

SAXOCELL®



**CLUSTERS
4 FUTURE**
Innovationsnetzwerke
für unsere Zukunft

GEFÖRDERT VOM



Bundesministerium
für Bildung
und Forschung

LIVING DRUGS

PRECISION THERAPY CLUSTER FOR SAXONY

SaxoCell Scientific Advisory Board Meeting
28.10.2022



TECHNISCHE
UNIVERSITÄT
DRESDEN



UNIVERSITÄT
LEIPZIG



Fraunhofer
IZI



KLINIKUM CHEMNITZ
gGmbH

The SaxoCell Scientific Advisory Board



Dr. Lorenz Mayr
CEO Vector BioPharma AG, Basel



Prof. Dr. Ute Modlich
Löwe Professorship and Head of
Research Group "Gene
Modification in Stem Cells" of the
Paul-Ehrlich-Instituts, Langen



Prof. Dr. Axel Schambach
Director Institute for
Experimental Hematology, MHH,
Hannover



Nadine Winter
Patient Advocacy

Experts from the fields of research, industry, regulatory and patient advocacy advise the SaxoCell cluster in general and provide assistance with their experience to the projects.

The SaxoCell Speakers and PIs



Speakers



Ulrike Köhl
Fraunhofer IZI
University of Leipzig



Ezio Bonifacio
CRTD
TU Dresden



Martin Bornhäuser
University Hospital
Dresden



Uwe Platzbecker
University Hospital
Leipzig

PIs

AlloCARTreg
Anke Fuchs, Martin
Bornhäuser, Anja Feldmann &
Frank Buchholz

CAR-NK 4.0
Ulrike Köhl, Ulrich Hacker,
Matthias Hänel, Sebastian
Huhn, Michael Albers, Paul
Franz & Sandra Palm

ZellTWund
Jan C. Simon, Yuval
Rinkevich, Marta Torregrossa,
Sandra Franz, Ravinder Kandi
& Ulrike Köhl

HemRec
Frank Buchholz & Thomas
Schäfer

OPTIX
Sandy Tretbar, Lilly Stahl,
Matthias Hänel, Martin
Bornhäuser & Stephan Fricke

areas



UltraCART
Michael Hudecek, Ulrike
Köhl & Jan van den Brulle



NK4Therapy
Achim Temme & Martin
Bornhäuser

CAReNK-AID
Torsten Tonn, Jiri Eitler &
Achim Aigner



xMac
Michael Sieweke & Frank
Buchholz

MSCPrestige
Mario Rüdiger & Tino
Hammer



ECP-CAR
Vladan Vucinic

TheraSTAR
Anja Feldmann & Marc
Schmitz

platforms



Kristin Reiche, Ulrike
Weirauch & Ezio
Bonifacio



Silke Gloaguen &
Matrin Bornhäuser



Ulrich Blache, Mario
Rüdiger & Stephan
Fricke



Ilka Henze, Anette
Bartsch, Stefanie
Binder, Maren
Henneken, Ira Illgen,
Sophia Kolbe, Dorit
Teichmann & Thomas
Tradler

What is SaxoCell?



Research institutions, hospitals and companies (mainly within Saxony) - funded by the BMBF – who work together to bring **efficient, safe and affordable** autologous and allogeneic **Cell and Gene Therapies** to patients who suffer from serious diseases.

Strategy

- Identify excellent local science and technology for **new areas** of Cell and Gene Therapy.
- Bring excellent Saxon **basic & applied research** to **industry- and clinical-ready stages**.
- Develop supportive **clinical** and **technology platforms** for projects and region.
- Create a cell and gene therapy dedicated **technology transfer** expertise for region.

And become a Gene and Cell Therapy lighthouse for Germany.

Who is SaxoCell?



2 Universities
1 Fraunhofer

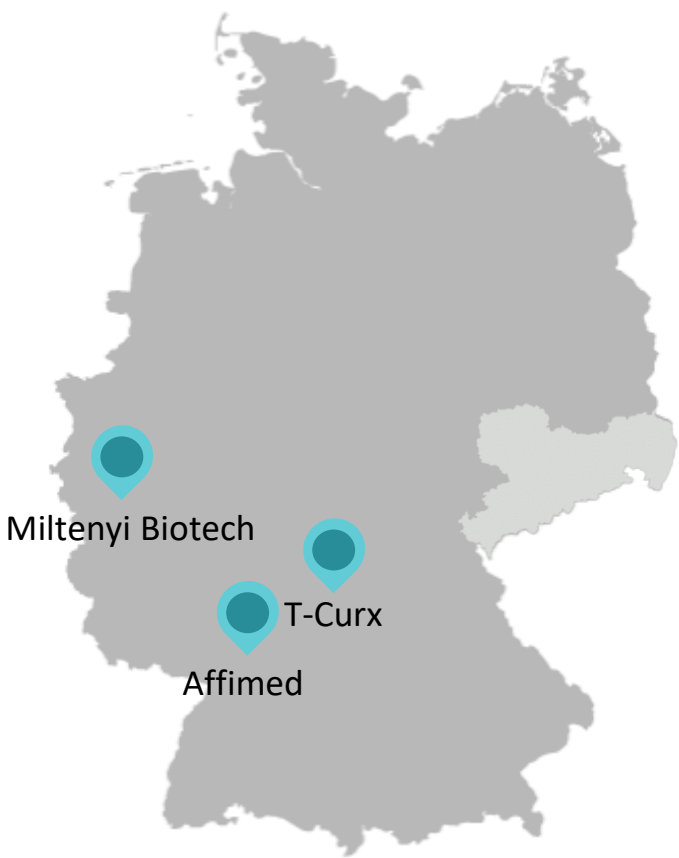


> 20 Academic partners



3 Hospitals

Who is SaxoCell?



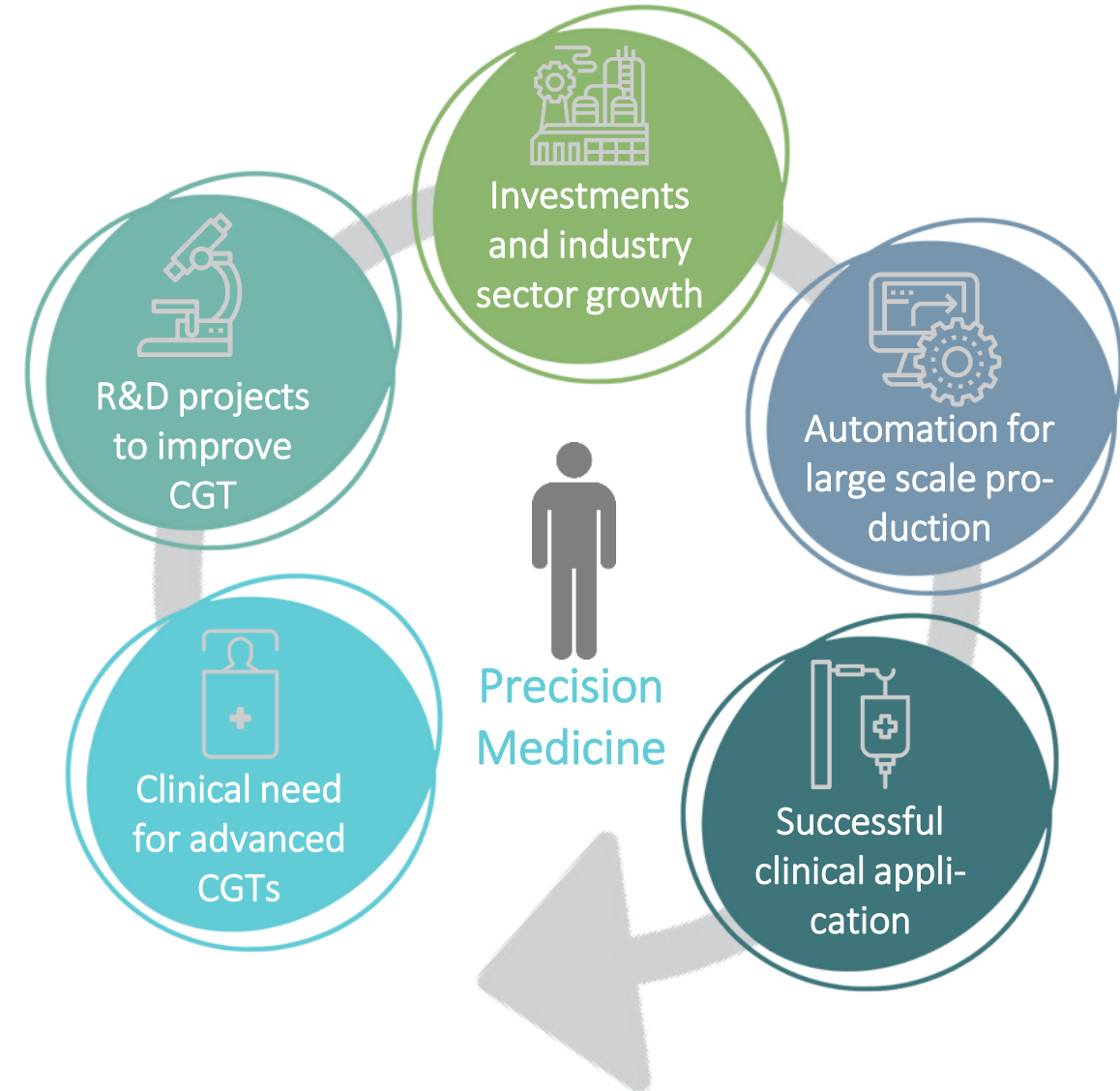
-  2 Universities
-  1 Fraunhofer
-  > 20 Academic partners
-  8 Industry partners
-  > 150 Members
-  3 Hospitals

The vision of SaxoCell

Novel gene and cell therapeutics i.e. "living drugs"

- Cluster technologies developed with local company partners and represent incentive for investors and industrial partners

Saxonian **science** and **industry** for effective, affordable, safe **cell therapy** to **cure** and **prevent disease** globally



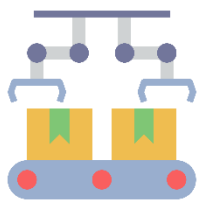
Long term vision

Technical & Clinical Innovations

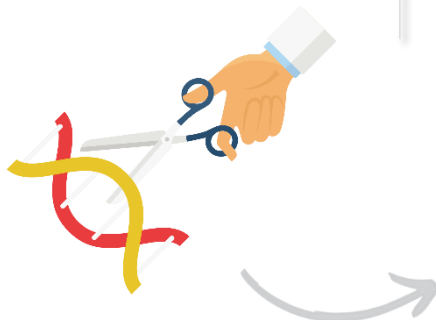


5 years

- Rapid translation of ATMPs & designer-recombinases to approval
- New optimized processes for production of ATMPs and vectors
- GMP Training centre for Europe
- External financed clinical studies
- Clinical application



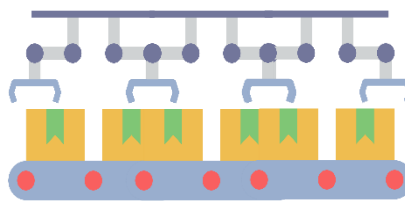
Partially automated production



Designer-recombinases

10 years

- Healing of other diseases
- Adaptable technologies for personalized medicine (in vivo & ex vivo therapies)
- Process lines, Robotics, AI, Industry 4.0 – Cost reduction
- Marketed clinical products



Full automation



ATMP studies phase III/IV

20 years

- Cost-effective healing of many diseases
- Universally applicable genome surgery and „off the shelf“ therapies



Increased quality of life

Long term vision

Economic & Social Innovations



5 years

- Establishment of the brand name SaxoCell
- Common position to politics (industry & academia)
- New jobs/ specialists



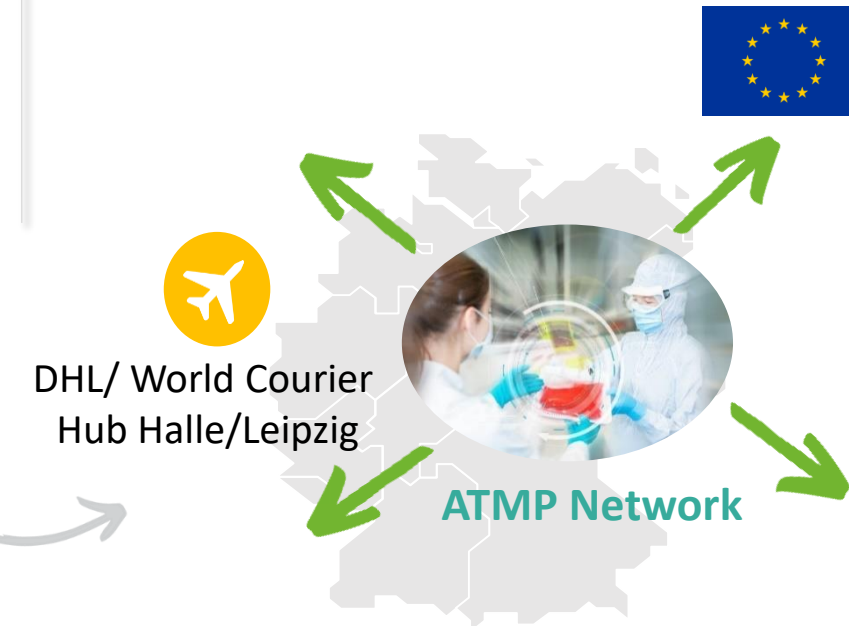
10 years

- Worldwide visibility
- New spin-offs and settlements
- Saxon training and university programs for ATMPs
- Consolidation & extension of the cluster

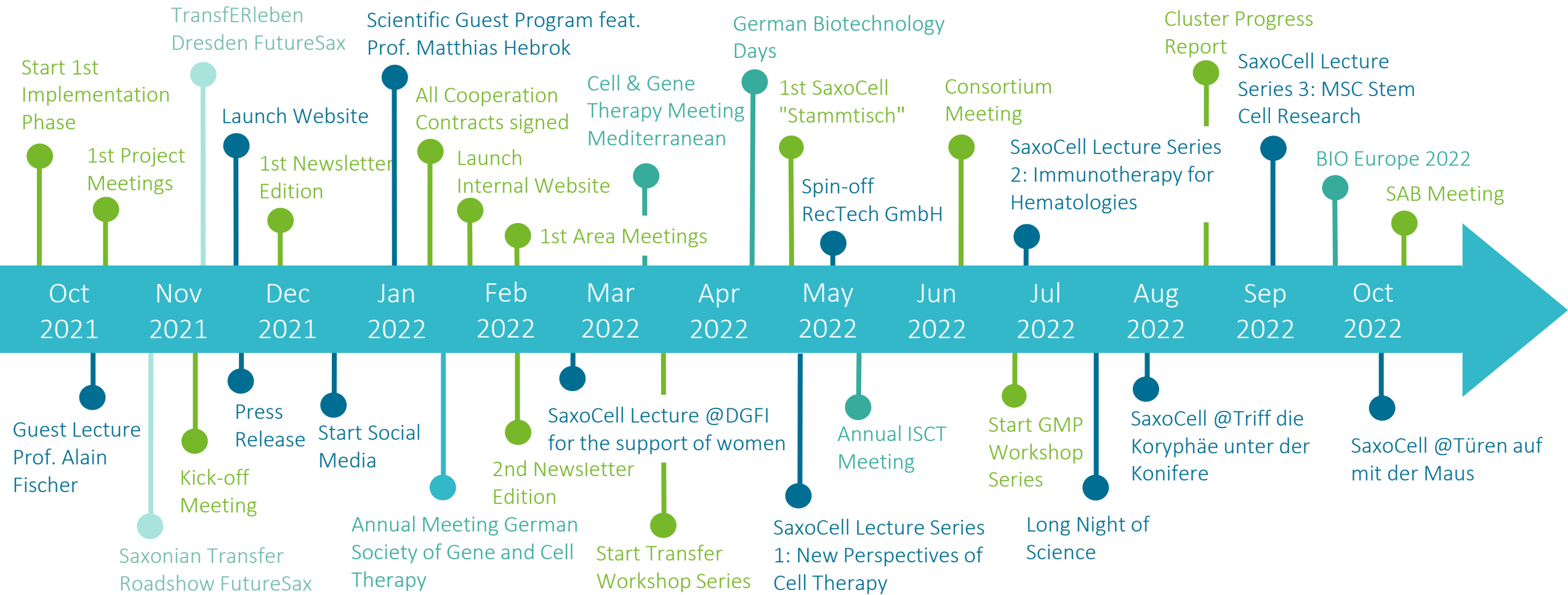


20 years

- Profiling of SaxoCell as leading cell and gene therapy location in Europe
- SaxoCell as new leading industry in Saxony – large investments



What we did in the first year



Measures of success in the 1st phase



Additional funding (5 Mio. €)



GO·Bio



Secured IP (6 patents) **one is applied**



Clinical studies (2 studies)



New partner (50 academic and industry)



Spin-offs (2)



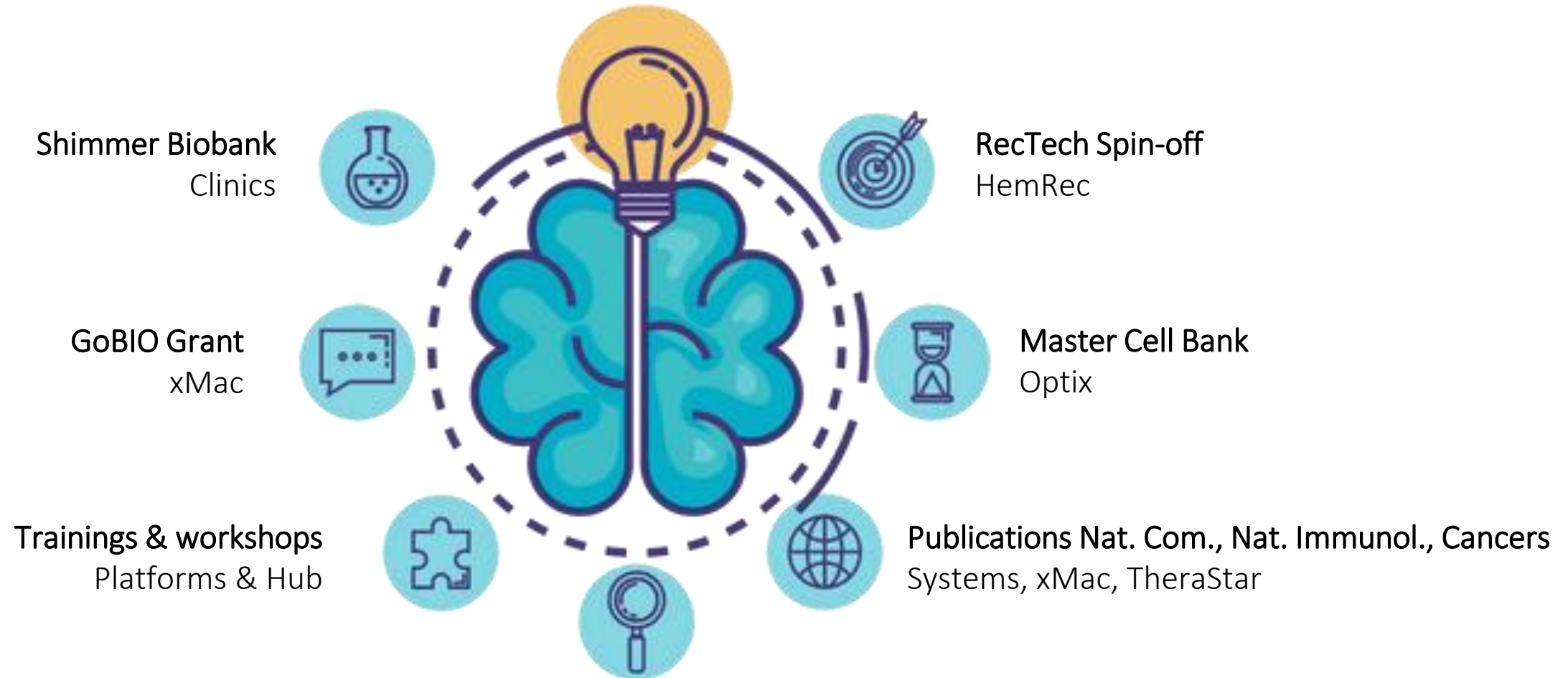
Settlement (1)



Visibility (5 workshops, conference participation, social media activities...)



Selected achievements



Strength & challenges

CHALLENGES

Additional regulatory requirements

Funding & time of clinical trials

Spin-offs & settlement of industry

Patenting by
scientists

STRENGTH

CGT expertise

Basic and applied research

Infrastructure

Established network: research, industry, service partners

Governmental Commitment

Saxony as nationwide beacon for CGT

SAB advice on current and new projects



- 1. Is the **portfolio of 12** projects sufficiently broad or **too diverse**?
- 2. Which **projects** are most likely to result in **industry cooperation**?
- 3. Are there **CGT areas** or projects that we should **focus** on and expand?
- 4. Are there **projects of concern** with respect to their
- 5. progress/competitiveness?

SAB advice on platforms and hub

- ❓ Does the approach of **platforms** make sense?
- ❓ Should we invest **more resources** into the **platforms**?
- ❓ Instead of individual entities should the **platforms** become **part of** the **projects** in the next phase with dedicated funding requests?
- ❓ Should we think about **more platforms**/other services?
- ❓ What are the **key areas** that the **Hub** should focus on?

The SaxoCell community



Outline SAB Meeting



12:45 am

Project Pitches part 1

2:00 pm

Coffee break

2:15 pm

Project Pitches part 1

4:15 pm

Discussion

4:40 pm

Discussion Board Members *(with coffee)*

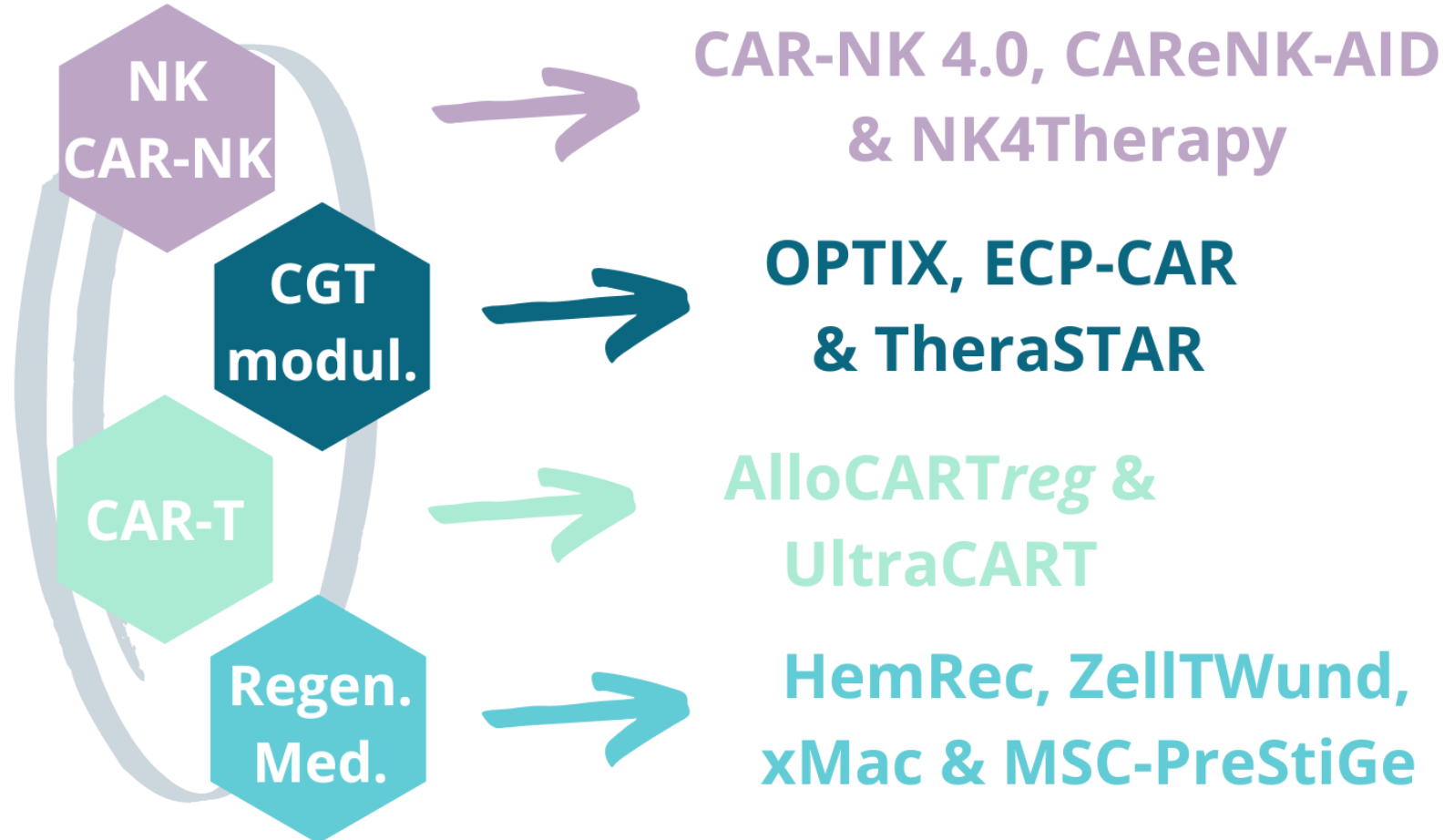
5:40 pm

Feedback to Speakers

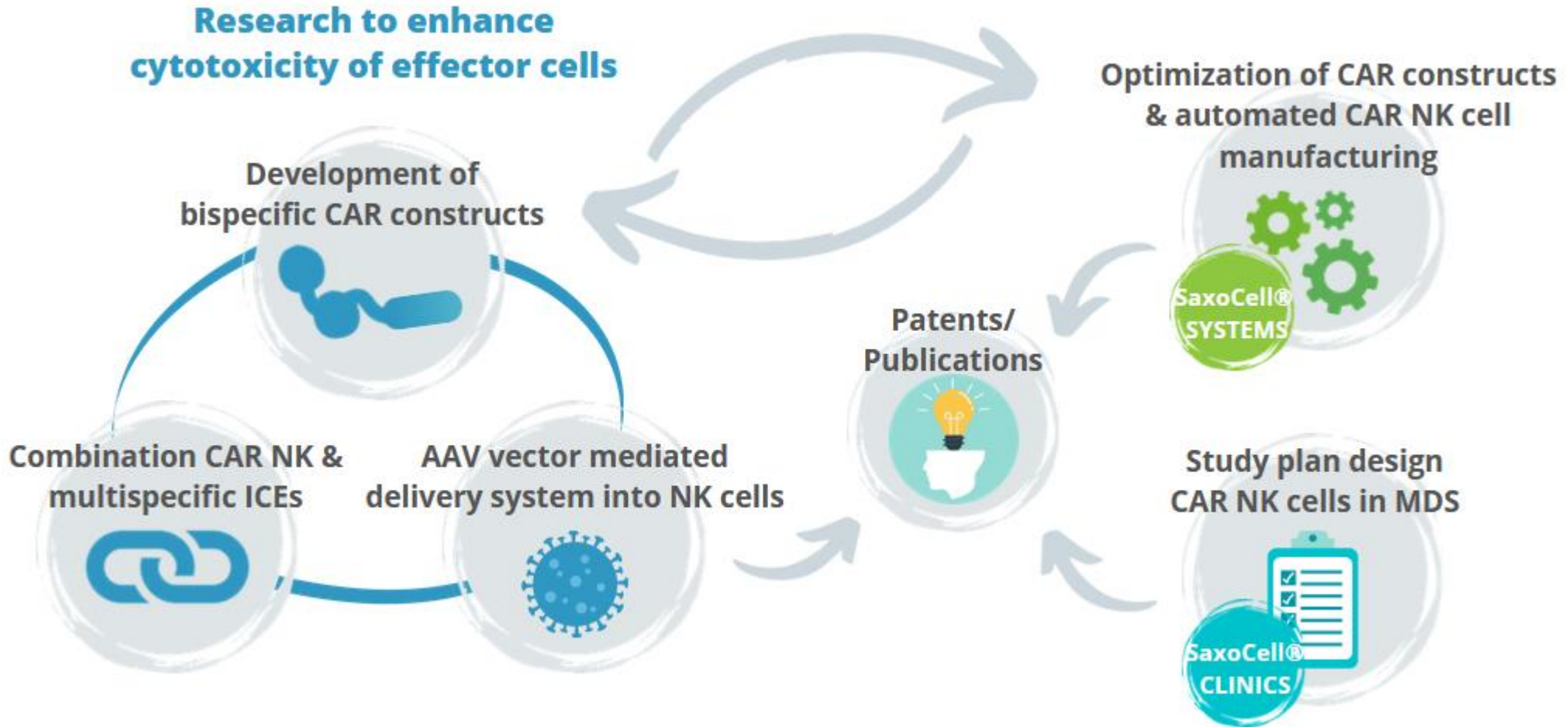
7:30 pm

Dinner

PROJECT PITCHES



CAR-NK 4.0 – Project Overview



CAR-NK 4.0 – Objectives

A: Platform technology for automated CAR-NK cell manufacturing

- +automated CAR-NK cell **manufacturing platform** (WP1)
- +prepared **study protocol** for the use of CAR-NK cells in MDS or AML (WP2)
- +**optimized** CAR-NK cell constructs (WP6)

B: Research program to enhance cytotoxic activity of effector cells

- +development of new **bispecific CAR constructs** (WP3)
- +NK cell product optimized for combination with bispecific **innate cell engagers (ICE®)** (WP4)
- +established **AAV vector-mediated CAR delivery** system into NK cells (WP5)

Indication: MDS or AML with minimal residual disease (MRD) and EMM

Executing affiliated partners:



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CAR-NK 4.0 – Results so far

WP1&6–Automated CAR-NKC manufacturing platform with optimized CAR constructs



MS1.1 (and 5.1) isolation and cultivation protocol is synchronized constantly and consortium is provided with NK cells from a **manual** isolation process

MS1.2 the final establishment of the **automated** process for the manufacturing of target-specific CAR-NK-cells will be finished in November 2022

MS1.3 the production of a target-specific CAR vector in preclinical quality is finished

MS1.5 data package for the *in vitro* analysis of target-specific CAR-NK cells has been collected

MS6.1 production of the 1st lot of improved target-specific CAR lentiviral vector finished



GRex[®]-System
by Wilson Wolf Manufacturing



CliniMACS Prodigy[®]
by Miltenyi Biotec



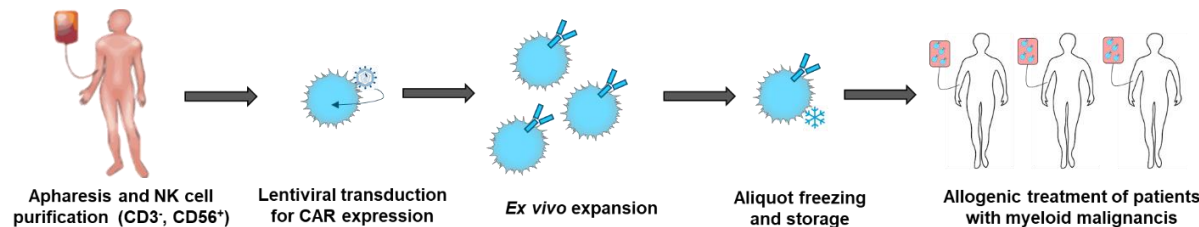
CAR-NK 4.0 – Results so far

WP2&3 – Design of study plan & Development of bispecific CAR constructs

Design of a study plan for the use of CAR NK cells in MDS/AML

- Preparation of a study protocol for a clinical phase I/IIa study to assess safety and efficacy of CAR-NK therapy in patients with myeloid malignancies

→ To achieve a fast clinical transfer of the ATMP after completion of the preclinical research



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Development of bispecific CAR constructs (focus: Extramedullary multiple myeloma (EMM))

- **MS3.1** Relevant antigen-binding domains have been identified and EMM-specific CAR-domains have been *designed*
- Organization of a Standard Operating Procedure (SOP) to standardize the sample collection in Chemnitz
- Current status: 4 EMM samples collected

CAR-NK 4.0 – Results so far

WP4 - Combination of CAR-NK cells with multi-specific innate cell engagers (ICE[®])



Successful generation of CD19 CAR-NK

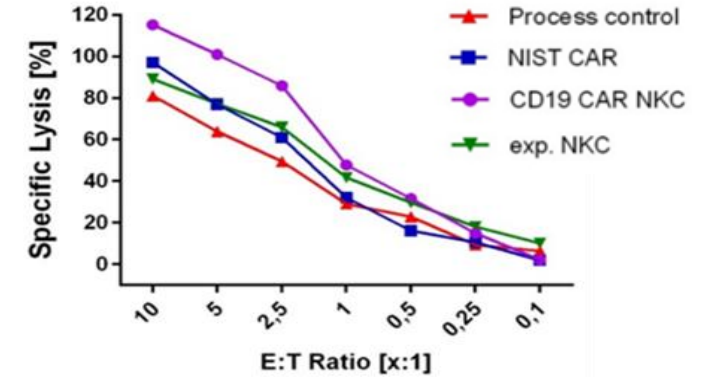
- Cloning and optimization of vectors ✓
- Optimization of γ -retroviral transduction and NK cell expansion protocols ✓
- > 40% CAR expression in primary NK ✓

CAR-NK cell phenotype

- Flow cytometric measurement of NK cell receptor profile of expanded (CAR-)NK cells ✓

Demonstration of CAR-NK activity

- Cytotoxicity in calcein release assays ✓
- Killing in InCucyte assays (kinetic assay) ✓
- Stimulation of degranulation activity ✓



3 anti-CD19 ICE[®] formats designed and produced

- Purity > 97% ✓
- Stability > 87% (7d, 37°C) ✓

Determination of ICE[®] binding affinities

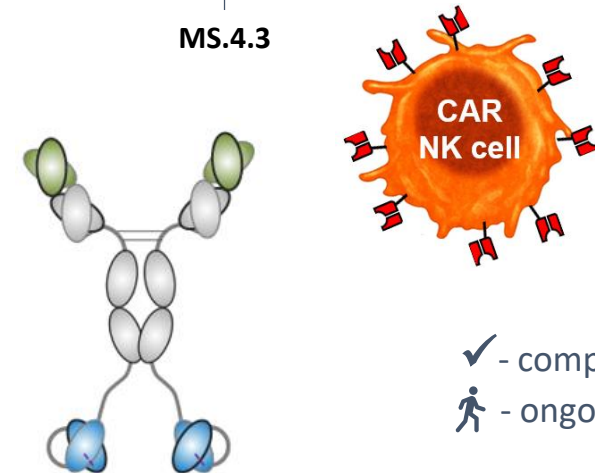
(ELISA, SPR, cellular binding)

- CD16 ✓
- CD19

Demonstration of in vitro functionality

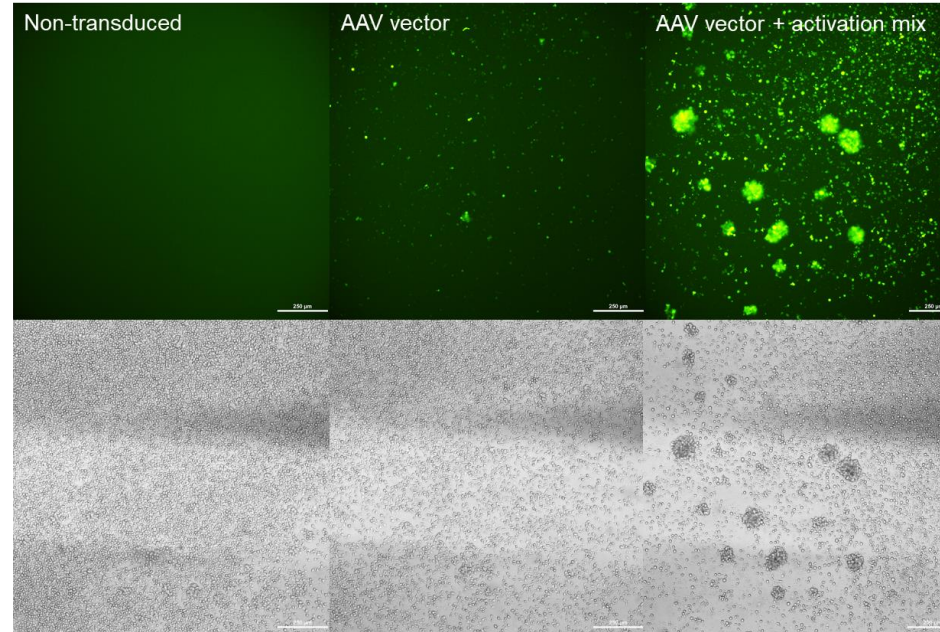
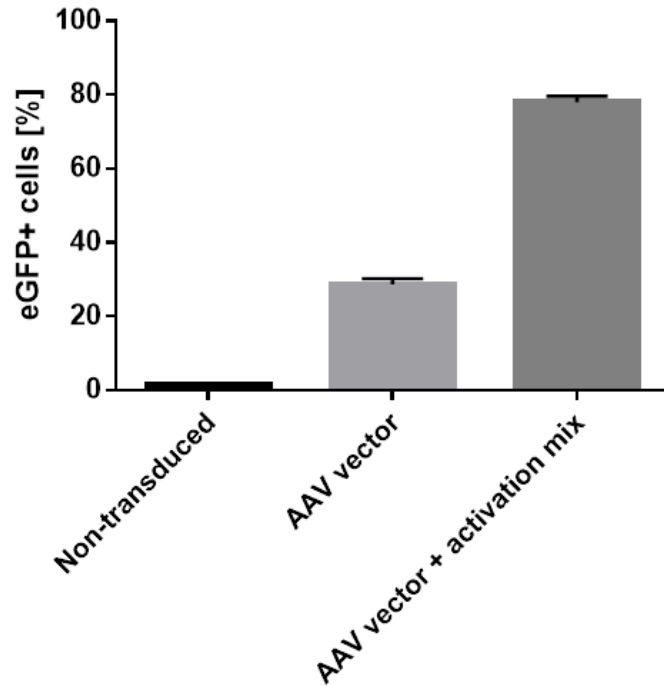
Activity of ICE[®] in ADCC:

- Calcein release killing assay ✓
- Time kinetics of killing (InCucyte) ✓



CAR-NK 4.0 – Results so far

WP5 – AAV vector-mediated CAR delivery system into primary human NK cells



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Fraunhofer
IZI

MHH
Medizinische Hochschule
Hannover

- **AAV vectors** for successful and efficient transduction and **transgene expression of human primary NK cells**
- Basal transgene expression level of AAV vectors is **highly donor-dependent** (mainly around 10-30%)
- Addition of **activation mix** increases transgene expression level to **~80%** → **independently of the donor!**
- **First AAV-CAR constructs (CAR-CD19, -CD4)** are produced and being tested

