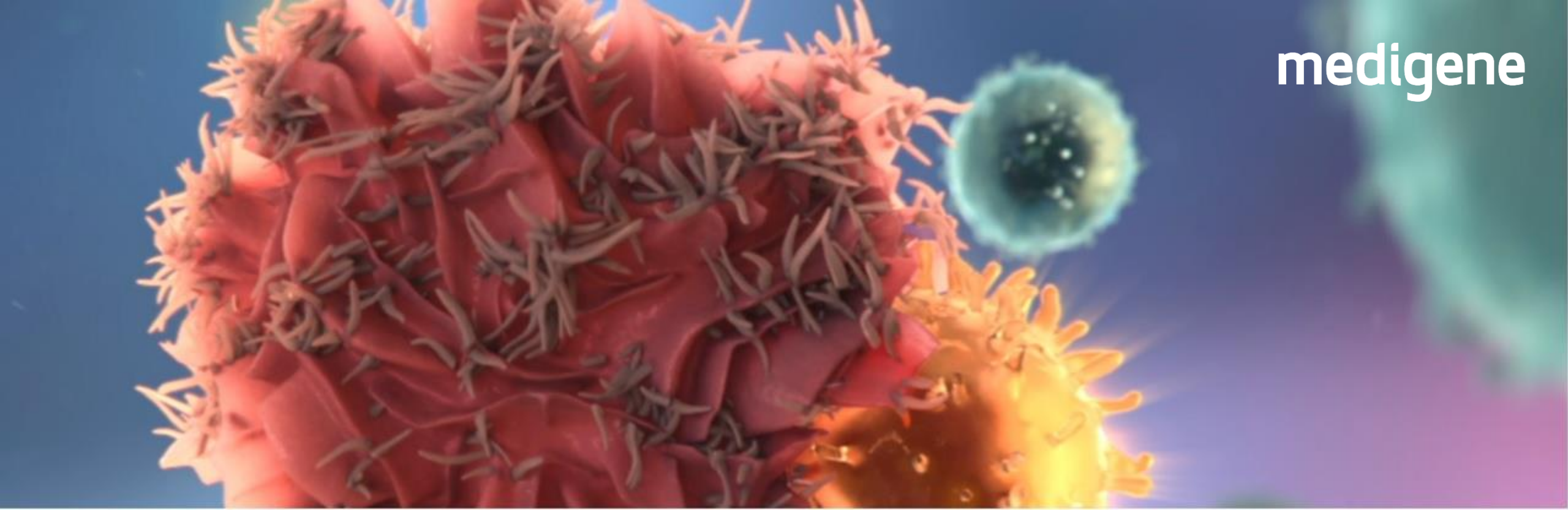

High Fidelity Production of TCR-T Cells from Elderly Hematologically-Challenged Patients With Blood Cancers

Cell UK 2022

London, 7-8 November 2022

Dolores Schendel, CSO Medigene AG

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MDG1011: Proof-of-concept phase I study of TCR-T therapy in blood cancer

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MDG1011: PRAME/HLA-A2-specific TCR-T therapy for blood cancers

