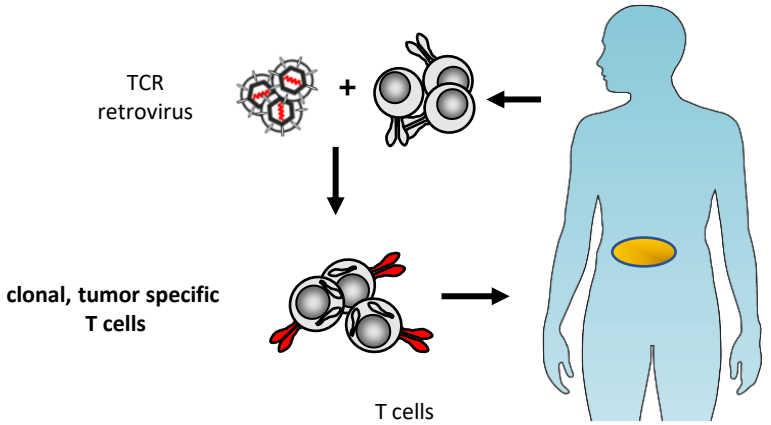
5th ForTra Workshop for Translational Research

Precision immunotherapy: Mutation-specific TCR-T-cell therapy for MyD88L265P mutated lymphoma – GMP-grade vector production and establishment of TCR-T cell manufacturing



Charité-Universitätsmedizin Berlin
Molecular Immunotherapy Research Group

PD Dr. med. Antonia Busse

Unmet Medical Need and Problems to be Solved

Diffuse Large B Cell Lymphoma (DLBCL)

Annual incidence ~ 7 / 100 000

Median age at diagnosis 66y

40% of patients are primary refractory or relapse

3y-PFS after HD chemotherapy and ASCT: 21%

mOS in patients who do not qualify for ASCT: 3.3 months

Primary CNS Lymphoma

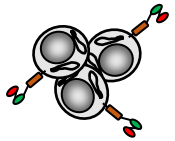
Annual incidence ~ 0.5 / 100 000

Median age at diagnosis: 67 years

Long-term remissions only reached with intensive HD-chemotherapy → high toxicity, mortality up to 12 %

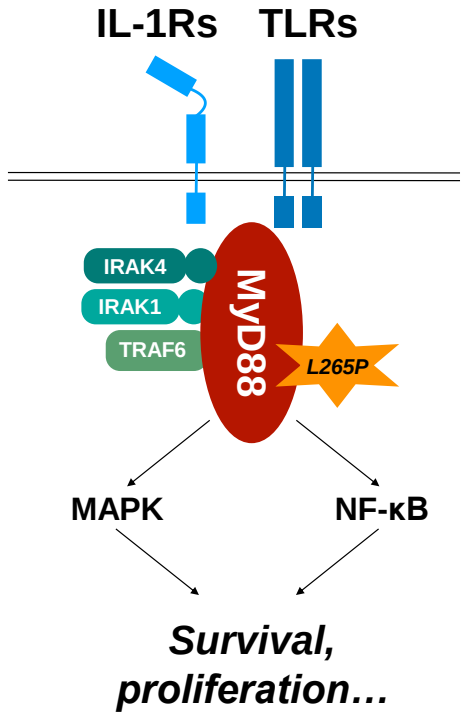
mOS in patients > 65 years: 7-19 months

CD19 CAR T cells



- **~ 50–60% of patients will not achieve a CR or will relapse after CAR T-cell therapy !**
- **pCNS have been excluded from CAR T-cell trials!**
- **NOT TUMOR SPECIFIC! "On-target" toxicity: B-cell aplasia, CD19 expression in mural brain cells**
- **Loss of surface expression (prevented by targeting multiple antigens?)**

Precision immunotherapy:
Targeting the tumor-specific driver mutation MYD88 L265P



	Mutation frequency of MyD88
All lymphoid malignancies	20 %
DLBCL ABC-like	15% 30%
Primary central nervous system lymphoma	50%
Testicular DLBC	72%
Waldenstrom Macroglobulinemia	90%