CAR-NK 4.0 – Synergies

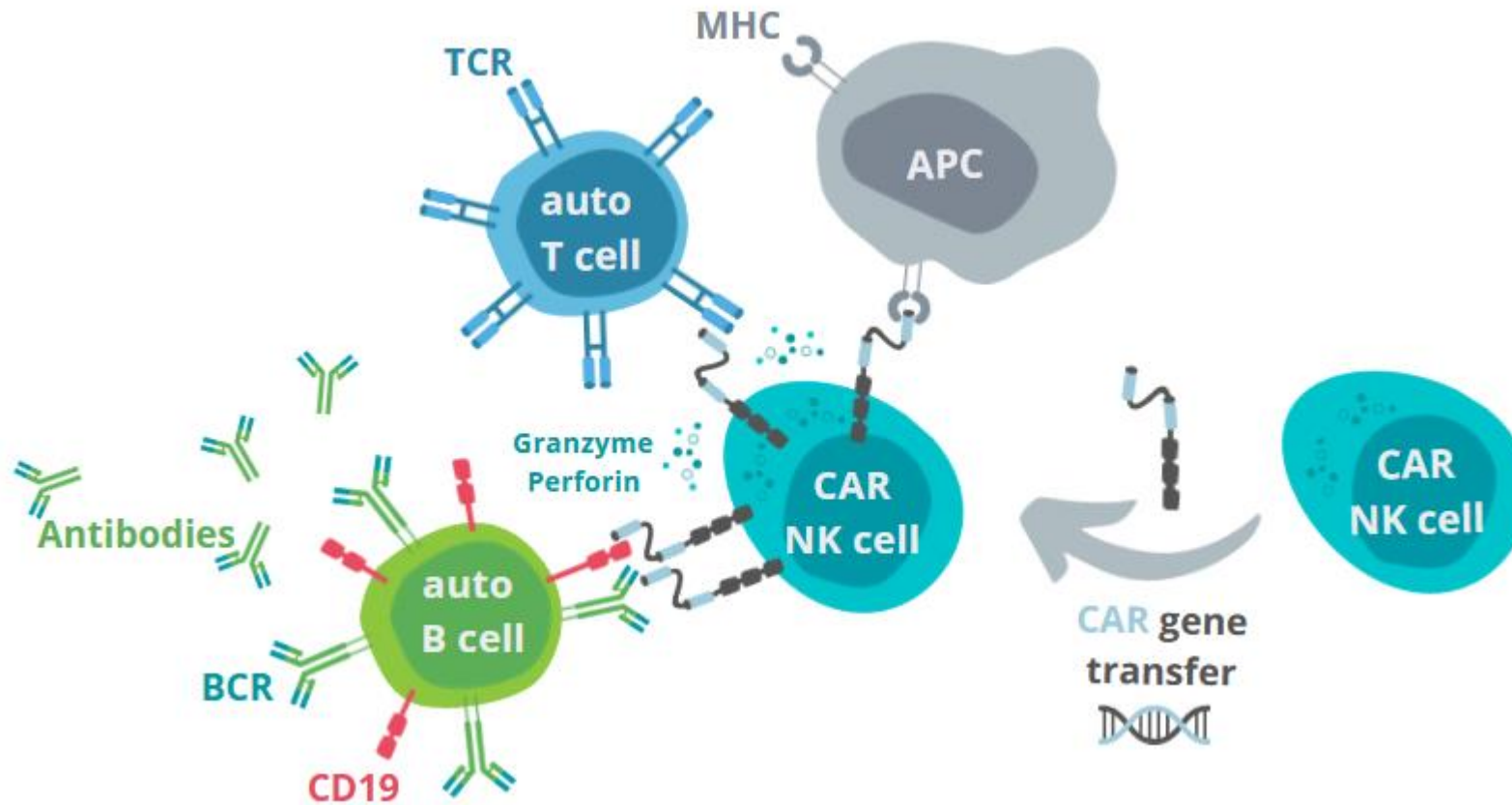


- Synergies within the different work packages (standardization of NK-protocols; centralized isolation of pNK cells)
- Support/Cooperation with **SaxoCellClinics** (WP2) on-going
- Support by **SaxoCellOmics** platform planned (WP3)
- **UltraCART** Project (Synergies in automation processes)
- Possible synergies **within Area 2**: Exchange of protocols, standardization of processes

CAR-NK 4.0 – Outlook

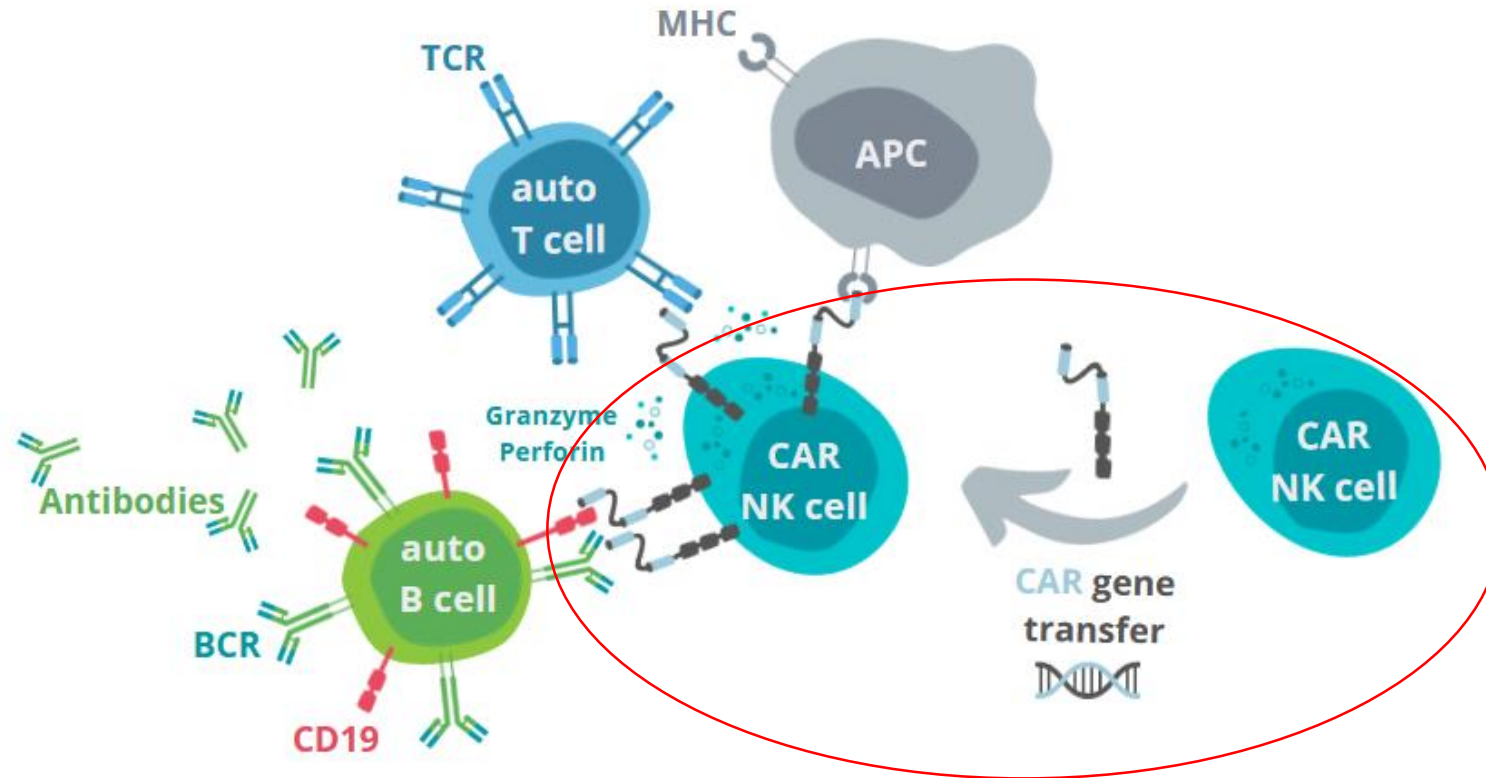
Work Package	Next steps
WP1	Finalization of the automated manufacturing process for target-specific CAR-NK cells at the CliniMACS® Prodigy® System, transfer of the process to Fraunhofer IZI Leipzig
WP2	Application for further funding to finance the planned clinical trial on MDS or AML with MRD, Ethics vote
WP3	Acquisition of sufficient number of EMM patient samples to search for novel targets via RNASeq and test the bispecific CAR constructs functionally
WP4	Generation of optimized CAR-NK cells, Affinity assays to check CD19 binding of ICE®; further <i>in vitro</i> and <i>in vivo</i> tests of cytotoxic CAR-NK cells in combination with ICE®
WP5	Investigation of the kinetics and the of transgen expression; Transduction of human pNKC with AAV-CAR-Vectors
WP6	Production of optimized target-specific CAR lentiviral vector in pre-clinical quality

CAReNK-AID – Project Overview



CAReNK-AID – Project Overview

CAR engineered NK cells for the targeting of severe AutoImmune Diseases



CAReNK-AID – Objectives

- High medical need for permanent treatment of autoimmune diseases
- SLE: recent success with autologous anti-CD19 CAR T cells is encouraging.
- Advantage of CAR NK cells:
 - Safety (GvHD, CRS)
 - Allogenic settings (reduced production costs)
 - Feasible transfer to non-malignant diseases

CAReNK-AID final product:

Off-the-shelf CAR-NK or CAR-T cells targeting (autoreactive) B/T cells for treatment of autoimmune diseases.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE



2021

CD19-Targeted CAR T Cells in Refractory Systemic Lupus Erythematosus

ARTICLES

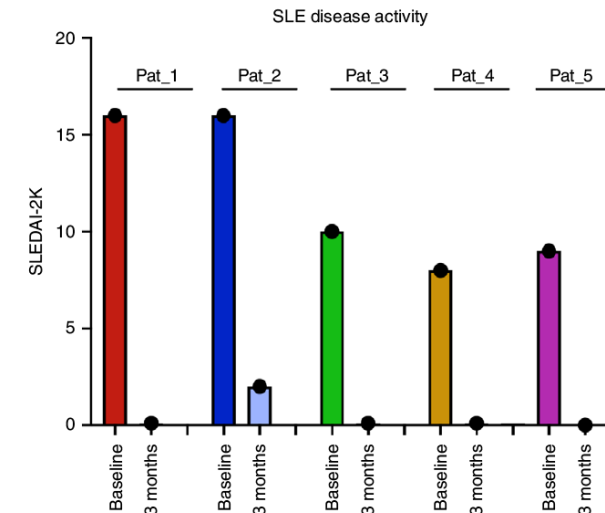
<https://doi.org/10.1038/s41591-022-02017-5>

nature
medicine

Check for updates

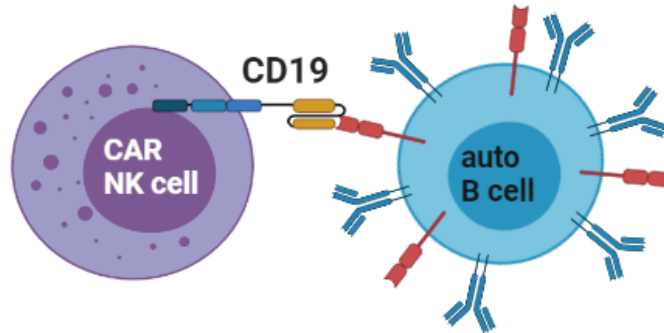
Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus

2022

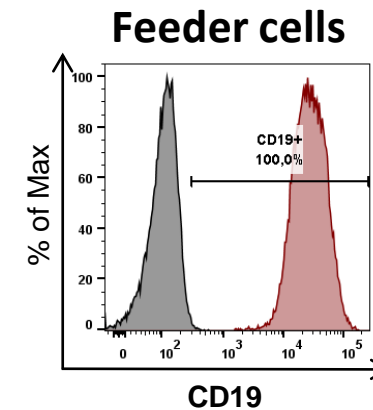
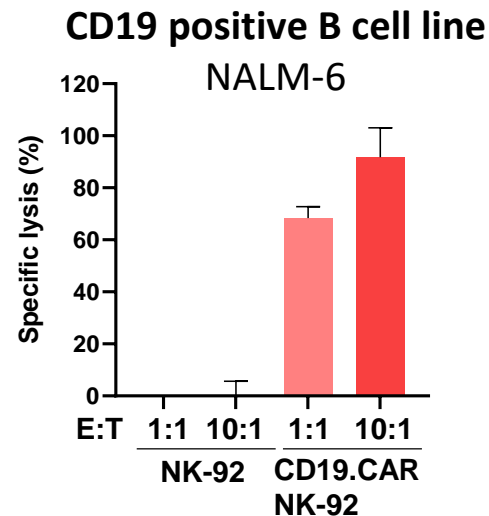
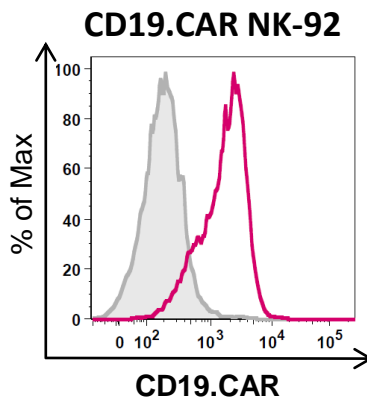
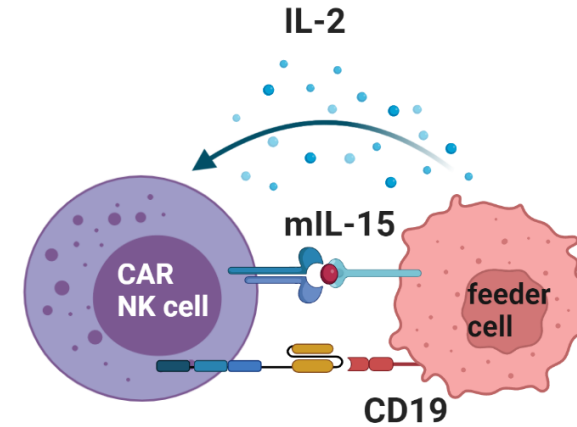


CAReNK-AID – Results so far

**CAR NK
Anti-Pan B cells**



Feeder cells for NK expansion



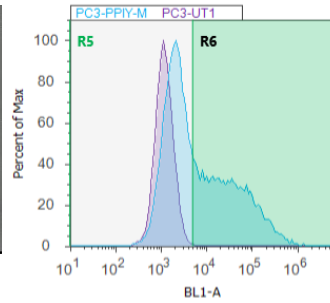
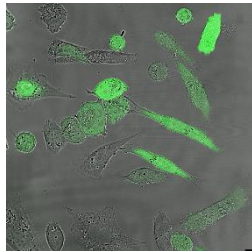
CAReNK-AID – Results so far

Virus-free NK cell transfection



nanoparticles

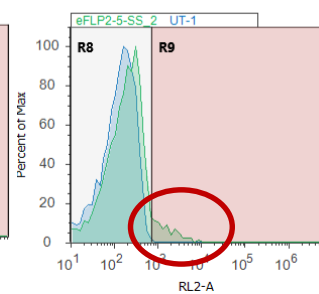
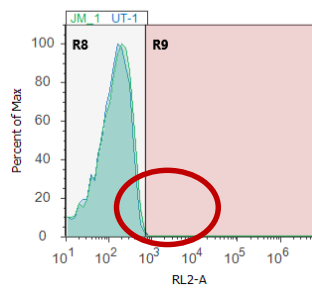
PC3



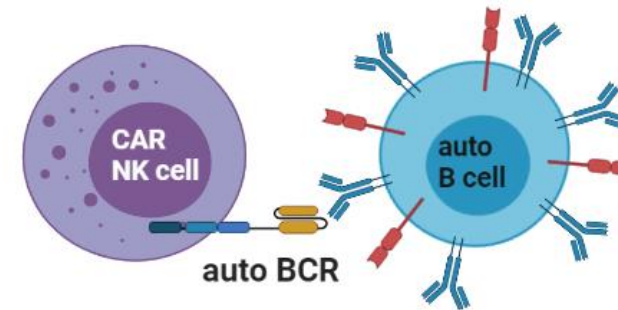
commercial ctrl.

nanoparticles

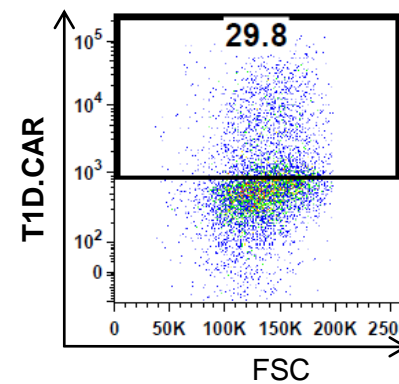
NK-92



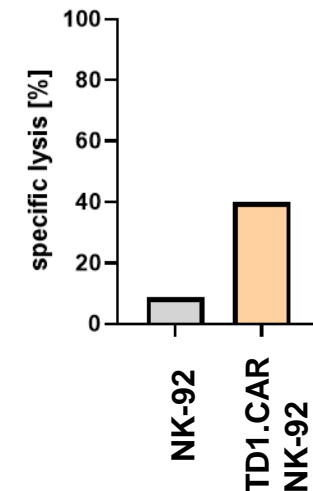
CAR NK Anti-autoreactive BCR - Type I Diabetes -



T1D.CAR NK-92

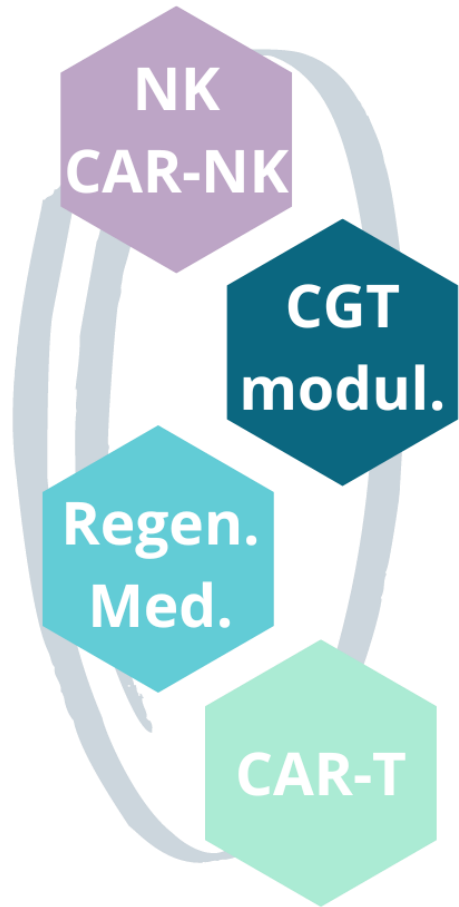


Cytotoxicity assay



E:T=10:1

CAReNK-AID – Synergies to other SaxoCell Projects



CAR-NK 4.0	●	●	●	●
NK4Therapy	●			●
AlloCARtreg		●	●	●
UltraCAR		●	●	●
TheraSTAR		●	●	●
EPC-CAR			●	●
OPTIX				●
HemRec	●			●
ZellWund				●
xMax				●
MSC-PrestiGe				●

❖ **NK cell expansion and production**

❖ **(CAR) gene transfer**

❖ **Transgenic GMP cell products**

❖ **Saxocell Omics, Clinics, Systems**

CAReNK-AID – Outlook

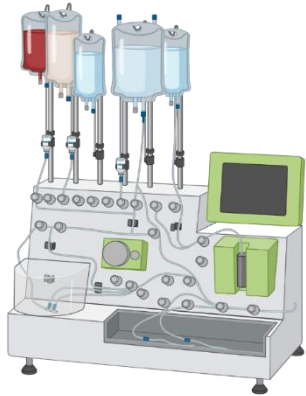
MaxCyte nanoparticles



virus-free gene transfer

Expansion

GMP



autoimmunity mouse model

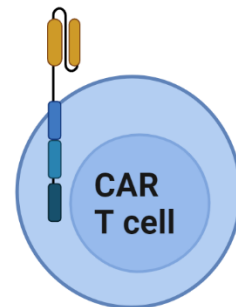
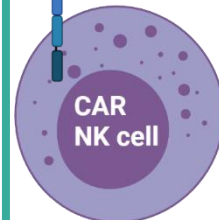
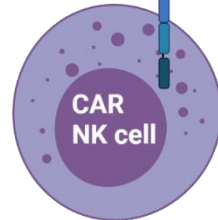


Pan B cell marker

Autoreactive B cell receptors

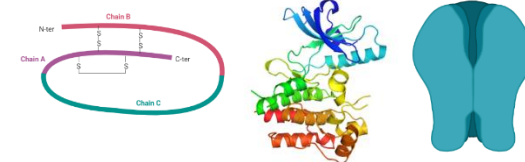
CD19.CAR

BCR.CAR

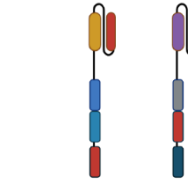


incl. targeting autoreactive T cells
APCs

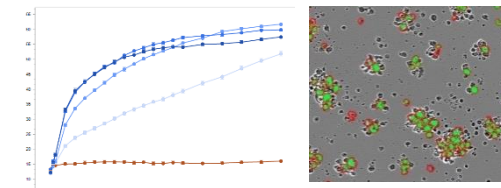
autoimmune targets



Myasthenia Gravis, Graves disease, SLE, T1D,...

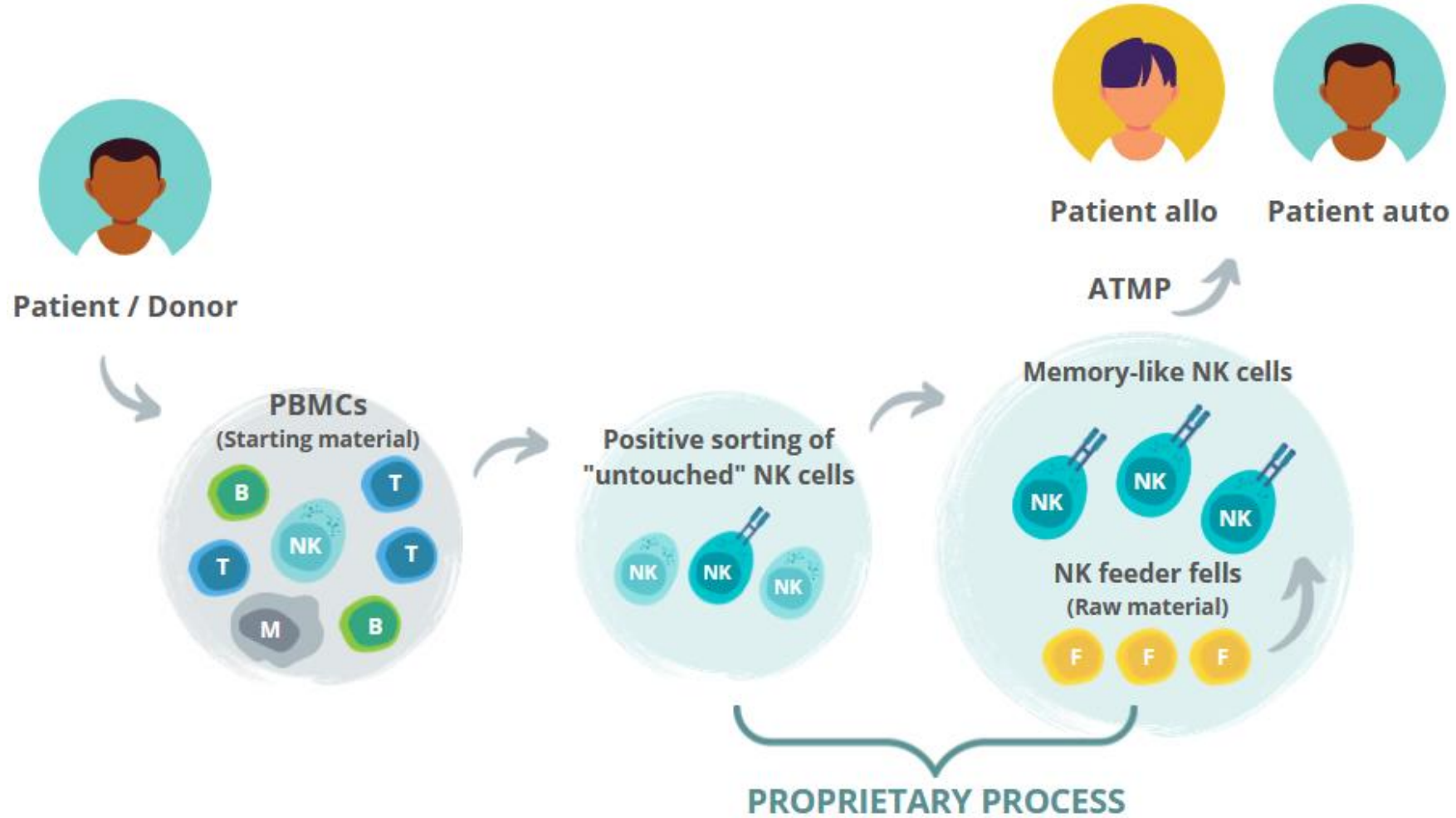


CAR generation



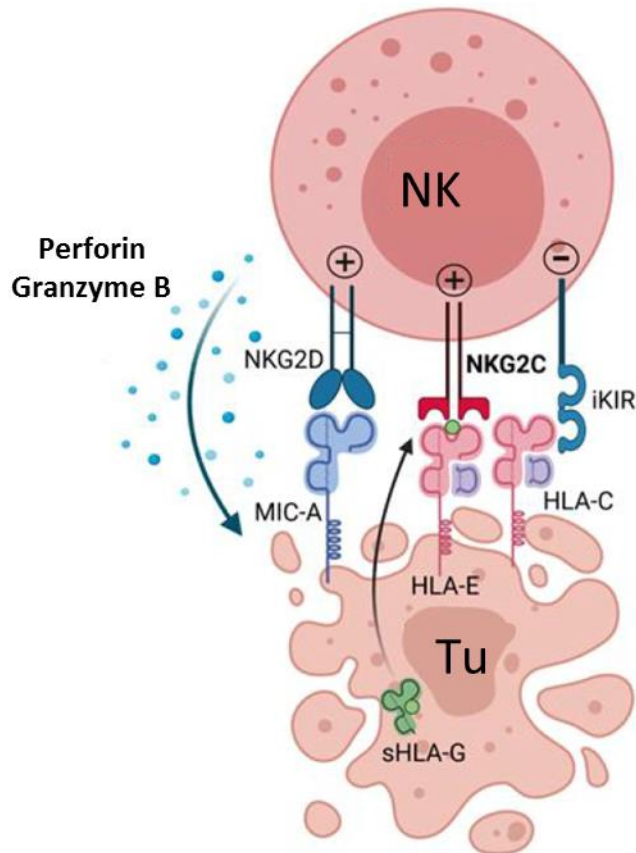
CAR-NK characterisation

NK4Therapy – Project Overview



NK4Therapy – objectives

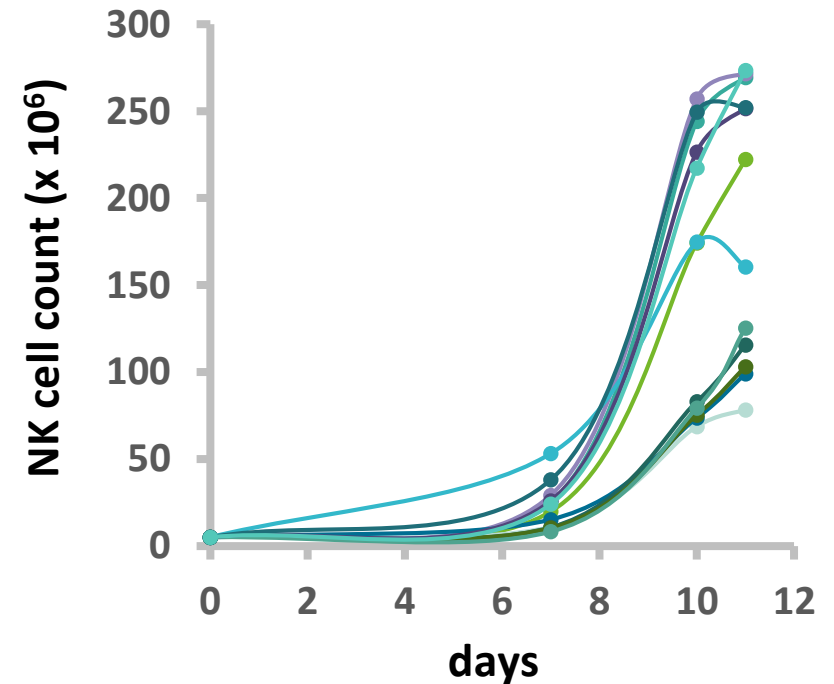
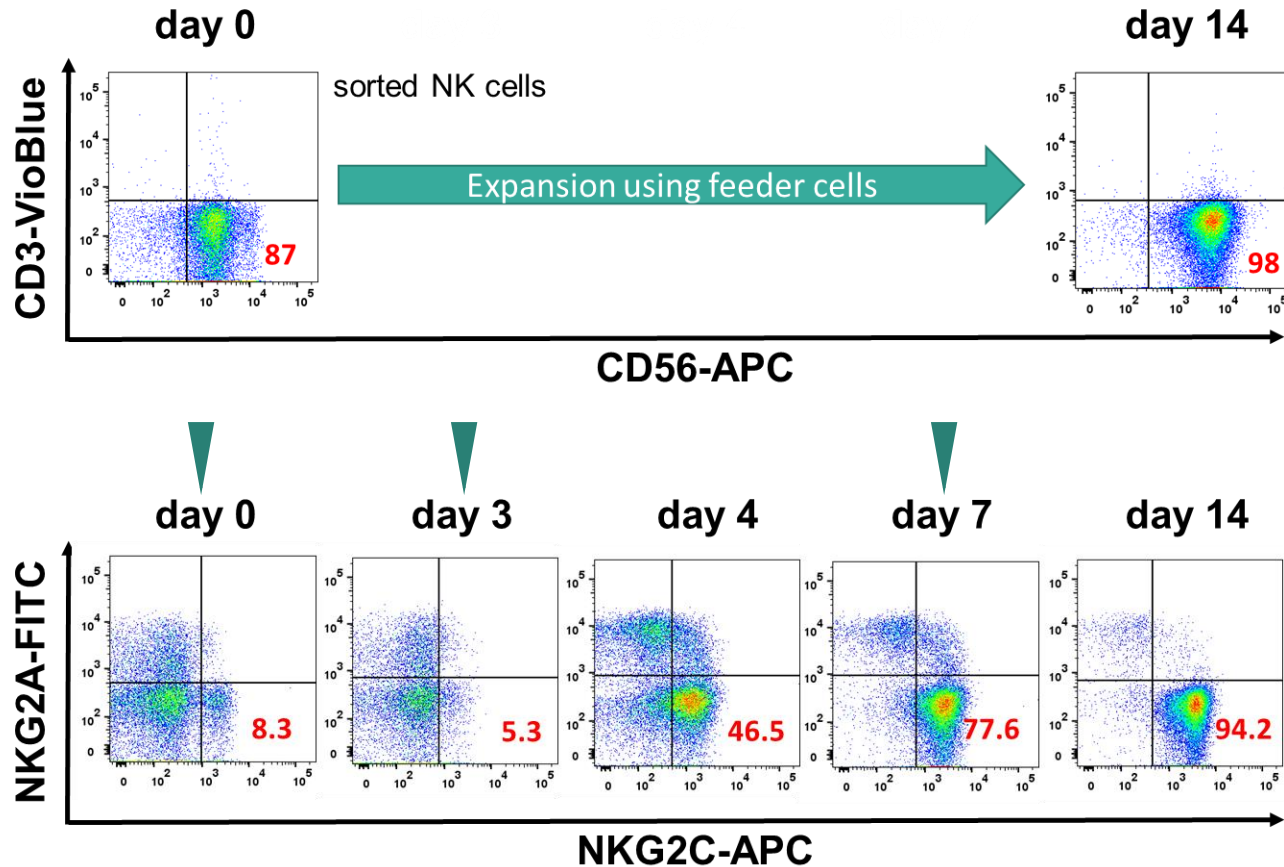
- **NK cells for immunotherapy of tumors**
 - Transplantable across HLA barriers (*no GvHD*)
 - Intrinsic anti-tumor cytotoxicity
 - Advantageous cytokine profile of differentiated CD56^{dim} NK cells (*no CRS*)



- **Focus on production and evaluation of differentiated NK cells for treatment of leukemia and solid tumors – final product: “Memory-like” NKG2C⁺ NK cells**
 - Recognition of malignant cells with deregulated levels of HLA-E and HLA-G (*broad applicability*)
 - Combinatorial „induced self“ and „modified self“ mechanisms of tumor cell killing
 - Increased cytotoxicity towards KIR/HLA-mismatched tumor targets
 - No genetic engineering needed (*cost effective*)
 - Can be combined with ADCC (*tunable*)

NK4Therapy – Results so far

WP3 „Large Scale Expansion of NK cells“ started with polyclonal feeder cells



Starting material: 5 x 10⁶ sorted NK cells

Expansion in disposable 6 well G-Rex bioreactor

NK4Therapy – Results so far

WP1 - Feeder cell clones and validation

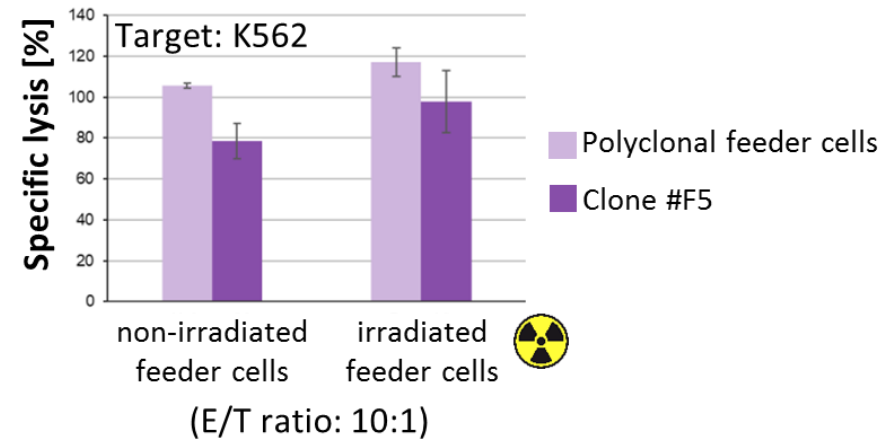
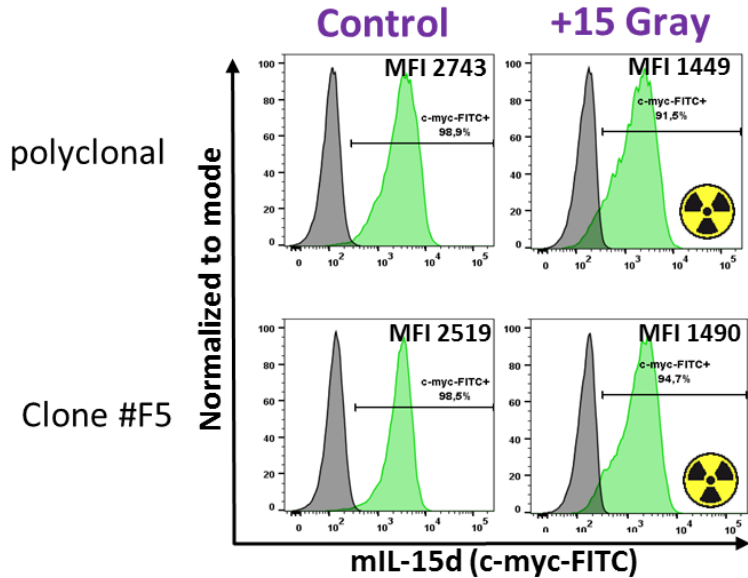
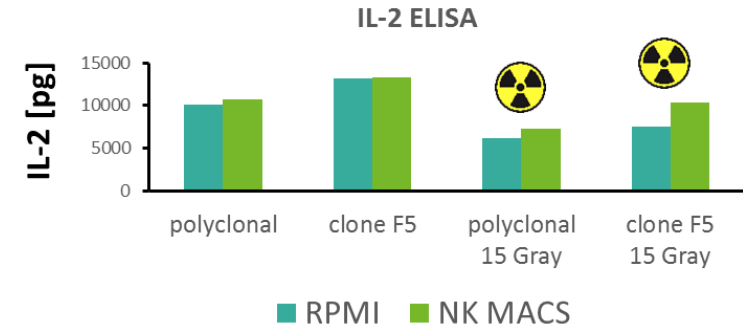
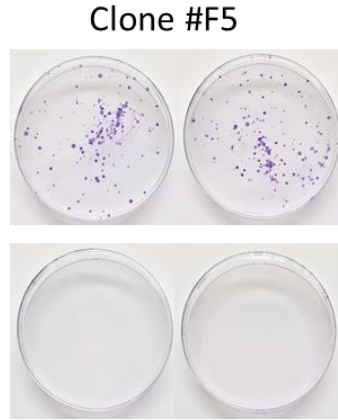


IMTEK
DEPARTMENT OF
MICROSYSTEMS ENGINEERING

Cell printing

Control

+15 Gray



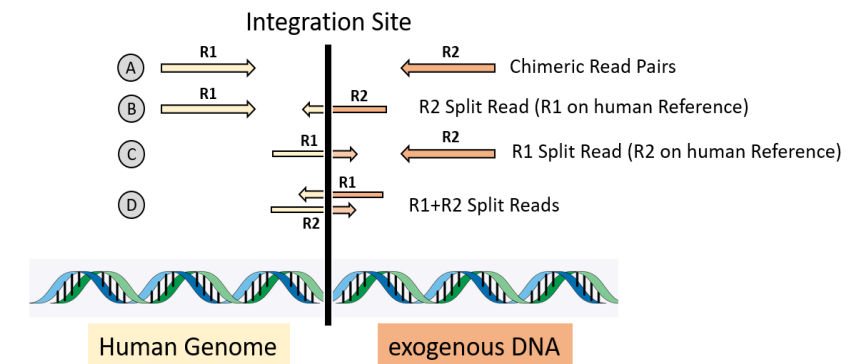
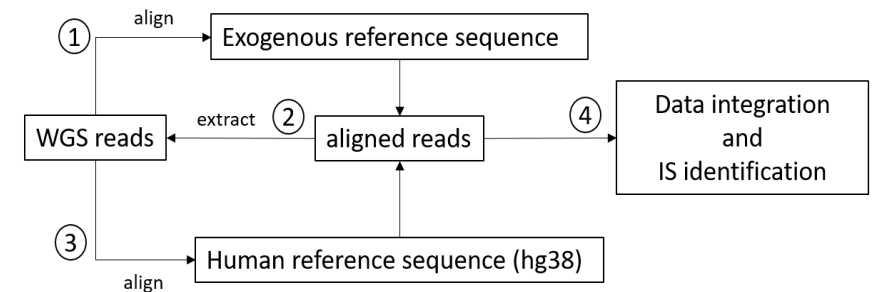
NK4Therapy – Results so far

WP2 - Feeder Cell Master Cell Bank (MCB)

- New optimized protocols and GMP raw materials for expansion of feeder cells
 - DMSO-free cryopreservation
 - Detaching with EDTA
 - Suspension culture

WP4 - GMP conformance

- Negotiations with contractors started (safety testing, identity)
- Whole genome sequencing of first feeder cell clones accomplished (*showcase for regulatory bodies*):
 - Development of proviral-loci-specific PCR
 - Sequence validation of transgenes
 - Assessment of DNA copy number
 - Analysis of „contaminating“ viral sequences (e.g. EBV, Adenovirus, Papillomavirus etc.)