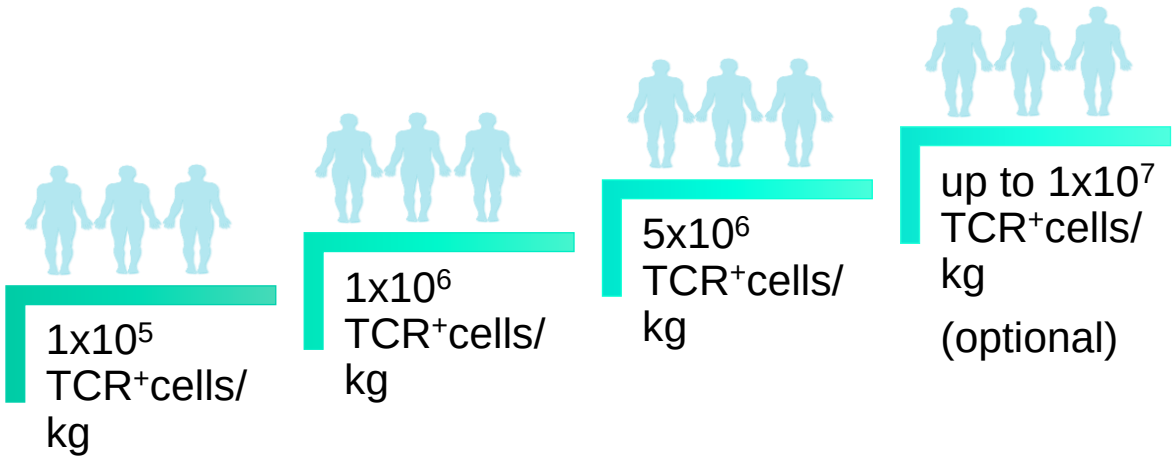
- PRAME – well-characterized, broadly expressed cancer-testis antigen
- CD8-enriched TCR-T drug products with multi-functionality

Phase I part of Phase I/II trial

- Patients with refractory/relapsed
  - Acute myeloid leukemia (AML)
  - Myelodysplastic syndrome (MDS)
  - Multiple Myeloma (MM)

Dose escalation study

- 3+3 clinical trial design
- Data Safety Monitoring Board reviews between cohorts



- **Single defined dose of CD8$^+$ TCR-T cells/kg BW**

https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000440-18/DE

MDG1011: Manufacturing challenges successfully met

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Patients with AML, MDS or MM with *relapsed or refractory disease* presented special challenges for manufacture of MDG1011

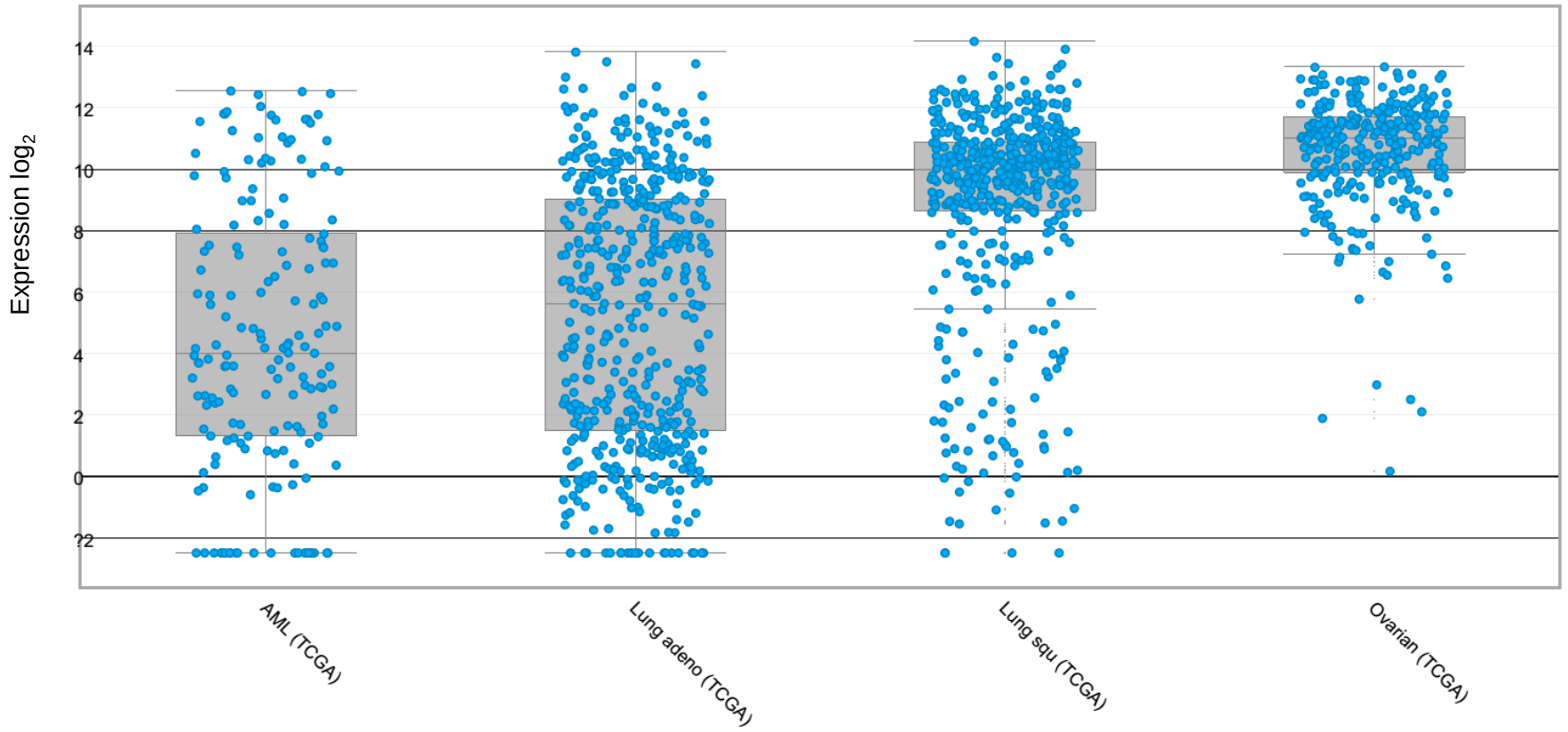
- Patients were mostly elderly
- Patients had cancer of the blood system
- Patients were heavily pretreated
- AML blasts present at substantial levels in leukapheresis starting materials, in several cases
- Patients had rapidly progressing disease, so time was of essence