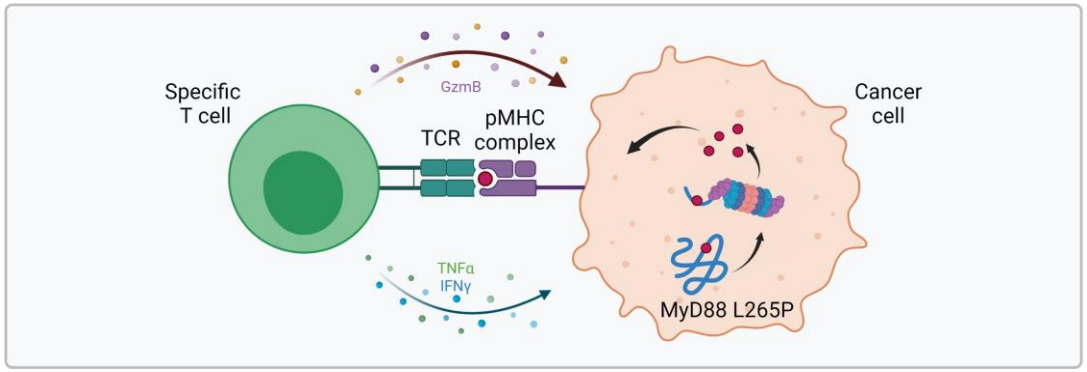
TRUELY tumor-specific,
not expressed in healthy tissue!

93% (2164/2330) of all mutant samples: p.L265P (c.794T>C)

Lee et al. 2017; Ngo et al. 2011; Rovira et al. 2016; Xu et al. 2013 Staiger et al. 2015; Drandi et al. 2018, Yizhak et al. 2019

Precision immunotherapy with a MyD88 L265P specific TCR for R/R lymphoma

Advantages compared to CARs or TCRs targeting B-cell antigens



Peptide	HLA type	Sequence	Affinity
WT	HLA-B*07:02	**RLIPIKYKAM**	3035 nM
Mut 10 mer	HLA-B*07:02	**RPIPIKYKAM**	12 nM
11mer (Pre-1)	HLA-B*07:02	**KRPIPIKYKAM**	156nM
12mer (Pre-2)	HLA-B*07:02	**QKRPIPIKYKAM**	219nM

- No “on-target”-toxicity
- Less risk of antigen loss when targeting a driver mutation
- Not subjected to negative thymic selection

  →isolation of high affinity TCR from the human repertoire without any affinitiy enhancement