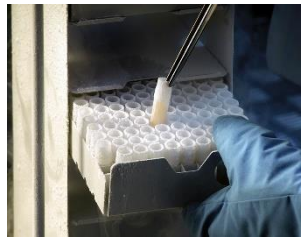


NK4Therapy – Synergies



- Exchange of isogenic target cell lines with deficient for HLA and with defined KIR-ligand settings between NK cell groups
- Feeder cell lines for production of CAR-NK cells (NK-CAR 4.0) and for production of NK cells engineered with reverse/epitope-CARs (i.e. for CARE-NK-AID)
- Streamlining of GMP processes and regulatory issues (Allo-CAR, NK-CARE-AID)

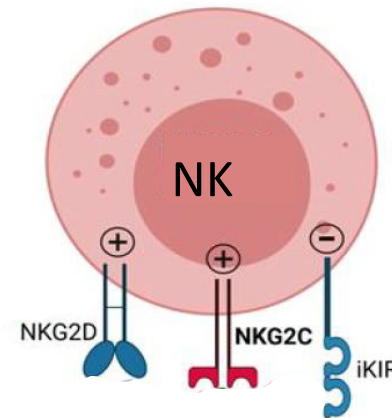
NK4Therapy – Outlook



GMP-compliant feeder cell MCB



GMP-compliant large scale NK cell production



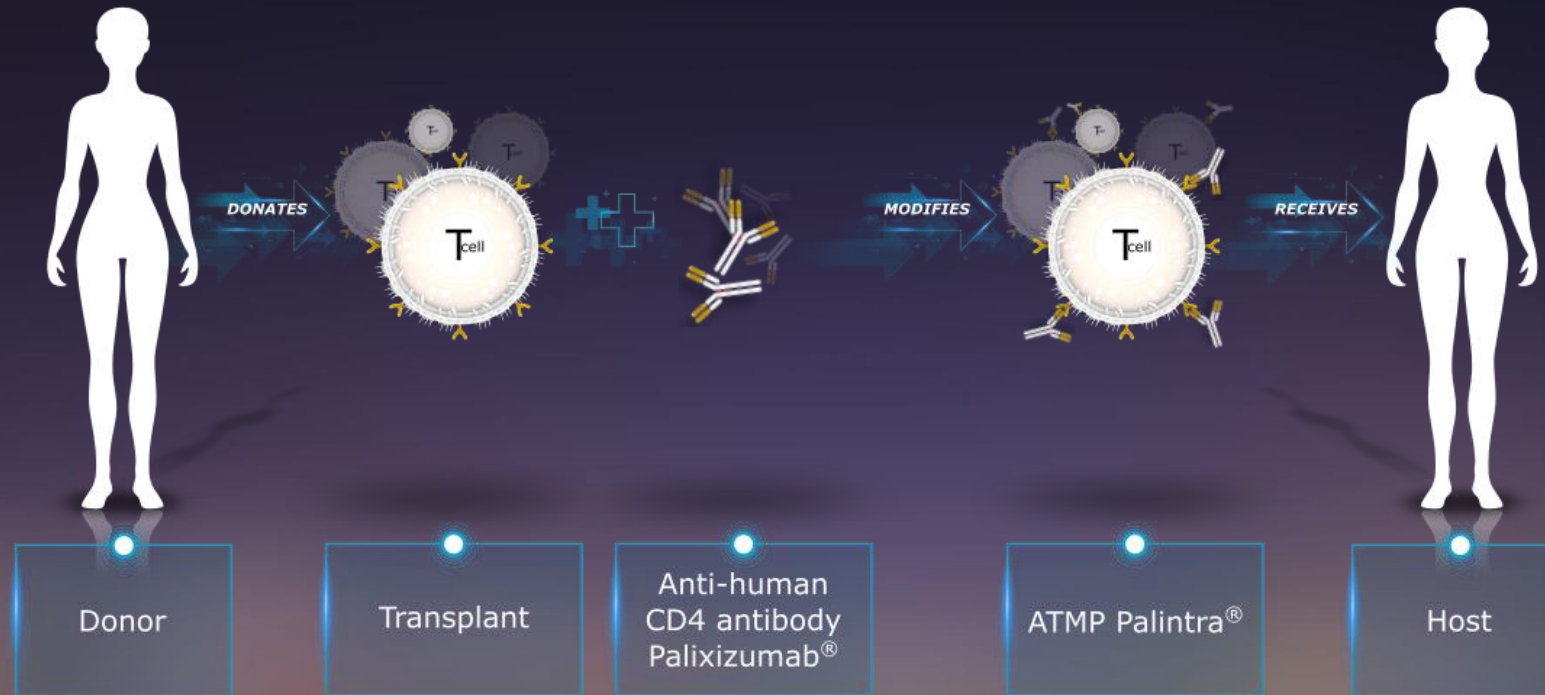
NK cell isolation (GMP)



in vitro / *in vivo* validation of NKG2C⁺ NK cells

- Platform technology for expanding NKG2C⁺-CAR-NK cells and CD19- and BCR-CAR NK cells

OPTIX—Project Overview



AREA 4 – CGT

Optimized GMP manufacturing and first-in-man phase 1 study of Palintra[®] as an ATMP for allogeneic hematopoietic cell transplantation (allo Tx)—**OPTIX**

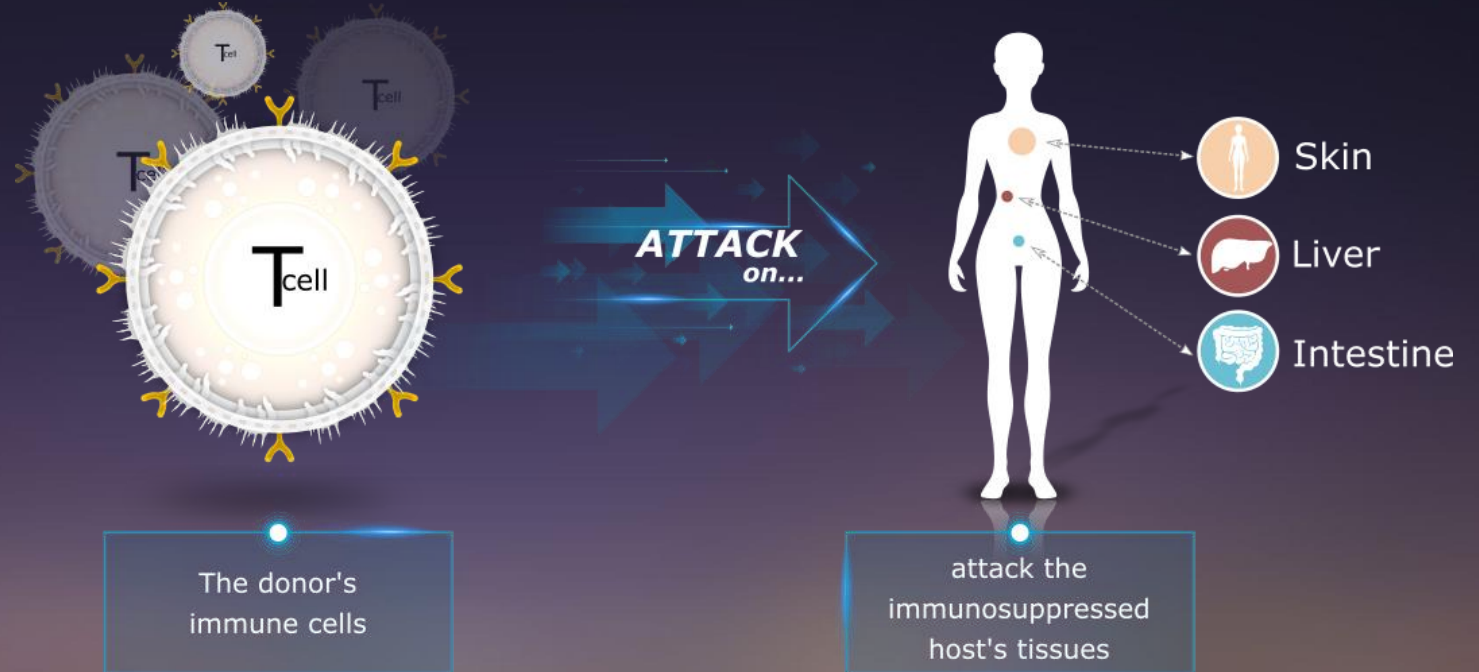
OPTIX—Problem Statement

Current treatment option:

- ❑ Systemic immunosuppression

Serious treatment related effects

- ❑ Infections
- ❑ Recurrence of Cancer
- ❑ Reduced Graft-vs-Leukaemia effect (GvL)



Graft-versus-host disease (GvHD) after allogeneic hematopoietic cell transplantation (aHCT)

→ Frequent occurrence, high mortality, serious side effects of counter therapy

OPTIX—Problem Scale

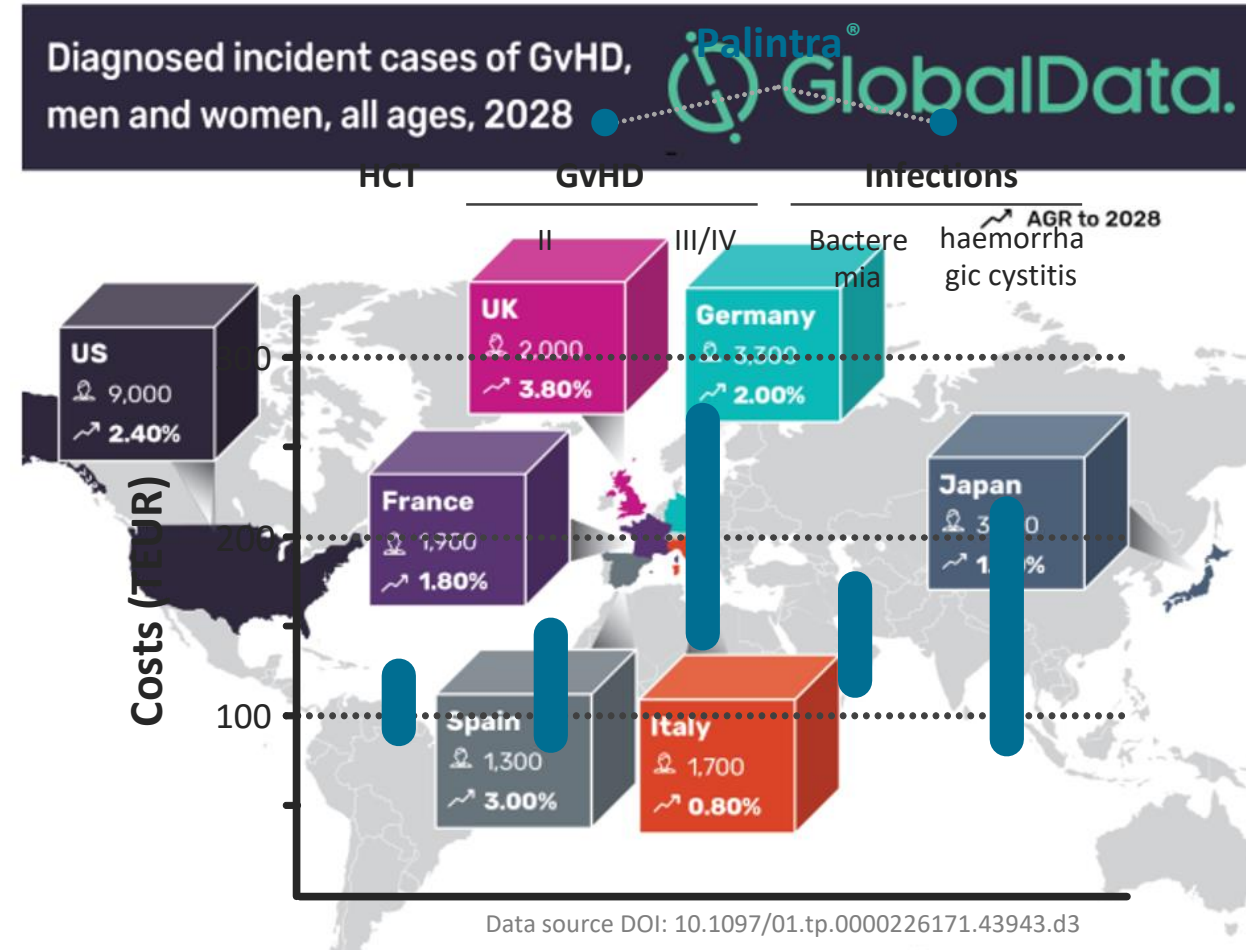
Allogeneic Hematopoietic Cell Transplantation (aHCT)

- ❑ Only curative approach for many hematologic malignancies
- ❑ World-wide appr. 40.000 transplantations annually (2016)

Acute Graft-versus-Host Disease (GvHD) Grade III/IV

- ❑ Appr. 50 % of all patients
- ❑ Mortality 15–30 %
- ❑ Current therapy causes relevant therapy associated morbidity and costs

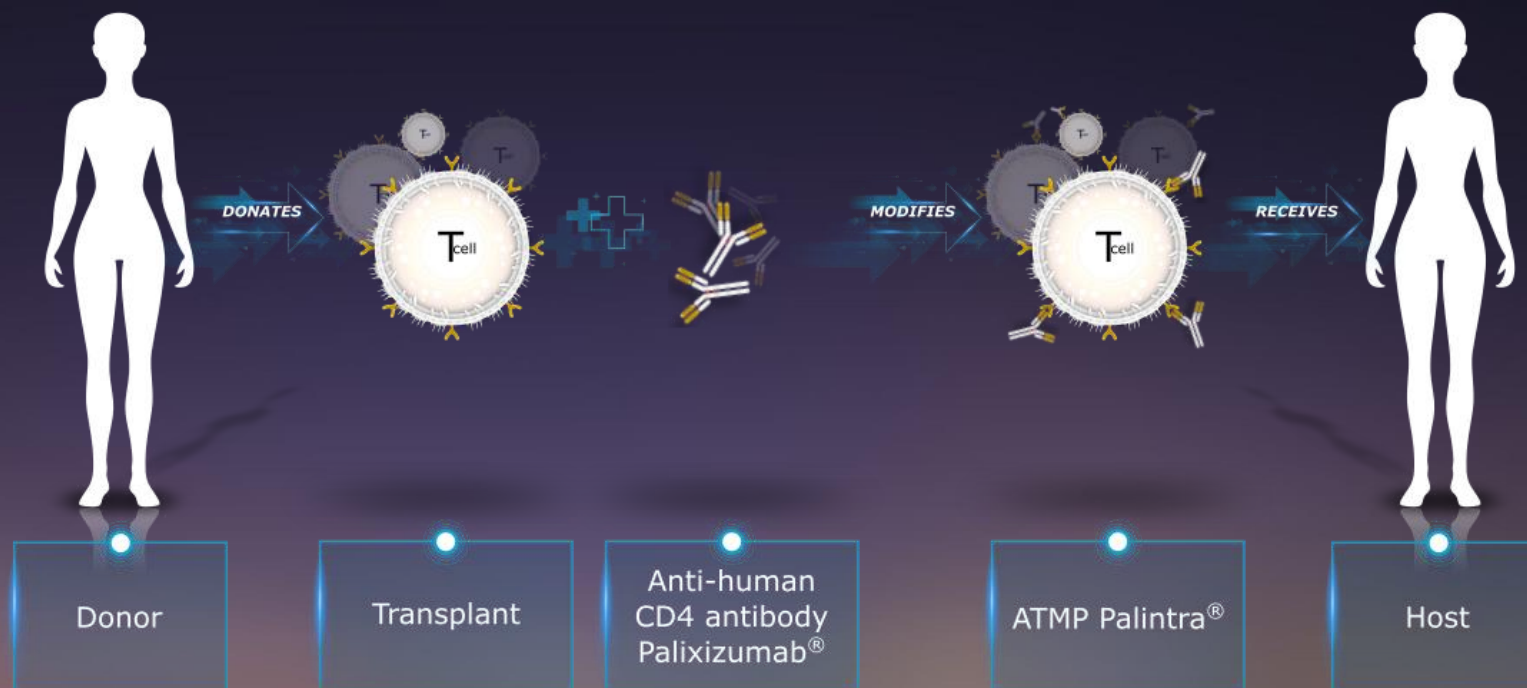
COST SPAN OF AHCT AND COMPLICATIONS



OPTIX—Solution: Tolerance Induction

Goals

- ❑ Prevent GvHD
→ prolong survival
- ❑ Avoid/Reduce immunosuppressive therapy
→ minimize side effects



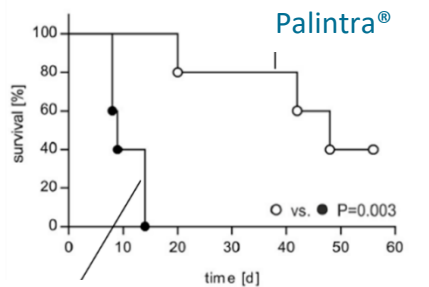
OPTIX – Pipeline from lab to clinics

Project Start



AREA 4 – CGT

In-vitro and in-vivo safety and efficacy



cell transplant

Acknowledgements

OPTIX Project Partners:

 **Fraunhofer**
IZI

 **Tcell Tolerance**

 **KLINIKUM CHEMNITZ**
gGmbH

Dr. Uwe Krasselt
Prof. Ulrich Räh
Florian Koch



PD Dr. Stephan Fricke
Dr. Sandy Tretbar
Dr. Ulrich Blache
Nadja Hilger
Kristina Roth
Bianca Zönnchen

PD Dr. Mathias Hänel
PD Dr. Stephan Fricke
Dr. Paul Warncke
Dr. Undine Meusch
Henriette Auerswald
Nadine Heimer



SaxoCell Hub (Fh IZI)

Dr. Thomas Tradler
Anette Bartsch
Ilka Henze
Sophia Kolbe

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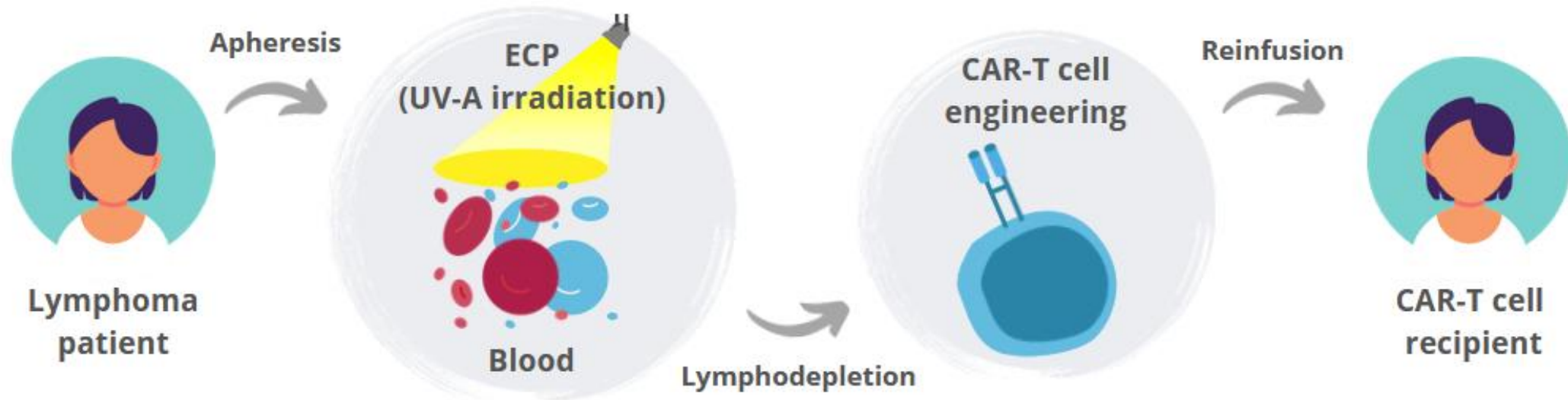


l.stahl@tcell-tolerance.de



www.tcell-tolerance.de

ECP-CAR – Project Overview

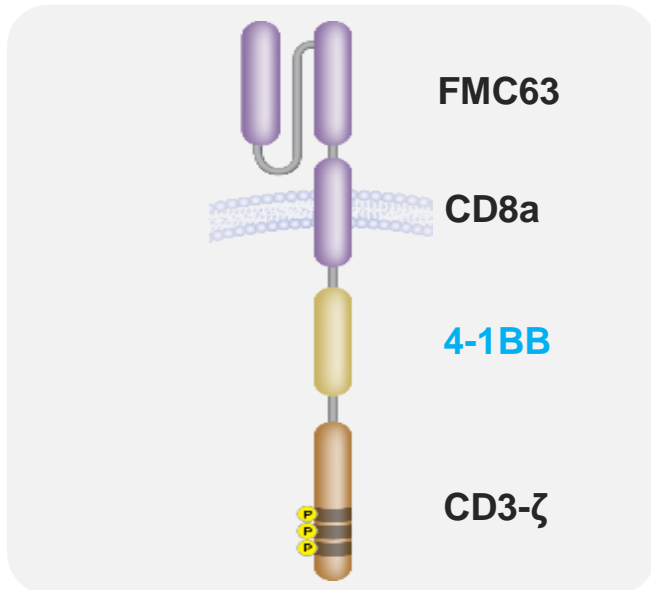


ECP-CAR – Project Overview

CAR T cells (aggressive lymphomas)



Tisagenlecleucel

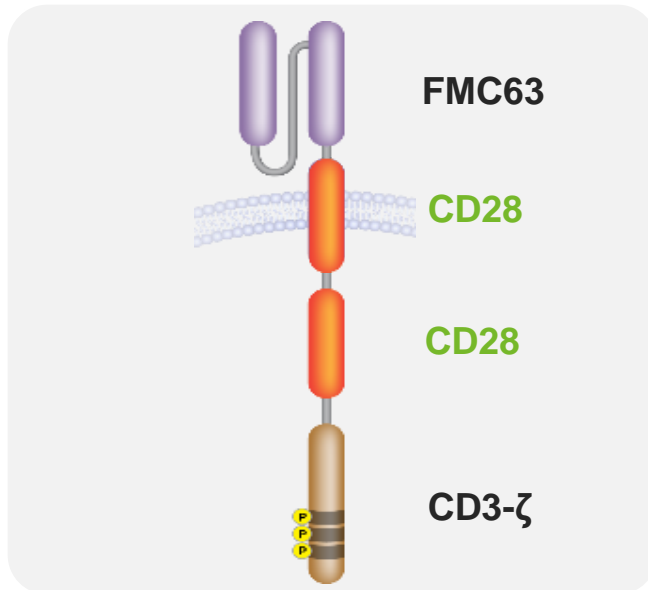


Lentivirus

Cryopreserved



Axicabtagene ciloleucel

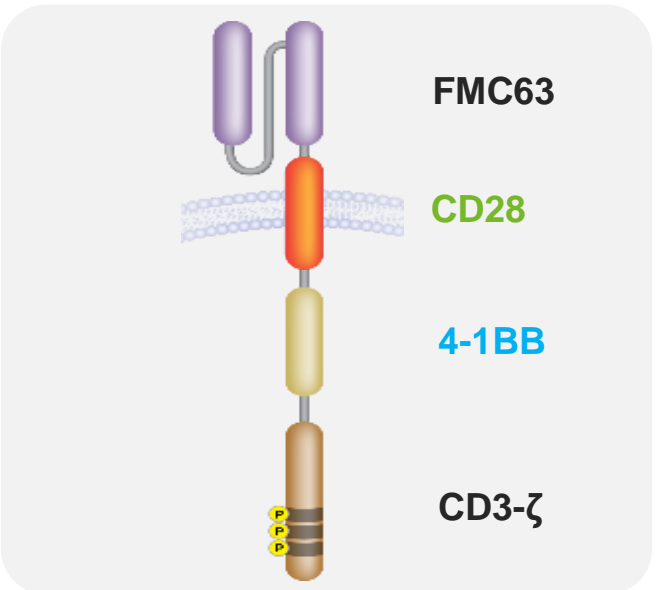


Retrovirus

Fresh



Lisocabtagene maraleucel



Lentivirus

1:1 CD4:CD8

Fresh

CD19 ANTIBODY

HINGE

COSTIMULATORY
DOMAIN

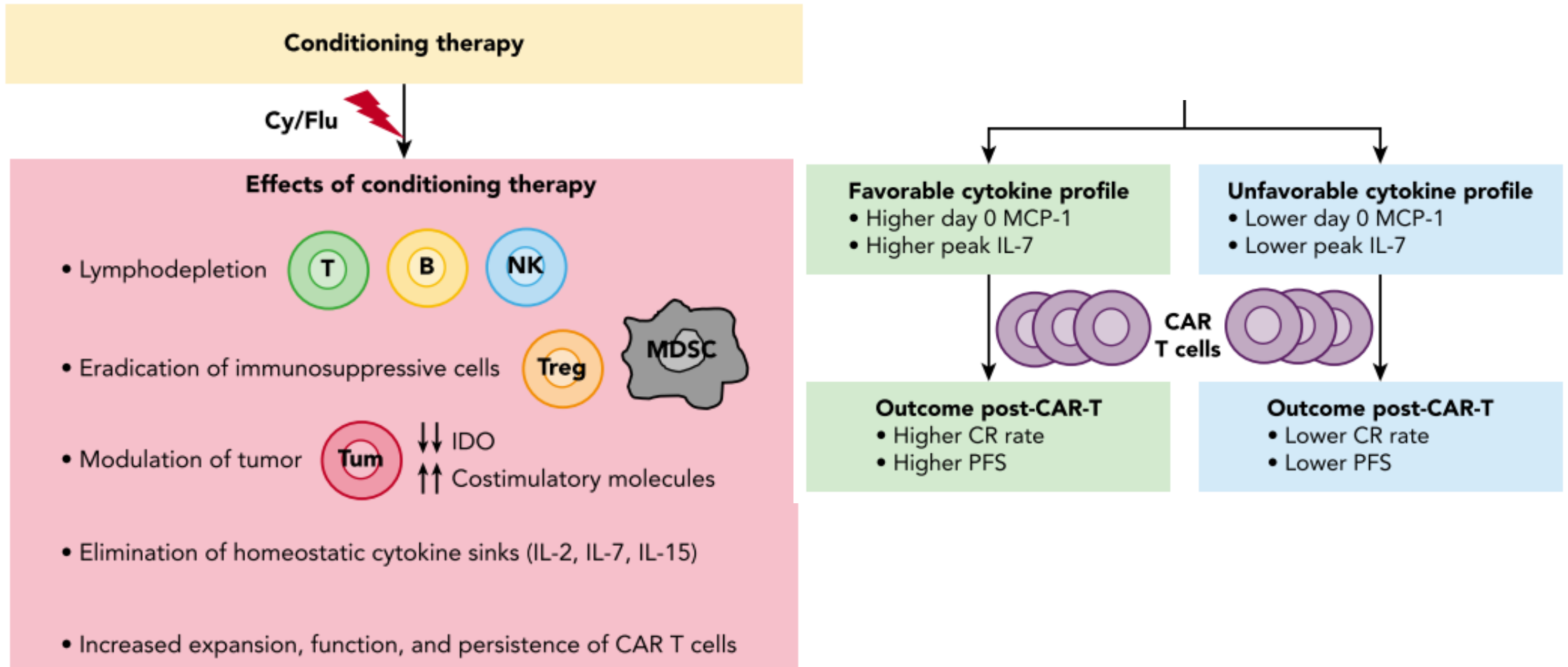
ACTIVATION
DOMAIN

GENE TRANSFER

APHERESIS
PRODUCT

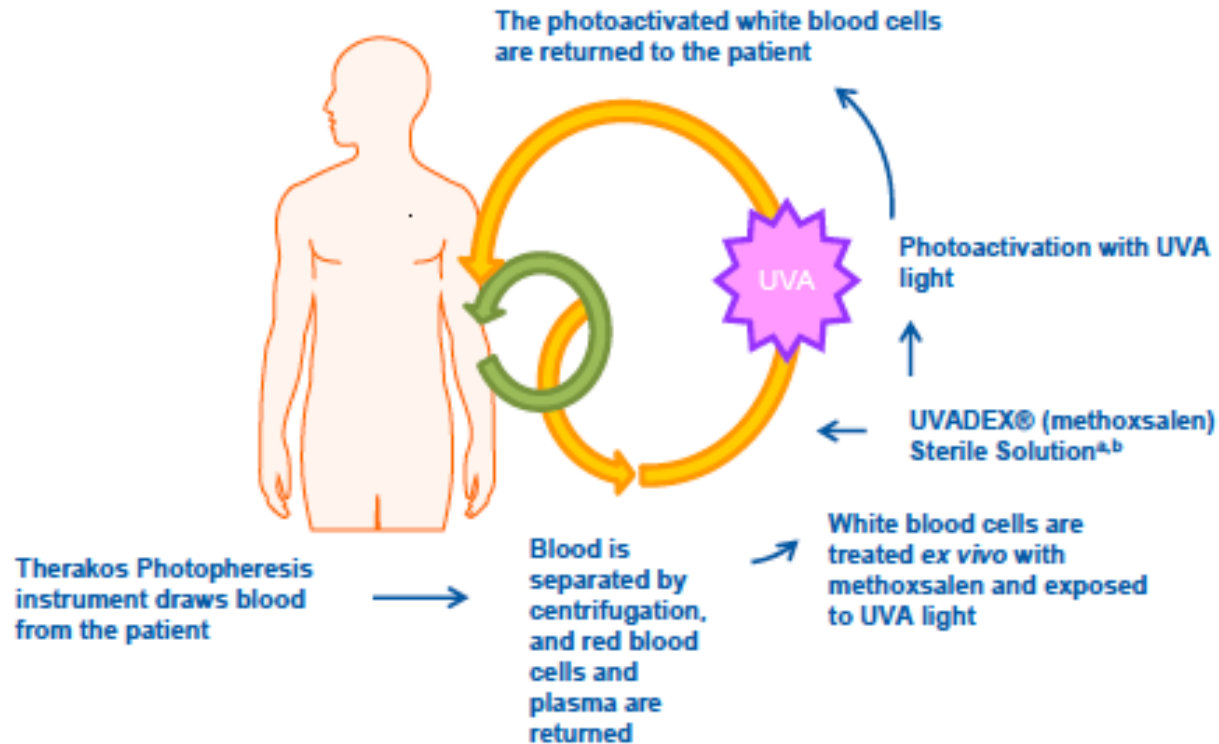
ECP-CAR – Project Overview

Lymphodepletion (is conditioning the key?)



ECP-CAR – Project Overview

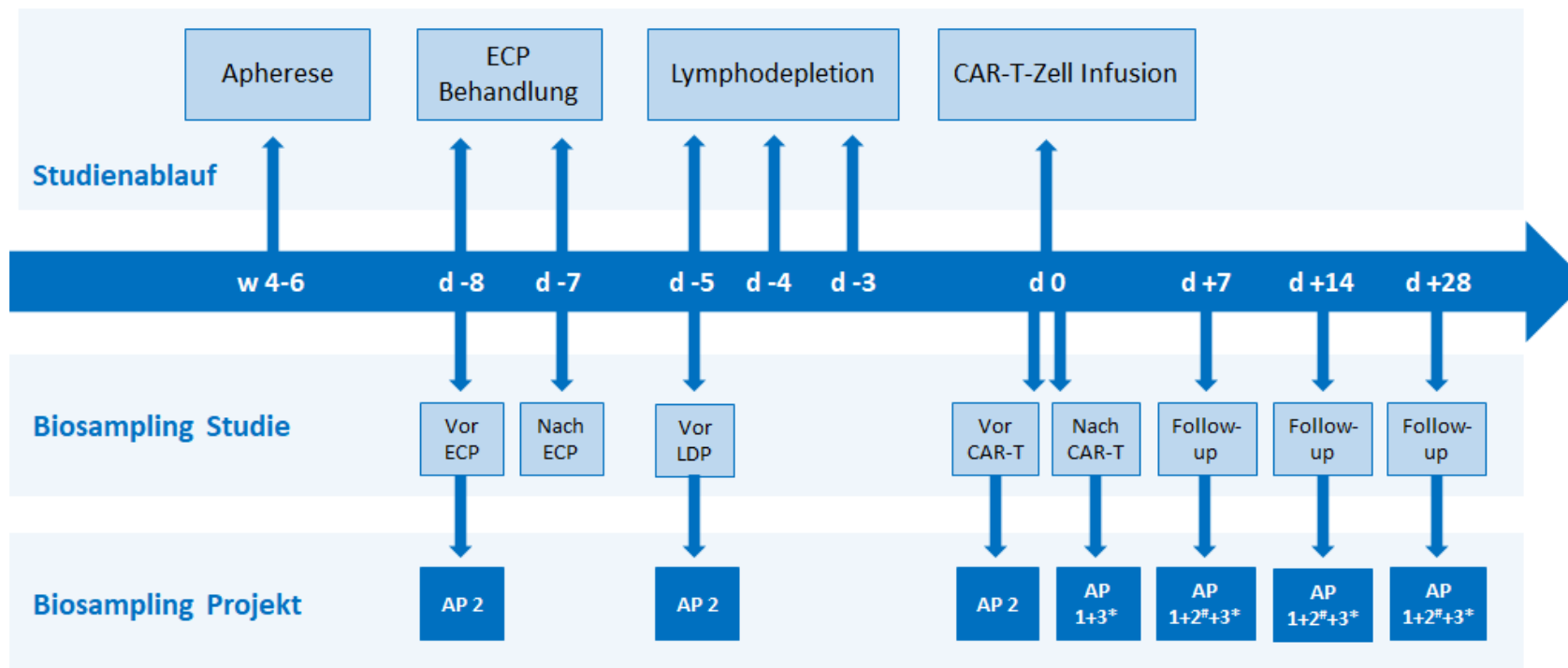
Extracorporeal Photopheresis (ECP)



R. Edelson et al. Treatment of Cutaneous T-Cell Lymphoma by Extracorporeal Photochemotherapy. N Engl J Med 1987 316:297-303

ECP-CAR – Project Overview

PhotoCAR clinical trial



Key inclusion criteria:

- age ≥ 18 years
- ECOG 0-2
- Diagnosis of aggressive B-cell lymphoma
- indication and planned treatment with licensed CAR T-cell therapies

Translational analyses (insights) of

- patients' CAR-T cells (quantitative and qualitative)
- ECP induced modulation of cellular and humoral microenvironment
- dynamics of cytotoxic effector functions and transcriptome-profiles

ECP-CAR – Results so far



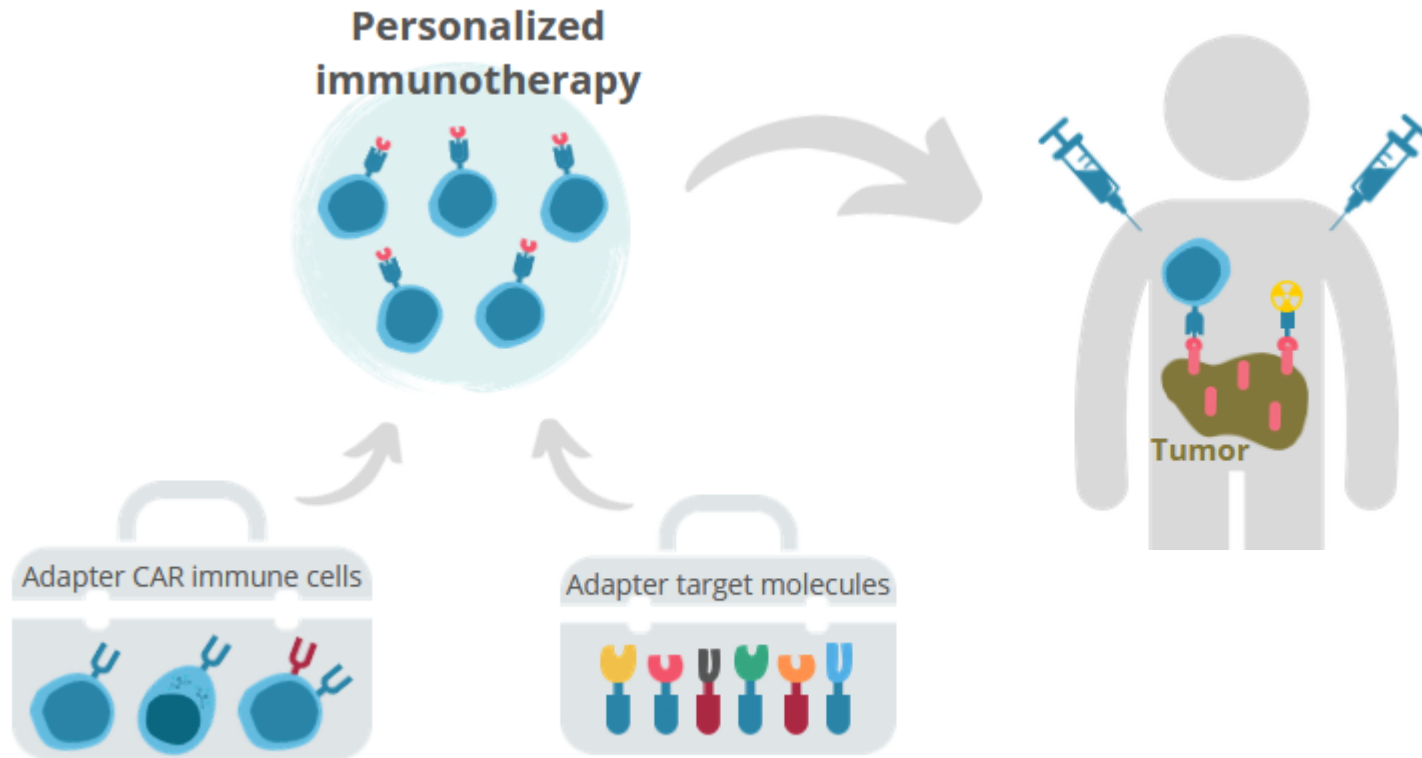
- Lab methodology (immunology) established
- Contract with Malinckrodt (PhotoCAR clinical trial) in discussion
- Manufacturing licence for ECP pending (request submitted)
- scientific advice with Paul Ehrlich Institute – scheduled on 1st November 2022
- trial start expected Q2 2023

Collaboration with:

- Institute for Immunology (Prof. Dr. U. Sack, Dr. R. Weiss)
- Saxocell Omics (Dr. K. Reiche)

- CAR-T treatment without toxicities of chemotherapy
 - applicable to all products and all entities
- reduction of immunological complications, e.g. CRS/ICANS through ECP-immunomodulation
- application of results of cellular kinetics and functional alterations of CAR-T to further developments of celltherapies

