
- ✓ ICT
- ✓ Partner institutes

Cross-networking of the 4D is an important unique selling point

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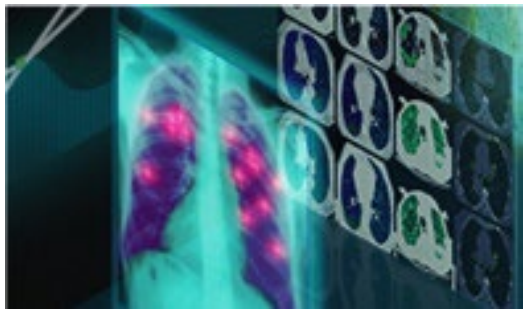
Fraunhofer Health Technology

Key Facts

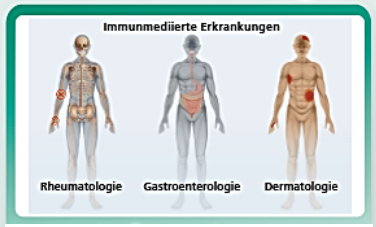
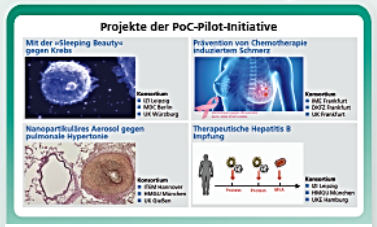
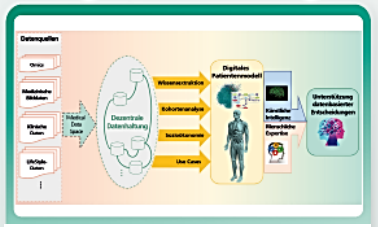
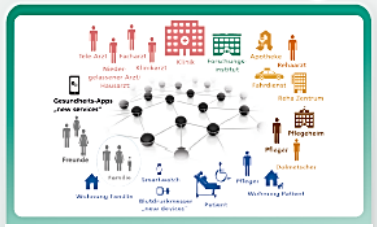
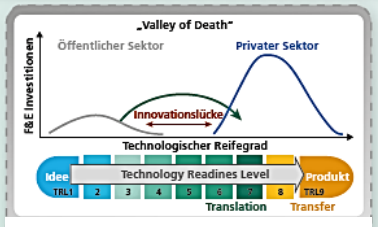
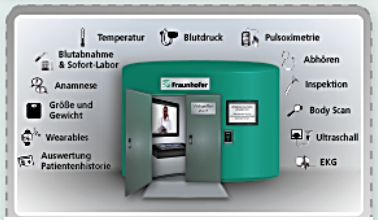
SPECTRUM	INDICATIONS	KEY POINTS
▪ Prevention ▪ Diagnostics ▪ Therapy ▪ Care	▪ Cancer ▪ Autoimmune diseases ▪ Common diseases ▪ Rare diseases	▪ Translational research ▪ Regenerative medicine ▪ Medical technology ▪ Medical informatics

STRENGTHENING RESILIENCE – Key impact for crisis management and innovative health research



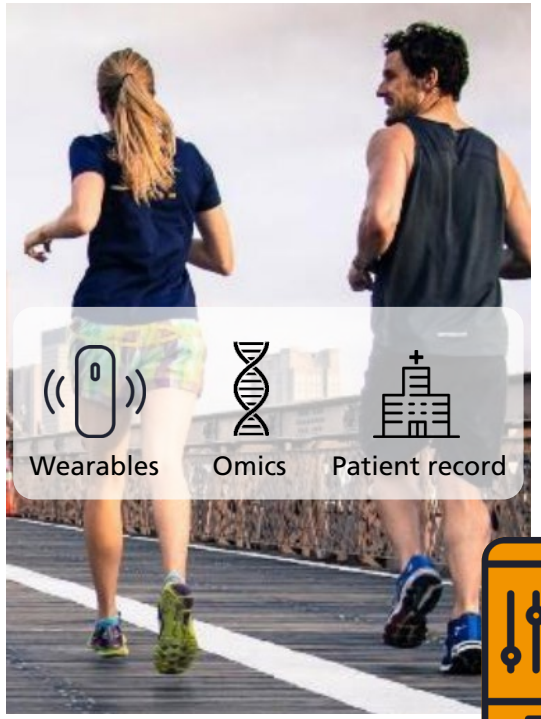



Examples of optimizing care to benefit patients

Immune diseases	Proof-of-Concept	Digital twin	Data networking	Cell therapeutics	Process technology
					
Fraunhofer Cluster of Excellence Immune-Mediated Diseases (CIMD)	Proof-of-Concept-Initiative	Fraunhofer Lead project MED²ICIN	Medical Data Space	CAR T cells	Stem cell processing technology
Decoding the immune system		**Innovation through digitalization**		**Efficiency through automation**	
					
National Alliance for Immune Diseases	PoC-platform	Digitalization for improved patient care	Virtual doctor	Pilot plant	Individualized therapies