International PCT-application PCT/EP2020/051405, Cinar et al., JITC 2021

Precision immunotherapy with a MyD88 L265P-specific TCR for R/R lymphoma

Preclinical development

Clinical development

Isolation

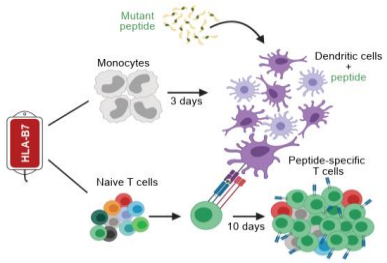
In vitro efficacy / safety testing

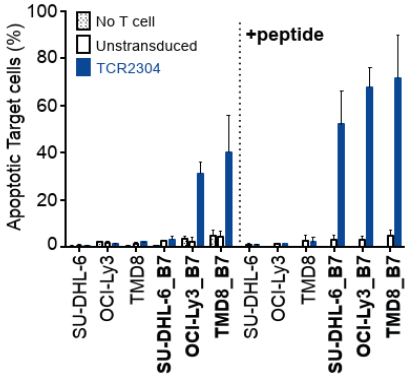
In vivo testing

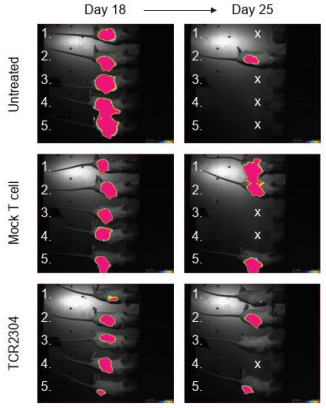
PEI *Scientific Advice*

NCT Multicenter Trial

Human, HLA-matched







- Berlin
- Heidelberg
- Würzburg

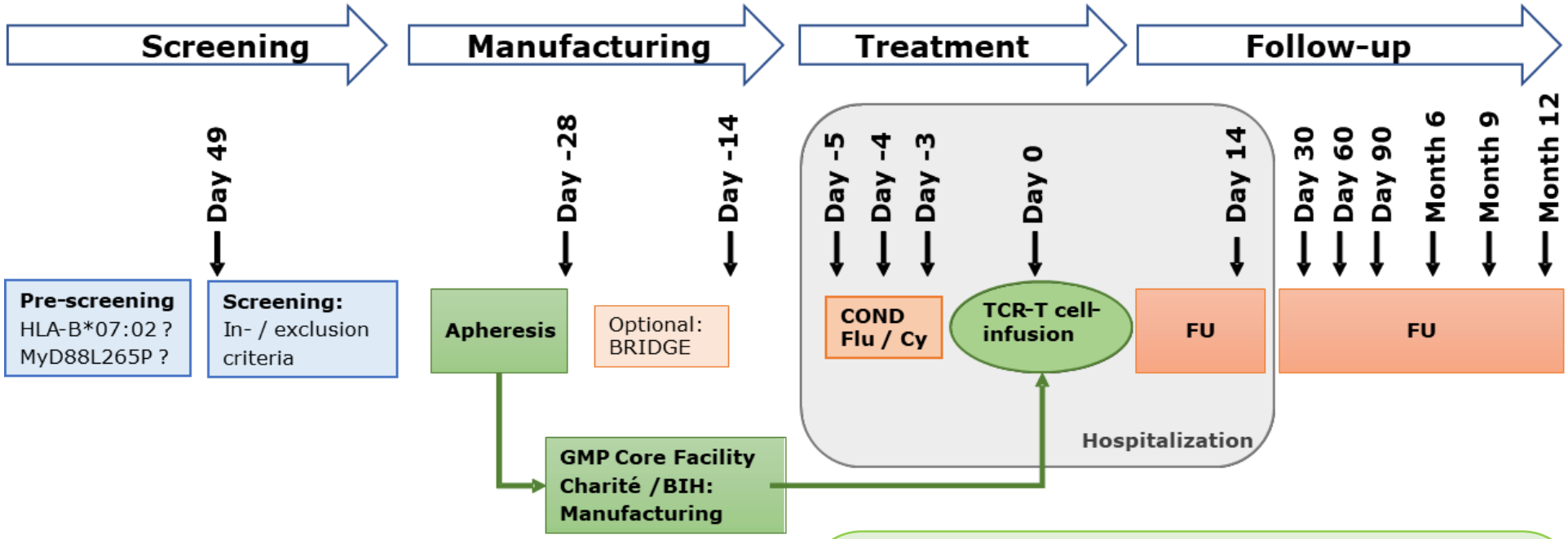
SPARK funding

BMBF funding

First-patient-in Q2/2024

International PCT-application PCT/EP2020/051405, Cinar et al., JITC 2021

First in human study in R/R MyD88L265P mutated, HLA-B*07:02+ B-cell lymphoma



Primary Objectives:

Safety and MTD

Secondary Objectives:

Pharmacokinetics of TCR-T cells;

Preliminary assessment of efficacy

Dose escalation of TCR-T cells ((BOIN Design)