TheraSTAR – Project Overview



Michael Bachmann,
HZDR, TUD

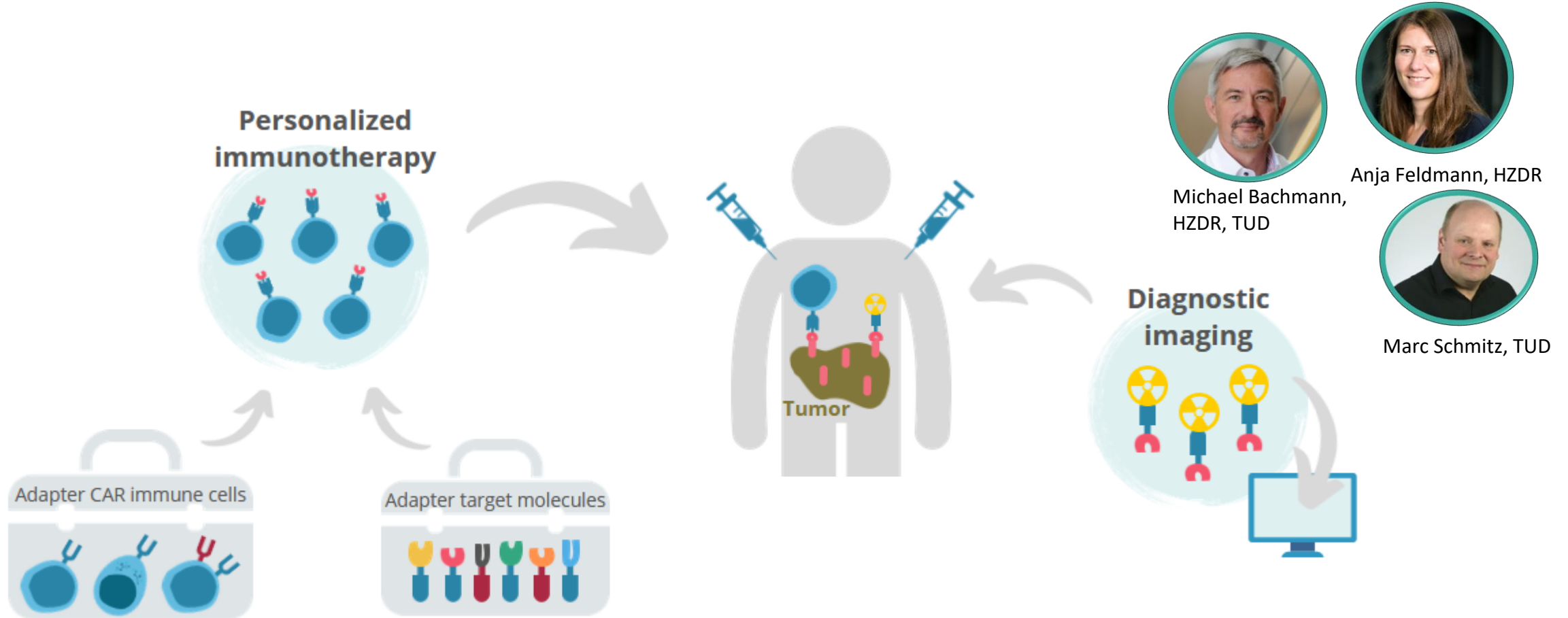


Anja Feldmann, HZDR

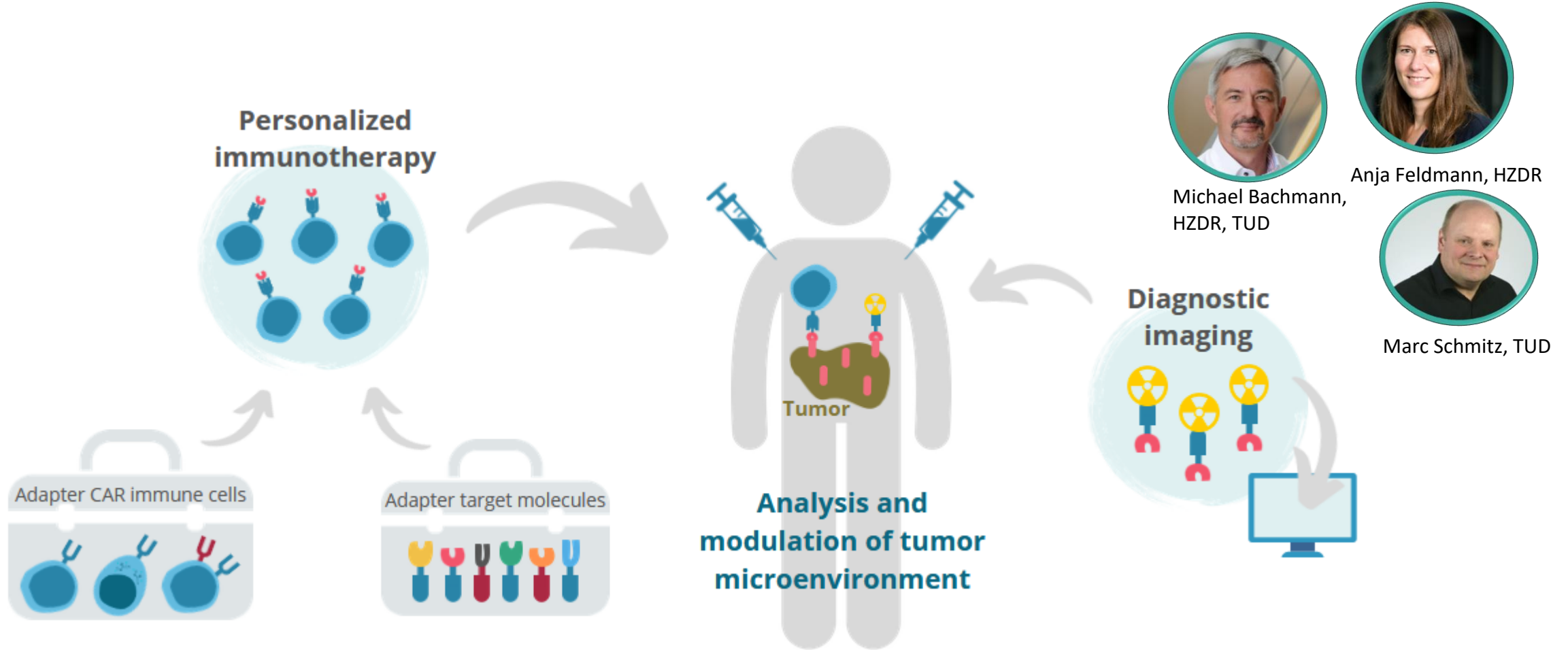


Marc Schmitz, TUD

TheraSTAR – Project Overview

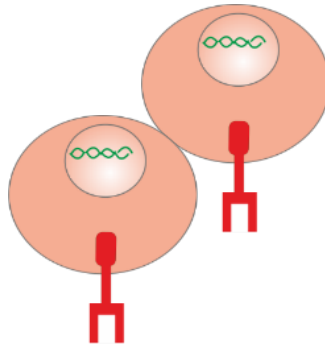


TheraSTAR – Project Overview

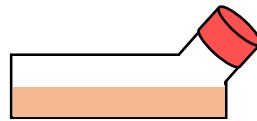


TheraSTAR – Results so far

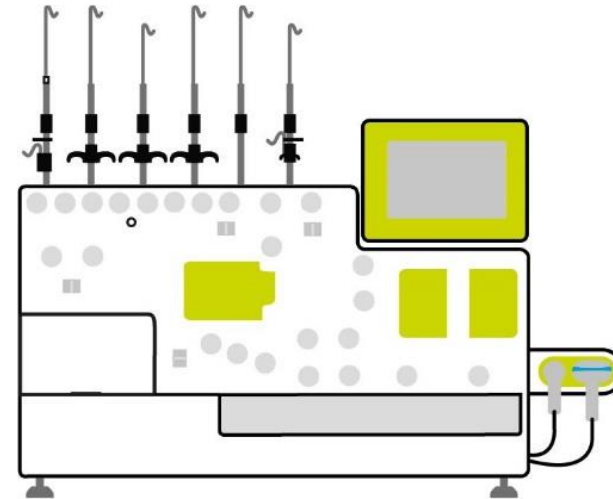
Generation of **Adapter CAR T cells**



Manual

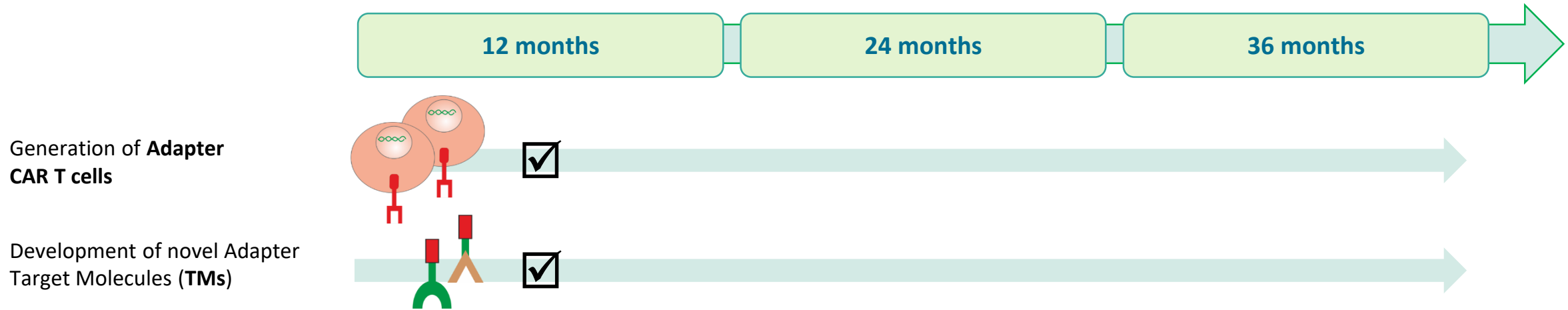


Automated scalable GMP-compliant



CliniMACS Prodigy® (Miltenyi Biotec)

TheraSTAR – Results so far

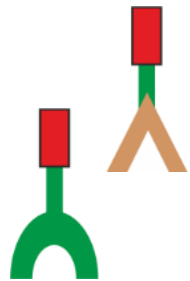


TheraSTAR – Results so far

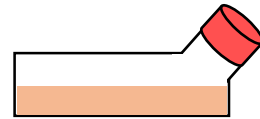
Development of novel Adapter Target Molecules (**TMs**) targeting immune checkpoint molecules



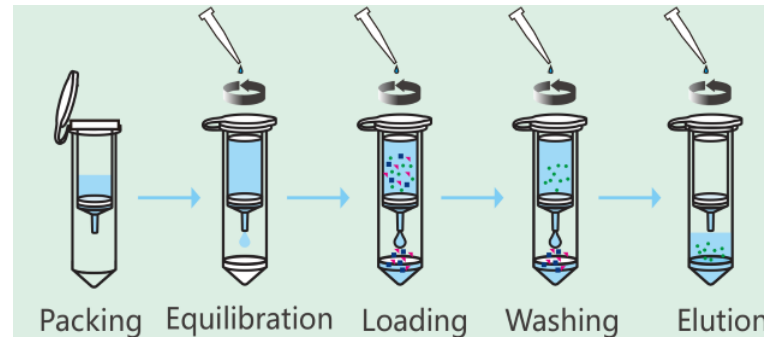
Design



Expression

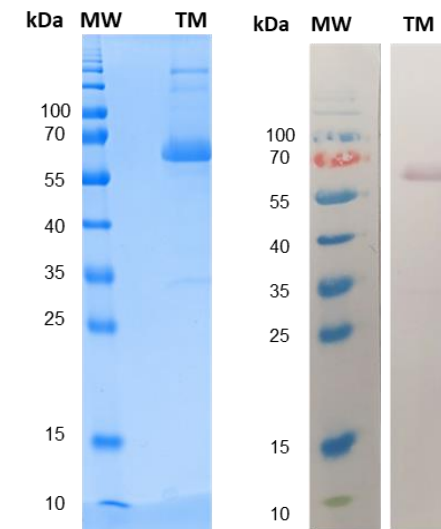


Purification



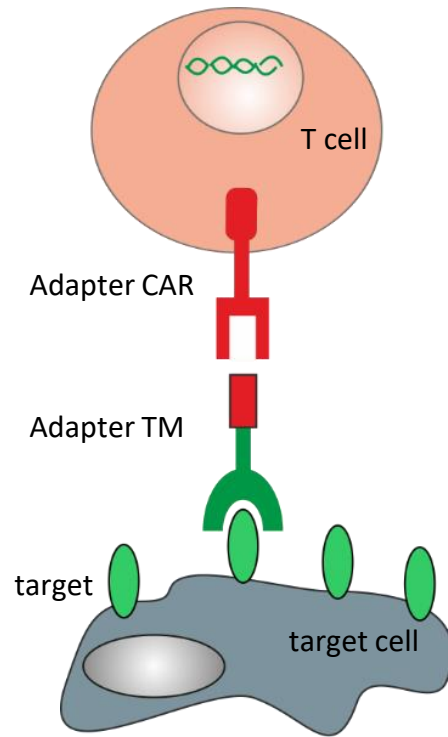
<https://www.biocomma.com>

Characterization

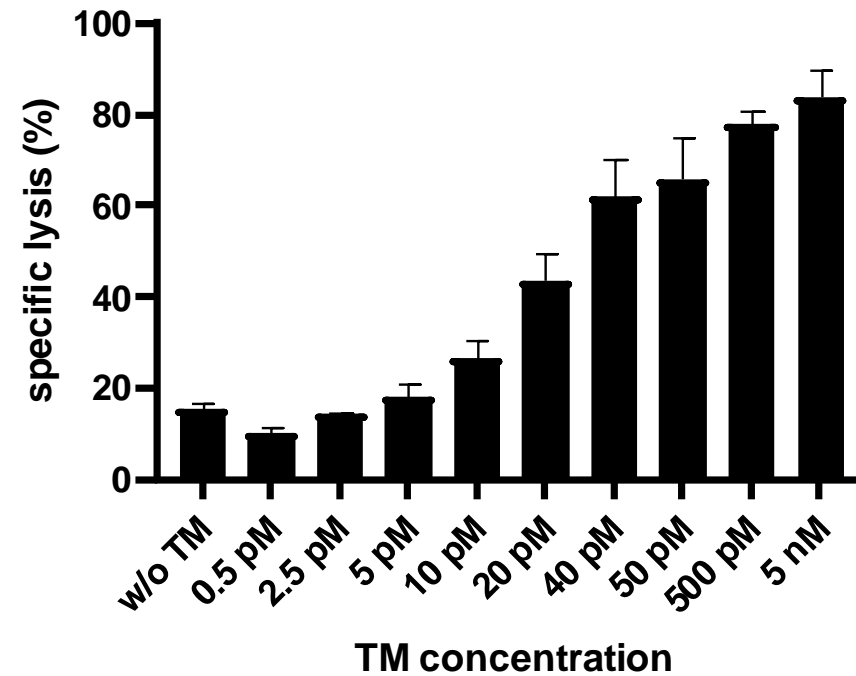


TheraSTAR – Results so far

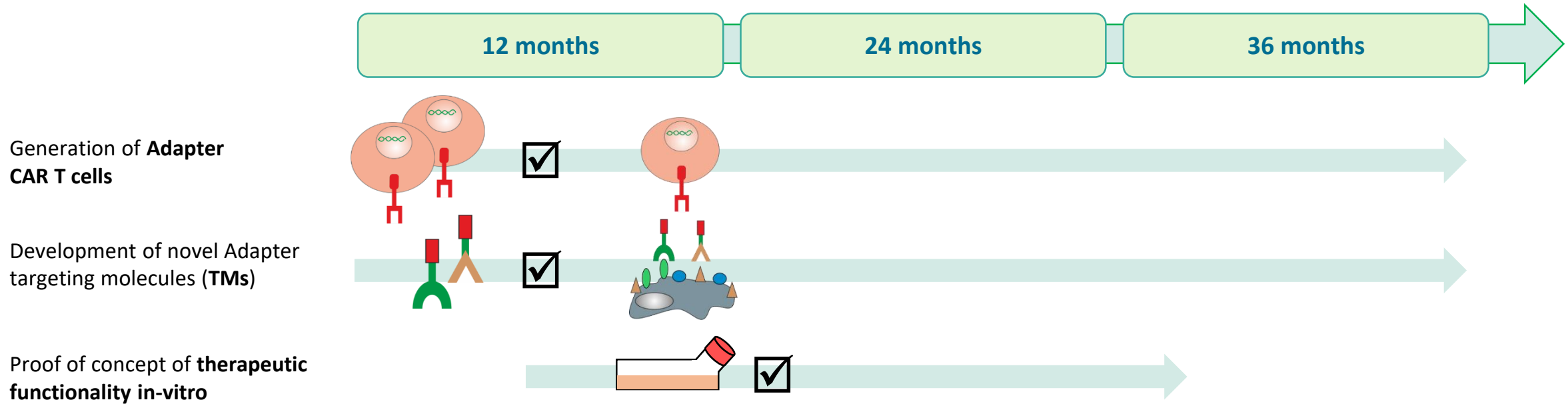
Proof of concept of **therapeutic functionality in-vitro** of Adapter CAR platform



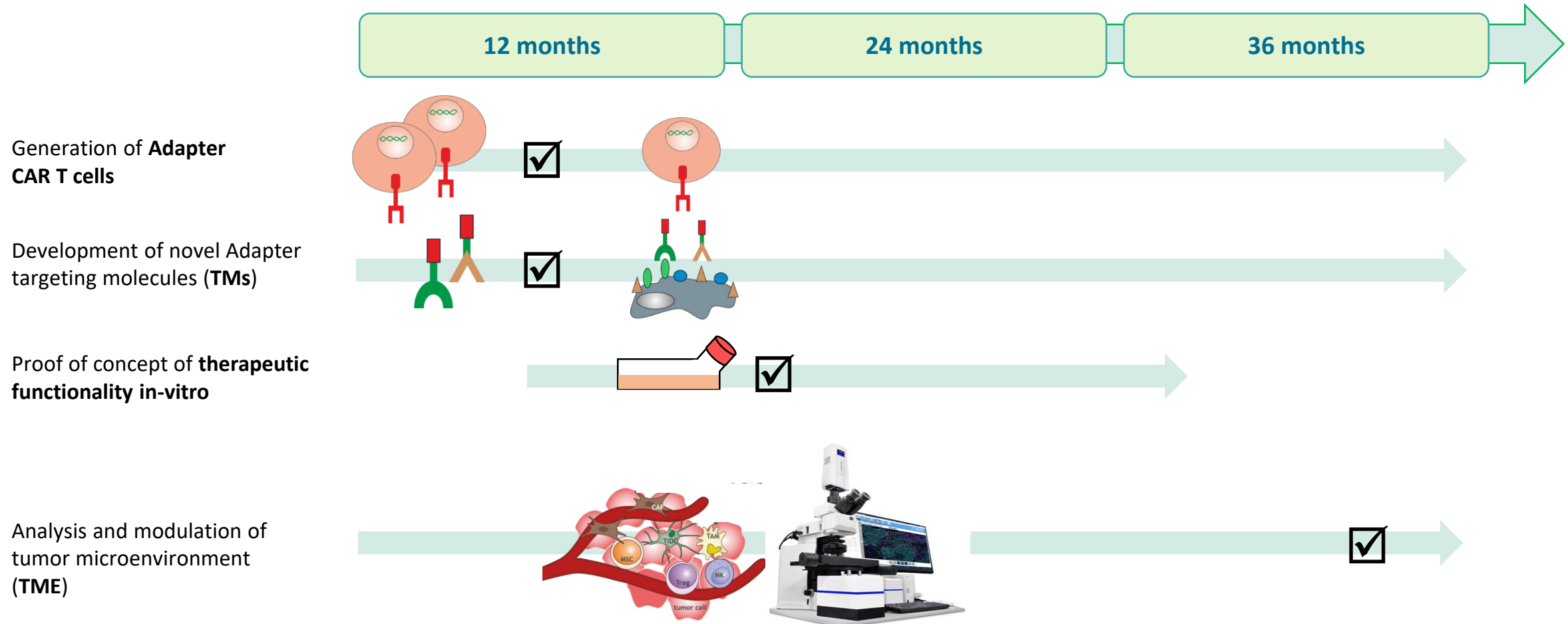
Killing of tumor cells



TheraSTAR – Results so far



TheraSTAR – Results so far



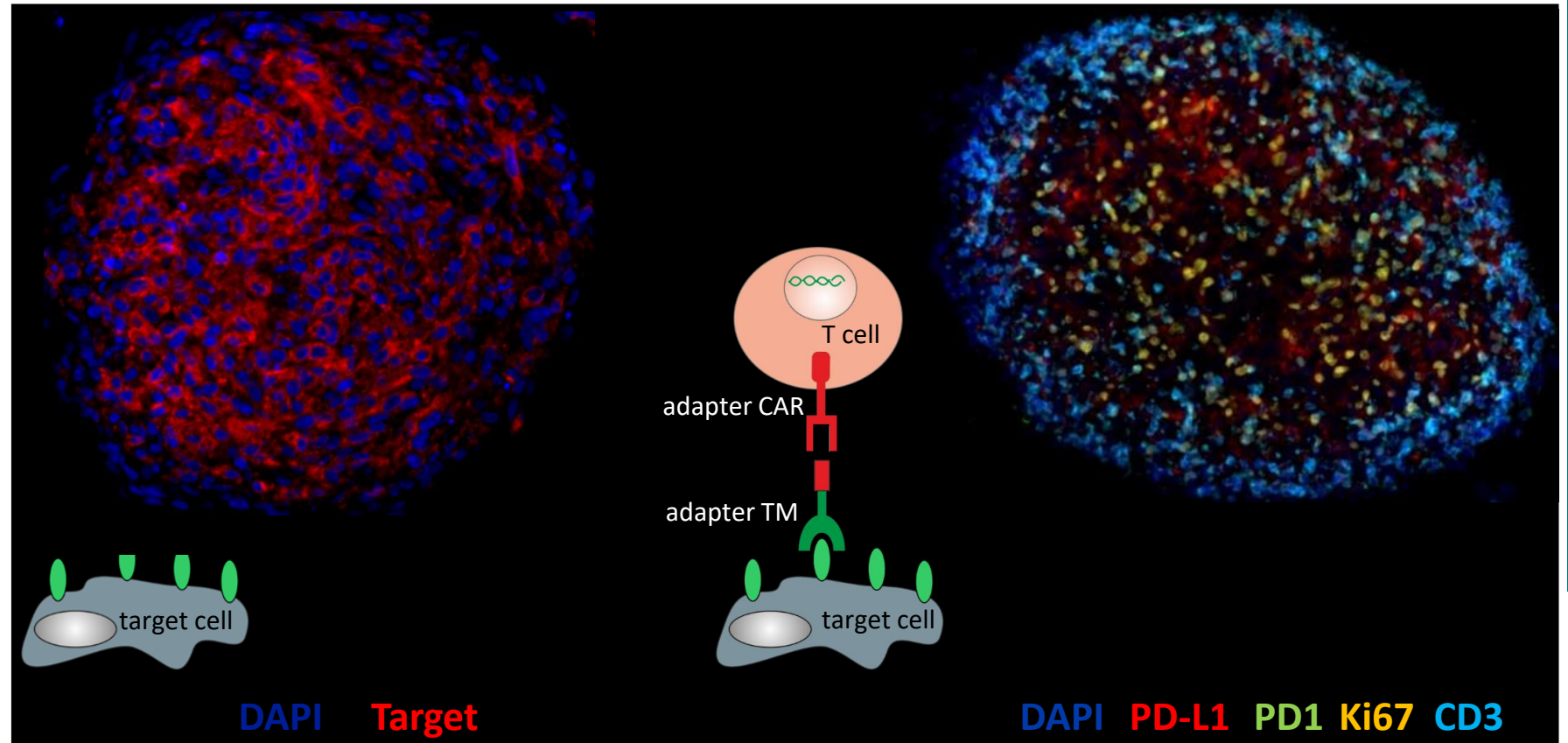
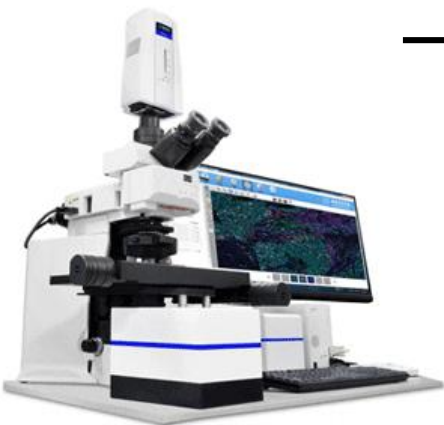
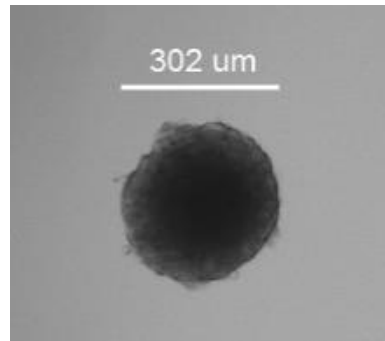
AREA 4 – CGT

TheraSTAR – Results so far

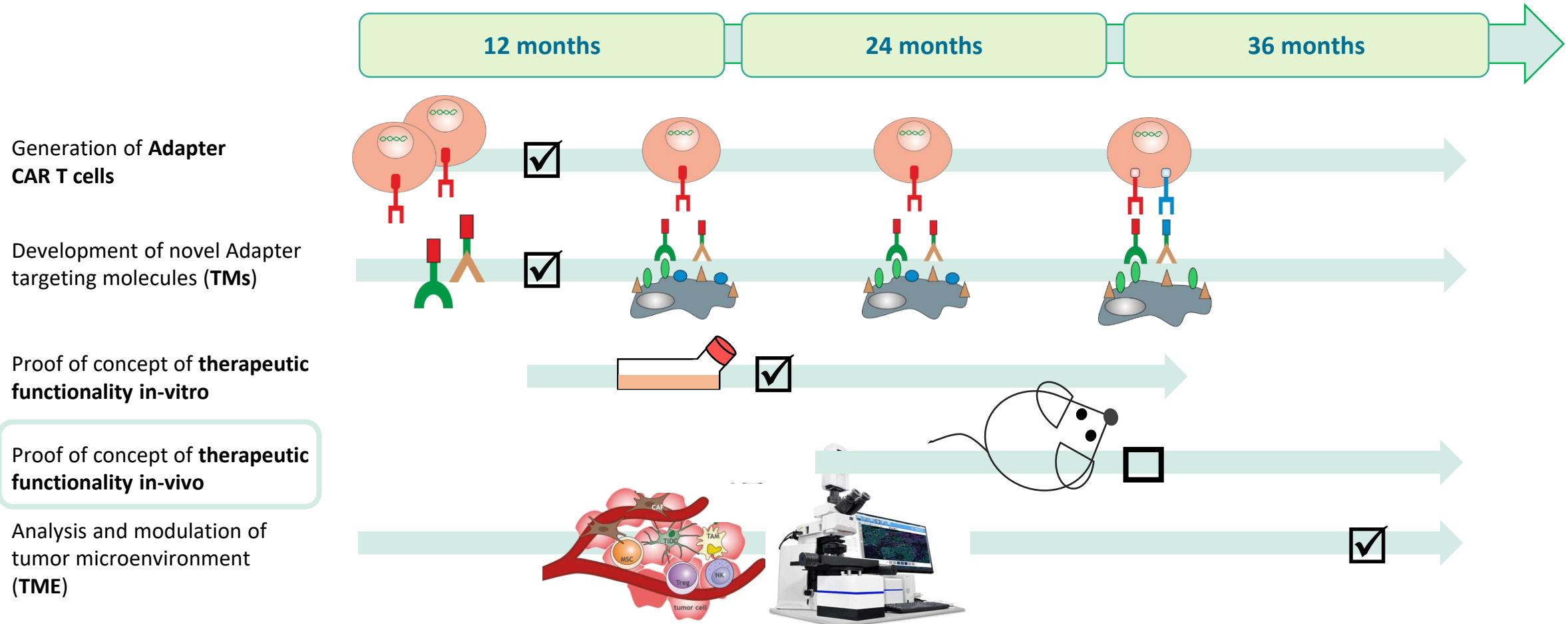
Analysis and modulation of tumor microenvironment (TME)

spheroid formation

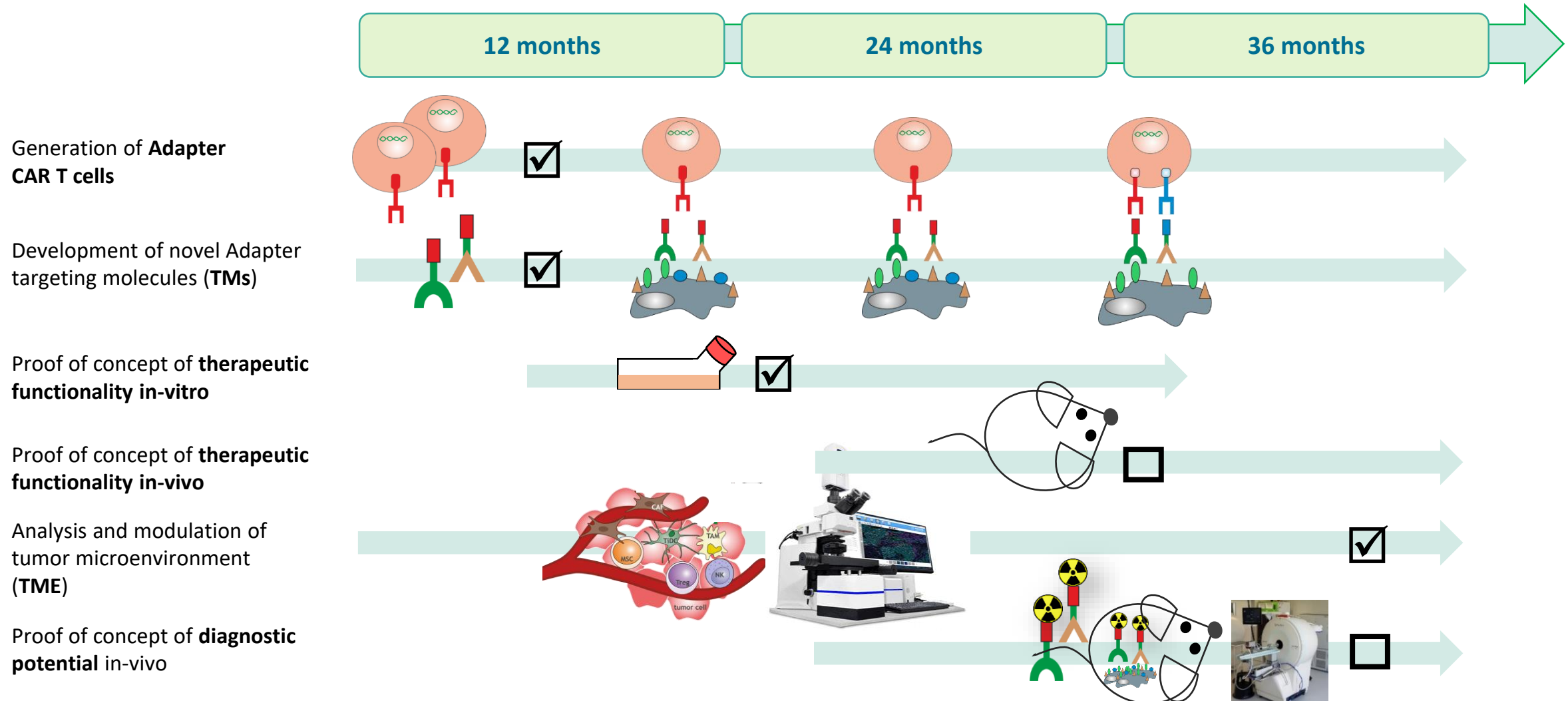
Vectra automated quantitative immunofluorescence imaging system