Using health data for research

People allow… use of data… for the research… for the benefit…



- consciously
- ethically
- sovereign
- safe
- revocable

➢ of the society

- new drugs
- new technologies
- cost-intelligent medicine

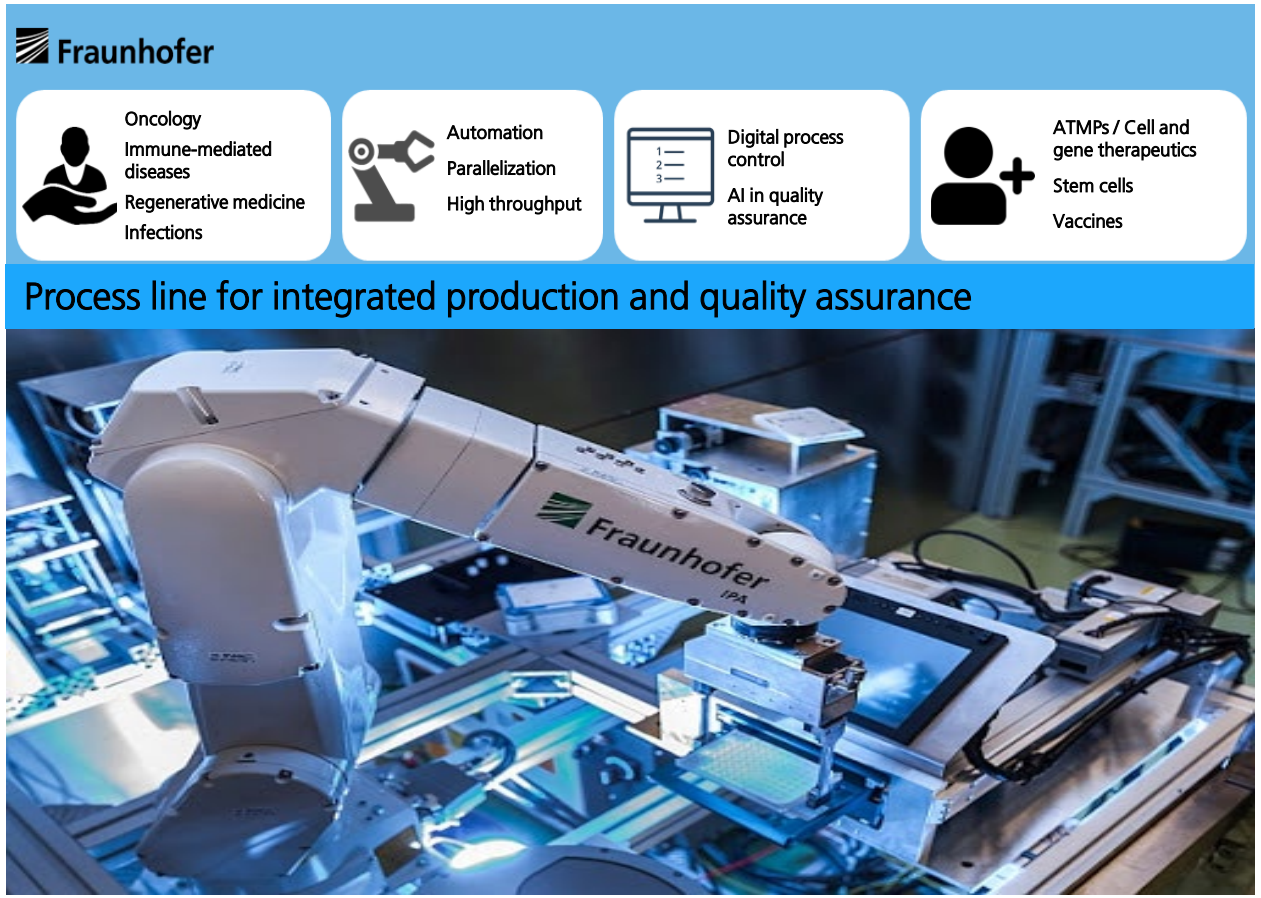
➢ for the economy

Data utilization concept for innovative health research

Example: Sovereignty for digital and automated pharma production

Fraunhofer consortium of 8 alliances

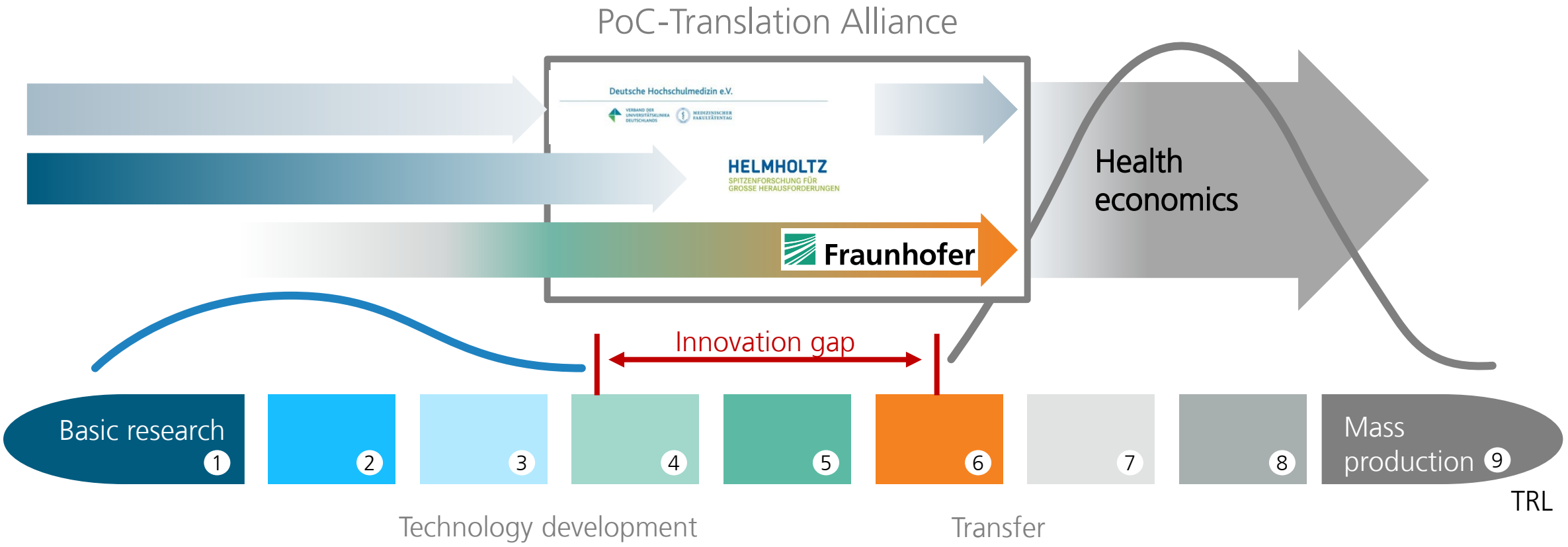
- Health
- Production
- Sensor Technology
- Materials and ICT
- Microelectronics
- Light & Surface
- Innovation
- Resource technologies and bioeconomy



Fraunhofer IZI

Closing the translation gap through strong networks

Universities & non-university research institutions & industry-academy partnerships



Fraunhofer IZI

Overview

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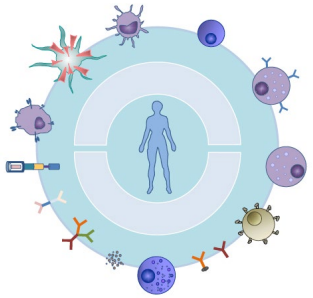
- Living Drugs in Cell and Gene Therapy

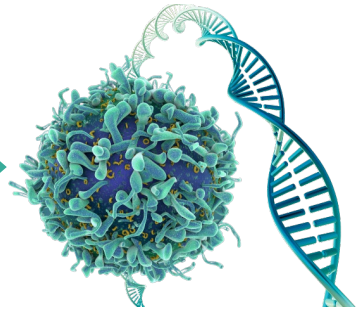


Medicine of the Future

Today
Treatment of diseases

Precision medicine

Tomorrow
Cure of diseases



- Chemical substances
- Regular intake
- Relief of symptoms

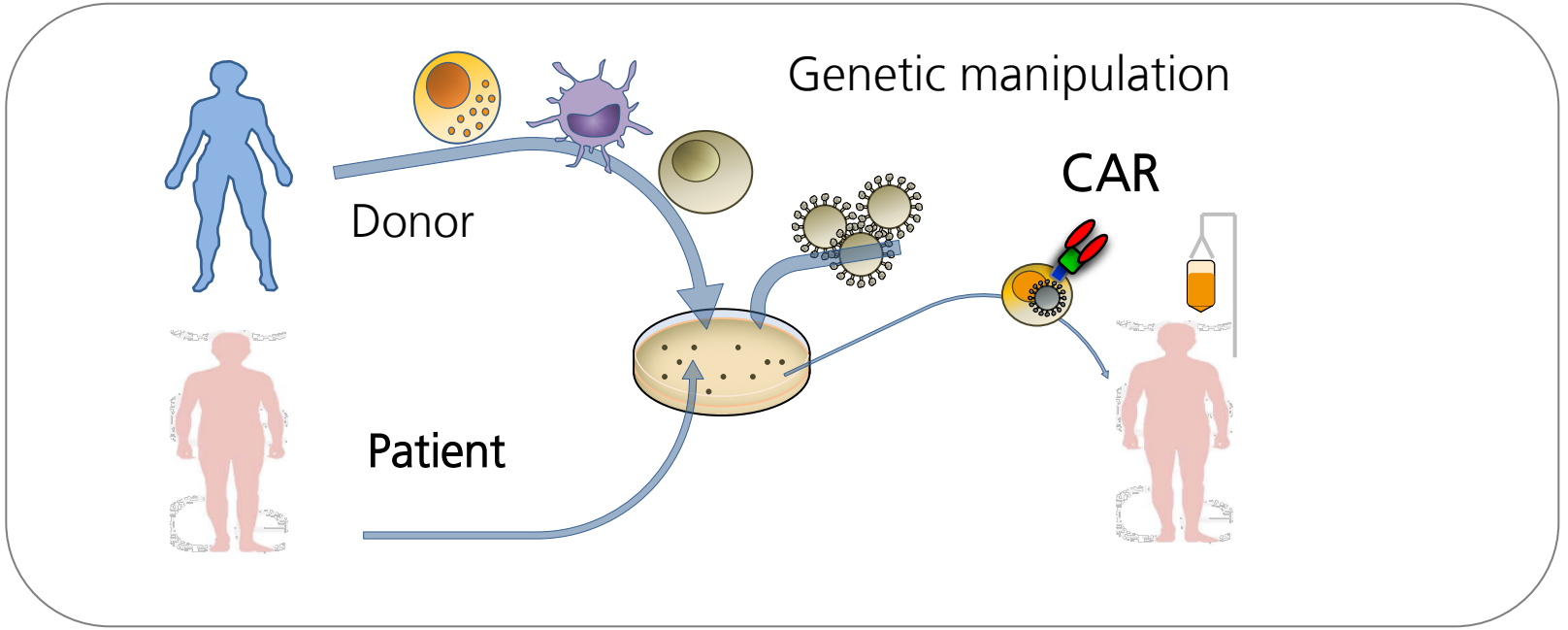
- Immunotherapies
- Cell and gene therapies (CGT)

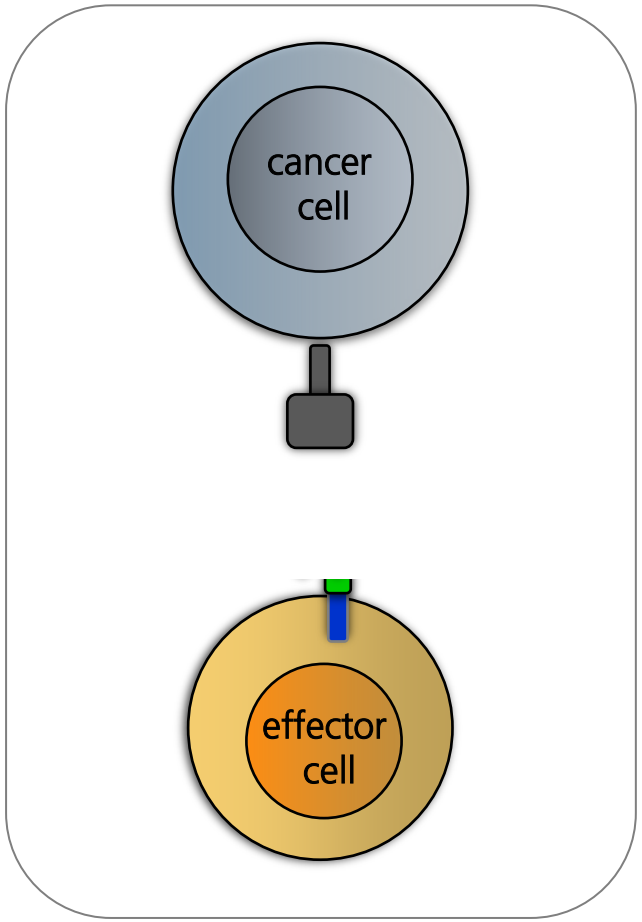
- One-off treatment
- Elimination of the cause
- Long-lasting effect