We achieved a 92% success rate in production of $CD8^+$ TCR-Ts

- Drug Products were derived from enriched cryopreserved $CD8^+$ T cells
- Leukapheresis was repeated for two patients only, with one success and one failure to get starting $CD8^+$ T cell numbers
- Vein-to-vein time of ~7 weeks: production ~3 weeks; QC ~3 weeks and patient preparation for infusion ~1 week
- Nine patients were successfully dosed, whereas four patients succumbed before IMP administration

The cryopreserved Drug Products showed functional activity *in vitro* and in patients *in vivo*

MDG1011: Background for development of TCR-T therapy for blood cancer and solid tumors – prevalence of PRAME



Scale is given as RSEM. RSEM quantifies gene and isoform abundances from single-end or paired-end RNA-Seq data.
Graphic compiled by Medigene, from publicly available TCGA-data.

MDG1011: Background for development of TCR-T therapy for blood cancer – relevance of PRAME

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	PRAME
Expression in bulk AML	Cancer-testis antigen
Expression in LSC	> 65 %
Expression in HSC / other cells	+-
Oncogenicity	-
Immunogenicity	++
Clinical efficacy	++
MRD Monitoring	++
Expression in bulk AML	Established by qPCR

Anguille et al, Leukemia 2012; Lichtenegger et al, Immunotherapy 2013

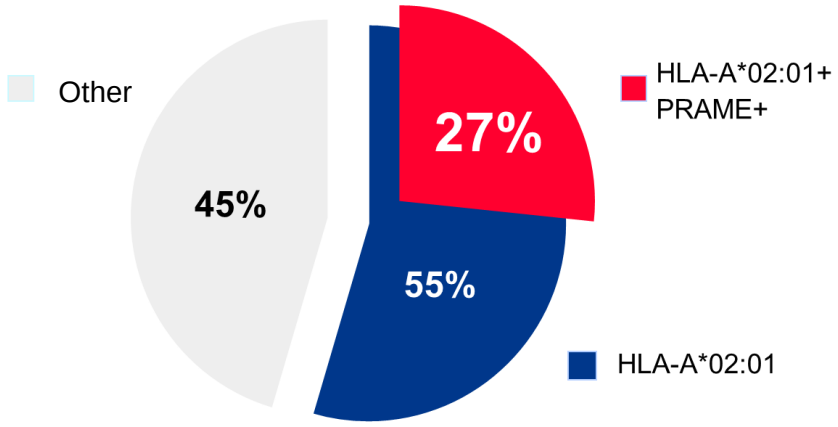
MDG1011: Background for development of TCR-T therapy for blood cancer – feasibility to recruit PRAME^{+} HLA-A*02:01^{+} patients