TheraSTAR – Objectives and Results

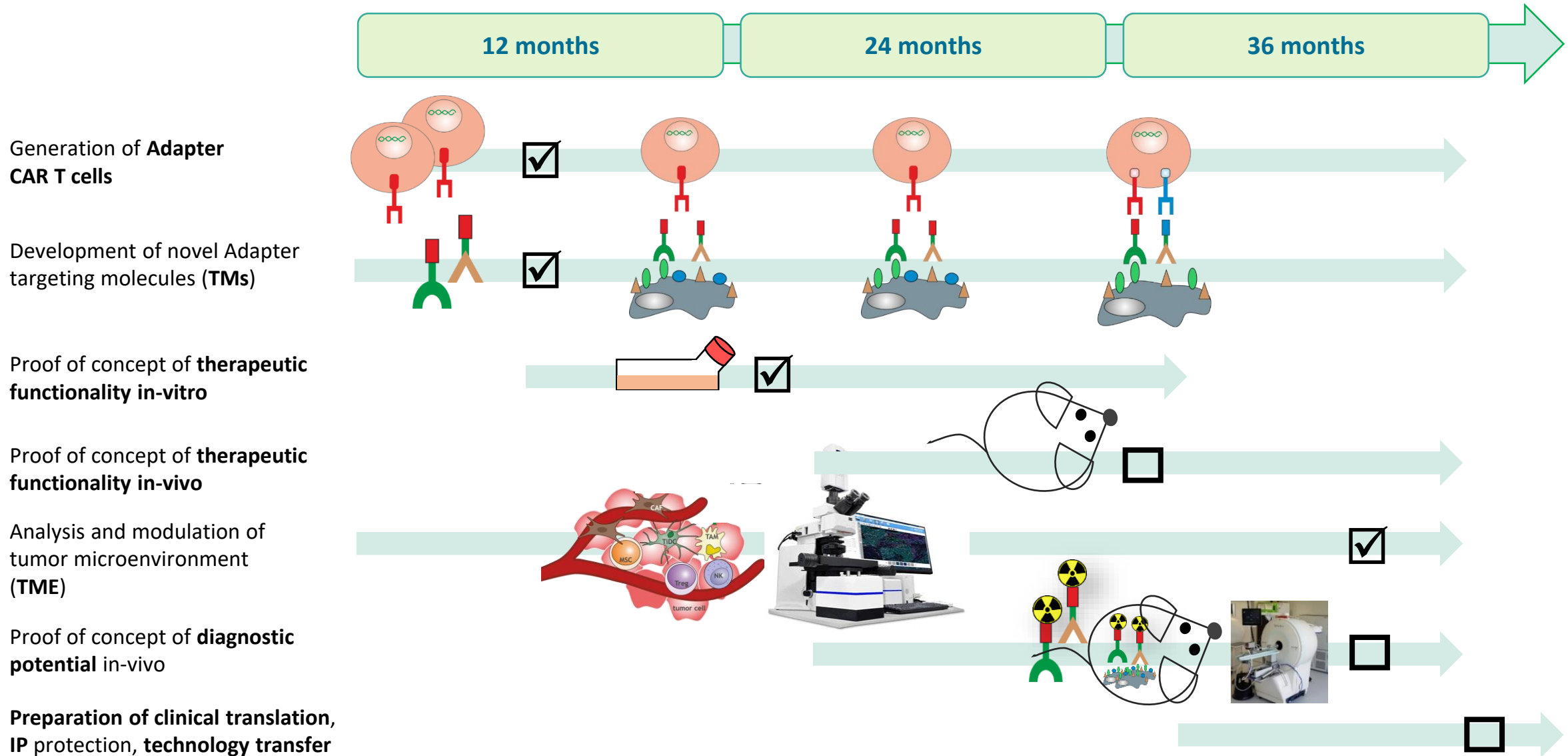


TheraSTAR – Objectives and Results

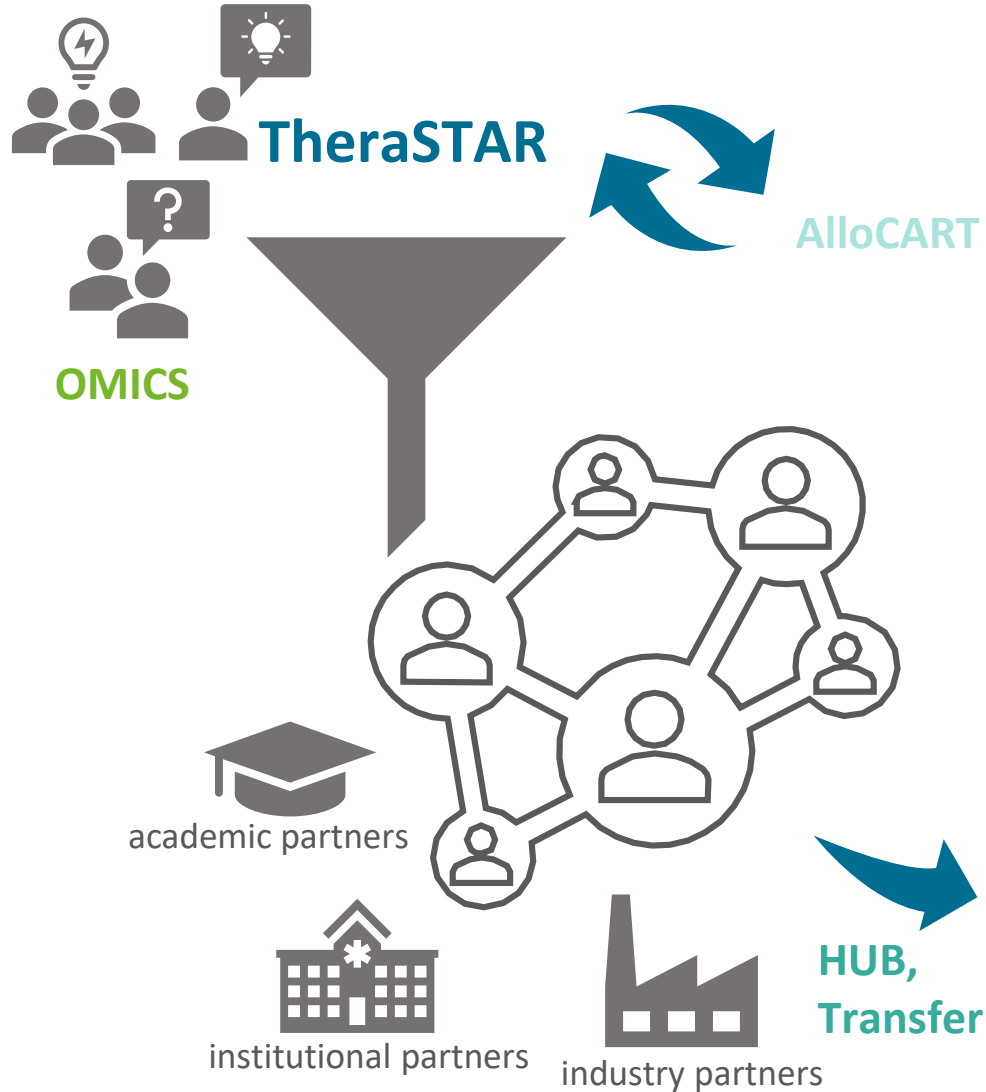


AREA 4 – CGT

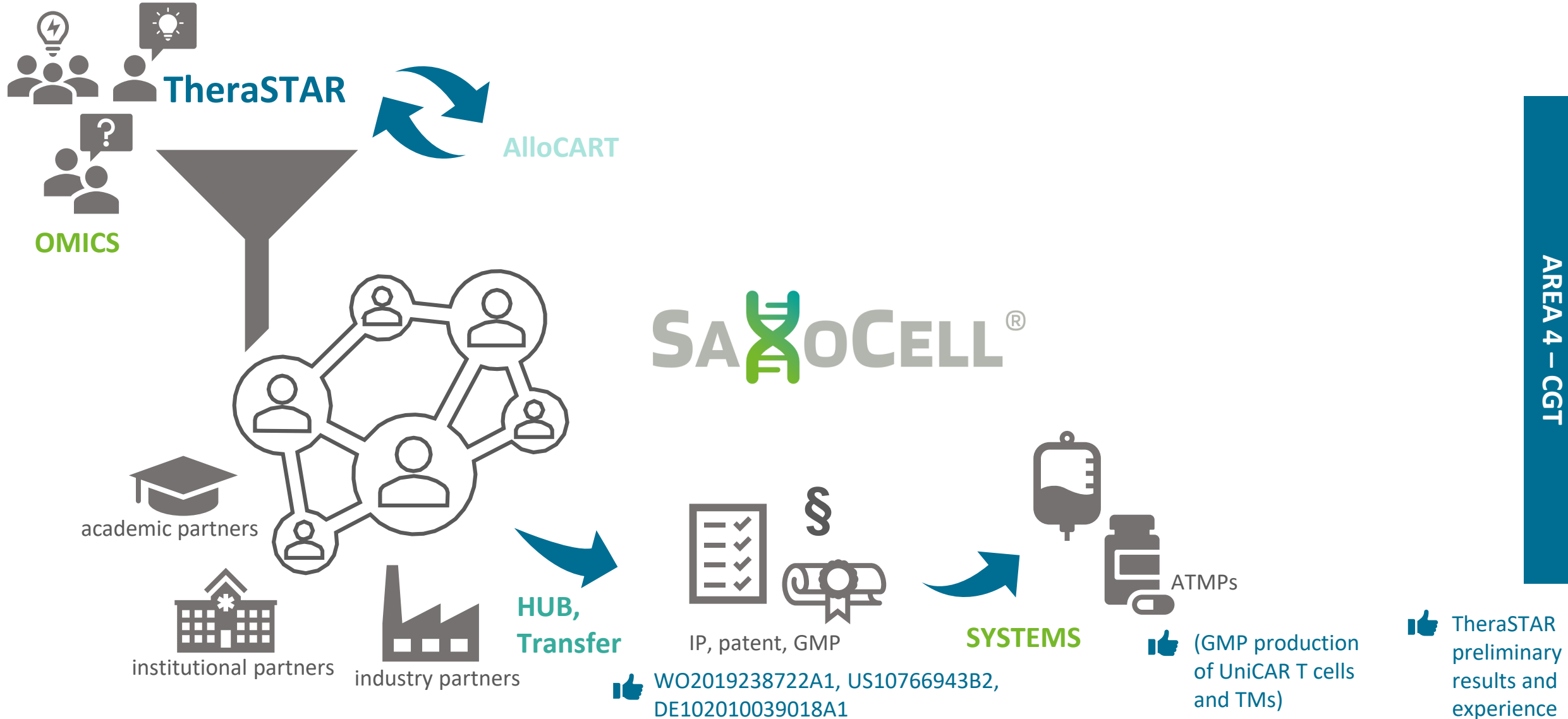
TheraSTAR – Objectives and Results



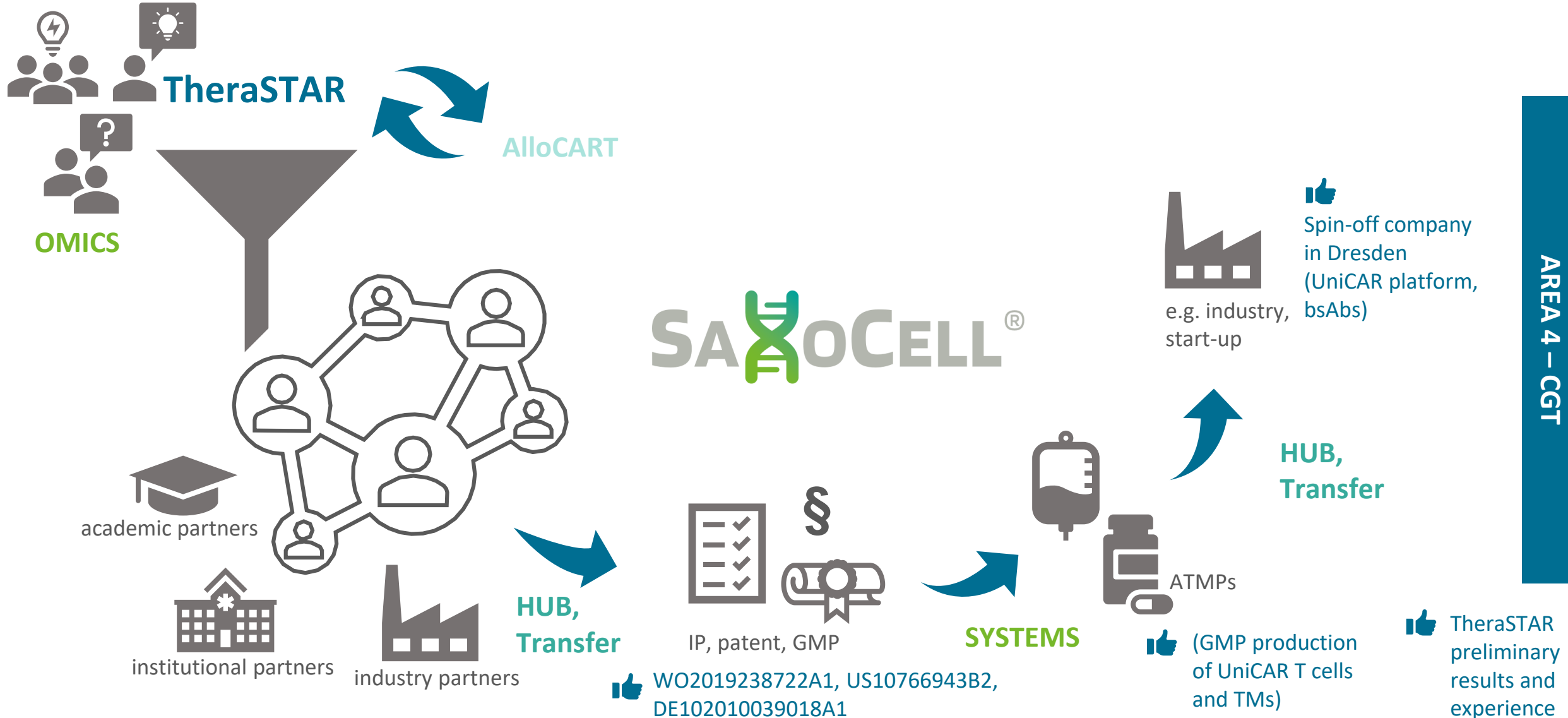
TheraSTAR – Synergies



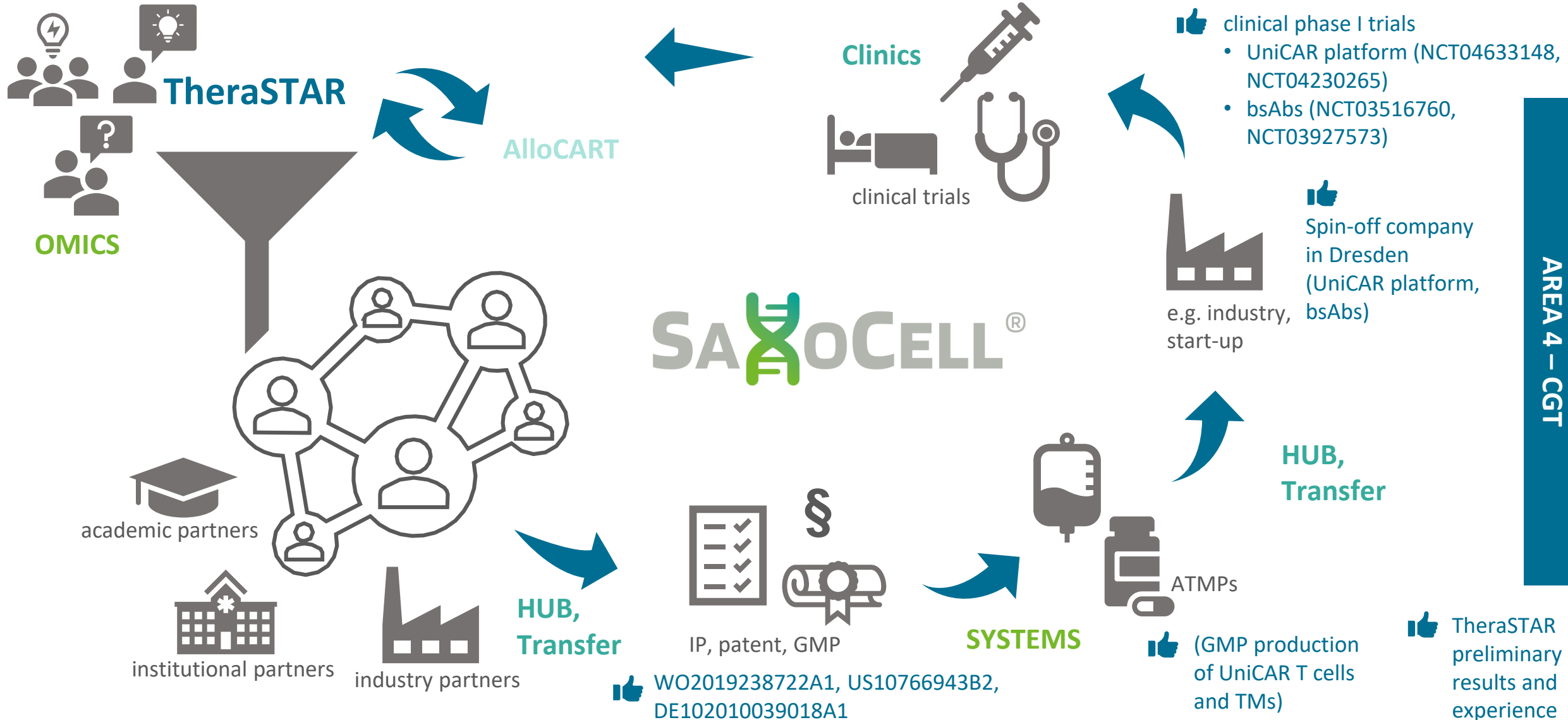
TheraSTAR – Synergies and Outlook



TheraSTAR – Synergies and Outlook

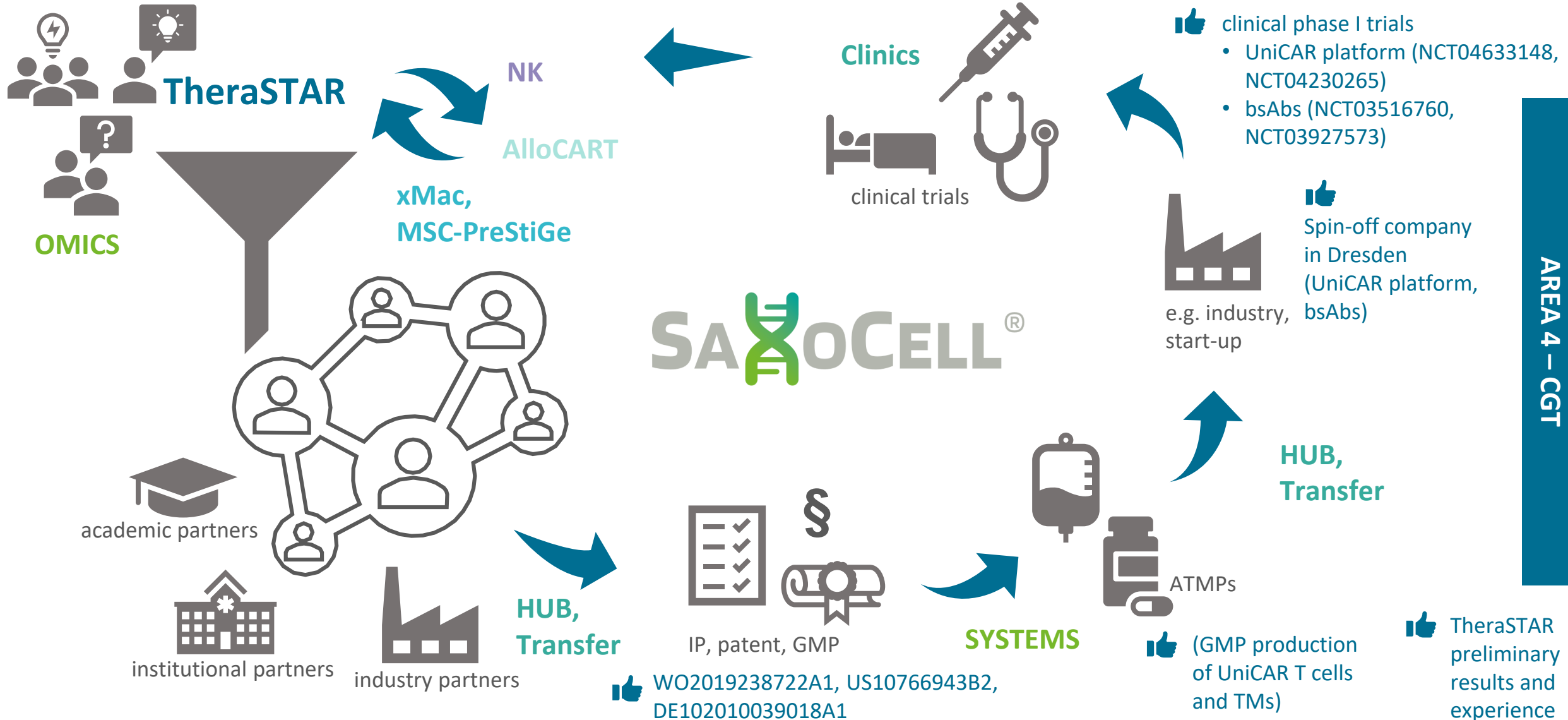


TheraSTAR – Synergies and Outlook



👍 WO2019238722A1, US10766943B2, DE102010039018A1

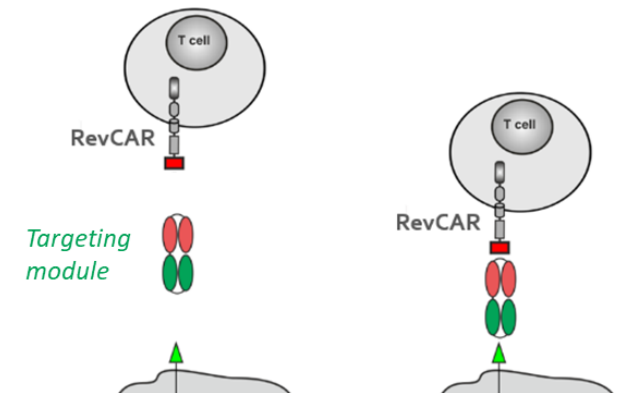
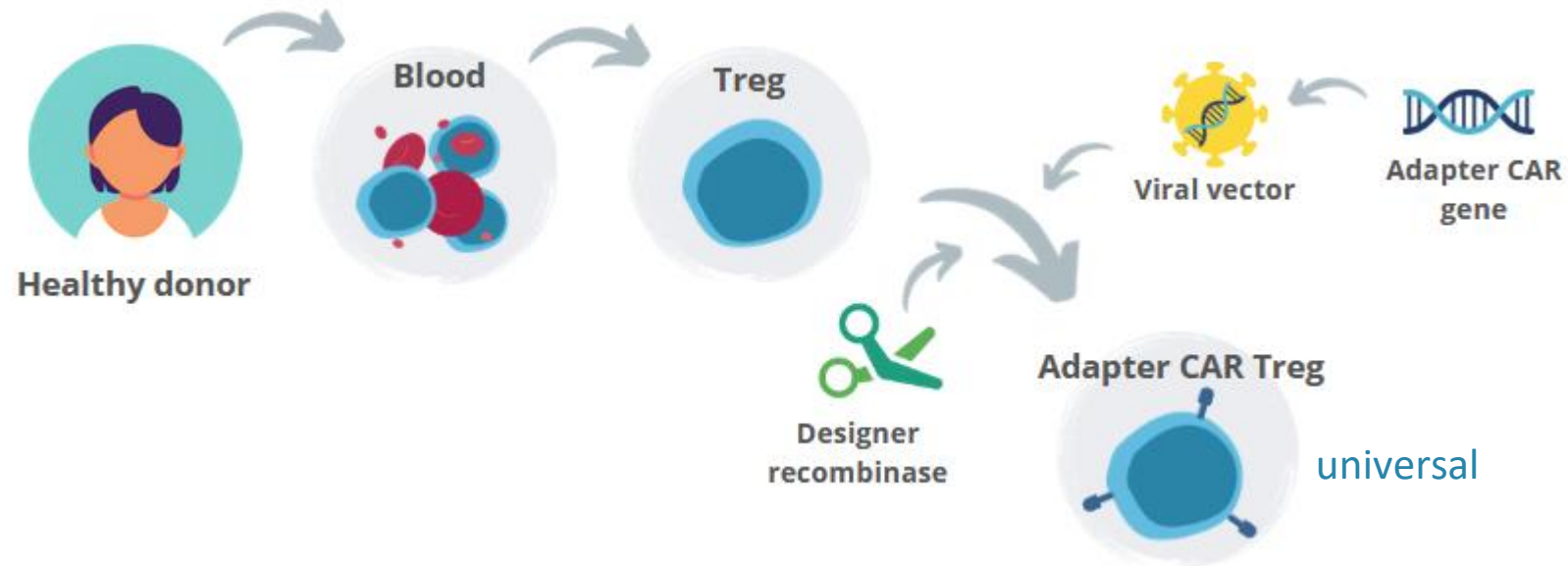
TheraSTAR – Synergies and Outlook



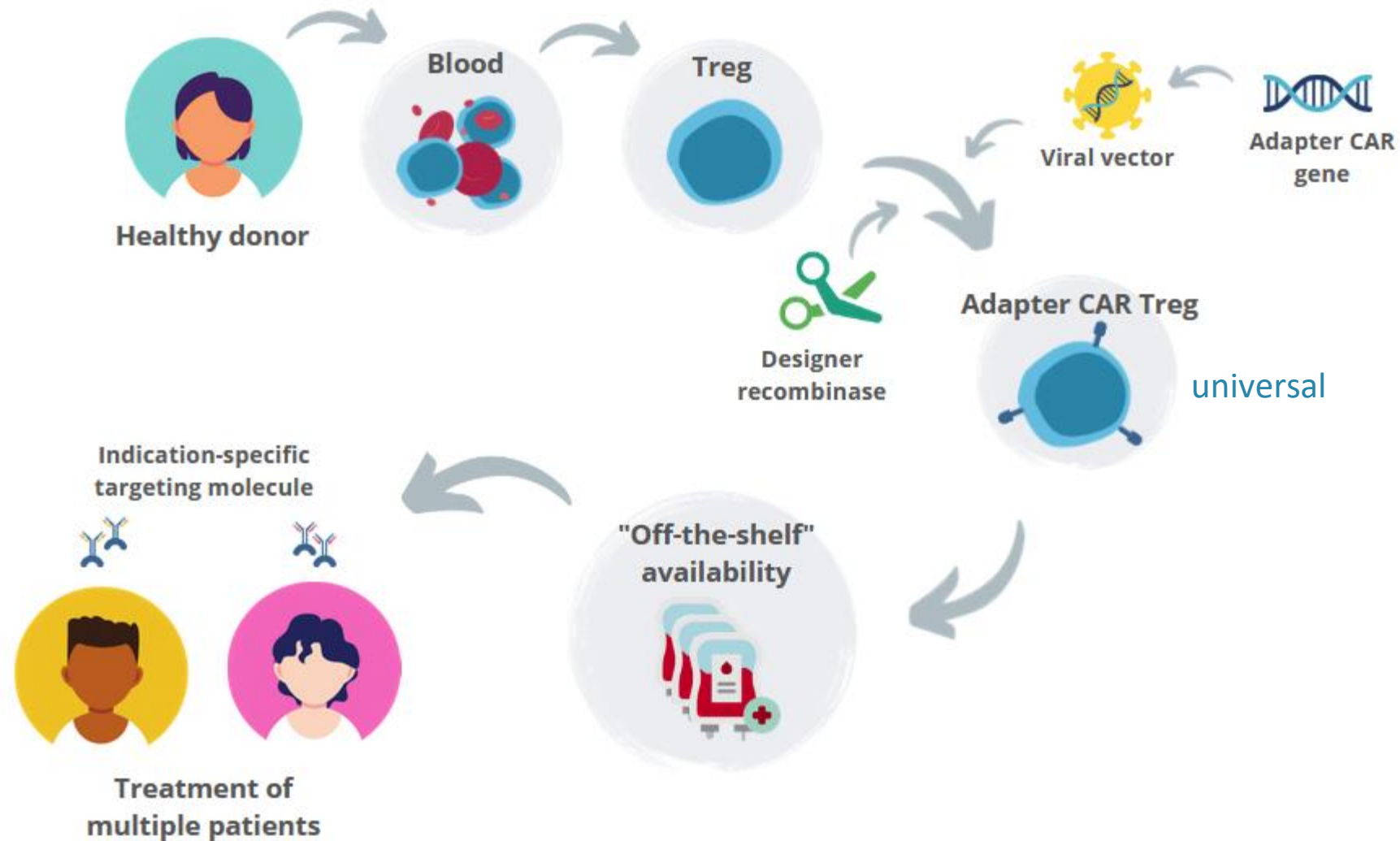
AREA 4 – CGT

Coffee Break

AlloCAR_{Treg} – Project Overview

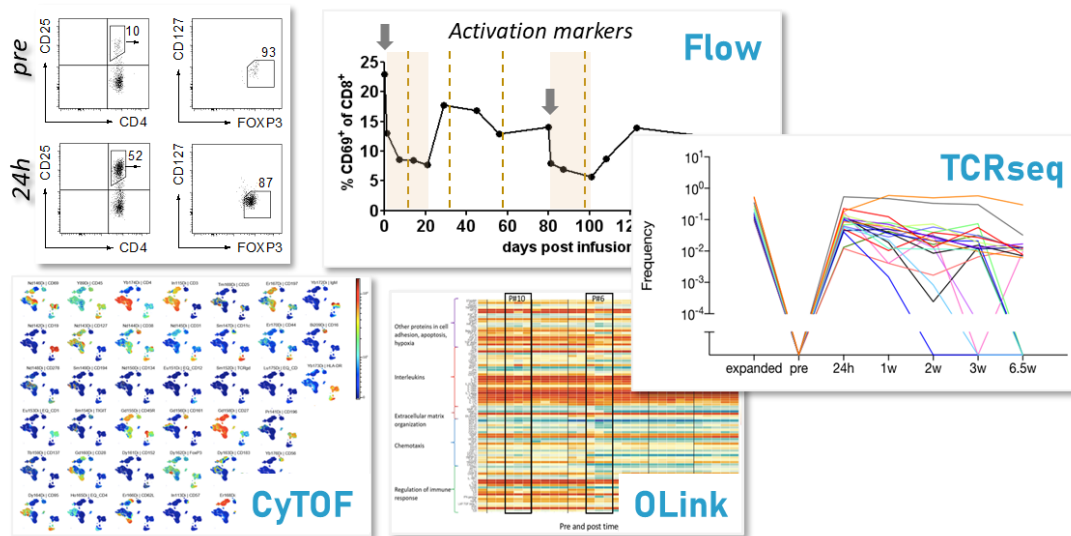


AlloCART_{reg} – Project Overview



AlloCART_{reg} – Objectives

Polyclonal Treg therapy for cGvHD



Transient response / late treatment
Systemic

Theil et al. 2015, Theil et al. 2017, Marín-Morales et al. 2019

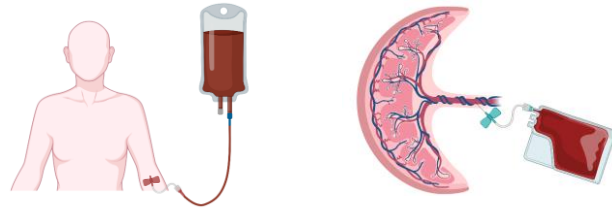
- „Off-the-shelf“ product allowing early treatment, multiple doses, prevention
- Targeted suppression

AlloCAR_{Treg} – Results so far

Samikshya



Treg source
Adult vs cord blood

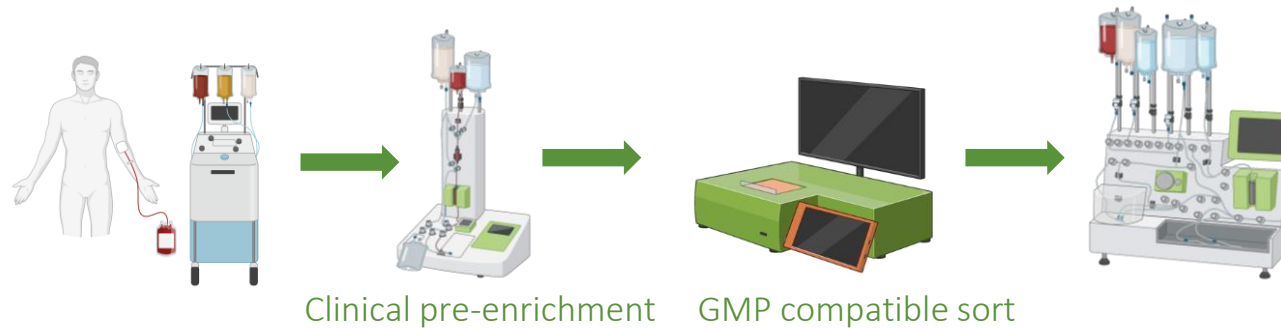


Expansion potential, yield ✓
Extensive phenotyping, QC ✓
Stability & Function ✓

Kavitha



Process
Optimizing purity
upscaling

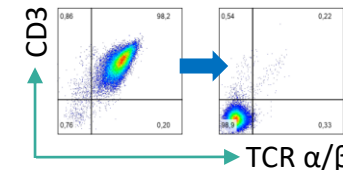
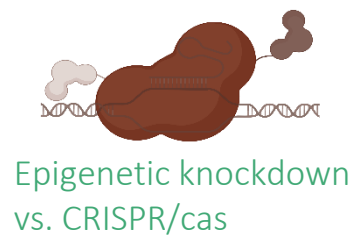


Isolation purity >95% ✓
High expansion ✓
Clinical scale ✓

Pascal

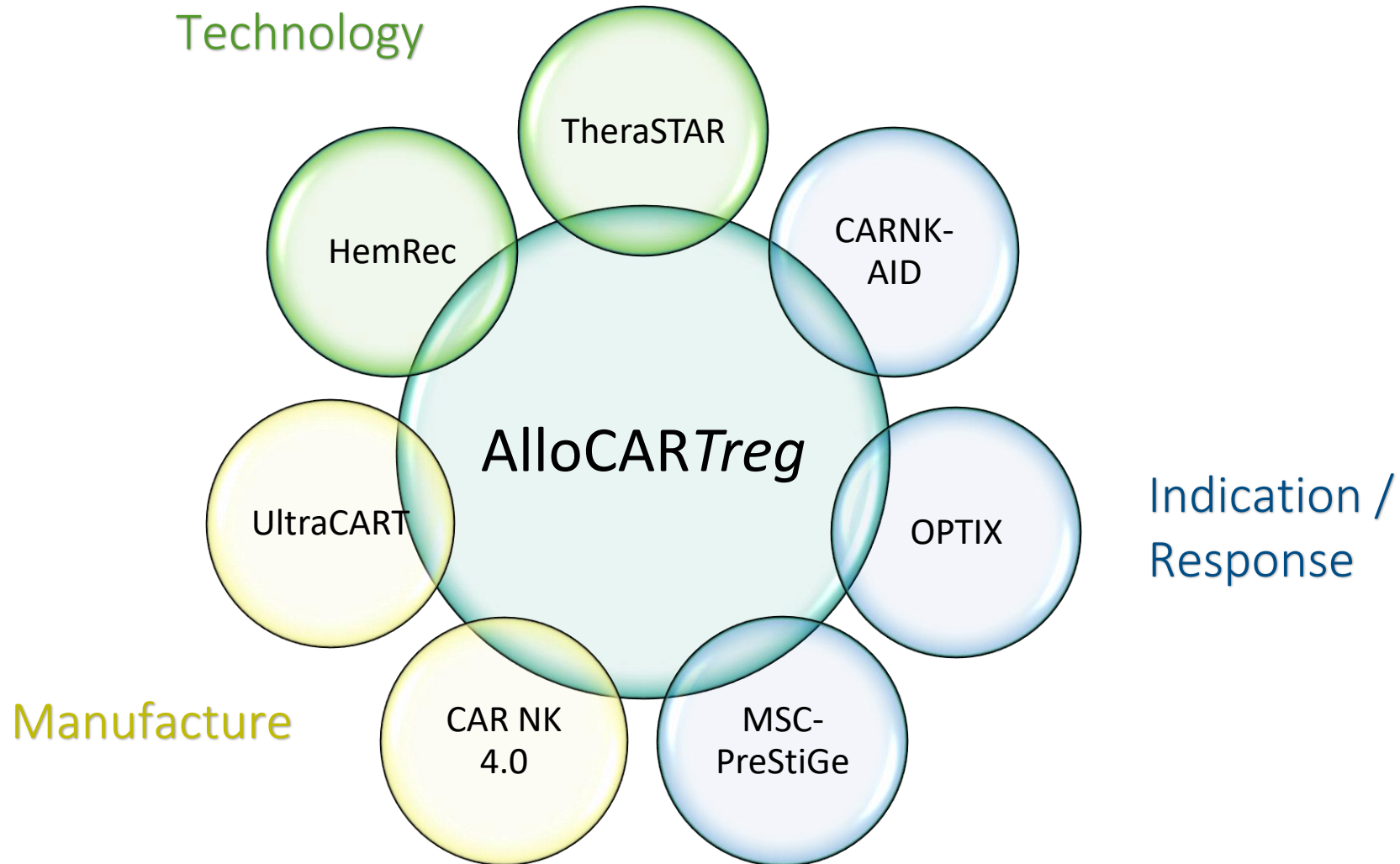


T cell receptor knockdown
Proof of concept



Tool comparison ✓
T cell lines, primary T cells ✓
Reporter lines for gRNA screen ✓
Transfection of Treg ✓

AlloCAR T_{reg} – Synergies to other SaxoCell Projects



AlloCAR^{Treg} – Outlook

Short-term

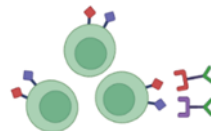
- Optimizing antigen-specific functional assays (Feldmann/Fuchs)
- Guide RNA screen for epigenetic TCR silencing (Buchholz)

Medium-term

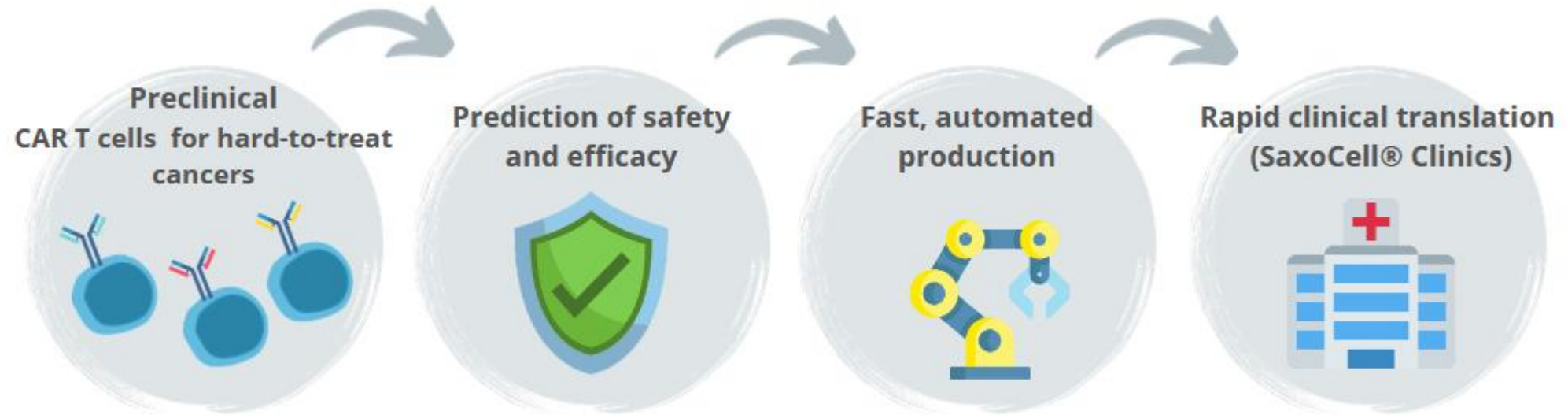
- Improved epigenetic editors (Buchholz)
- Designer recombinase for TCR excision (Buchholz)

Long-term

- Novel targeting modules for autoimmune indications
- Dual targeting CARs to enhance specificity



UltraCART – Project Overview



UltraCART – Objectives

Validation of novel target antigens and corresponding CART products with optimal anti-tumor efficacy

Shortening of development time by optimization of novel pre-clinical models to assess safety and efficacy of CART products

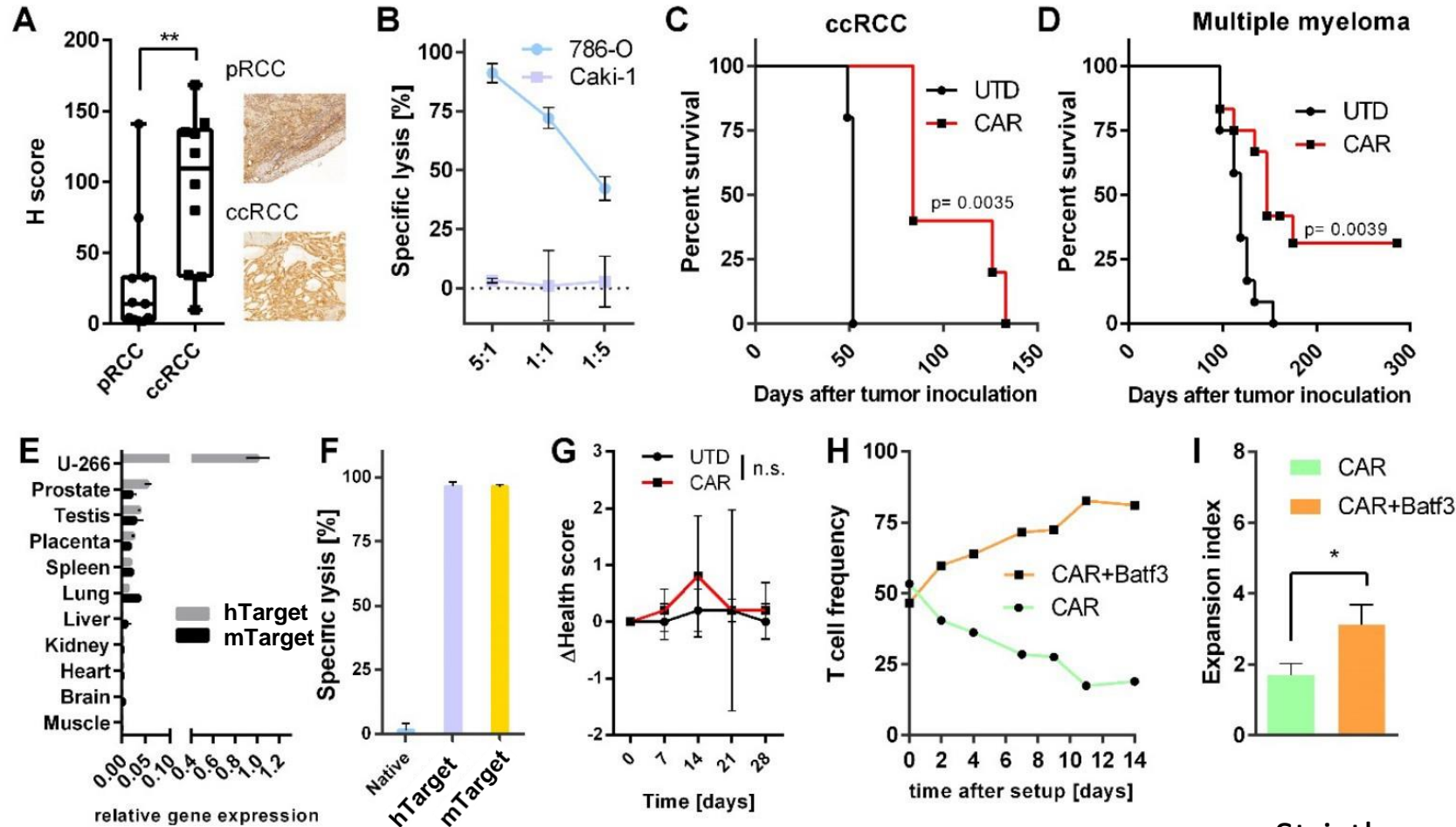
Shortening of delivery time by application of optimized scalable manufacturing processes

Standardization of therapeutic management and monitoring to allow for the deployment of artificial intelligence



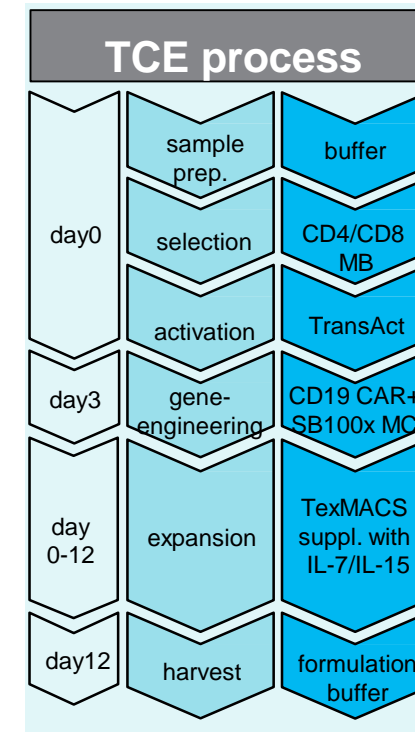
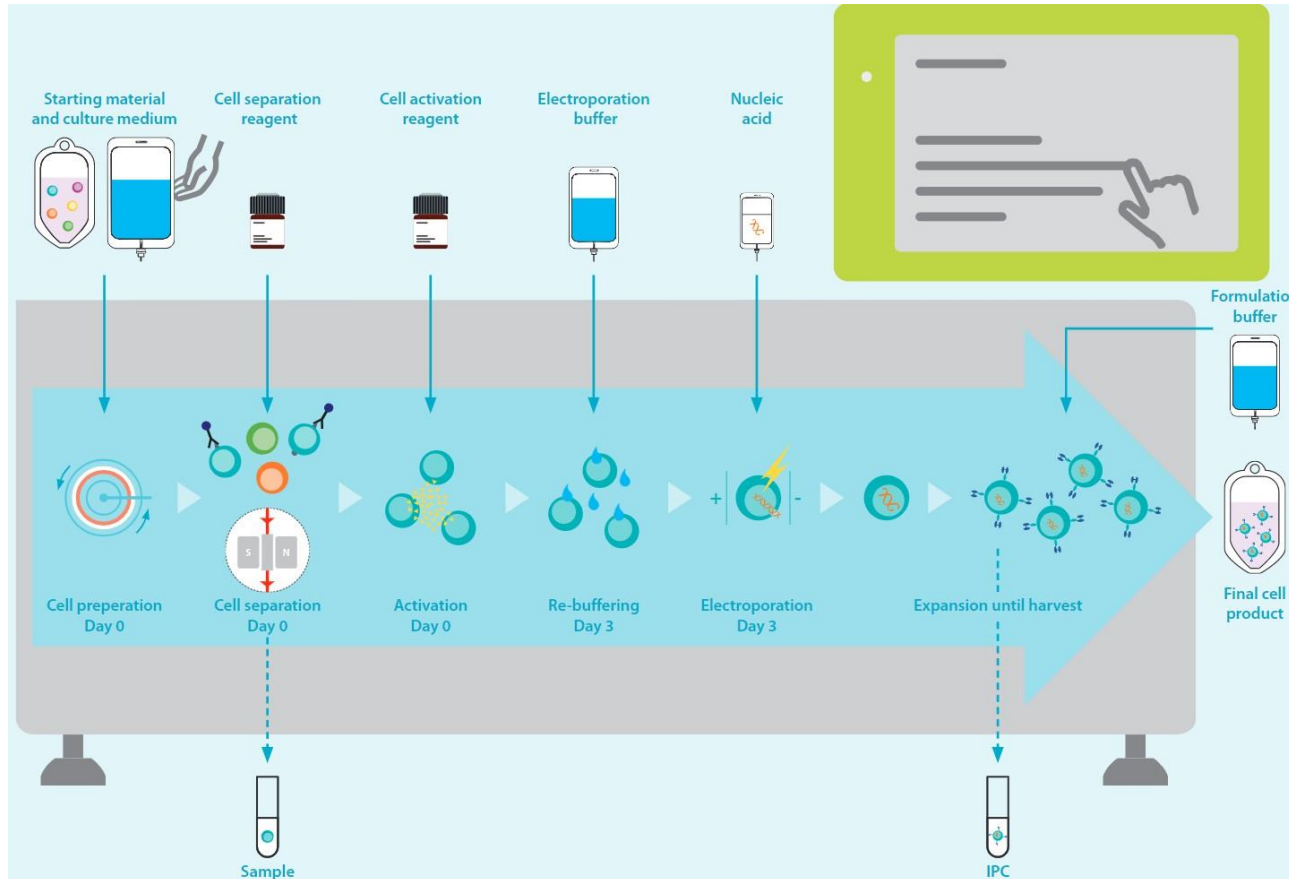
UltraCART – Results so far

New targets and CAR T cell products → Top target: addresses liquid and solid tumors



UltraCART – Results so far

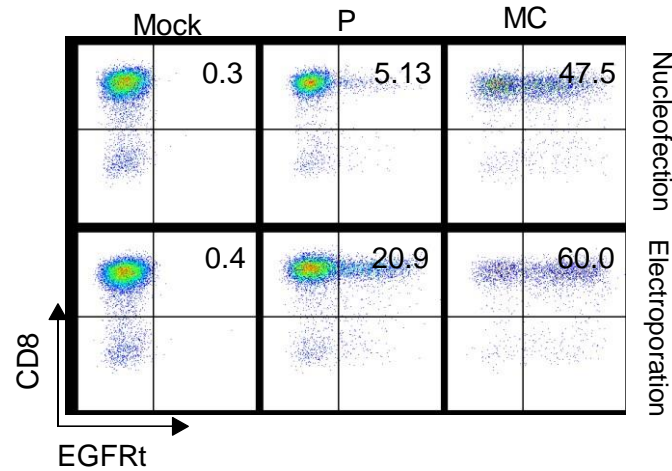
Manufacturing & automation → Fully automatic production of virus-free transposon-based CAR-T
(Miltenyi Prodigy + EP)



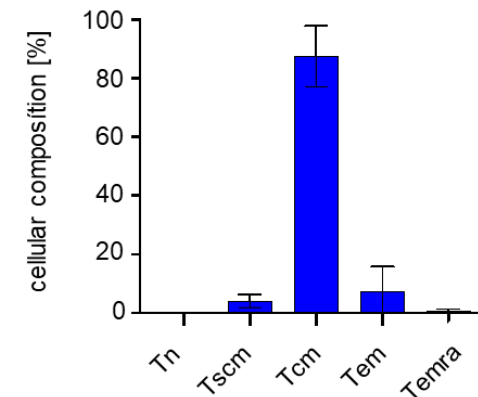
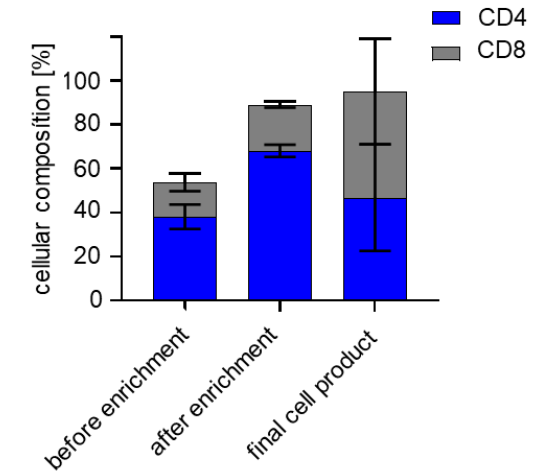
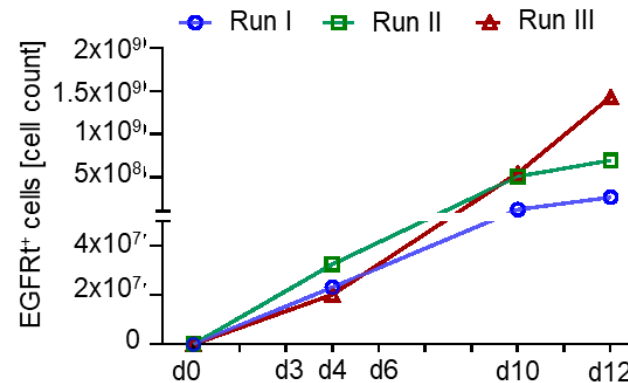
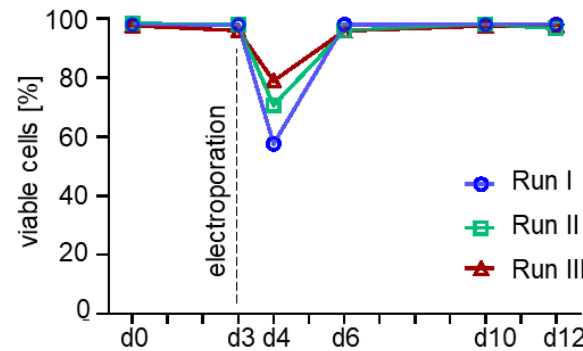
AREA 1 – CAR-T