Healing of Infectious-, Cancer-, Monogenetic-, Cardiovascular- and Neurological Diseases using **viral** and **non-viral gene transfer**

Chimeric antigen receptor (CAR)-expressing effector cells

Autologous CAR T cells are state of the art, but first trials with allogeneic CAR effector cells are ongoing



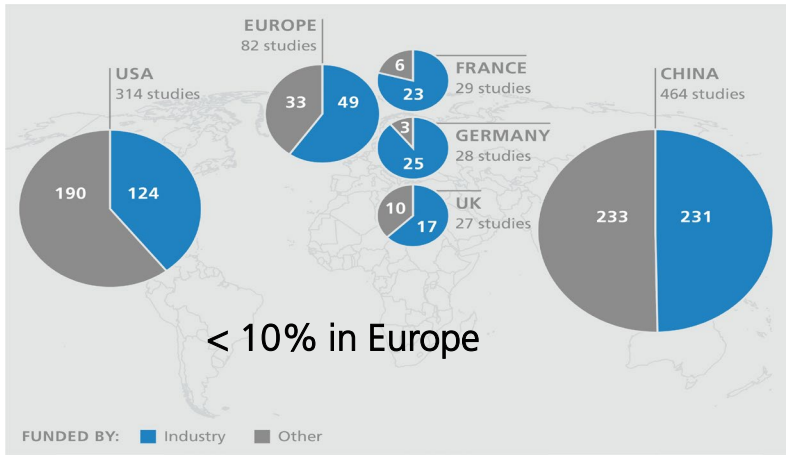


- Collection of patient or donor cells; ***ex vivo*** **gene modification & cultivation of cells**; re-infusion of genetically modified cells
- **Regulatory**: Advanced Therapy Medicinal Products (**ATMPs**)

CAR = chimeric antigen receptor

The world of personalized CAR T cell treatment

Emily Whitehead Foundation



- **Outstanding benefit** in haematological cancer CD19+ ALL and DLBCL, followed by MM
- **> 1000 clinical trials**, less than 10% in Europe (~ 5% GER)[1,2]
- **6 approved CAR T** products for cancer (anti-CD19, anti-BCMA); > ¼ Mill € per batch
- **High growth rates** in market: 40 Bill € up to 2026[2,3]
- Currently **> 40.000 patients** treated[2,4,5]
- **Successful results** also in **autoimmune diseases**[6]

[1]Vucinic V .. Koehl U. Frontiers Medicine 2021

ALL = Acute lymphoblastic leukemia
DLBCL = Diffuse large B cell lymphoma
MM = Multiple Myeloma

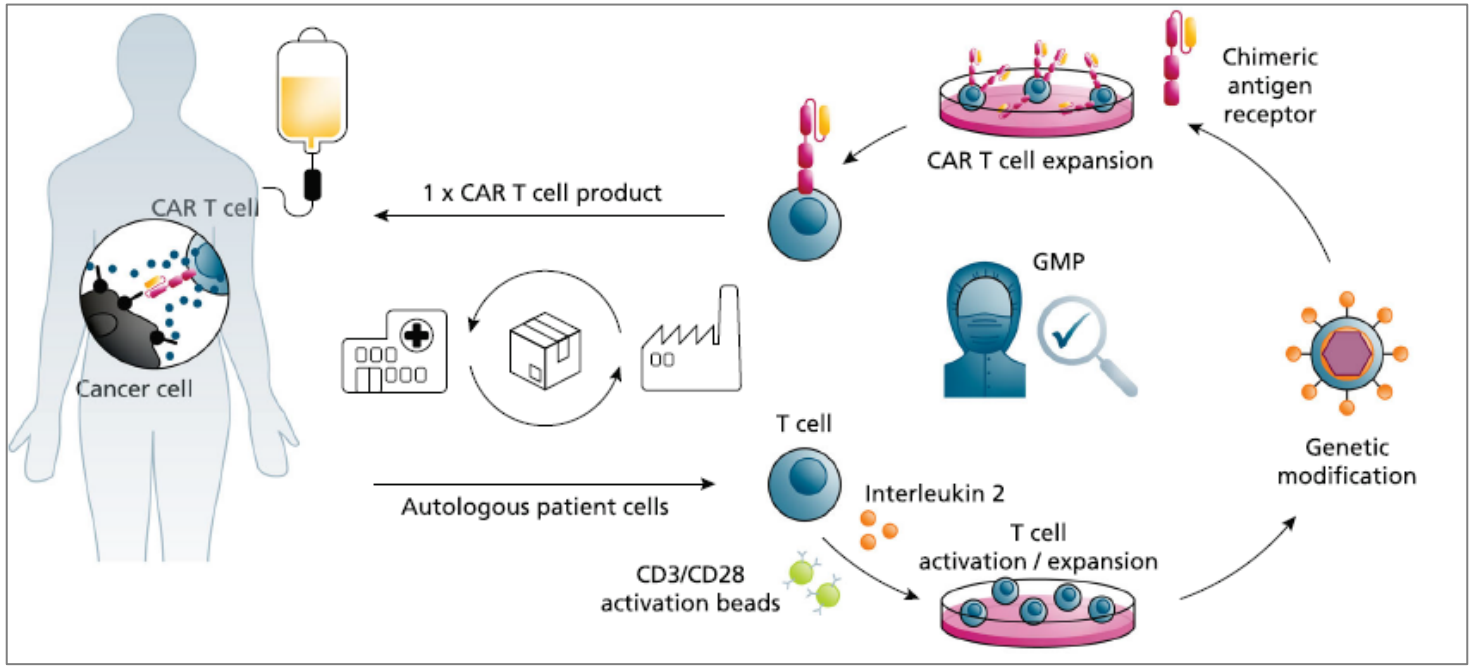
[2] https://clinicaltrials.gov/ Update 11/2024
[3] Pharmaevaluation I Roland Berger GmbH, Feb 2023
[4]Levine et al. Nat Med 2024

[5]Willyard C Nature Feature May 2024
[6]Mougiakakos D et al. New Engl J Med 2021

Manufacturing of CAR T cells is complex: State of the art

Process worldwide[#]:
Manual up to automated

1. stimulation
2. transduction
3. expansion
4. formulation



Blache U, Popp G, Dünkel A, Koehl U & Fricke S. Nature Communication 2022

- Time consuming, complex, expensive / facility running cost and operational cost
- Complex quality control (QC)
  Identity, purity, impurity, quantity, safety, potency …
- <u>Centralized manufacturing</u> 12 days (range 7-22)* with previously, vein-to-vein time 4-6 weeks; currently: shortened protocols up to 2 days
- <u>Decentralized manufacturing</u> 12 days (optimized 7) with vein-to-vein time around 2 weeks

[#] Maschan M et al. Nat Communication 2021 I Fowler N et al. Nature Med 2021 I Schuster S et al. Leukemia & Lymphoma 2022
*Koehl U et al, HGT 2018 | Roddie et al. Cytotherapy 2019 | ten Haml R et al. Cytotherapy 2020

Fraunhofer IZI

Own experiences in manufacturing of cell and gene therapies

IZI GMP Clean Room Facility II > 110 staff members

Facility No. 1 (8 clean rooms, 410 m²)
Facility No. 2 (5 clean rooms, 222 m²)
all: Grad A in B, S2

CAR T cell manufacturing at Fh IZI

AAV manufacturing
from Q1/2026
Facility No. 3 *(350 m² under construction)*

U. Köhl

Film CAR T cell manufacturing at Fraunhofer IZI:
https://www.izi.fraunhofer.de/content/dam/izi/de/Videos/Beitrag_CAR_T_Extern_2018.mp4

CGT = Cell and Gene Therapy
GMP = Good Manufacturing Practice
GMPDU = GMP Development Unit
AAV = Adeno associated Virus