Pre-screening for general eligibility

Screening for HLA-A2 and PRAME mRNA in bone marrow or blood

Inclusion and treatment

HLA and antigen frequency is critical



MDG1011: Establishment of safety profiles of antigen and TCR-T cells

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Target Antigen and HLA-Peptide Ligands at Molecular and Cellular Levels

→

TCR Specificity and TCR-T Functionality at Molecular and Cellular Levels

Target antigen expression in cancer

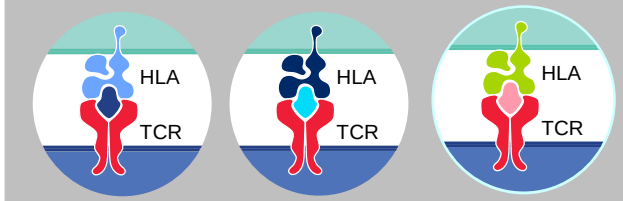
- Genetic isotypes, RNA, protein, peptide expression
- Expression in cancer cell lines and tumor specimens
- Expression in cancer databases
- *In vitro* models for functional testing

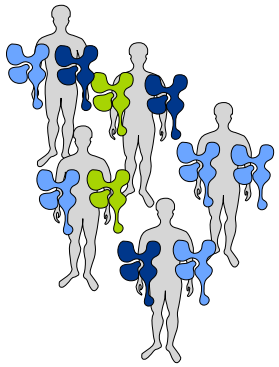
Target safety

- Expression from databases of healthy tissues
- *In vitro* models for functional testing