Cohort 1: 1 x 10^6 TCR-T cells/kg BW ± 20%

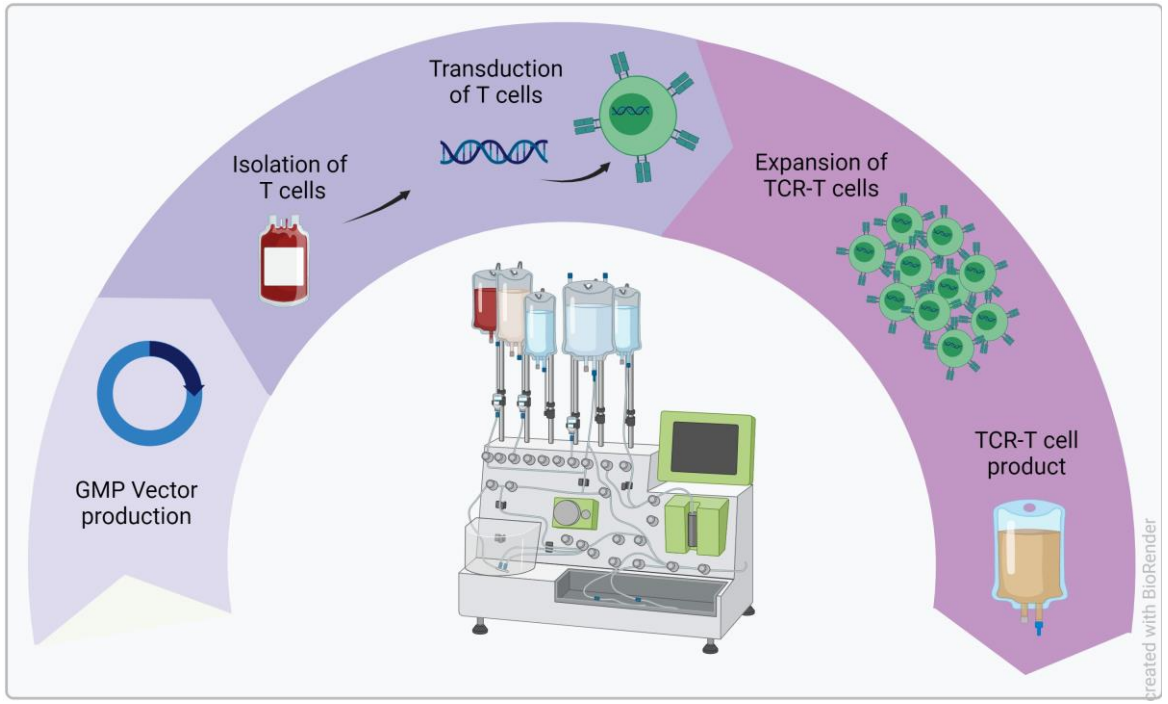
Cohort 2: 1 x 10^7 TCR-T cells/kg BW ± 20%