Dep. GMP CGT: G. Schmiedeknecht K. Kebbel
Dep. GMP development : S. Fricke, T. Schmid

Fraunhofer IZI

ATMP manufacturing: Centralized and decentralized

Own experience with a special view to CAR T cells

Centralized academic manufacturing

- Phase I-IV studies up to translation commercial – CAR pipeline (Academia & Industry)
- Fraunhofer IZI: large GMP team (>110 staff members) – very high standard

Examples:

1) CL019/ Kymriah® & YTB323/T-Charge (Fraunhofer IZI – coop. Novartis) > 500 CAR-T cell products[1,2]
2) Clinical CAR T cell trials in Europe (Fraunhofer IZI – coop. Bristol-Myers Squibb)

Requirement for highly technology platforms → multiple patients

Decentralized academic manufacturing

- Early phase I/II trials
- possible only with successful training of staff members

Examples:

1) CD20 CAR T cells[3,4] – manufacturing at MHH *(coop. Miltenyi and H. Abken)*
   Team experience: 200 stem cell products & >60 virus-specific T cell products/ year
2) ROR1/ROR2 CAR T cells using sleeping beauty – manufacturing Fh IZI (coop. M. Hudecek[*])

Fast transfer of new innovation from academia

Blache U, Popp G, Dünkel A, Koehl U & Fricke S. Nature Communication 2022

[1]Vucinic V. … Koehl U. Frontiers Medicine 2021
[2] Koehl U et al, HGT 2018

[3]Aleksandrova K et al. Transfusion Medicine and Hemotherapy 2019
*M. Hudecek, H. Einsele, Würzburg and Z. Ivics, MDC Berlin

Fraunhofer IZI

ATMP manufacturing: Centralized and decentralized

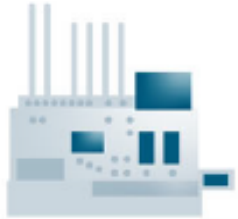
Own experience with a special view to CAR T cells

Overall > 3,500 released products:

- ~ 550 CAR T cell products
- ~ 430 dendritic cell vaccines
- ~ 330 stme cell-based-engineered tissues
- ~ 1,400 allogeneic cell products
- ~ 900 autologous stem cell products

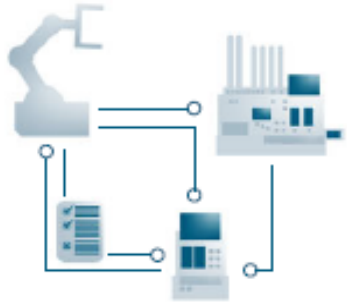
Manufacturing devices & principles

Manual manufacturing



All-in-one bioreactors
Semi-automated

Scale out
Semi-automated / automated



Modular process street
Automated

Pharma 4.0

Blache U, Popp G, Dünkel A, Koehl U & Fricke S. Nature Communication 2022

[1]Vucinic V. … Koehl U. Frontiers Medicine 2021
[2] Koehl U et al, HGT 2018

[3]Aleksandrova K et al. Transfusion Medicine and Hemotherapy 2019
*M. Hudecek, H. Einsele, Würzburg and Z. Ivics, MDC Berlin

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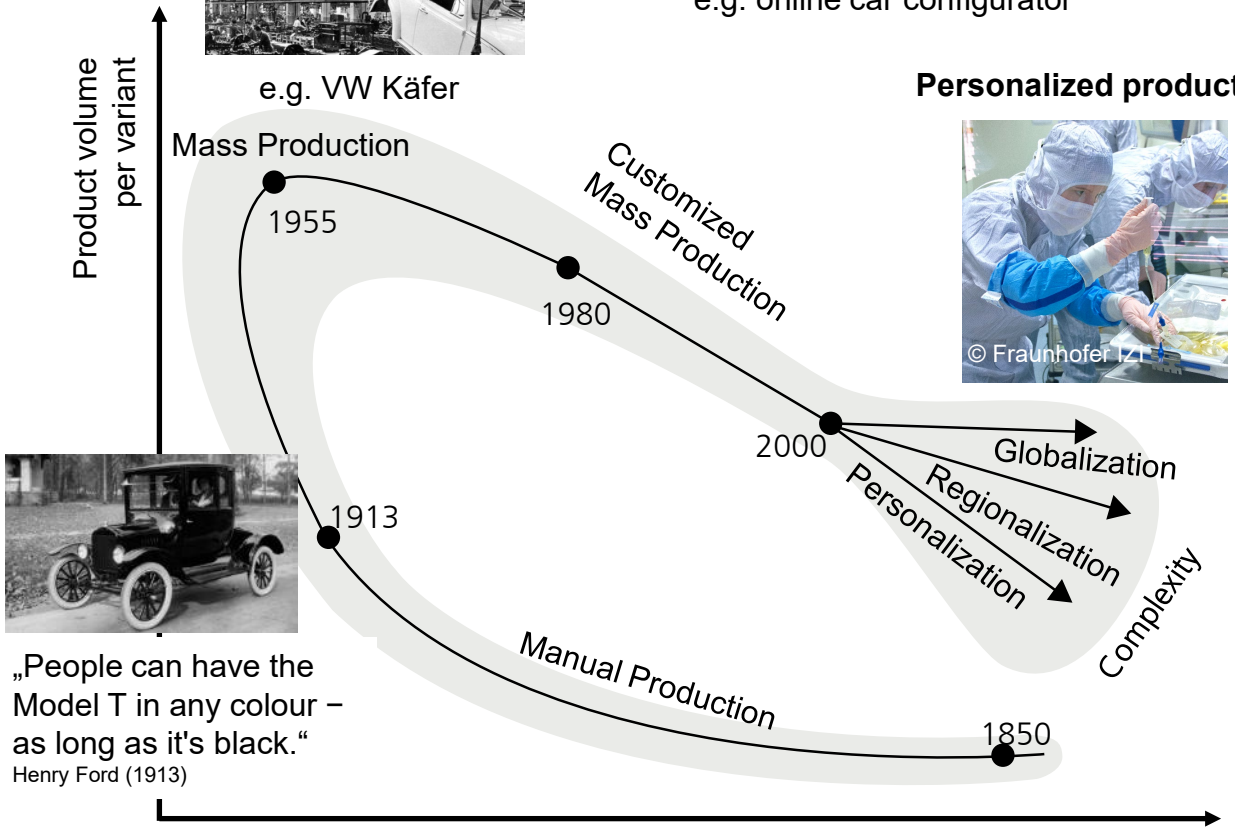
Mass Personalization – future challenge for ATMPs

In order to address 100-fold more patients

e.g. VW Käfer

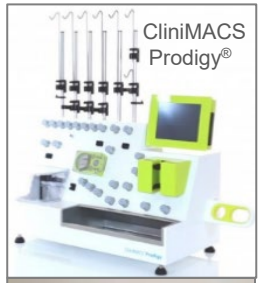
e.g. online car configurator

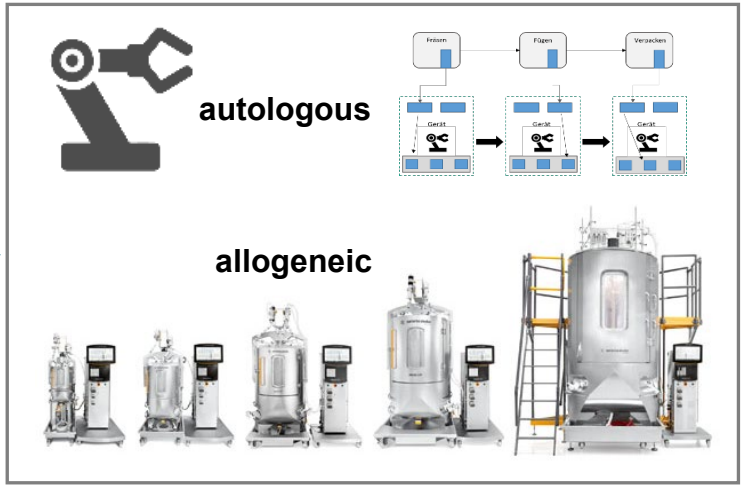


„People can have the Model T in any colour − as long as it's black.“
Henry Ford (1913)

Personalized production

Automation





AI-mediated industry 4.0

- Automation & robotics
- Digitally controlled modular production lines
- Sensor Technology
- Inline sensors
- Machine learning
- Traceability
- …

According to Yoram Koren: The Global Manufacturing Revolution; source: Ford, beetleworld.net, bmw.de, dw.de

Fraunhofer Lighthouse Project »RNAuto«

Automated production technologies for mRNA based drugs and cell and gene therapies