UltraCART – Results so far

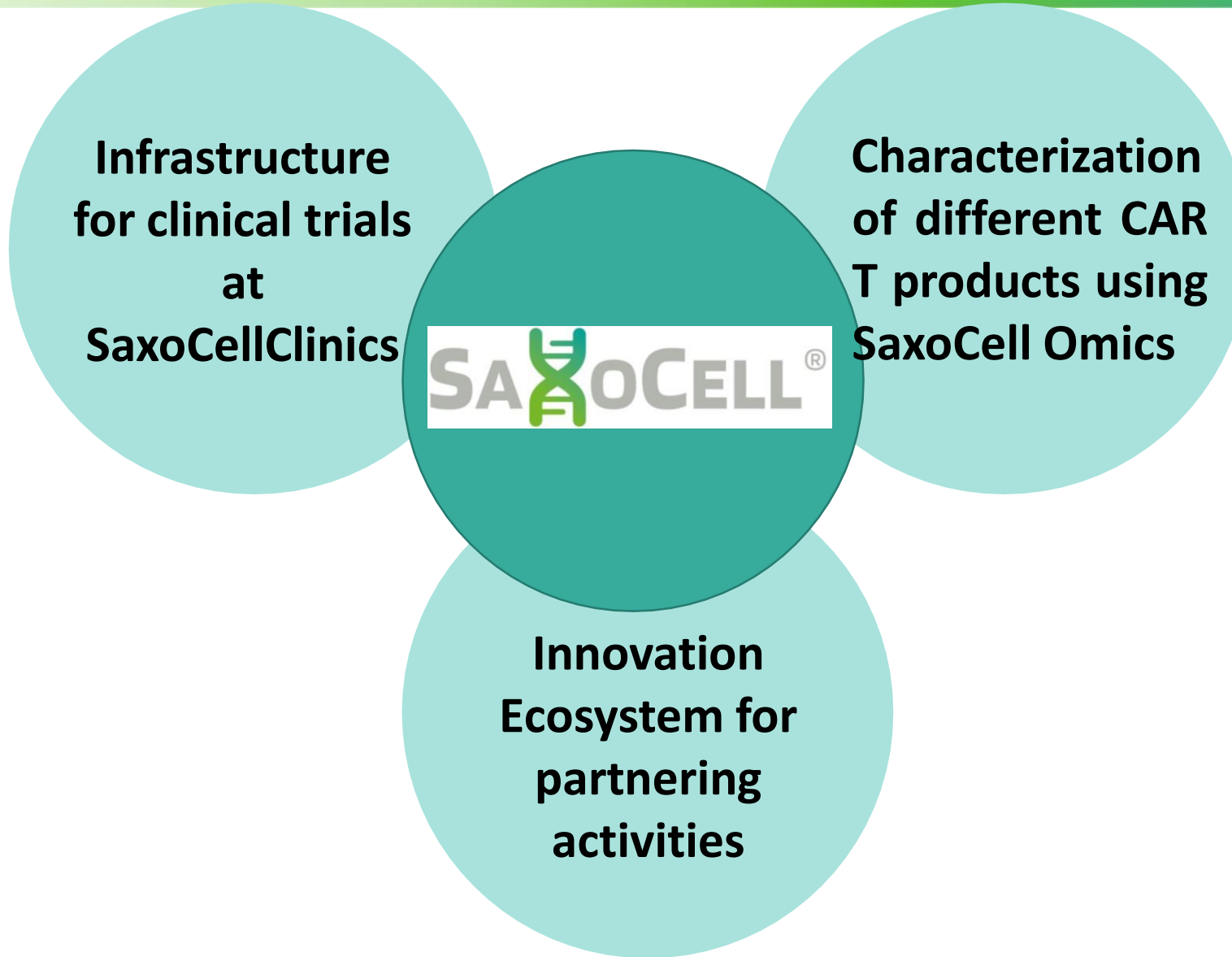
Manufacturing & automation → Fully automatic production of virus-free transposon-based CAR-T (Miltenyi Prodigy + EP)



Gene transfer rate: 60%
Therapeutic dose
TCM phenotype, CD4/CD8 Ratio 1:1



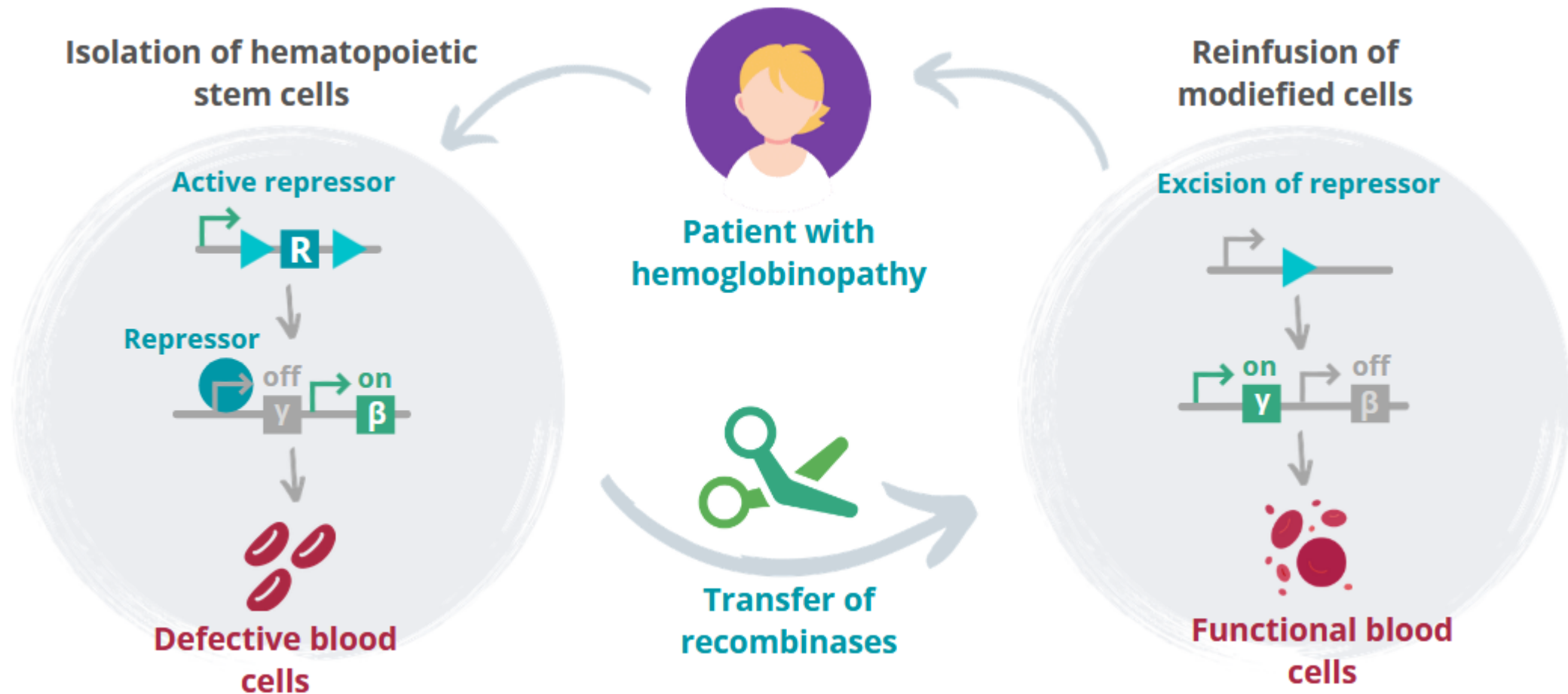
UltraCART – Synergies to other SaxoCell Projects





- Standardisation of*
- 1. translational development
(test systems for safety and efficacy)*
 - 2. clinical development*
 - 3. data collection*

HemRec – Project Overview



SICKLE CELL DISEASE (SCD) AND β -THALASSEMIA (β -THAL)

Blood disorders caused by *mutations* in the β -globin gene



Significant worldwide burden

300,000 Annual births in SCD and β -thal, respectively
60,000

High morbidity and mortality



Anemia



Pain



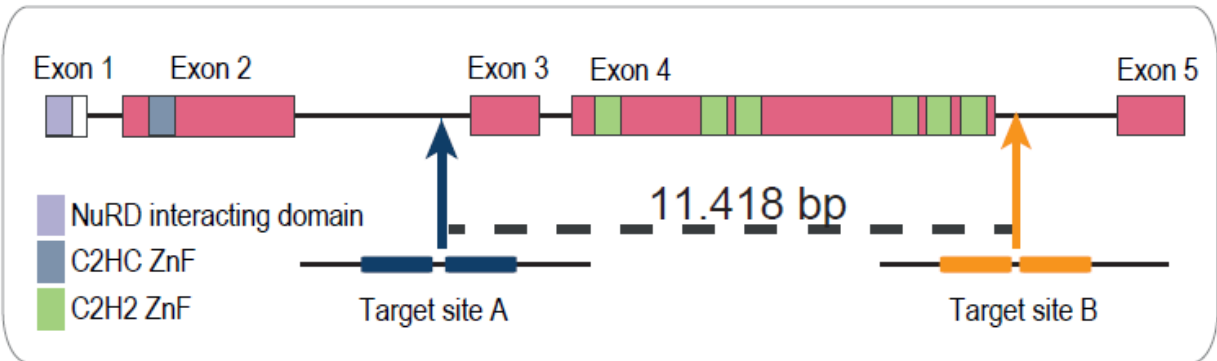
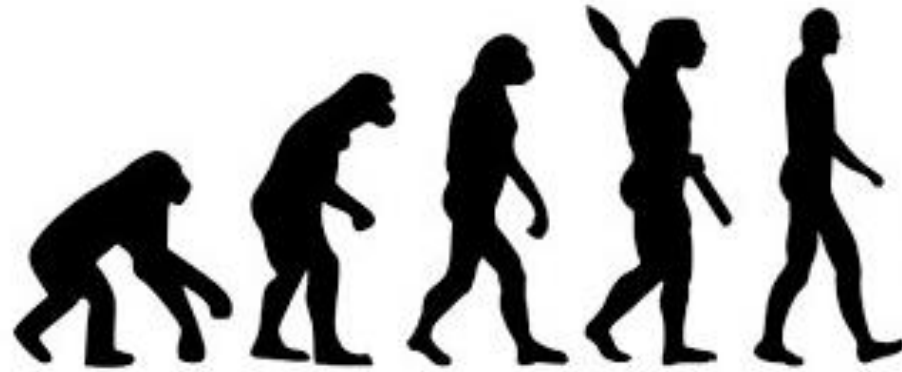
Early death

Heavy burden of patient care

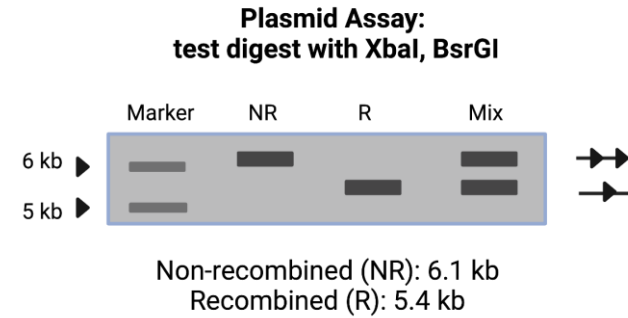
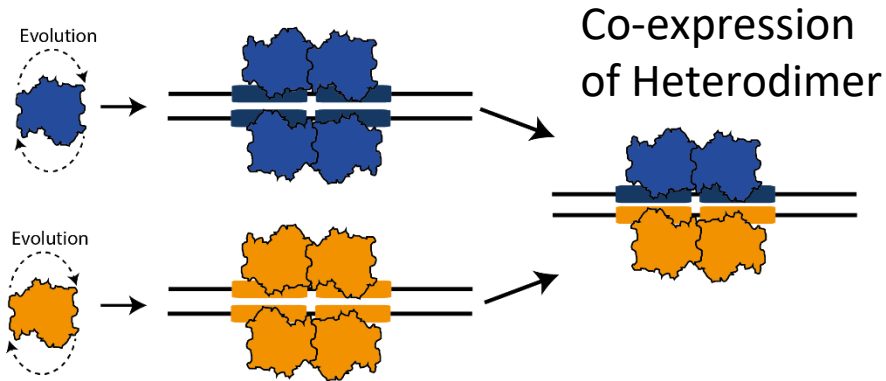


Frequent transfusions & hospitalizations

HemRec – Target site for BCL11A excision



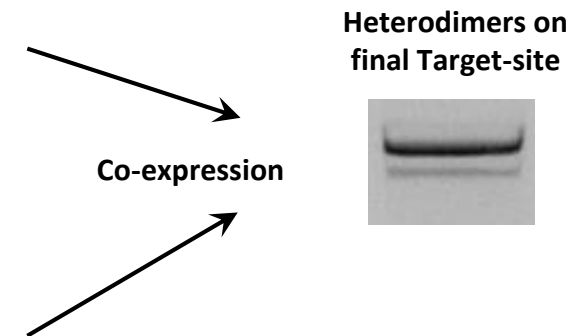
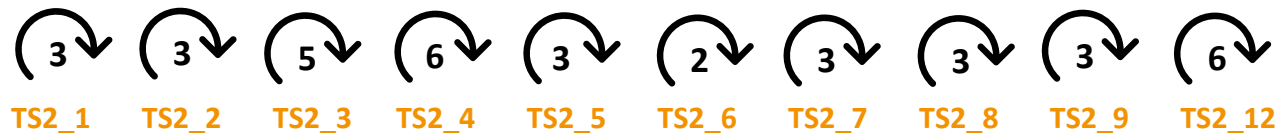
HemRec – Results so far



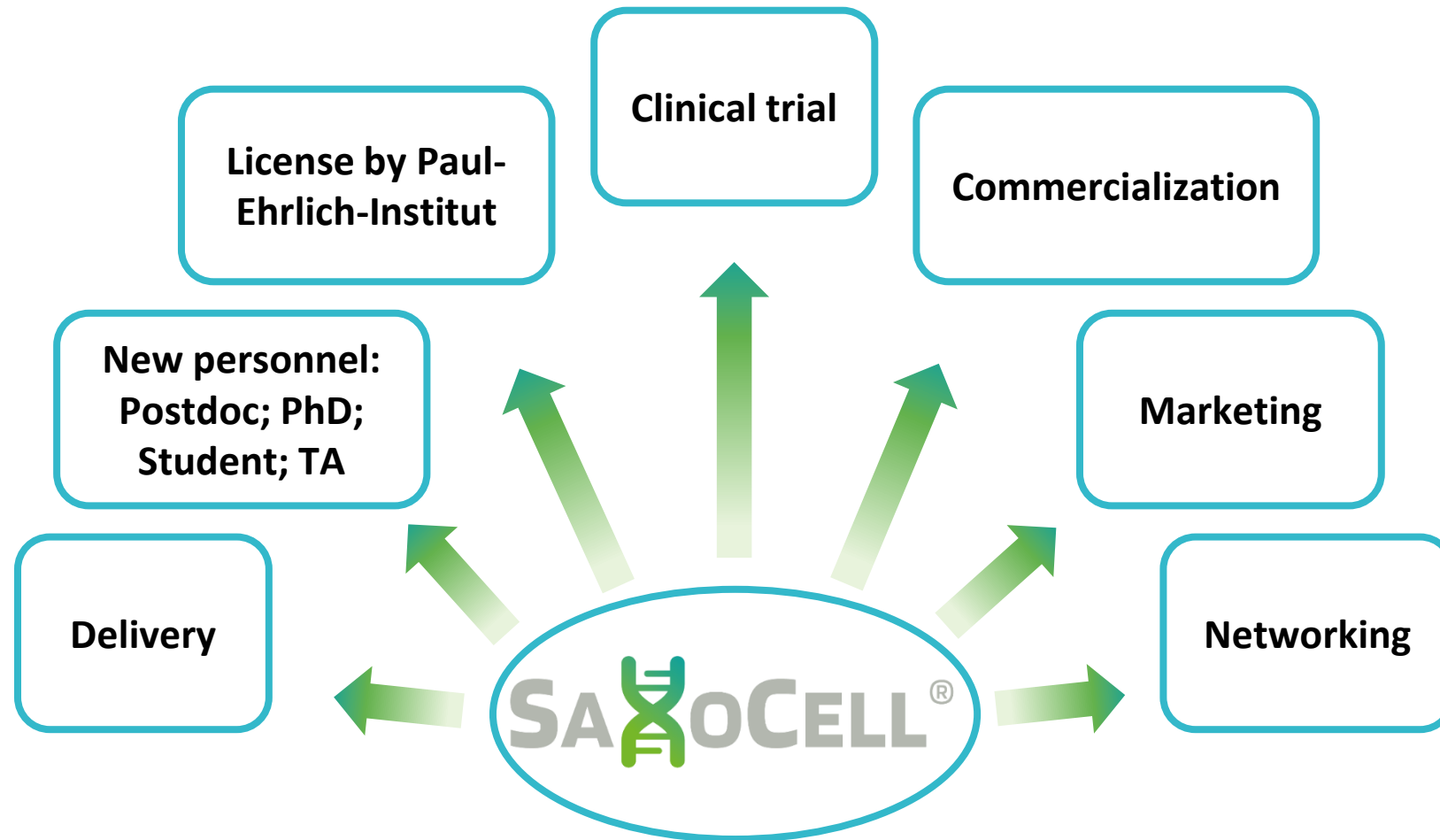
Total cycles: 36



Total cycles: 37



HemRec – Synergies



HemRec – Outlook

- Evolving hetero-specific recombinases for final BCL11A target site -> *Dec.2022*
- Deep sequencing based screening of the libraries to test efficiency for on-target and potential off-targets in the human genome -> *Feb. 2023*
- In depth-analysis of single clones in bacteria -> *May 2023*
- Testing most promising clones in cell culture in a reporter cell line -> *Sept. 2023*
- Analysis of the BCL11A deletion at the endogenous locus using adult erythroid cell line -> *Feb. 2024*
- Analysis of the BCL11A deletion in patient cells with support from DKMS -> *Feb. 2024*
- Preparation for clinical study with support of DKMS -> *Dec. 2024*

Universitätsklinikum
Carl Gustav Carus



DKMS x
Life Science Lab

Universitätsklinikum
Carl Gustav Carus



DKMS x
Life Science Lab

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DKMS x
Life Science Lab

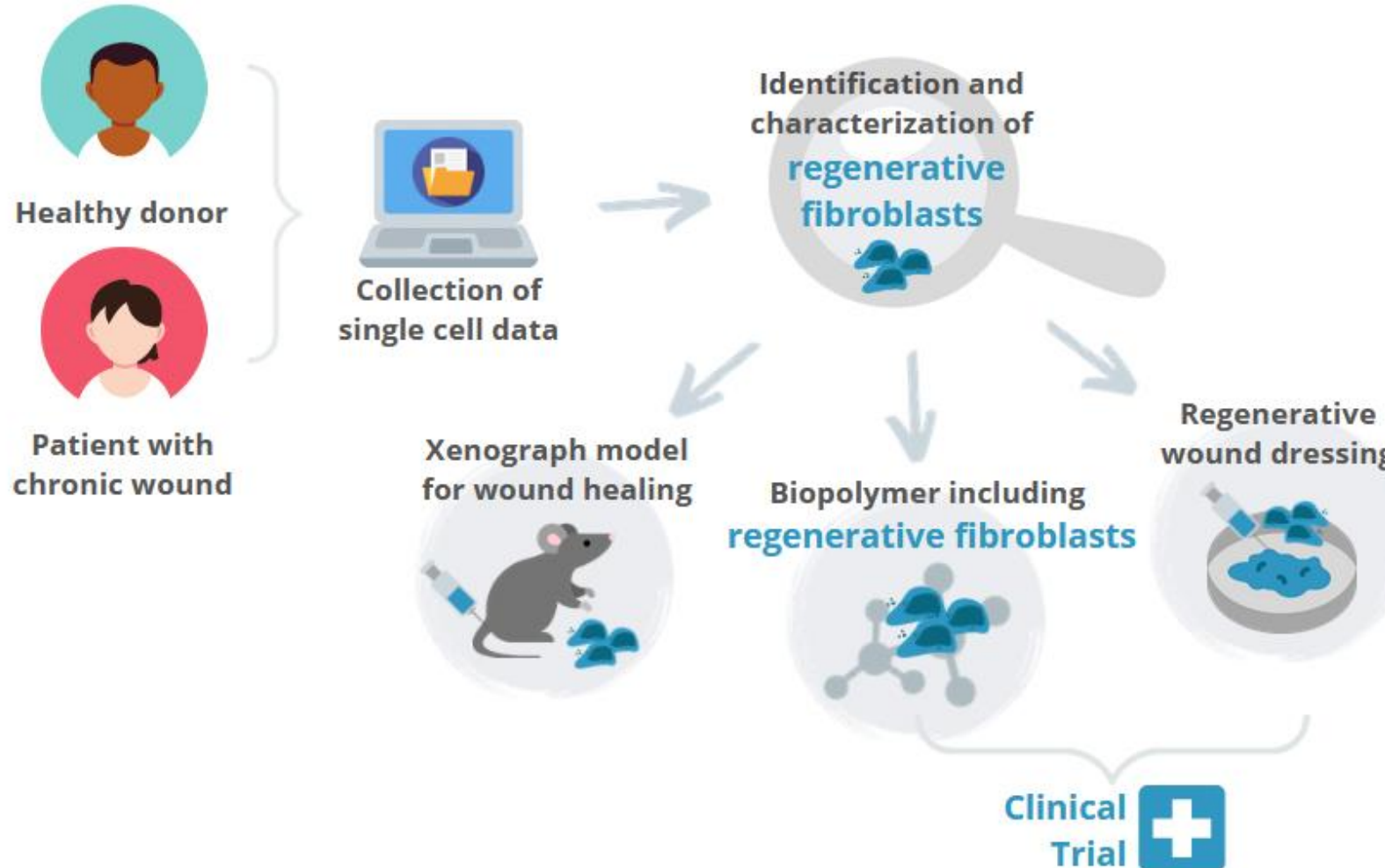
Universitätsklinikum
Carl Gustav Carus



DKMS x
Life Science Lab




ZellTWund – Project Overview



ZellWund – Problem

Wound healing disorders



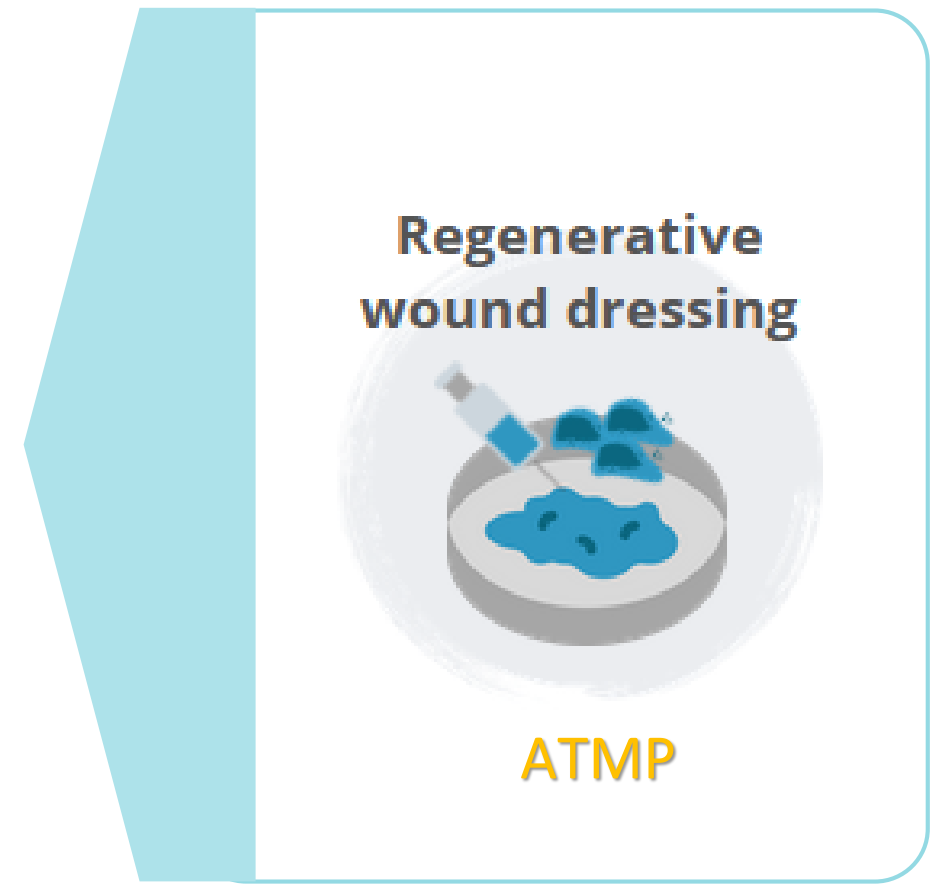
Incidence chronic wounds in Germany¹: 2010 2012
0,13% **0,26%** 

Aging population / Comorbidities 

Direct treatment costs² : 9000 € / patient / year



Insufficient therapeutic success



AREA 3 – ATMPs

¹ Heyer et al., WoundRepairRegen, 2016

² Augustin et al.; IntWoundJ, 2014

Innovative cell therapy to promote skin regeneration



Marta Torregrossa



Dr. Ravinder Kandi



PD Dr. Sandra Franz



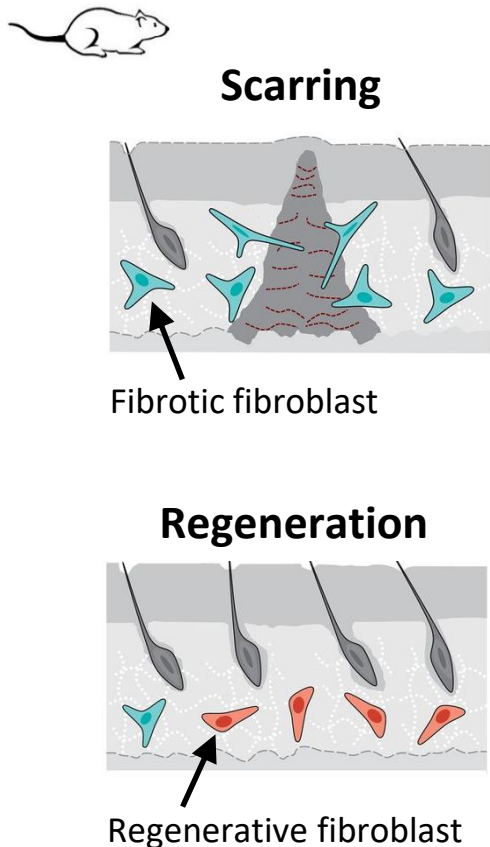
Prof. Dr. JC Simon



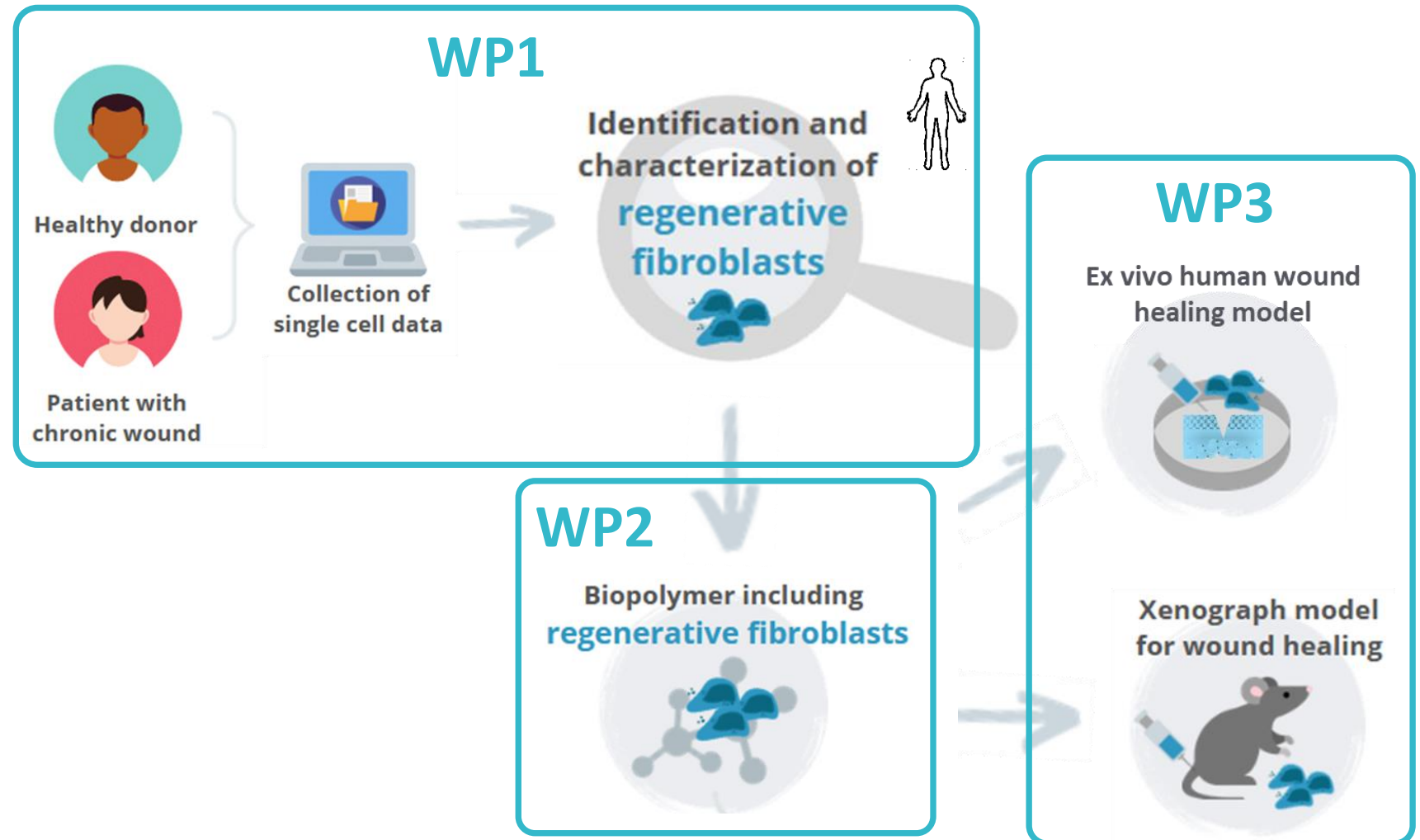
Dr. Yuval Rinkevich



ZellTWund – Project Plan



Shamik et al., Science, 2021
Rinkevich et al., Science, 2015
Correa-Gallegos et al., Nature, 2019
Phan et al., Exp. dermatology, 2020



Identification and characterization of regenerative fibroblasts



Definition of human fibroblast subtype transcriptomic landscapes



- 2022 Gur et al., Cell
- 2021 Reynolds et al., Science
- 2021 Tabib et al., JID
- 2020 He et al., JACI
- 2020 Sole-Boldo et al., Nat Com.
- 2020 Vorstandlechner et al., FASEB J.



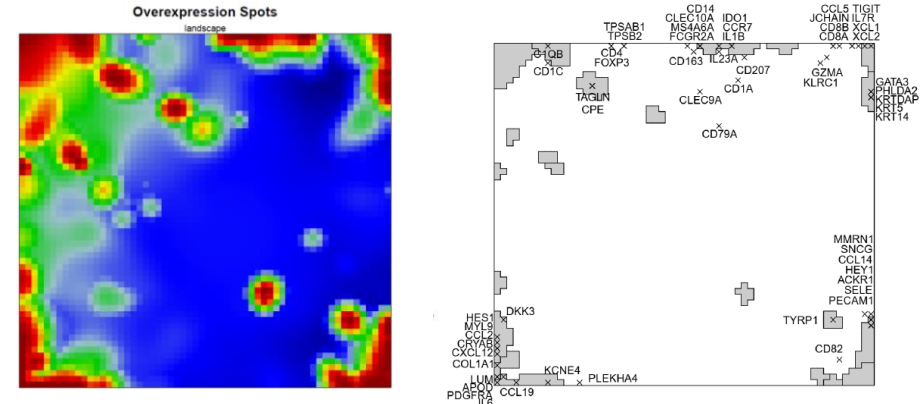
- 2022 Thompson et al., JID
- 2021 Mascharak et al., Science
- 2020 Phan et al., eLife
- 2019 Guerrero-Juarez et al., Nat Com
- 2018 Lim et al., Nat Com



INTERDISCIPLINARY CENTRE FOR BIOINFORMATICS

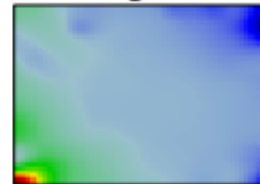
Analyses by H. Löffler-Wirth & M. Schmidt, Interdisciplinary centre for bioinformatics, University Leipzig

whole skin (human)

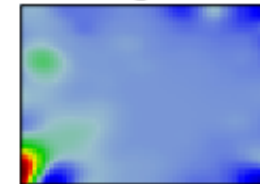


fibroblast subtypes (human)

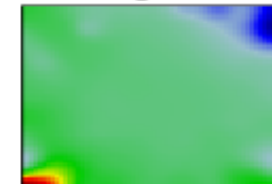
Fibroblast 1
logFC



Fibroblast 2
logFC



Fibroblast 3
logFC



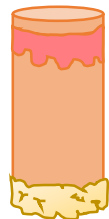
Identification and characterization of regenerative fibroblasts

Identification of human fibroblast subtype and characterizing marker

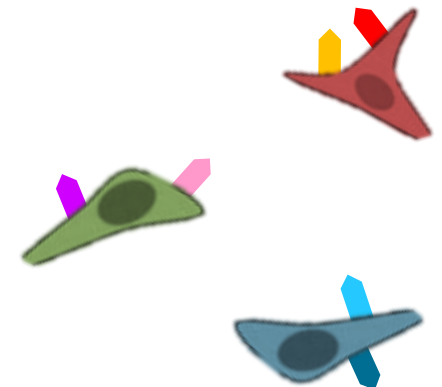
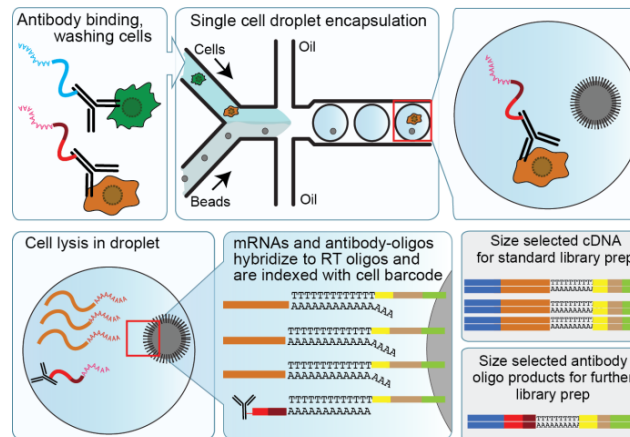
Skin biopsy collection:

healthy
diff. location
young
old

wound
normal
chronic
scarring

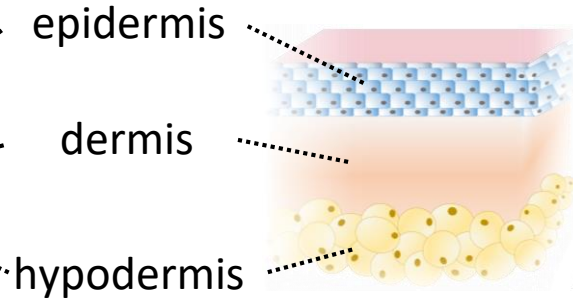
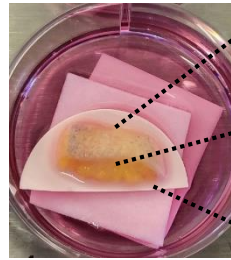


CiteSeq

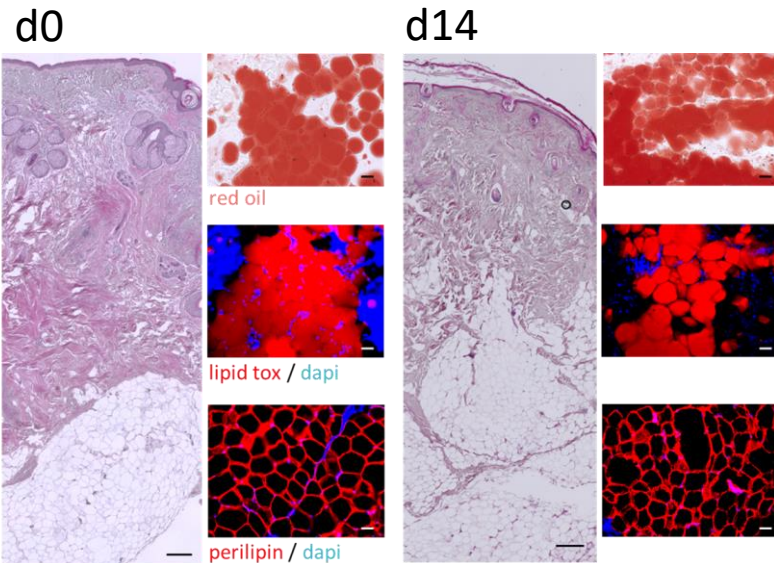


ZellWund – WP3 ahead of schedule

Ex vivo human wound healing model



Long-term ex vivo culture



H&E

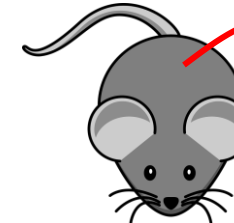
Wounding



Biomaterial injection



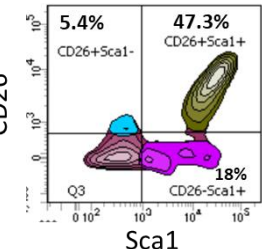
Xenograph model for wound healing



TM4 mice

FACS

Shamik et al., Science 2021



Papillary Fb

Lin- CD26+
Sca1-

Reticular Fb

Lin- DIK+
SCa1-/+

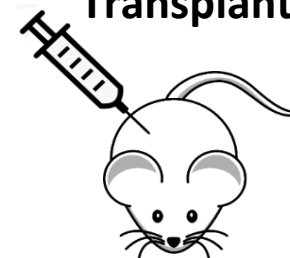
Hypodermal Fb

Lin- DIK-/ +
SCa1+

Fascia Fb

Lin- CD26+
SCa1+

Transplantation into dorsal skin



SCID mice

Fibroblast engraftment
Viability
Immune cell response

ZellTWund – Synergies/Partners

Science

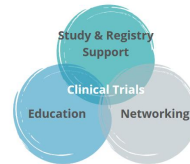
MSC-Prestige



OMICS



Clinics



xMac



Macrophage

Systems



Industry

existing



new



Current project

- Integration of regenerative fibroblasts into biomaterial
- Testing of fibroblast-biopolymer in ex vivo human wound healing model and xenograft mice model

Biopolymer including regenerative fibroblasts



Ex vivo human wound healing model



Xenograph model for wound healing



In future funding periods

- Optimization of innovative ATMPs (preclinical testing)
- Clinical trial

Regenerative wound dressing



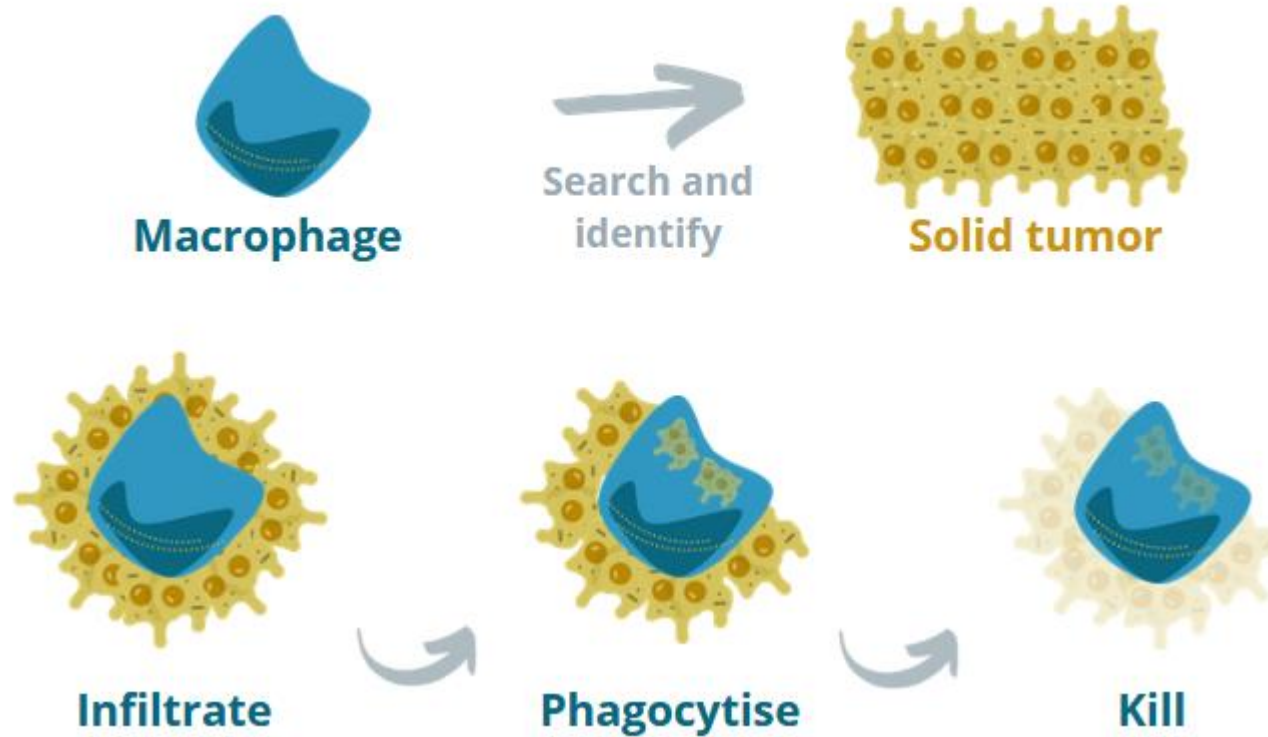
Clinical Trial 

ZellTWund – Discussion

- 8 months delay
- Reduce the objectives within this funding period:

WP3: In vivo murine wound healing models (MS8)

xMac – Project Overview



WHY MACROPHAGES?