Cohort 3: 1 x 10^8 TCR-T cells/kg BW ± 20%

Cohort 4: 5 x 10^8 TCR-T cells/kg BW ± 20%

GMP-grade vector production and establishment of TCR-T cell manufacturing

ForTra gGmbH für Forschungstransfer der EKFS



Reservation of GMP production slot

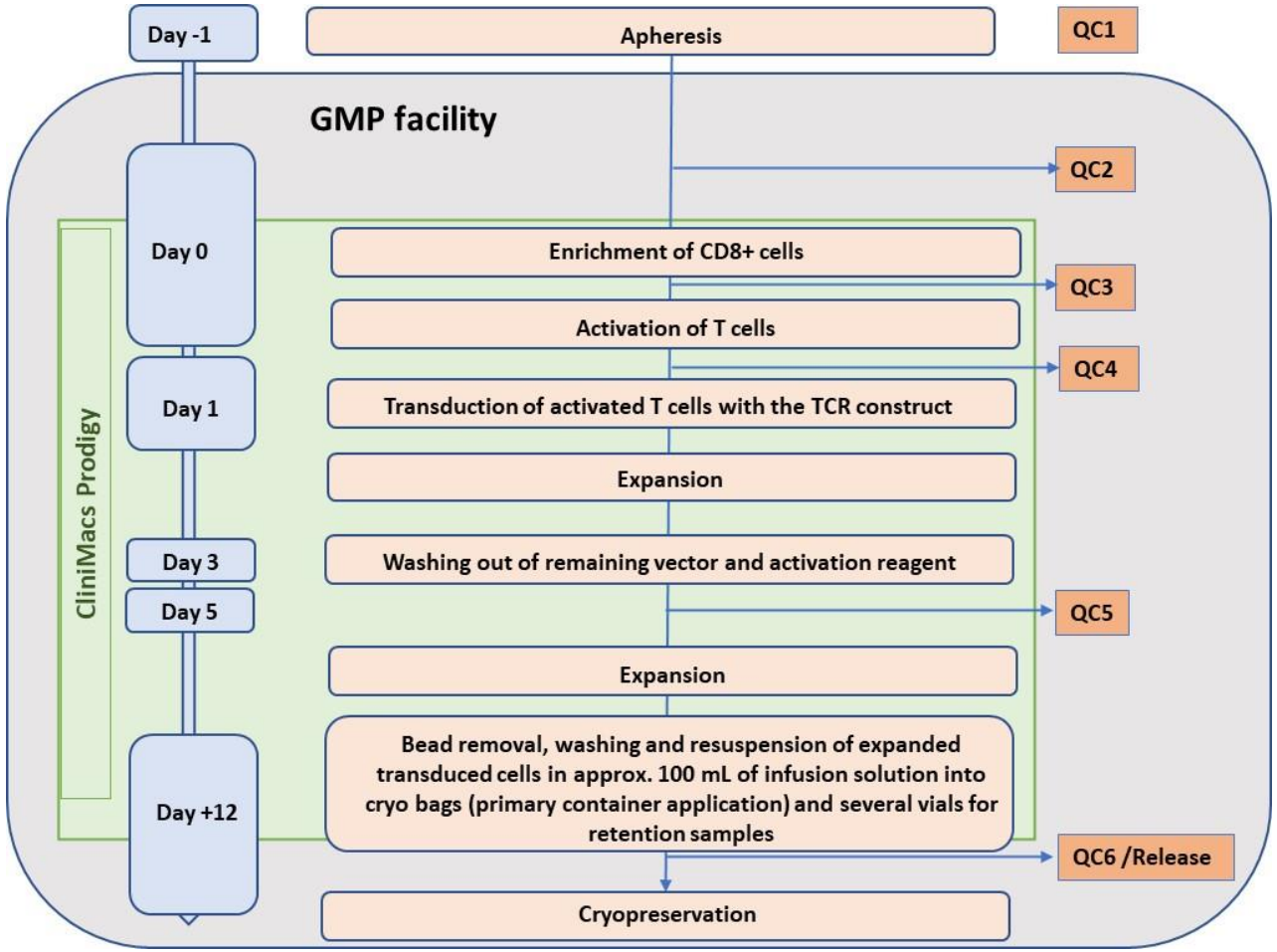
GMP production of SIN-γ-retroviral vector for TCR gene transfer

Establishment of T cell production by Prodigy technology

Comparability and safety studies

Establishment of TCR-T cell manufacturing

Establishment in non-GMP environment @MDC



Manufacturing for clinical trial @Charité

Thank You

Molecular Immunotherapy Research Group

Sarah Al-Tabatabaee
Oezcan Cinar
Nese Cakmak
Falk Fabian
Caecila Freund
Corinna Grunert
Gustav Heynen
Ulrich Keller
Ran Li
Antonio Pezzutto
Paula Schmidt
Simone Rhein (EPO Berlin Buch GmbH)

BIH Innovation

Julia Hütter, Tanja Rosenmund and **SPARK team**
Anette Schröder and team, **Technology Transfer**

Ascenion

Ansgar Santel, Elisabeth v. Weizäcker

Cooperation Partners

Charité/ DKTK
Björn Chapuy
Sebastian Ochsenreither
Gerald Willimsky

MDC
Thomas Blankenstein
Felix Lorenz
Clemens Schmitt

EPO Berlin Buch GmbH
Bernadette Brzezicha, Simone Rhein

ATMP Lab
Lars Bullinger, Anette Künkele

Charité-CTO
Roman Weimann, Mario Lorenz

NCT Trial Centers
Carsten Müller-Tidow, Heidelberg
Hermann Einsele, Würzburg

Biostatistic, BIH@Charité
Frank Konietschke

Patient Advocates
Deutsche Leukämie- & Lymphomhilfe"
Patient Advisory Board CCCC, Ulla Ohlms

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Thank you !

Questions?

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