Fraunhofer CIMD

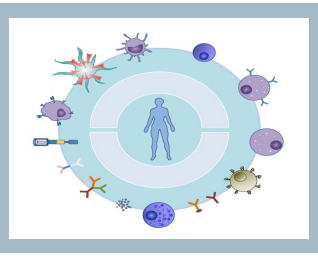
Fraunhofer Lighthouse Project »RNAuto«

Partners and key competencies

- Microelectronics
- Materials
- Health
- Production
- ICT-Technology

Health

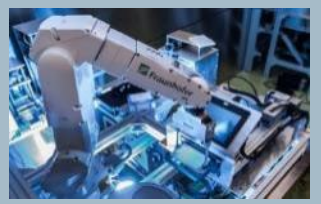
- Vaccines and ATMPs
- GMP Process development



Fraunhofer IZI
Fraunhofer ITEM
Fraunhofer IMM

Automation

- Production technologies
- Robotics and sensor technology



Fraunhofer IPA
Fraunhofer IPT
Fraunhofer IESE

Artificial intelligence and sensor technology

- Digital twins
- Virtual engineering & quality assurance

Fraunhofer IESE
Fraunhofer IMS
Fraunhofer IMM

Fraunhofer CIMD

Fraunhofer Lighthouse Project »RNAuto«

Project goals and technologies

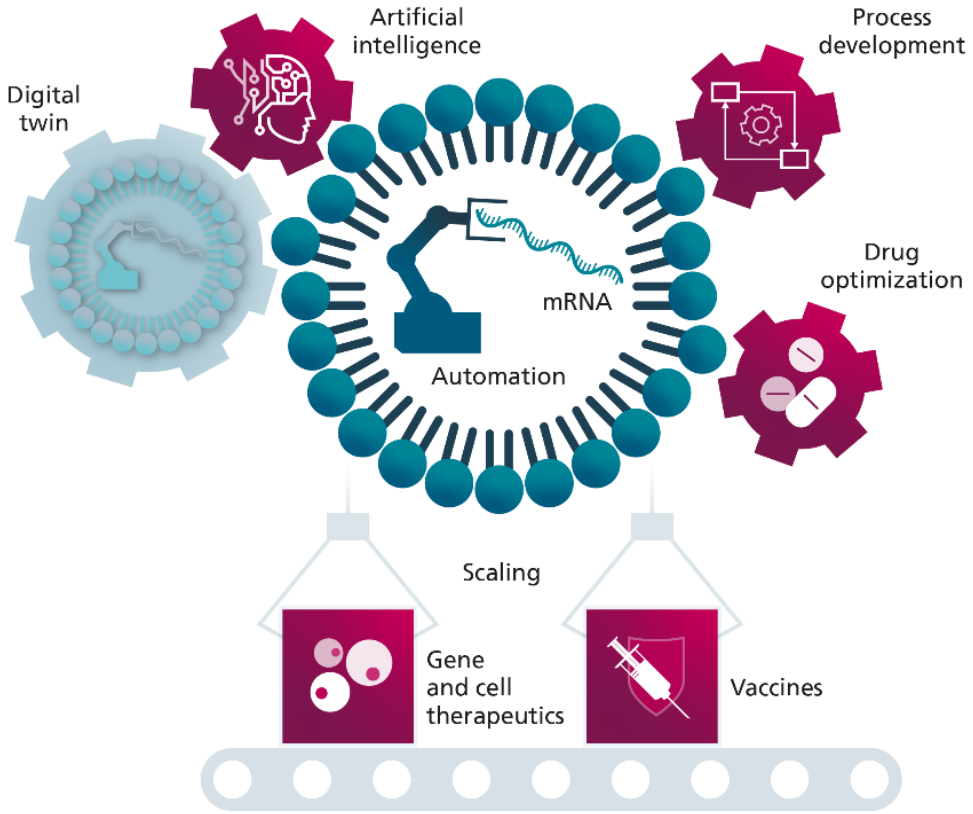
Project goals

1. Automatable method for packaging mRNA into nanocarriers

2. Development of a **screening platform** for automated mRNA encapsulation with integrated online analytics for quality assurance and documentation for accelerated bioprocess development

3. Expansion module with integrated quality control for the production of allogeneic gene and cell therapeutics

4. mRNA drug candidates: West Nile Virus vaccine, gene and cell therapeutics for the treatment of hematologic cancers

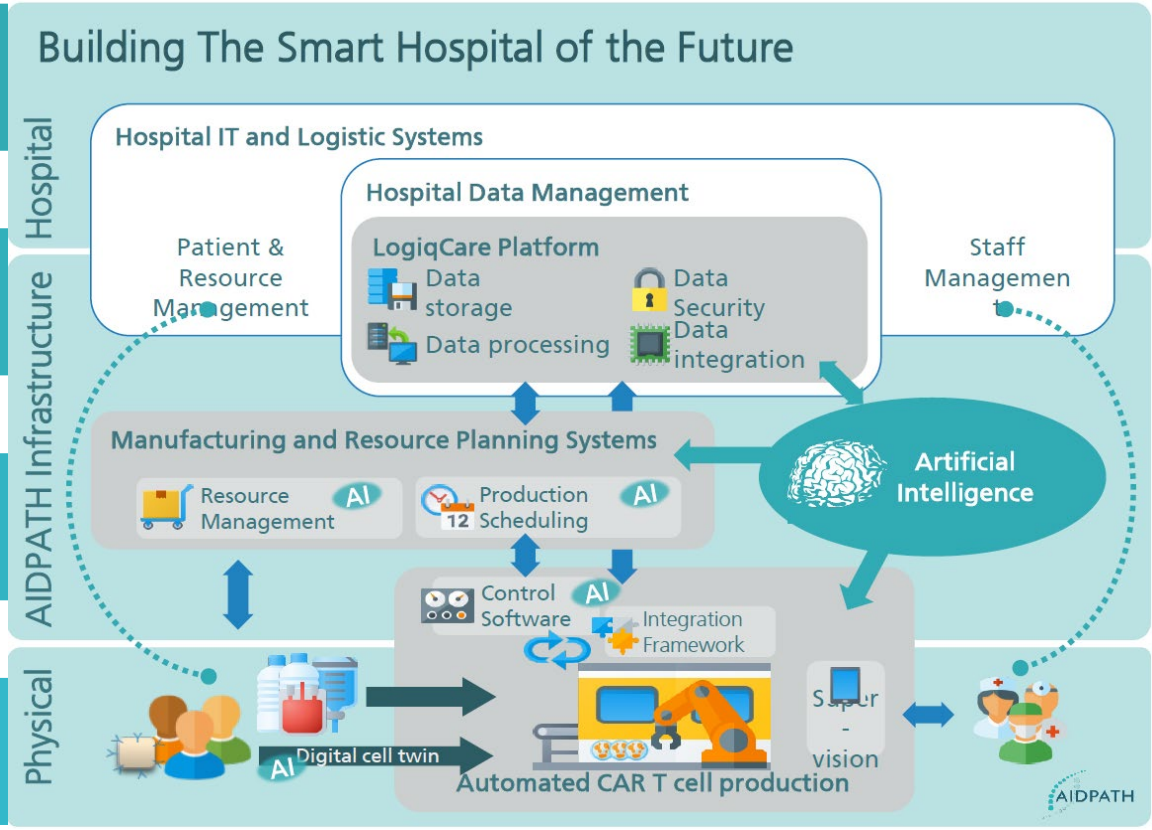


Fraunhofer CIMD

Artificial Intelligence (AI) and CAR T cell manufacturing

AIDPATH

- Automated robotic, modular manufacturing platform for CAR-T manufacturing
- Artificial Intelligence solutions supporting the end-to-end manufacturing process
- Data Architecture enabling a continual AI learning and CAR-T process optimization
- Business model and Innovation Ecosystem



* leadership: Fh-IPT, Aachen

Cooperation: Aachen, Würzburg, Leipzig, London, Brüssels ….