TCR selectivity

- Vetting of multiple TCRs to select Lead TCR





HLA-peptide ligands for lead TCR

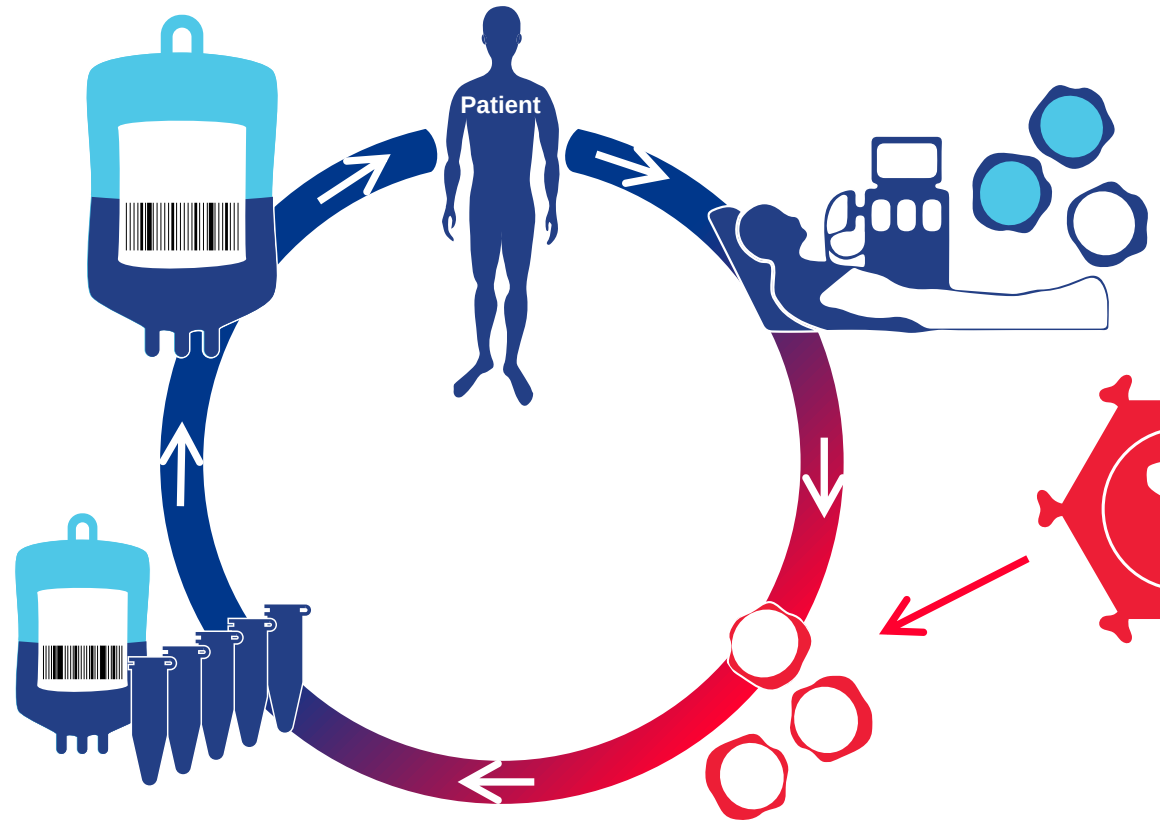
→

Safety Profile

„Go/no go“ studies of TCR-T cells in final Drug Product formulation

MDG1011: GMP production of personalized TCR-T therapy

Medigene's TCRs are delivered via a vector to genetically modify autologous patient T cells to express the desired tumor-specific TCR



1 Leukapheresis and T cell isolation

TCR vector

2 Activation of T cells and transfer of TCR

3 Expansion, freezing and quality tests

TCR drug product and analytical samples

4 Thawing and infusion into patient

MDG1011: Manufacturing process based on multi-modular system

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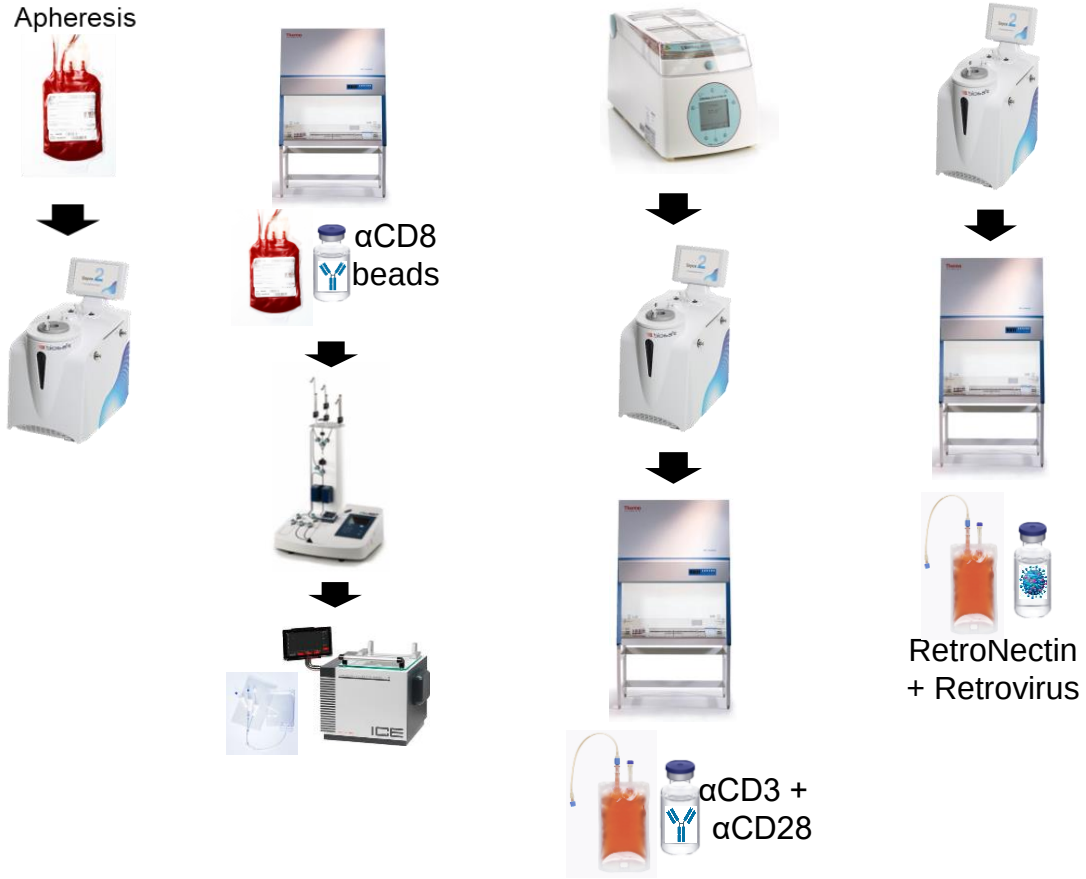
Cell preparation → Selection → Activation → Transduction → Expansion → Harvest → Final Formulation → Cryopreservation