Macrophages are able to infiltrate solid tumors and execute various functions:

- Phagocytosis of tumor cells

- Oncolytic activity

- MHC II-dependent antigen presentation

- Activate adjacent immune cells within the tumor microenvironment

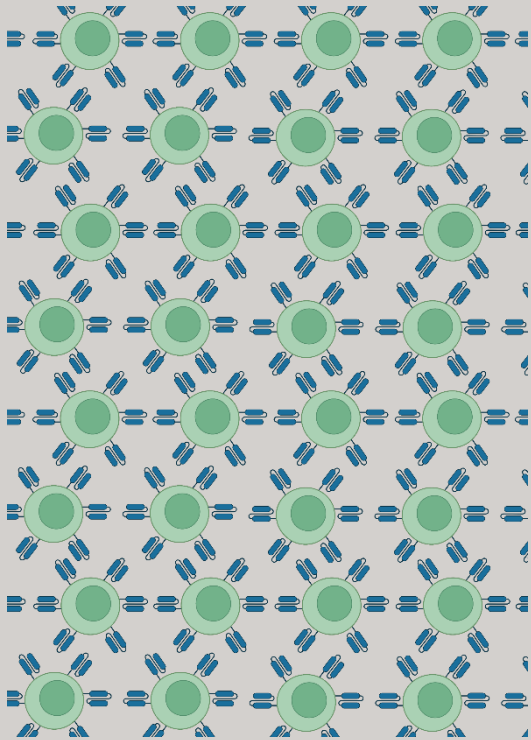
Current roadblocks:

1. Lack of expansion in cell culture → limited availability for therapy
2. Conversion by the tumor milieu (M1->M2 polarization) → promotes tumor growth and metastatic spread

- Genetically engineered human macrophages
 - High ex vivo proliferation capability
 - Prevention of tumor induced M2-like polarization
 - Stable anti-tumor activity
- Human iPSC-derived macrophages
 - allogeneic „off-the-shelf“ products
- POC: Anti-tumor activity of the corresponding mouse macrophages

xMac – Results so far

Vermehrung – ex vivo



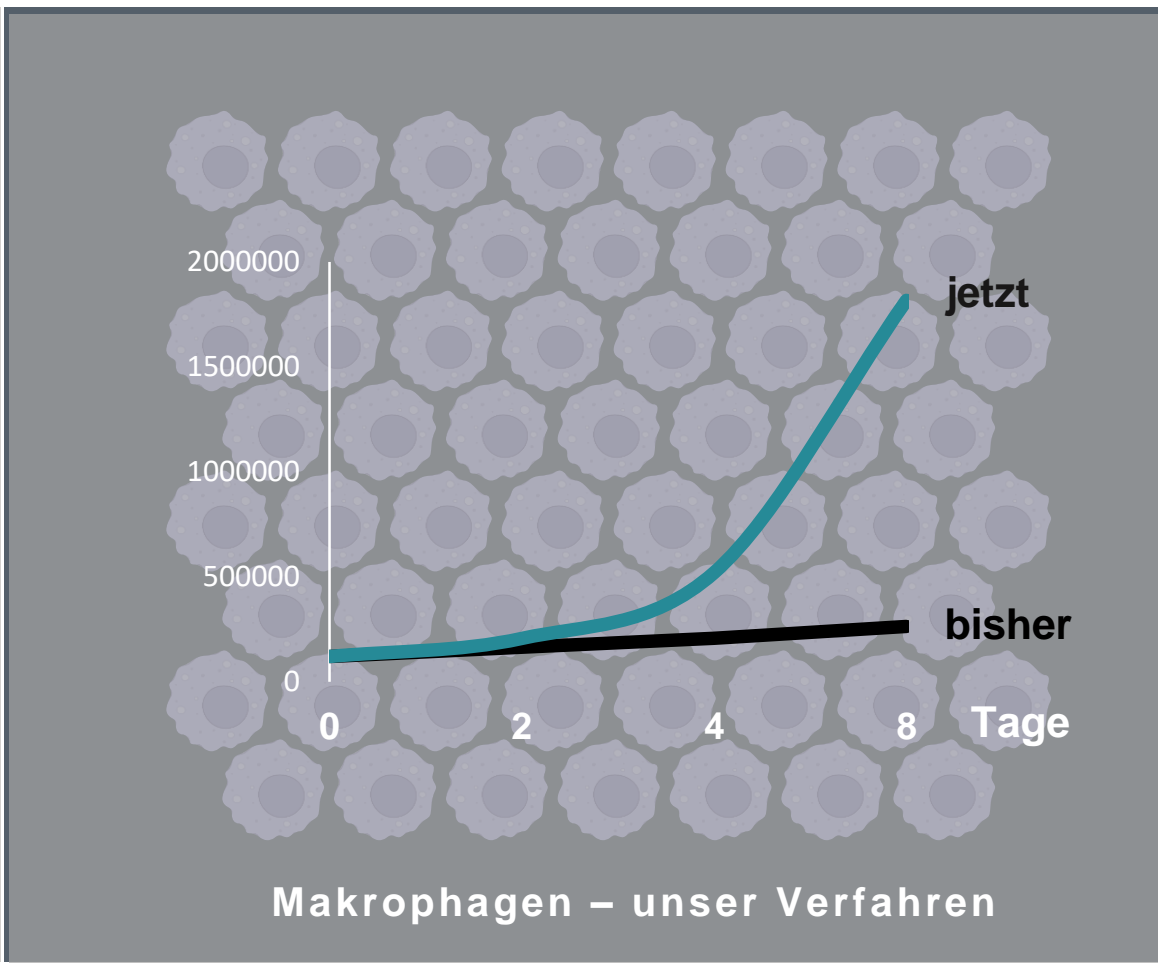
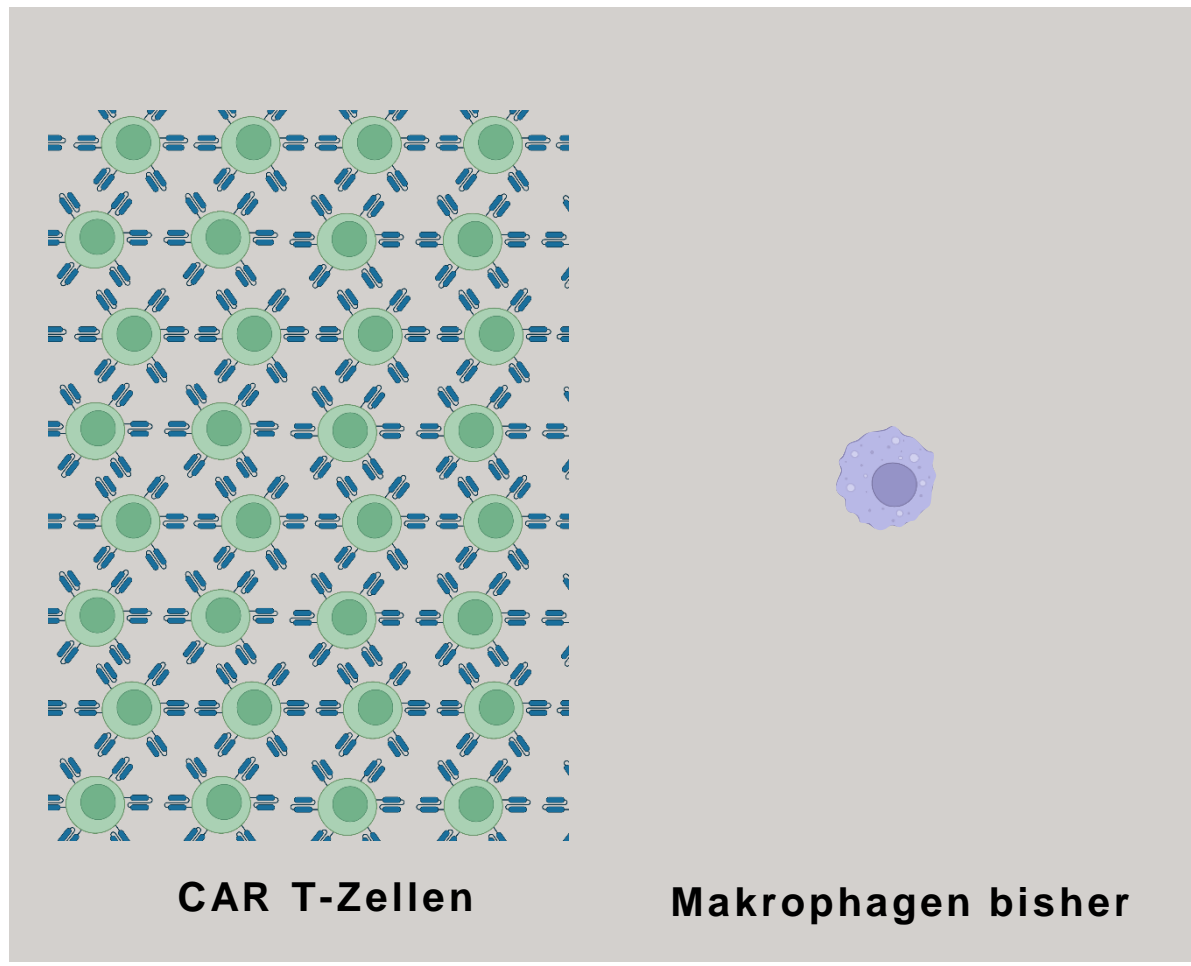
CAR T-Zellen



Makrophagen bisher

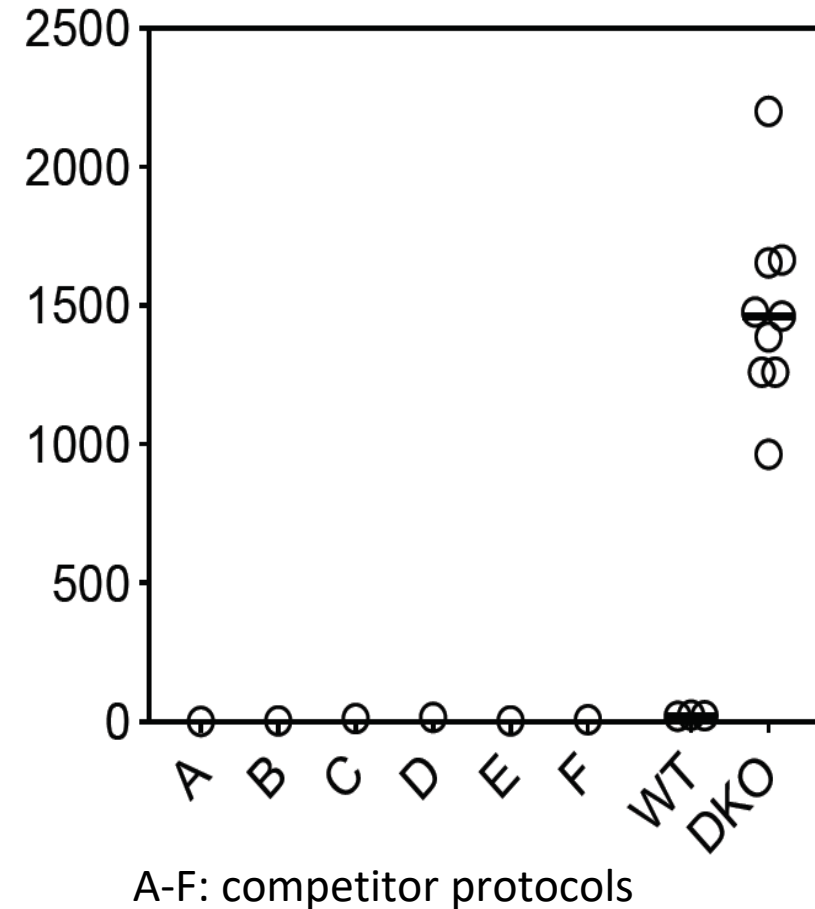
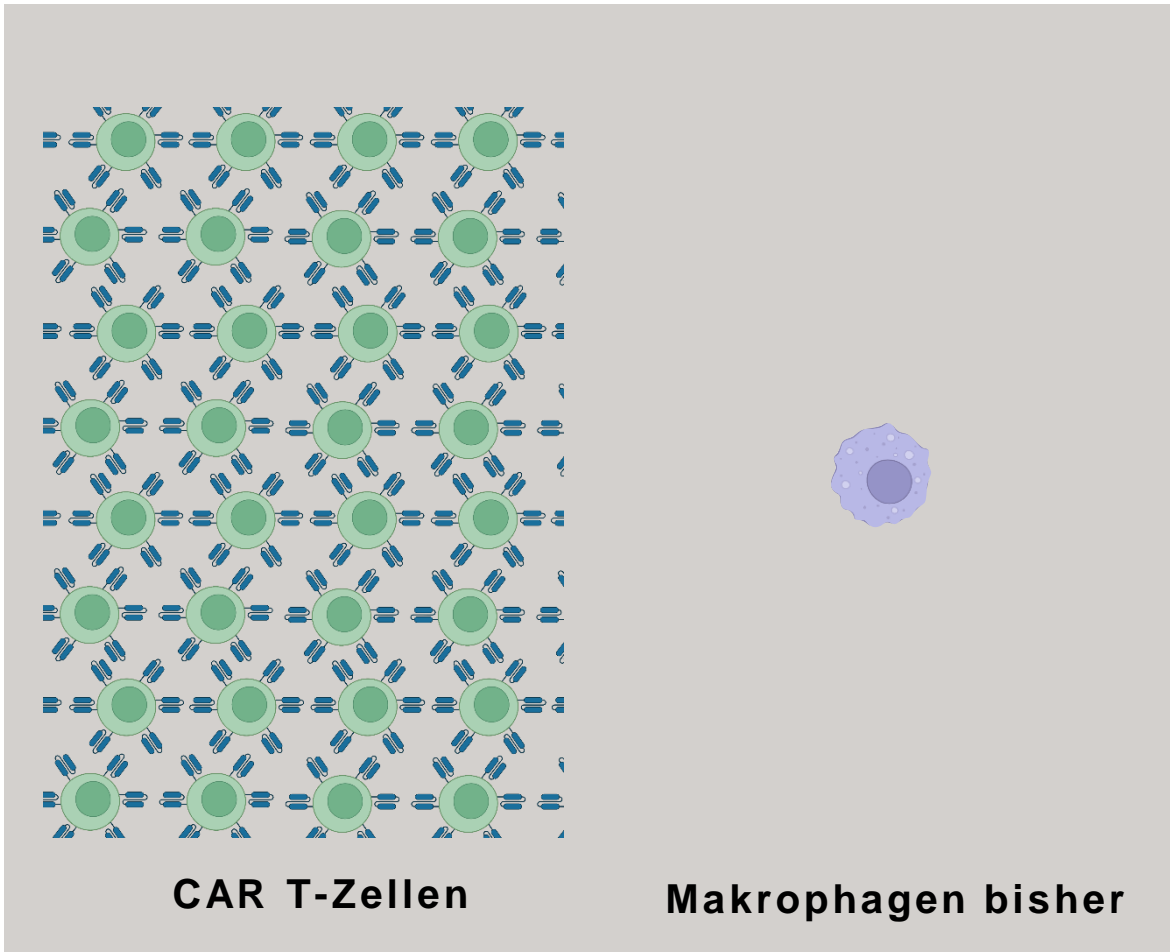
xMac – Results so far

Vermehrung – ex vivo

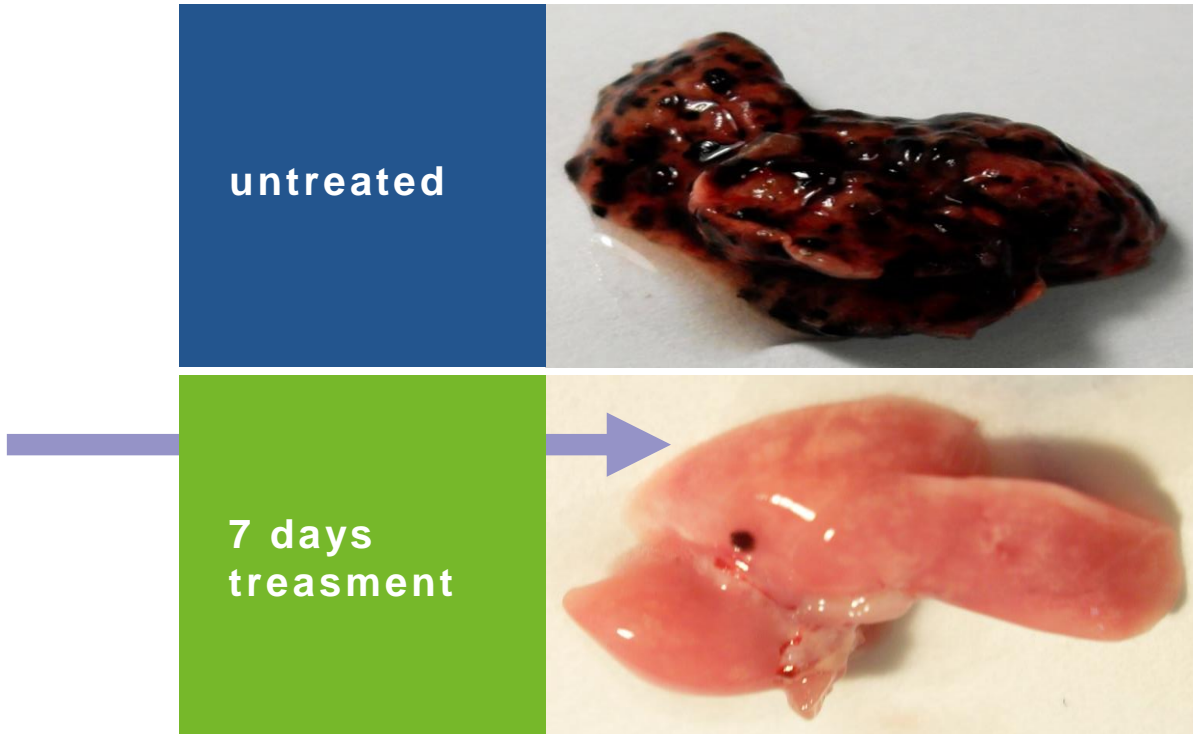
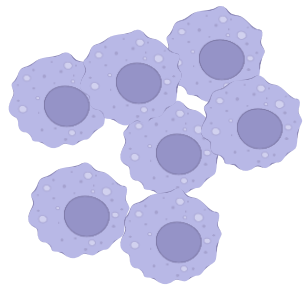


xMac – Results so far

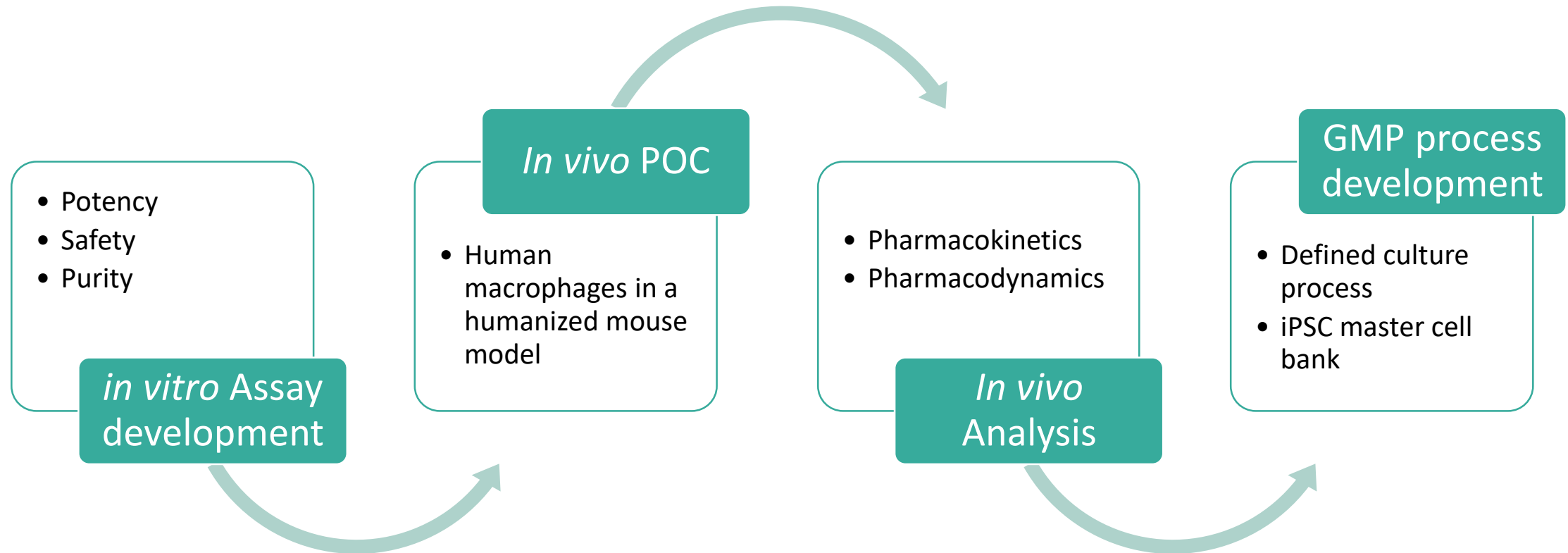
Vermehrung – ex vivo



xMac – Results so far

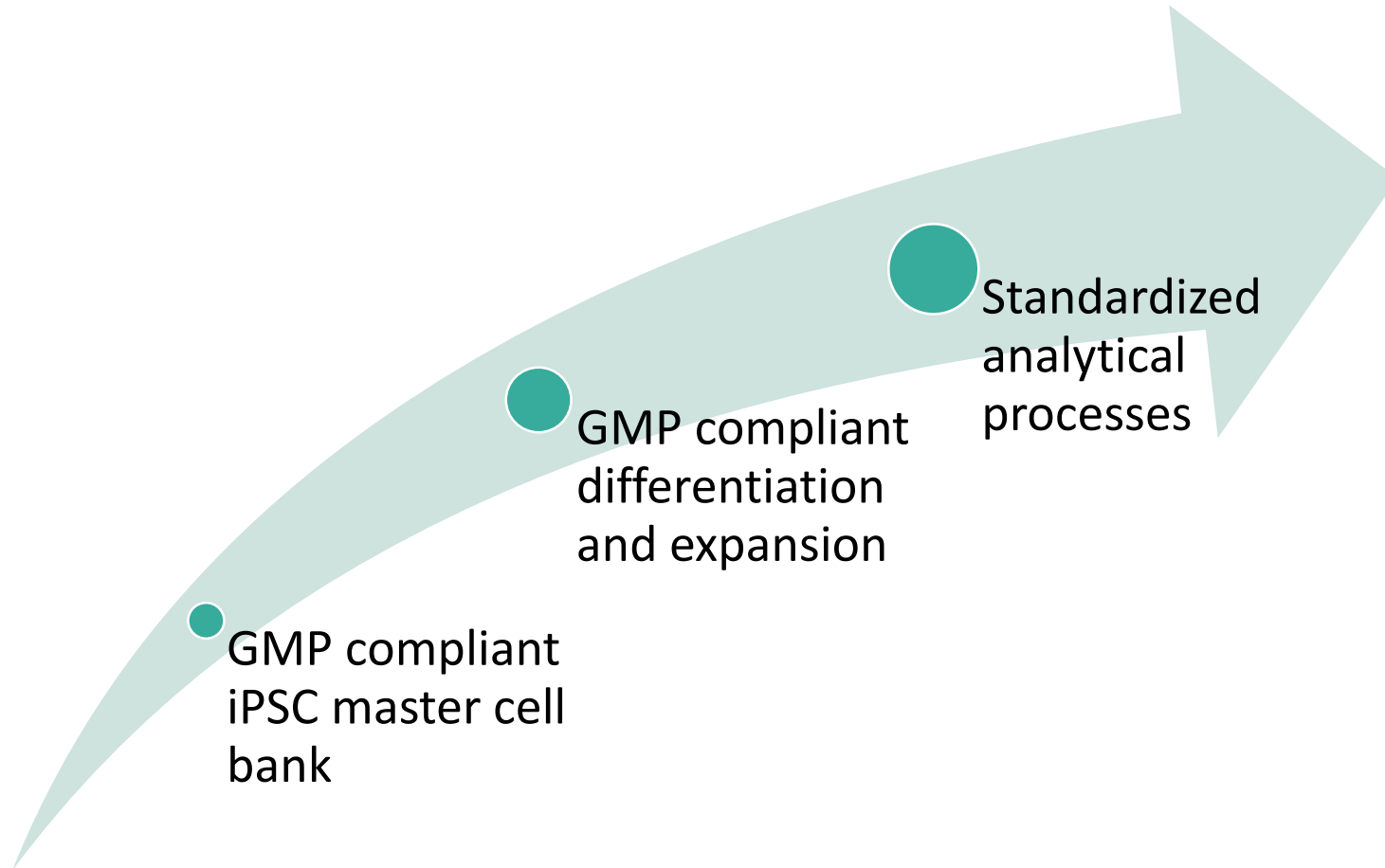


B16 Melanoma



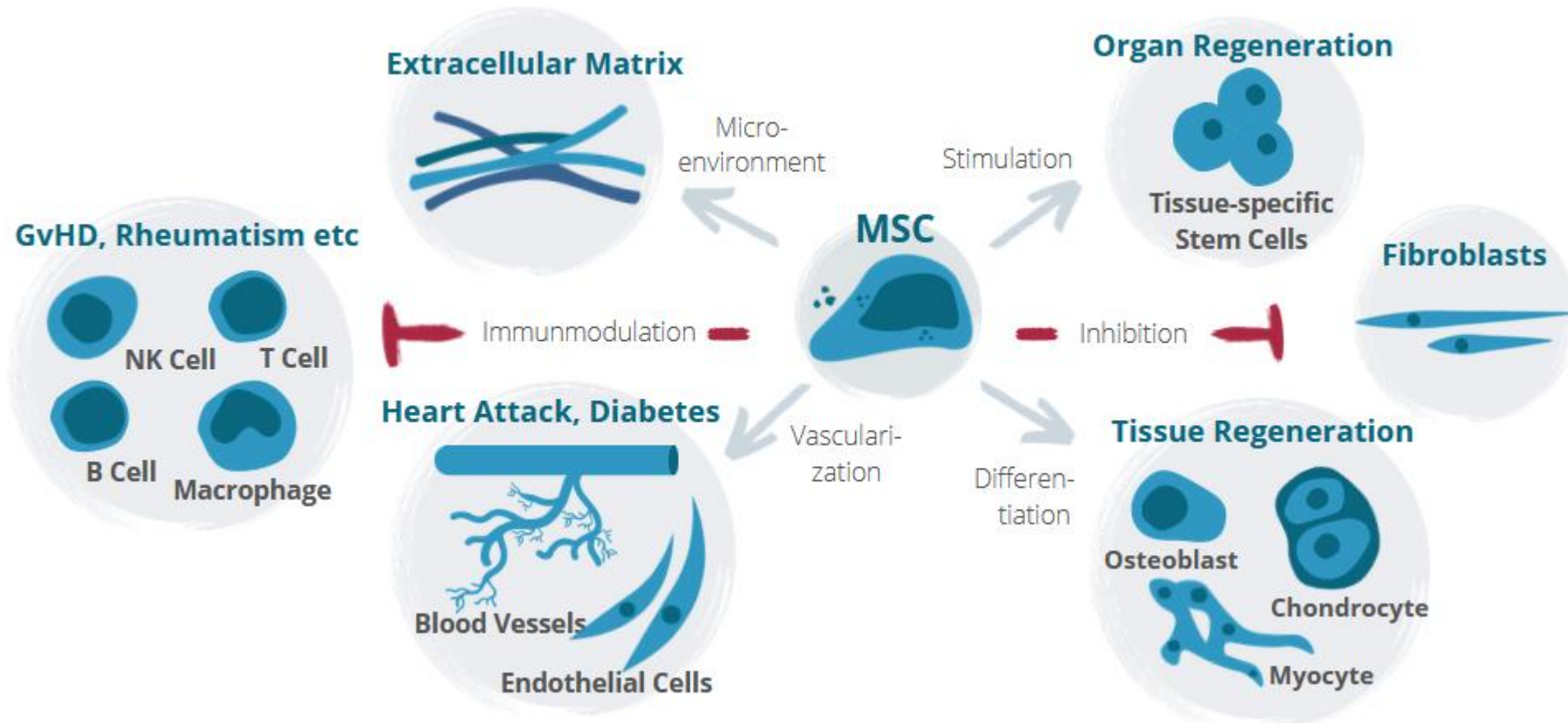
Background info:

- Patents applications are filed; two PCT applications are already published
- Considerable funding from competitive programs for other aspects of product and process development is granted (ERC POC, GO-Bio initial)

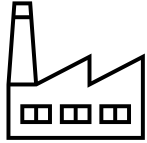


PEI approved ATIMP for „First-in-human“ studies

MSC-Prestige – Project Overview



MSC-Prestige – Objectives



✓ industrial

- ✓ establish an **industrial pharmaceutical MSC Cell Manufacturing**

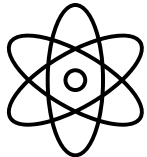


✓ clinical

- ✓ produce the **Investigational Medicinal Products (Prüfpräparate)**
- ✓ prepare a Phase I/II Trial (GvHD)

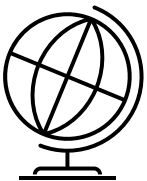
MSC-PreStiGe = Phase I/II trial of human umbilical cord derived Mesenchymal Stromal Cells to Prevent Steroid-refractoriness in acute Graft-versus-Host Disease

Controlled, randomized, single-center, double-blind



✓ scientific

- ✓ further characterization
 - > active profile of the drug substance
 - > immune profile of patients



✓ international

- ✓ set up a base in North America

MSC-Prestige – Results so far

✓ intensive cooperation



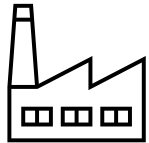
✓ Academic/Clinical Partner



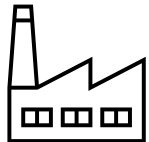
Universitätsklinikum
Carl Gustav Carus
DIE DRESDNER.



Prof. Rüdiger, Prof. Bornhäuser



✓ Industrial Partner



✓ Industrial Partner (associated)



MSC-Prestige – Results so far

✓ on schedule, objectives will be achieved

WP 1

✓ **Industrial Process Transfer from CRTD/TUD to DKMS ongoing**

WP 2

✓ specification and SOPs

✓ investments at associated Industrial partner ongoing

WP 3

✓ **Accompanying scientific research in progress**

✓ characterization drug substance, immune profiles

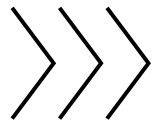
WP 4

✓ **Spin-off of a subsidiary in preparation**

✓ will be in Canada, province of Ontario

MSC-Prestige – Synergies

✓ **To all platforms!**



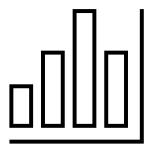
✓ **Systems**

✓ MSC-Prestige is an initial use case for Systems



✓ **Clinics**

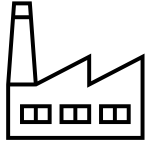
✓ future clinical trials with MSC for other indications are interested in



✓ **Omics**

✓ MDTB is interested in a 1st work package (scheduled 2023)

MSC-Prestige – Outlook



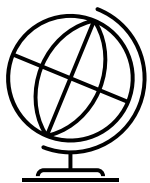
- ✓ **industrial infrastructure**
- ✓ DKMS is an **industrial partner** for **Cell Manufacturing**



- ✓ **clinical impact**
- ✓ MDTB is a **leading company** for MSC-drugs for international trials
- ✓ **Advanced Therapies** for GvHD, Sepsis, Chronic Lung Disease are in clinical testing



- ✓ **unique products**
- ✓ **Desacell®** is the **MSC drug substance** for allogeneic, off-the-shelf, ready-to-use cellular drug products at reasonable costs



- ✓ **international impact**
- ✓ **Transatlantic** long-term cooperation is prepared

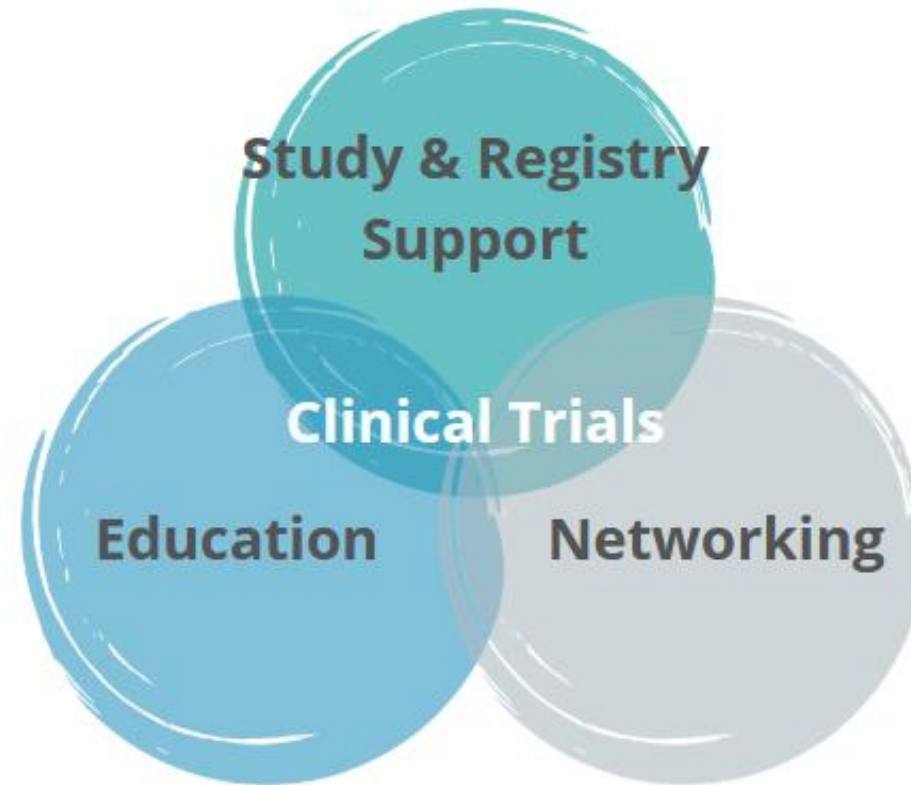
Clinics – Overview



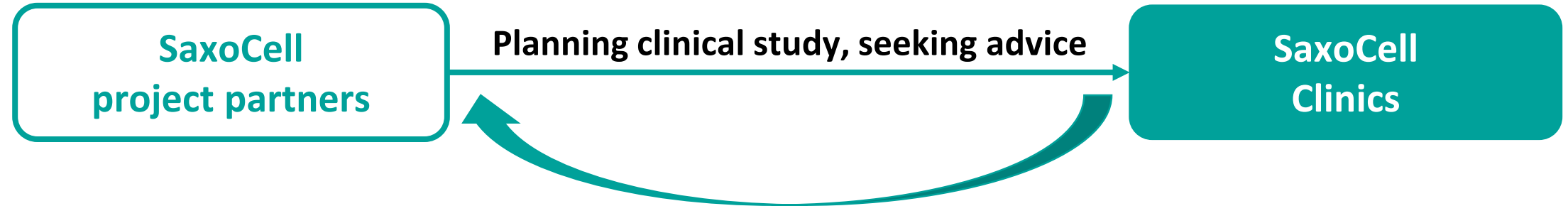
Silke Gloaguen
University Hospital Leipzig



Prof. Dr. Uwe Platzbecker
University Hospital Leipzig



Clinics - Objectives



Clinics supports with



Clinics - project-related activities





Support preparation of PHOTOCAR study (the study will provide samples for ECP-CAR)

- Collaboration with project team / Dr. Vucinic and regulatory bodies
- PEI advice on November 1st - get clarification on:
 - Role of ECP → classified as ATMP in Germany
 - Regulatory consequences
 - Need manufacturing license (work in progress with Landesdirektion)
 - Get PEI opinion on pre-clinical analyses and results available to date
 - Perceived (regulatory) role of CAR-T cell therapy in the trial → our understanding = non-IMP

Support pipeline on the way to a CAR-NK study

- Development of an anti-CD123 CAR construct
 - Pre-clinical work ongoing
- Anticipate PEI advice for pre-clinical work (tox / safety / quality) in Q3/Q4 2023:
 - Collaborate with project team – Clinics to coordinate PEI advice efforts
- Outlook → based on PEI advice results start working on study concept(s)
 - AML / MDS / both?
 - Request for funding with DKH once study concept is final



- **SHIMMER biobank**

- Registry / biobank of patients treated with ATMPs and/or SCT. Status as of mid October:
 - **Leipzig:** Baseline: 28 patients FU28d post Tx: 22 patients
 - **Chemnitz:** Baseline: 4 patients FU28d post Tx: 4 patients

- **Working paper (WP) on ATMPs**

- Summary on classifications, landscape, regulatory aspects etc.
- As general informational and SaxoCell reference document
- Work in progress - final until end of year

- **Workshop „clinical studies on ATMPs“**

- 16-17 March 2023
- Location: UKL (anticipated is *kleiner Hörsaal im Studienzentrum*)
- In collaboration with the HUB, ZKS Leipzig and KKS Dresden
- Preparations ongoing
 - Finalize program & speakers
 - Organize technical aspects (hybrid)
 - Financing