Fraunhofer IZI

Cluster for cell and gene therapy

Cooperation approaches & networks - 38 academic PIs and 23 industry partners

One of the winners

CLUSTERS 4 FUTURE
Innovationsnetzwerke für unsere Zukunft

Fraunhofer CIMD

Cluster for cell and gene therapy

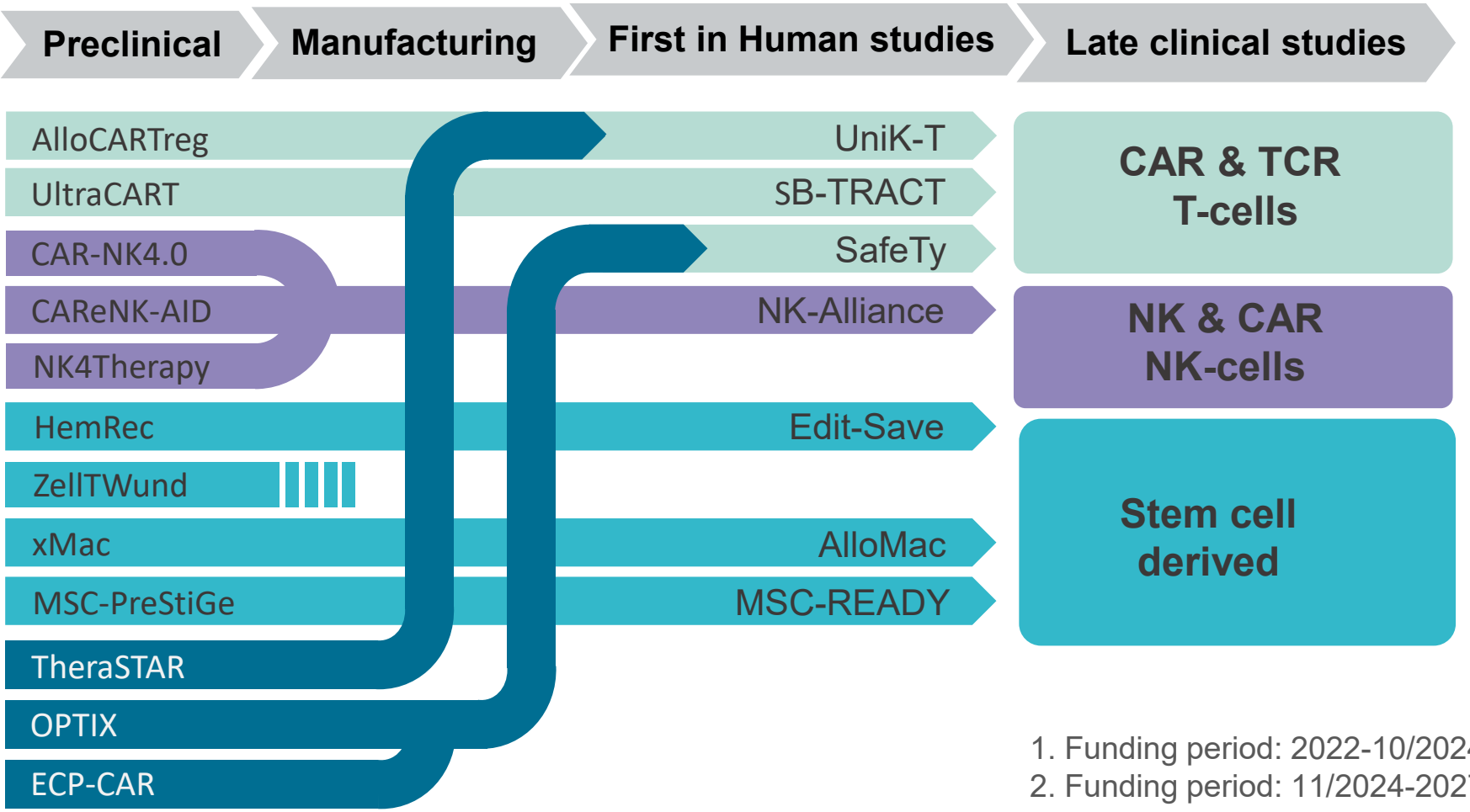
Goals and projects

Complete Value Chain

Automation
Robotics
Artificial intelligence

Viral Vectors

Non viral gene transfer



1. Funding period: 2022-10/2024
2. Funding period: 11/2024-2027

Speaker Leipzig & Dresden: U. Köhl & F. Buchholz

Co-Speaker U. Platzbecker & M. Bornhäuser

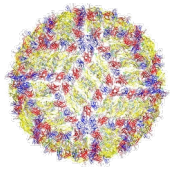
Strategies for genetic modification

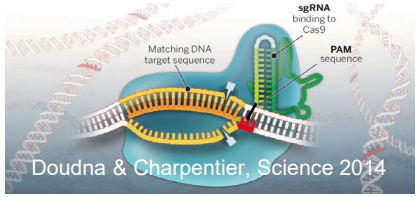
From viral to non viral gene transfer for CAR effector cells

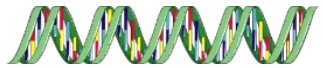
Viral vectors

Non viral gene transfer

Lentiviral/ retroviral vectors	Adeno-associated virus (AAV)	CRISPR-Cas, Talen, ZFN Sleeping Beauty …	Plasmid DNA/RNA







genomic integration

stable expression

extra chromosomal/ episomal

transient expression

Risk for genotoxicity

Manufacturing costs

Büning et al,
Human Gene Therapy 2021

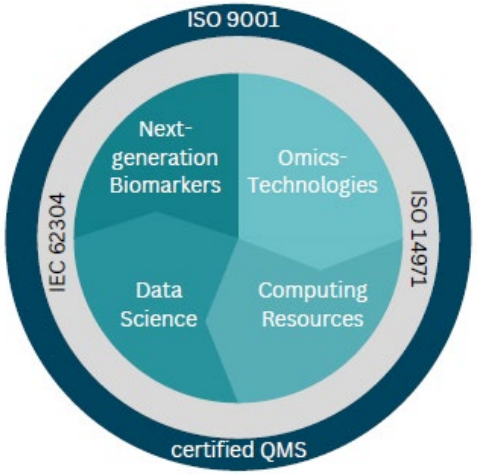
Doudna and Charpentier,
Science 2014

AI: From manufacturing to managing personalized therapies

Biomarker and predictive calculation models for planning and implementation of clinical trials

- Optimization of patient selection
- Support therapy management including predictive parameters for

  (i) therapy response
  (ii) undesirable side effects and
  (iii) occurrence of secondary malignancies

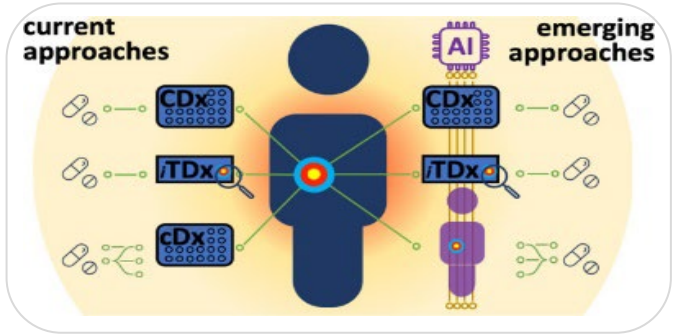


Omics
RNAseq
…

Fh IZI Biomarker Center

FDA reported 22 cases sec. malignancy out of 27.000 people after CAR T treatment (Updated March 2024: 33 of 30.000)[1,2,3]

Real-world evidence analysis (2018-2022) to investigate incidence and prevalence of TCL in patients: **MM 0.06%, DLBCL 0.62%**



➡ Risk of secondary T-cell malignancies following CAR-T therapy is relatively rare → Further investigations are required, FDA requires lifelong monitoring of patients[1,2,3]

AI = Artificial Intelligence

[1]Levine et al. Nat Med 2024
[2]Willyard C Nature Feature May 2024
[3]Gurbakhash K. et al. Fonseca Online Newsletter 2024

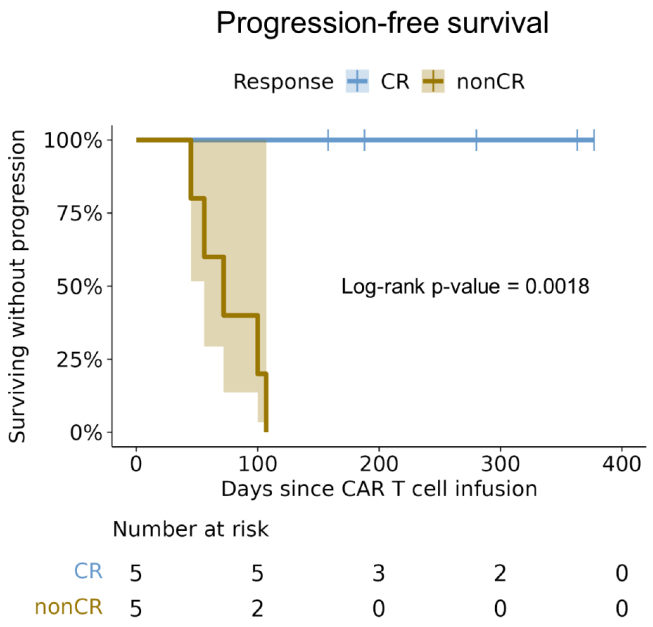
Derraz B…Koehl U
… Gilbert S NP
J Prec Oncology 2024