Advantage:

- Modular semi-automated system provides flexibility
- Up- and down-scaling possible

Disadvantages:

- High manual interventions with risk of contamination
- Multiple handling steps → highly skilled personnel needed
- Difficult process to standardize
- Clean room class A and B required

MDG1011: Diverse testing was performed for Drug Product release and Drug Product characterization at CMO and MDG

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Release at BioNTech

- Safety Parameters
- Identity
- Potency
- Quantity / Cell Dose
- Purity / Impurity
- Appearance

Characterization at BioNTech

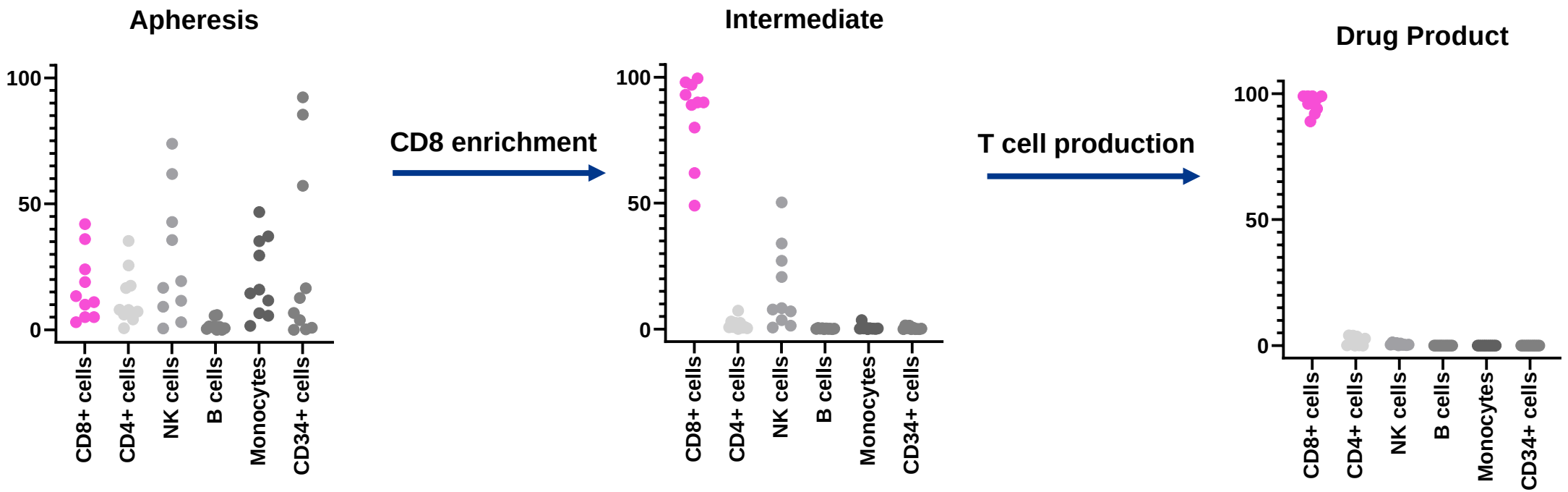
- Cellular Impurities / Cell Composition
- T Cell Subsets
- Viability and Cell Count (during entire process of drug production)