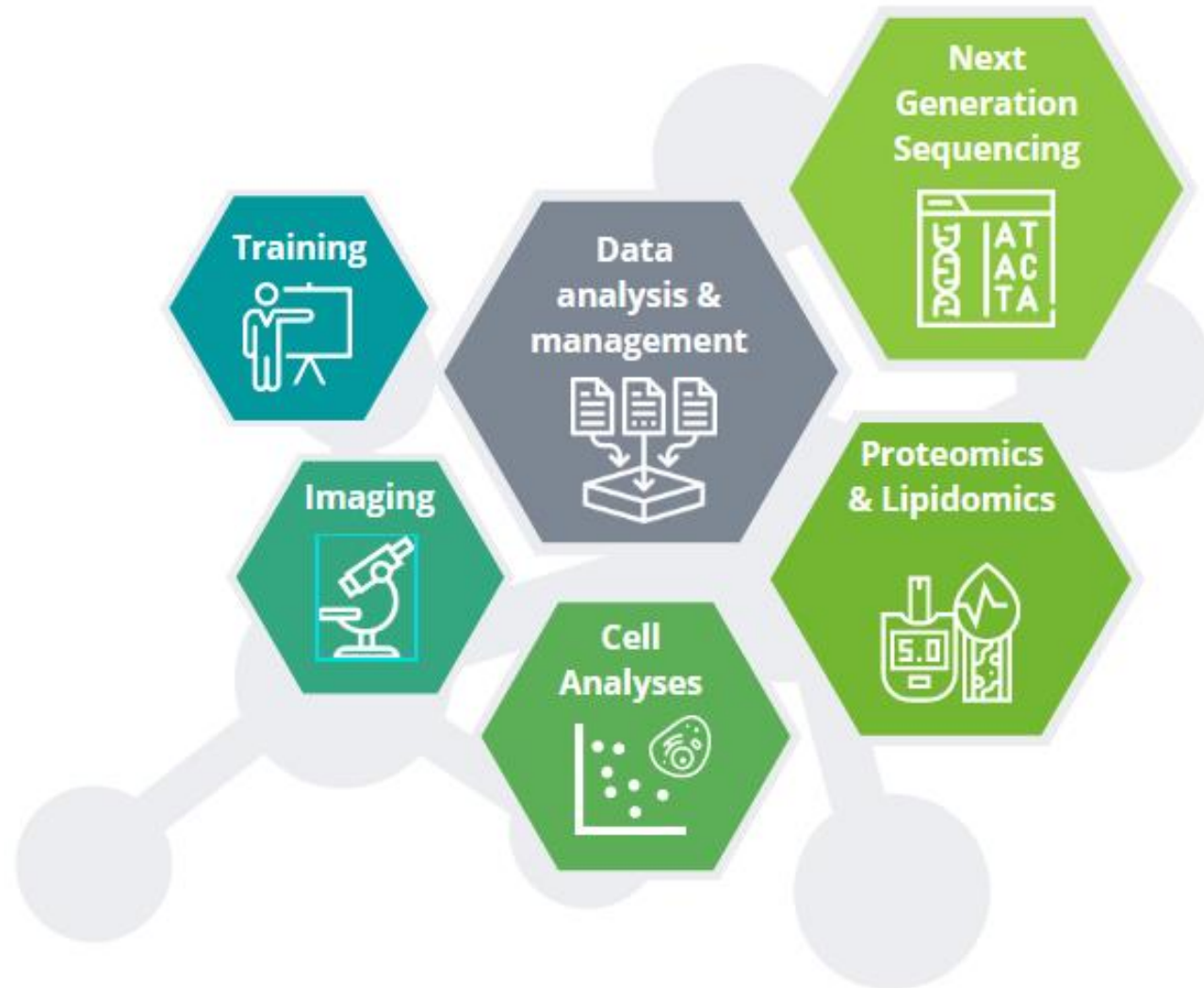
PLATFORM – OMICS



Dr. Kristin Reiche
Fraunhofer IZI



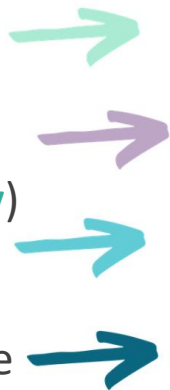
Prof. Dr. Ezio Bonifacio
CRTD / TU Dresden



OMICS – Objectives

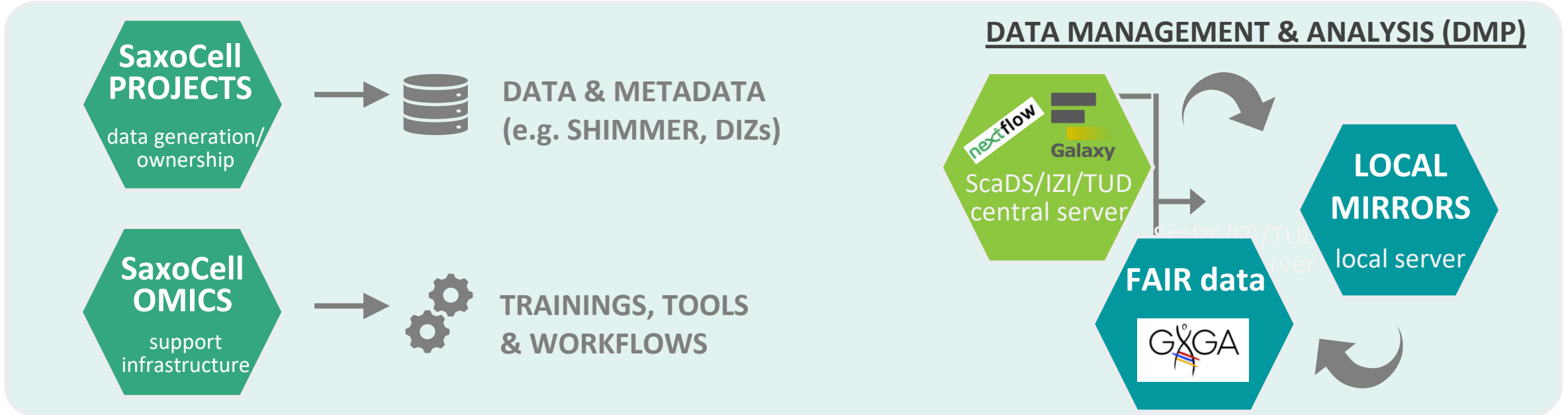
Specific needs of „Living drugs“

- ✘ Understand mechanisms of action, resistance and adverse effects (**molecular and cellular**)
- ✘ Assess quality of novel targets (e.g. **target-specificity**)
- ✘ Identify the right patient at the right time for treatment
- ✘ Characterize cells prior to manufacturing and release



SaxoCell Omics

Improved evaluation of cell and gene therapies **through** standardized and documented **high-throughput measurements & cutting-edge ex-vivo tools, bioinformatics tools, workflows and trainings**



OMICS – Results so far

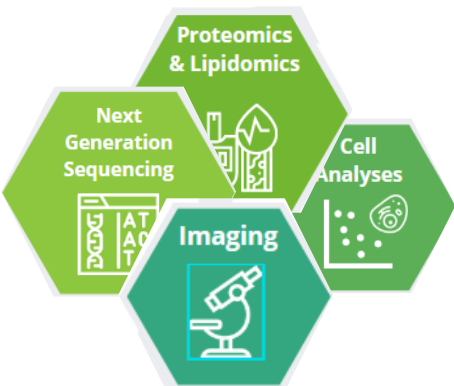
Preparatory actions and establishment of workflows and services of platform for SC projects



Educational courses and trainings are offered to SaxoCell by **ecSeq**
- theme-specific courses are in preparation, following identified demand



Data management plan describes a **concept for data production, storage & sharing and analysis**
- data storage and management in accordance with FAIR principles
- implementation of an dedicated analysis server (Galaxy platform) started.



Identification of **Omics assays and workflows** relevant for SaxoCell projects (DD, LE, C)
Patient consent and data protection in collaboration with SaxoCellClinics (SCC)

OMICS – Synergies to other SaxoCell Projects

- Contact with SaxoCell projects – better understand project objectives and needs, and plan how SaxoCellOmics can support them
- Proactive project interactions beyond projects in proposal



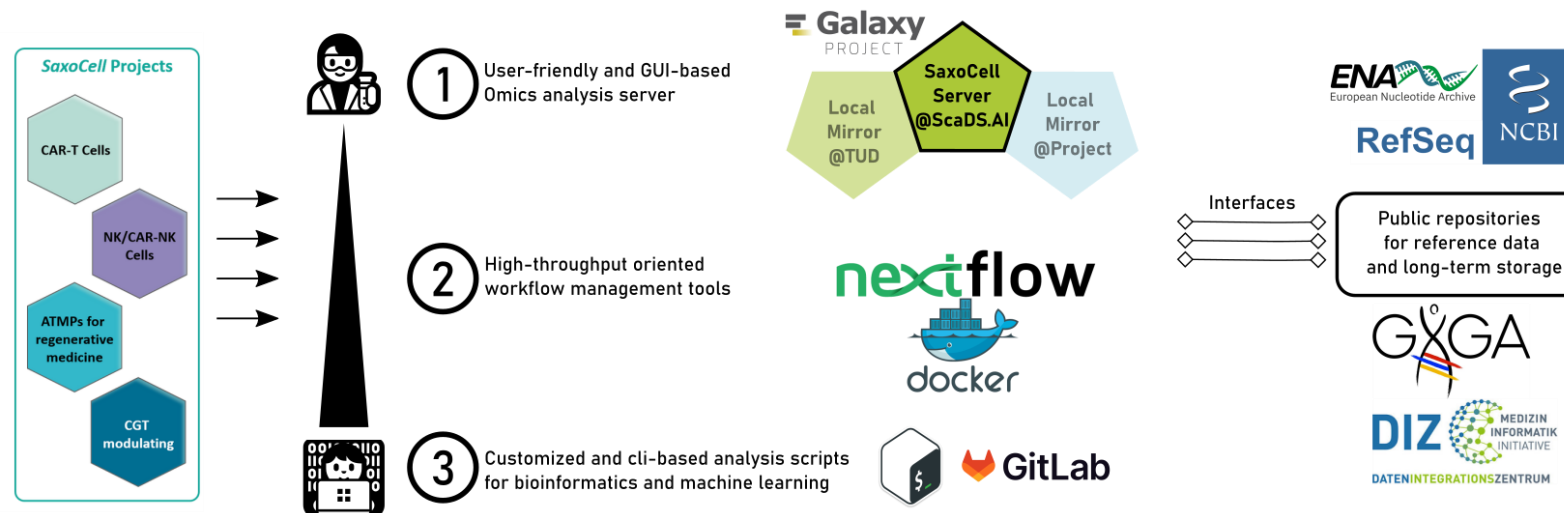
OMICS – Outlook

Short term goals:

- Provide analysis platform for data analysis (galaxy server)
- Conduct theme specific courses/training (NGS/(single cell) transcriptomics, galaxy server/Nextflow)
- Partner a SaxoCell project on a funding application with OMICS cooperation

Mid/long term goals:

- Provide custom analysis support and algorithm development (issue: financing)
- Integrate data storage and management approach into existing strategies
- Approach SME/industry partners for cooperation with SaxoCellOmics



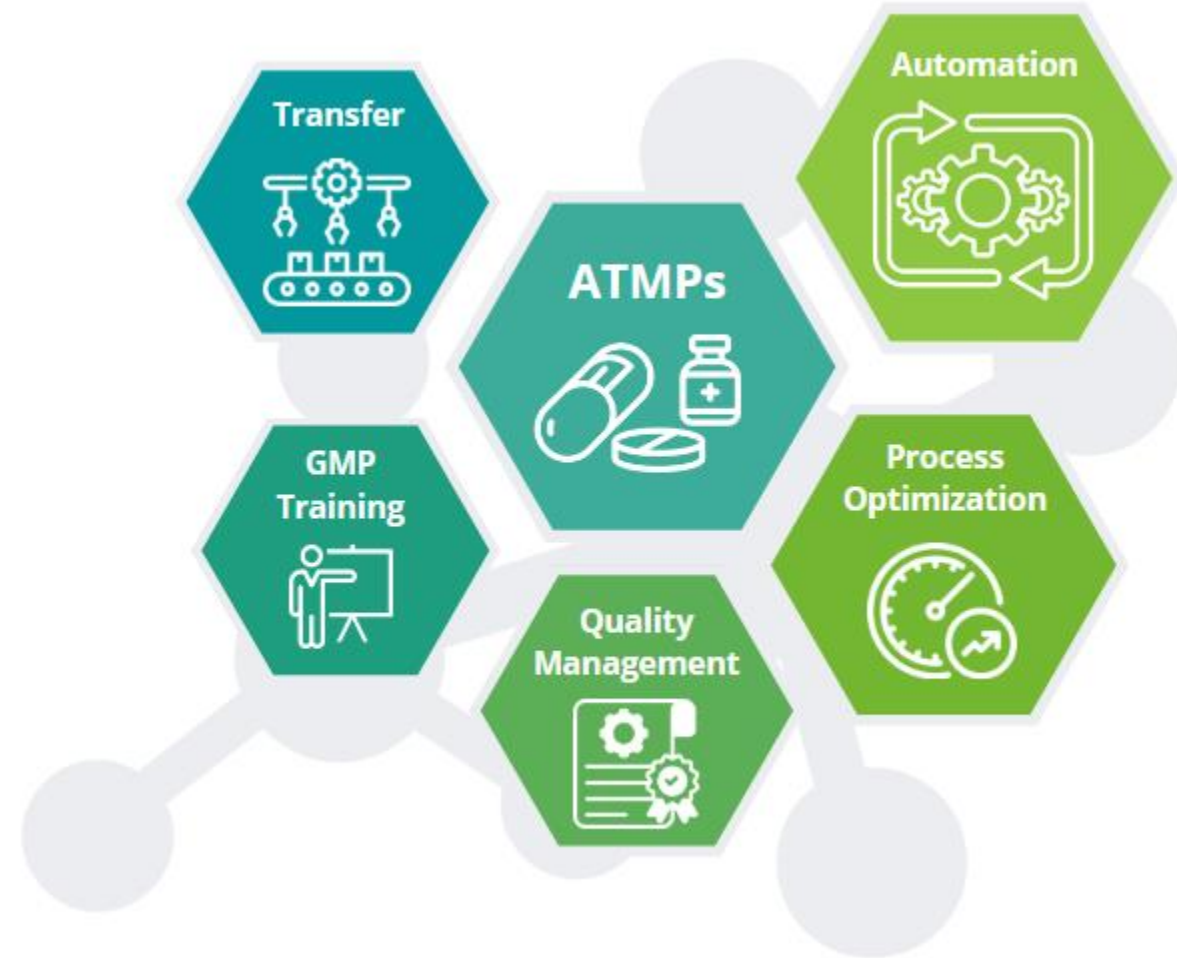
PLATFORM – SYSTEMS



PD Dr. Stephan Fricke
Fraunhofer IZI



Dr. Ulrich Blache
Fraunhofer IZI



PLATFORM – SYSTEMS

Prof. Dr. Rüdiger, Dr. Freund
TU Dresden



Prof. Dr. Neumuth
Uni Leipzig, ICCAS



Prof. Dr. Rahm
Uni Leipzig, ScaDS.AI



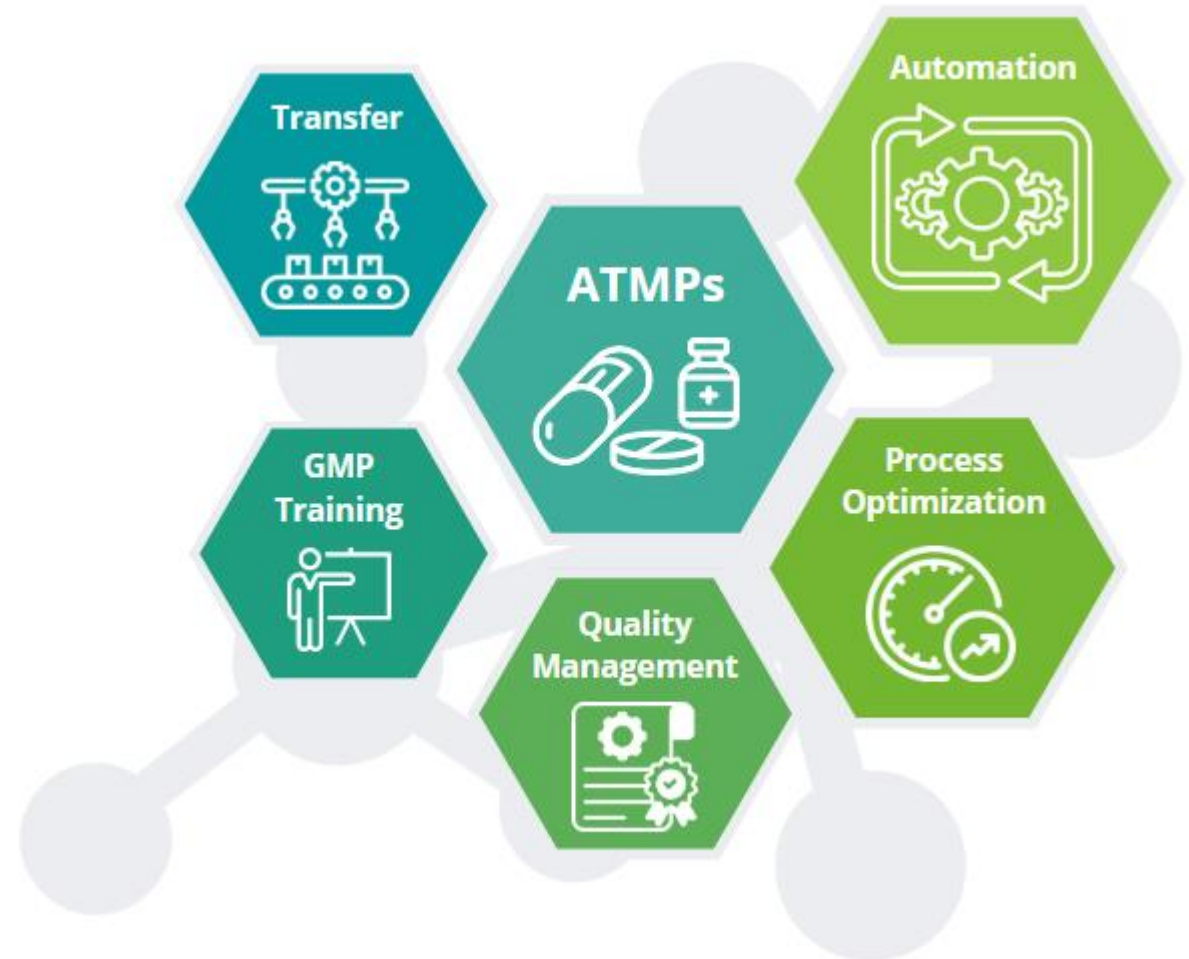
Prof. Dr. Henschler
Uni Leipzig, UKL



Prof. Dr. Pompe, Dr. Jahnke
Uni Leipzig, BBZ



PD Dr. Fricke, Dr. Blache
Fraunhofer IZI, Coordination



Overarching Goal

Building a competence platform for the intelligent (i.e. automated, digitalized) manufacturing of ATMPs (from the SaxoCell Cluster and beyond)

Objectives

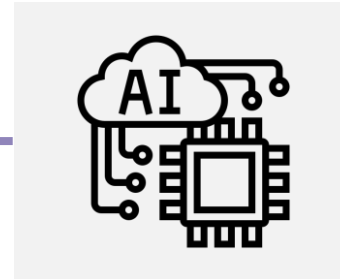
- Concepts and protocols for automated ATMP manufacturing
- Intelligent quality management and process optimization including artificial intelligence (AI) methods (digital twin concepts)
- Development of next-generation quality controls
- Good Manufacturing Practice (GMP) compatibility
- GMP training courses for staff in the field of ATMP and automation

SYSTEMS – At a glance

WP 1+4: GMP compatibility

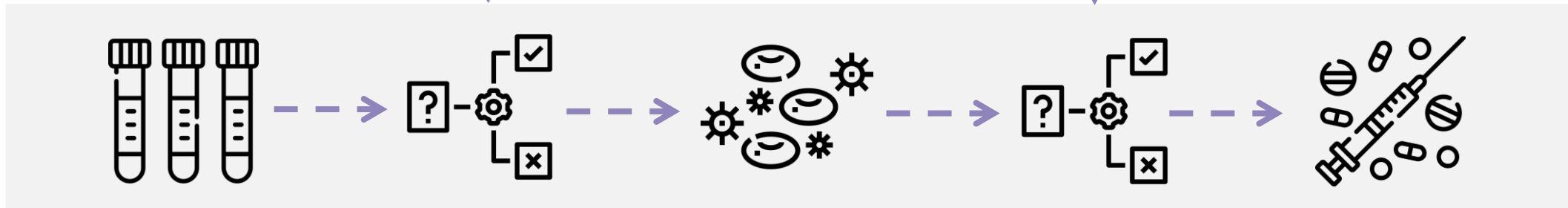


WP 4+5: GMP training

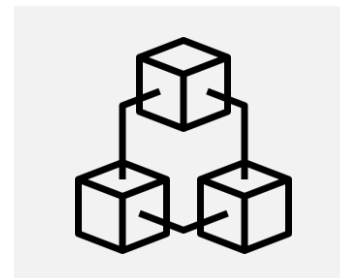


WP 1: ATMP use case (MSC)

WP 3: AI for process optimization



WP 2: Quality management

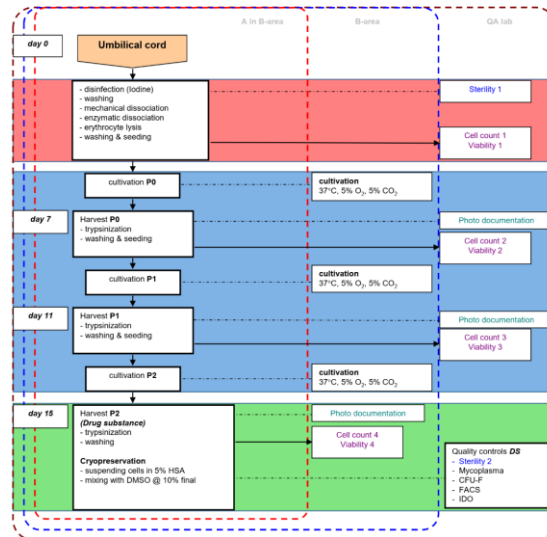


WP 6: Next-gen quality controls

SYSTEMS – Results so far

WP 1+2+3

ATMP process definition, requirement specifications

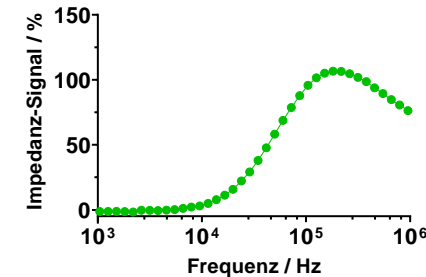
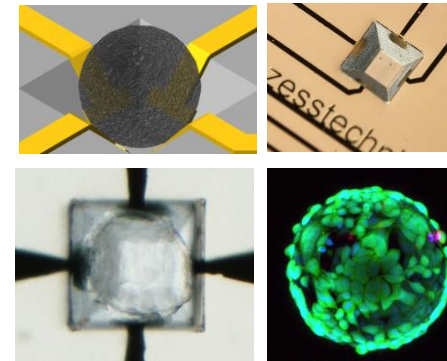


- Ongoing semantic definition of all assets (devices, substances) related to the ATMP process
- Deployment of a testnet (blockchain) infrastructure to allow for validated data management and exchange

- Development of AI-based modules for process optimization: cell confluence and potency prediction based on images and impedance data
- Integration of documentation and optimization modules into a software prototype

WP 6

Bioelectronic Monitoring



- First microcavity array based analysis of impedance signals in the identified use case (successful)

WP 4+5

Course Theory (40h)



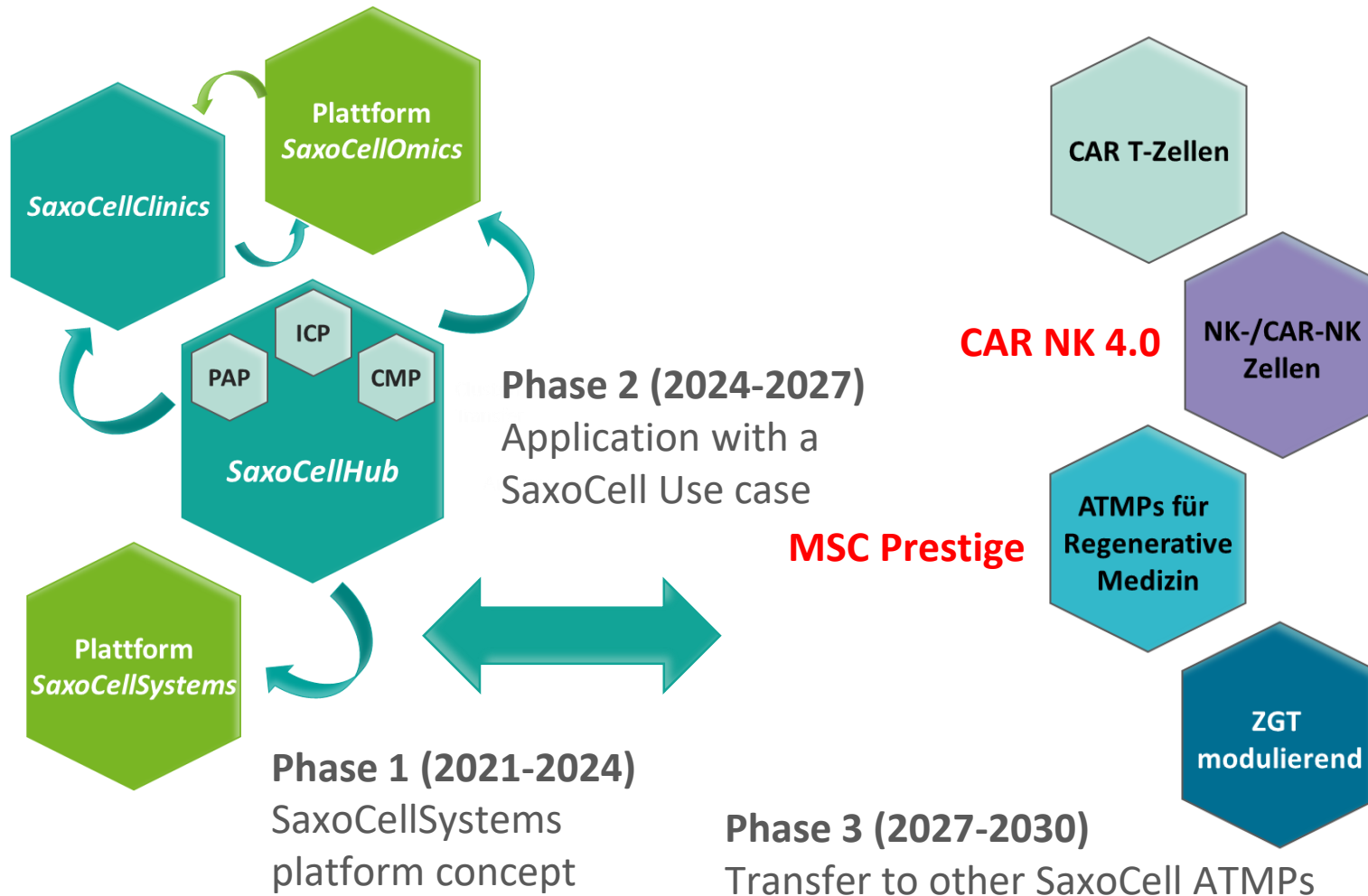
Course Praxis (160h)



Under construction:

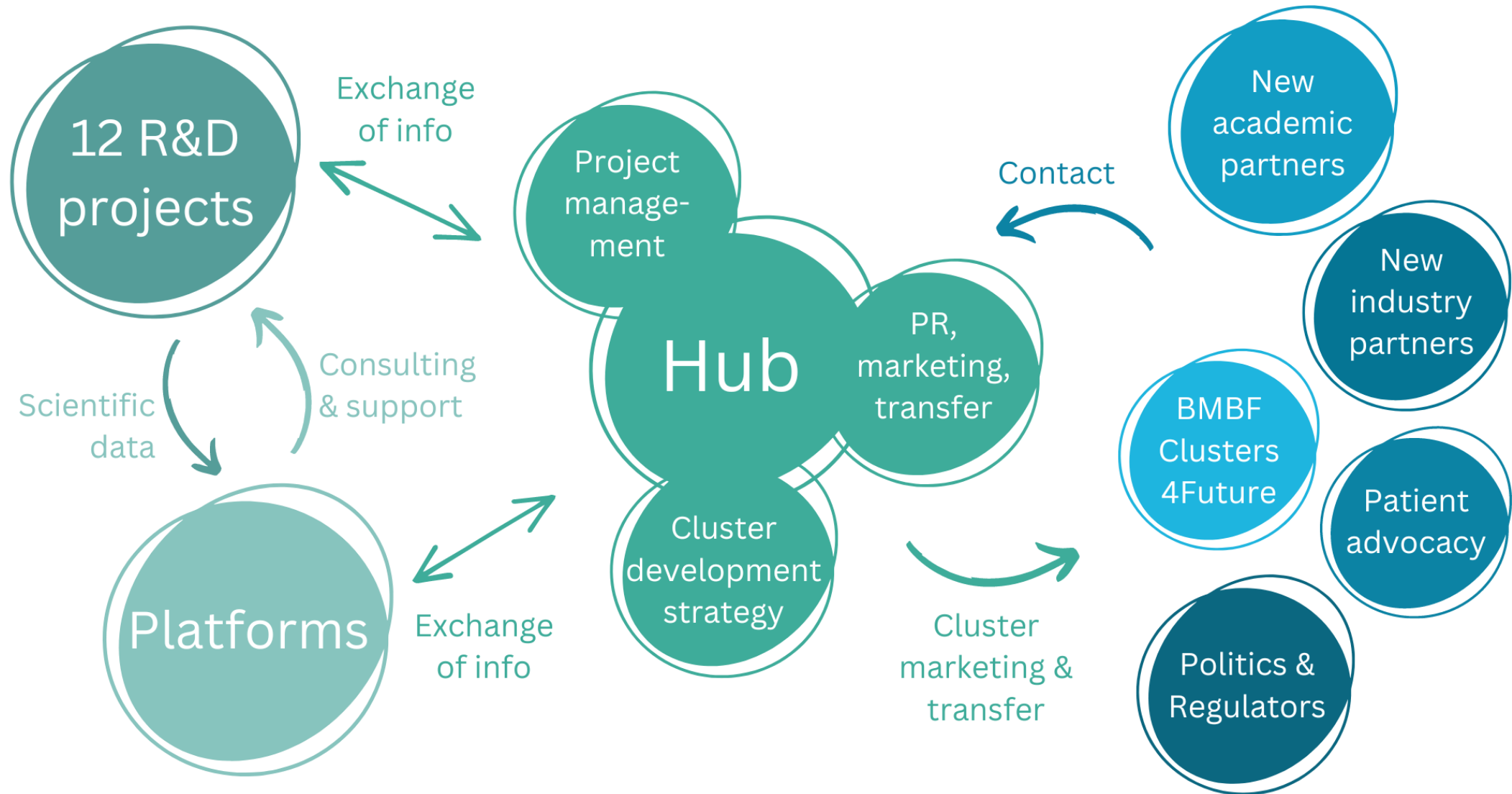
- Automation module
- Online training platform

SYSTEMS – Synergies & Outlook



Miscellaneous

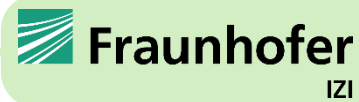
- Commitment of MDTB CELLS as industry partner for SaxoCellSystems in Phase II
- SaxoCellSystems ‘Competencies and offer’ Atlas (December 2022)
- First milestones are achieved (MS1, MS10)
- Further milestones are due end of the year (Dec 2022, MS2, MS4, MS7) and will likely be achieved in time



SaxoCell Hub

the central structure to enable connections,
interactions and visibility

Hub members



Fraunhofer IZI



Ilka Henze



Thomas Tradler



Anette Bartsch



Sophia Kolbe



Paul Starz



TECHNISCHE UNIVERSITÄT DRESDEN



Maren Henneken



Ira Illgen



Franziska Friebel-Viebach



Dorit Teichmann



Luisa Brückner



Stephanie Wieneke



UNIVERSITÄT LEIPZIG



Beatrice Berneck



Stefanie Binder



Nicole Modler

PAP

Pipeline Accelerator Program

Project management
Identification of new projects
Reporting

CMP

Cluster Matching Program

Cluster strategy development
Cluster sustainability
Joint research infrastructure

ICP

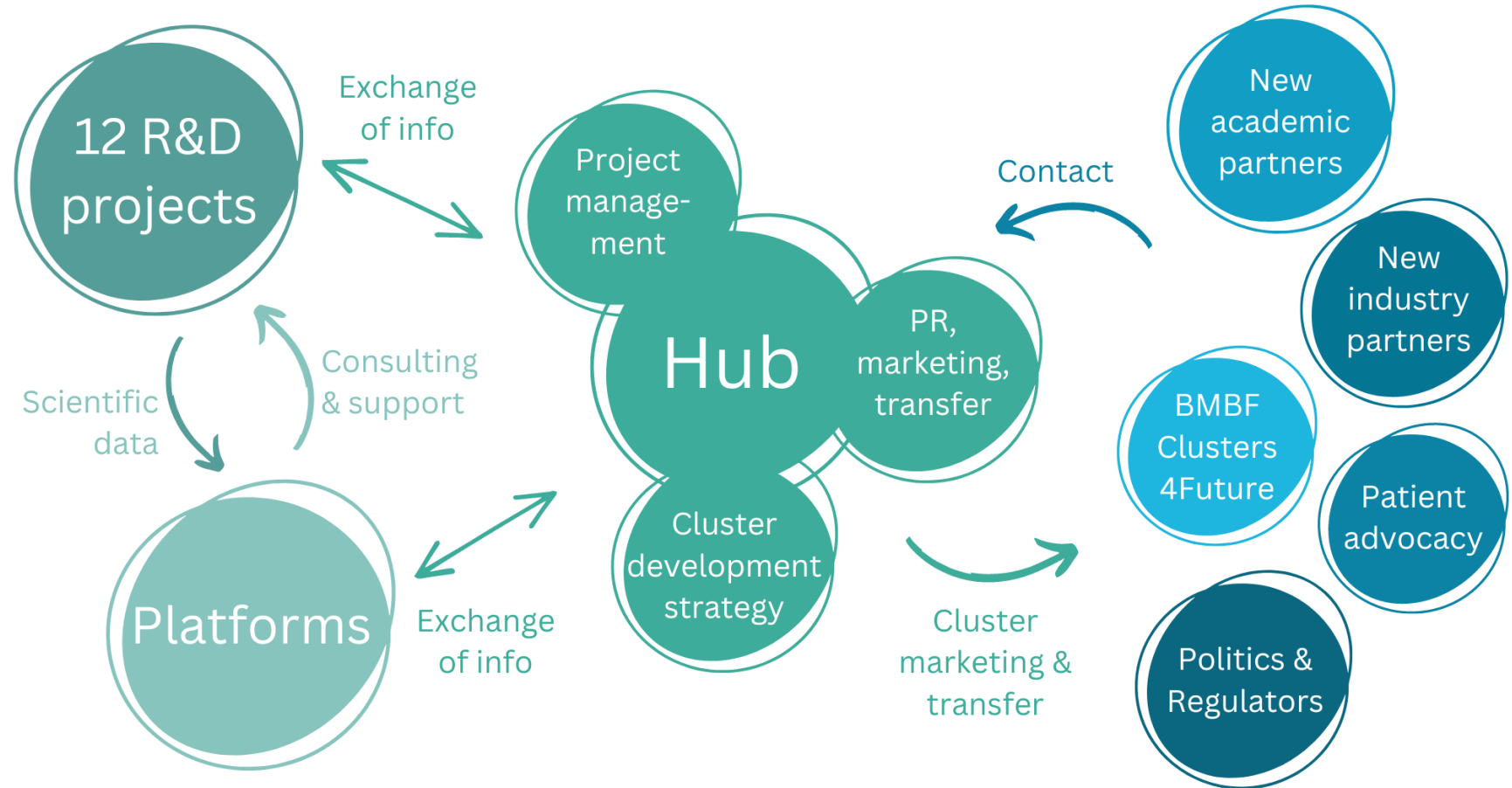
Innovation Culture Program

PR, marketing & transfer
Contracts & patents
Trainings & innovation culture

Hub program

SaxoCell's Innovation Hub

- Interdisciplinary & strategic approach to support cluster development & R&D activities
- Focus on fostering transfer friendly cluster culture & on workshops/trainings



What we did in the first year

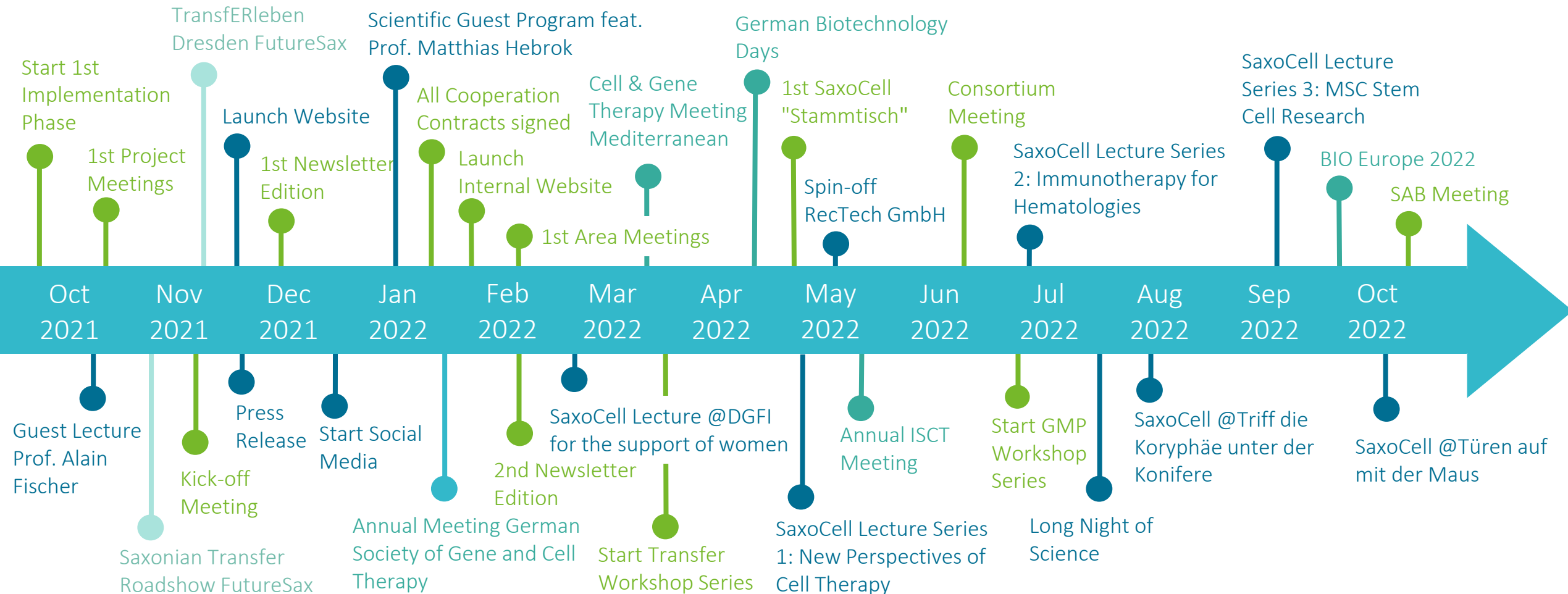


Public event

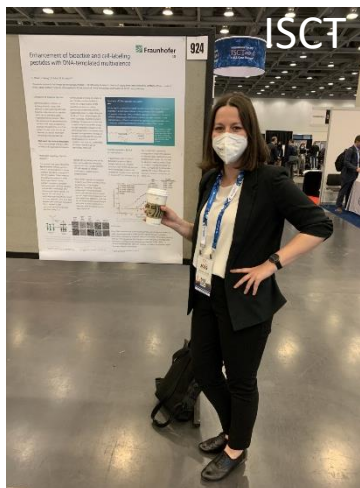
Transfer

Conferences

Cluster-internal



We transfer!




- DBT 2022
- ARM-MED 2022
- ISCT 2022
- BIO-Europe 2022

We support our projects!



Hub

Challenges

- **Few proprietary assets** available yet due to short project duration
 - Increase awareness of importance of **IP assets** amongst scientists
 - **Regulatory requirements** regarding manufacturing, animal and clinical studies in parts unpredictable → early involvement of existing expertise
 - Next rounds of funding **require higher industry commitment**
 - **Strict guidelines from PtJ**
 - Establishment of a **Cluster-Spirit** (different locations and institutions, confidential aspects...)
- 
- A faint, light gray illustration in the background shows a stylized human figure climbing a hill. At the top of the hill, a flag is planted on a pole. The figure is in a dynamic, forward-leaning pose, suggesting effort and progress.

Questions to the SAB



Regulatory aspects

- How to establish appropriate project plans in the 2nd phase of SaxoCell considering regulatory aspects?

Industry aspects

- How to better motivate projects to get in contact with industry for collaboration?

Patient engagement

- What are the expectations of patients from a Cluster like SaxoCell?

Advice required

- Any advice to identify interesting institutes, speakers, topics to include in SaxoCell is welcome
- Further conferences, meetings or partners to increase visibility
- Any support to identify CGT companies willing to establish a business in Saxony

Stay in touch with SaxoCell!



Website + Members Area

<https://www.saxocell.de>



LinkedIn

<https://www.linkedin.com/company/saxocell-cluster/>



Twitter

<https://www.twitter.com/saxocell>



Instagram

<https://www.instagram.com/saxocell/>



**In future: external
Newsletter**

Discussion