Fraunhofer IZI

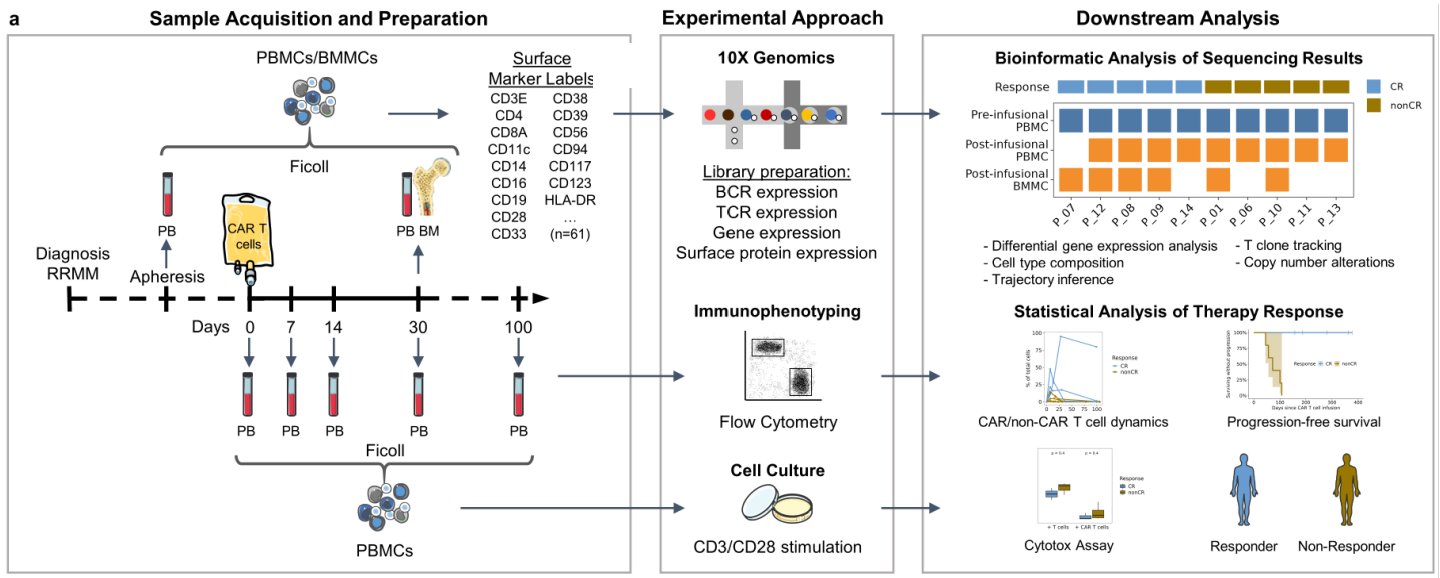
Predictive markers for treatment response

Real-world analysis of 61 patients treated BCMA-directed CAR-T cells

Survival curve



Overview work plan



To date, still missing predictive marker

➡ Differences between CR and nonCR could already be identified at the time of leukapheresis

CR = Complete response
nonCR = non Complete response
PB/KBM MC = Mononuclear cells from peripheral blood or bone marrow

Rade M, …Koehl U, …Platzbecker U,…Reiche K,…Vucinic V,…Merz M.
Nature Cancer 2024

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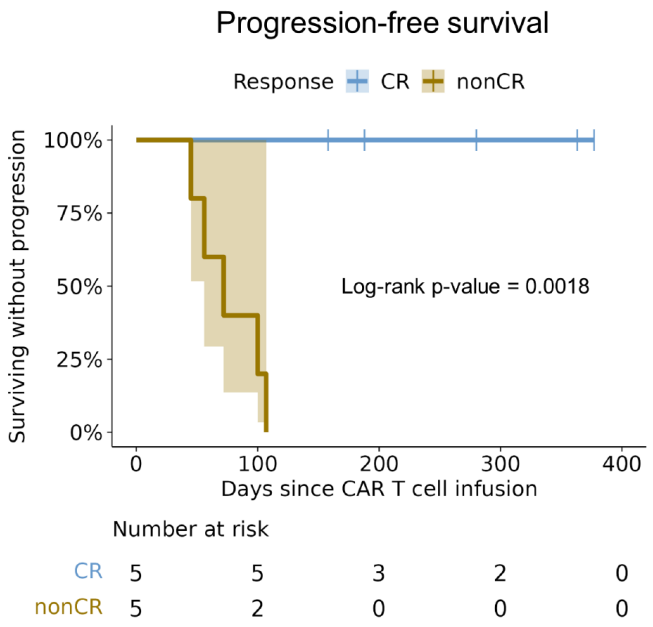
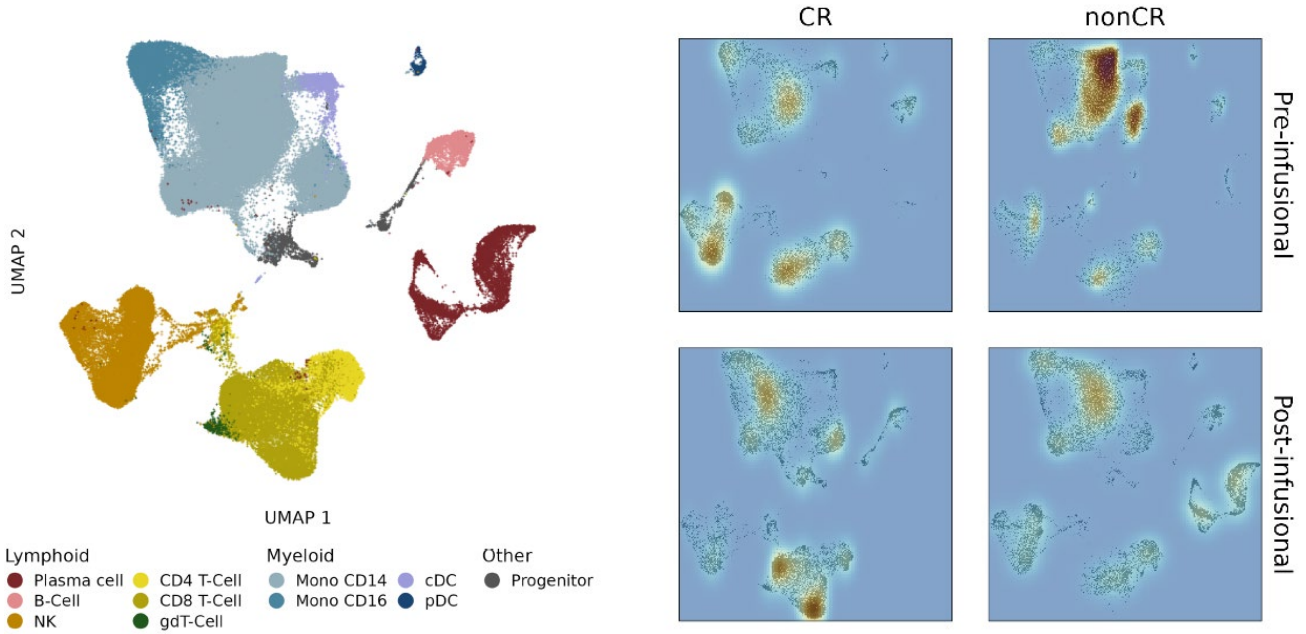


PB/BM MC at the timepoint of apharesis and 30 days post CAR T cell therapy



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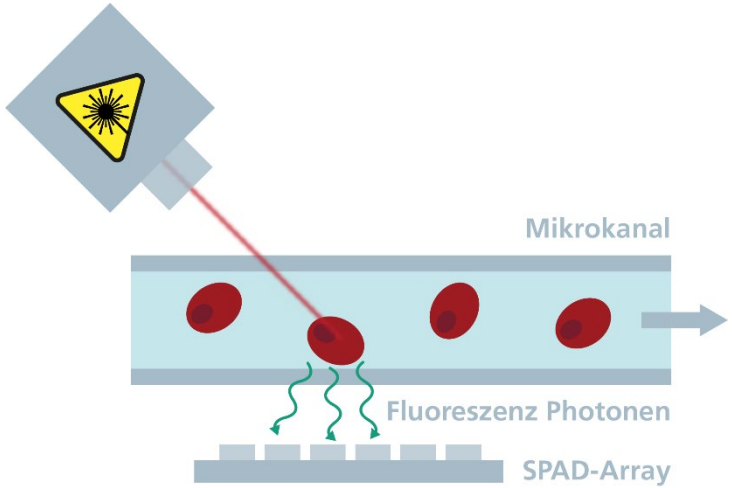
Online quality control, sensoric and AI for prediction

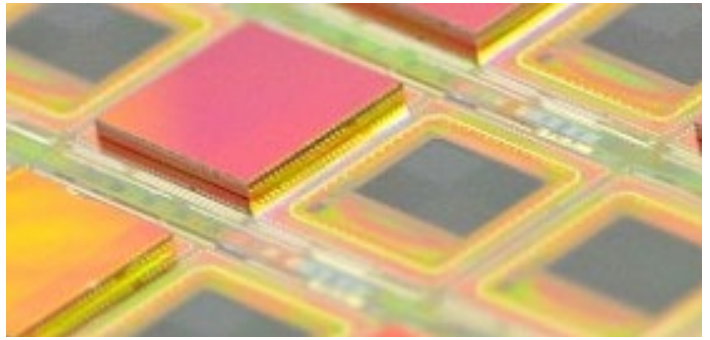
Microfluidic flow cytometry with integrated AI analysis

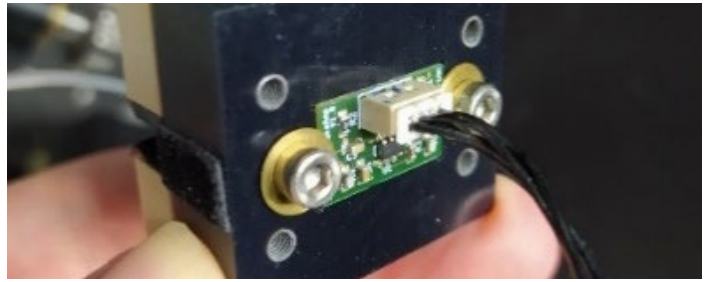
Online flow cytometry



Module for the detection of single photons (SPADs)

Microsystems technology





Data analysis

AI f ES

Multi-parameter analysis (cell count, viability) using embedded AI and digital twin

Miniaturization and high integration (optics, fluidics)

Organ on the chips and integration of sensoric for prediction

Future cooperation Fraunhofer IZI, MicroDiagnostic and ENAS

Goal: Orgon on the Chip

Reproduction of human organs on a microfluidic chip

Why:

- ➢ Drug testing
- ➢ Personalized medicine
- ➢ Reduction of animal testing through preclinical disease models

Goal: Integration of sensor technology

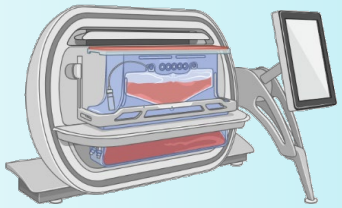
- ➢ Collection of “real-time data”
- ➢ Improving the understanding of disease mechanisms

Requirement

- ✓ Integration of e.g. optical or electrochemical sensors

Summary:
The furture of health technology requires interdisciplinarity

Automation & technical improvements

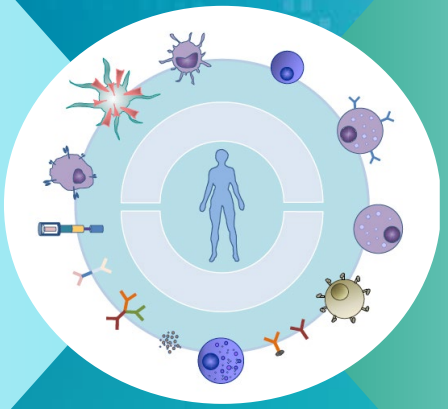


GMP-in-a-box devices

Modular solutions

Robotics

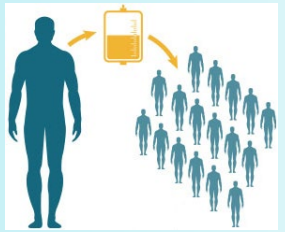
Sensor technology



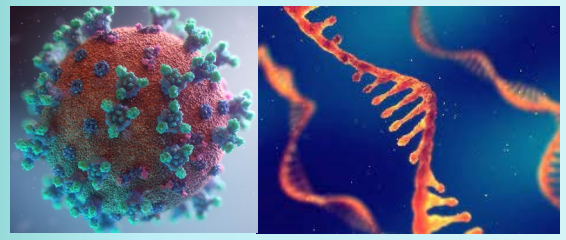
Living Medicine

Biological optimization and process design

Shorter process design



Allogeneic CGT



Smarter genetic modification

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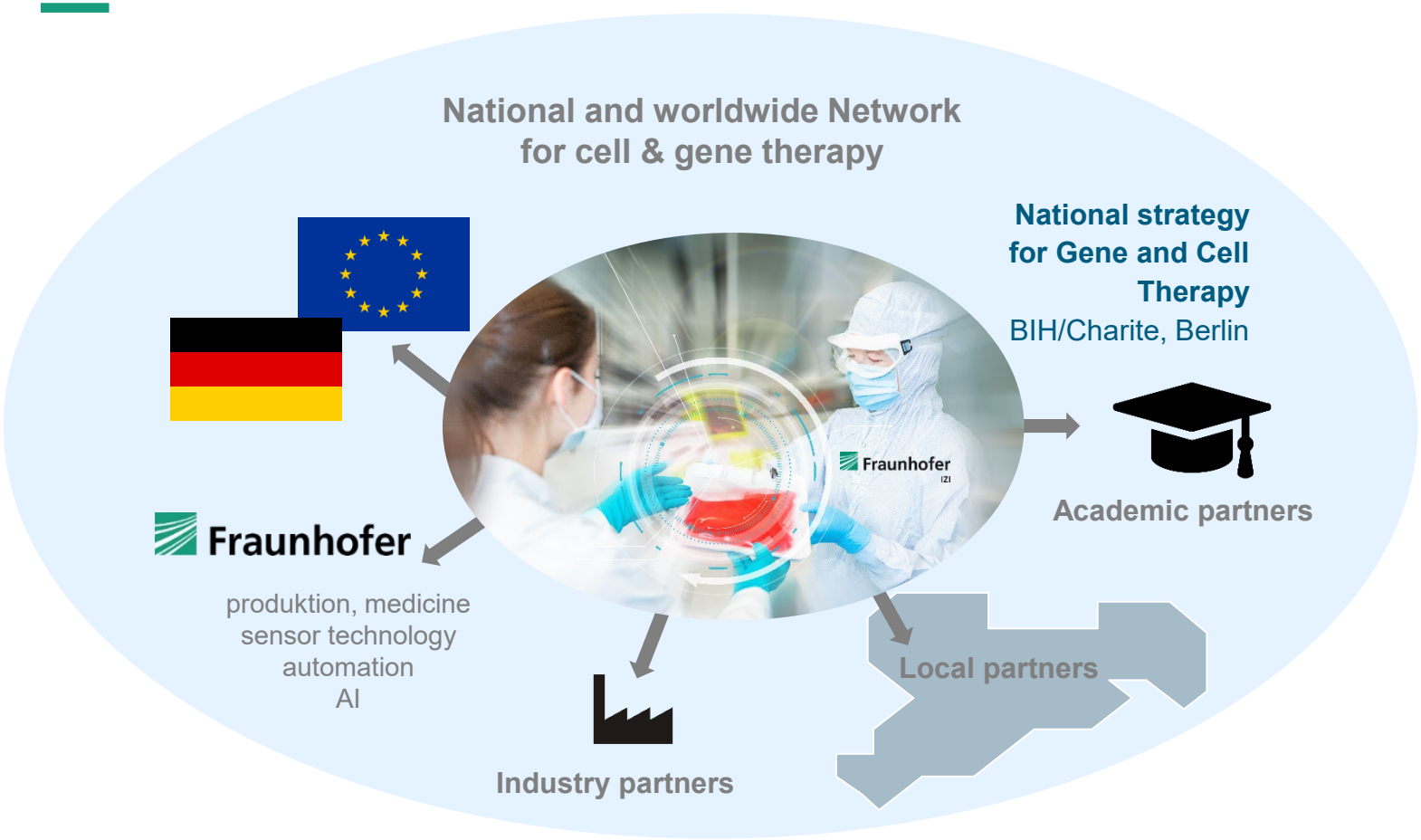
NOVARTIS

… and thank you for listening



imSAVAR	CAR T safety assessment
T²EVOLVE	Next generation CAR T
AIDPATH	ATMP production with AI
REANIMA	iPS-deriv. cardiomyocytes
Certanty	Digilal Twins and ATMPs
Creatic	GMP Training
SAXOCELL	New Cell and Gene Therapies
WIR! sind DIANA	Point of care diagnostic
ICON	Designer NK cells
RNAuto	Automated manufacturing

Our ongoing EU and local cluster