Characterization at Medigene

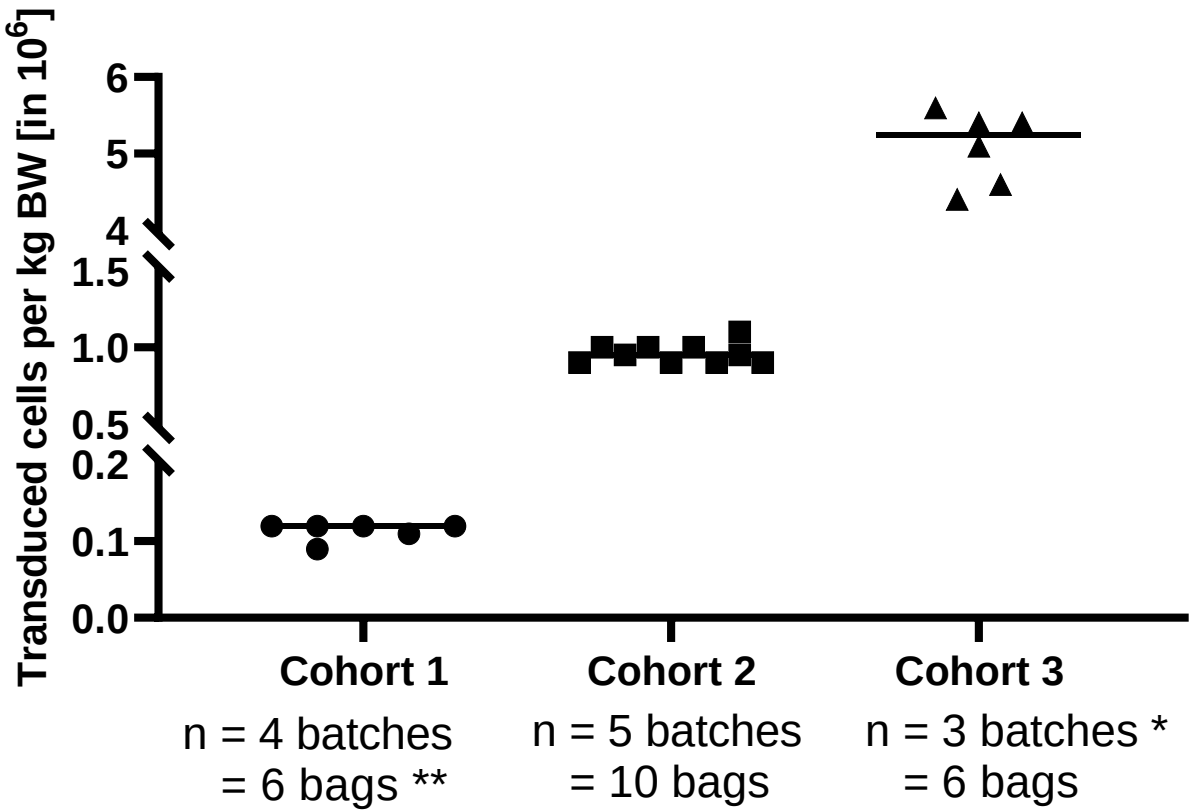
- Process-Related Impurities
- T Cell Subsets
- IFNγ Secretion (ELISA)
- Intracellular Cytokine Staining
- Cytotoxic Activity

CMO for this study was BioNTech IMFS at Idar-Oberstein, Germany. The GMP process for TCR-T Drug Product manufacture was co-developed with the Departments of Translational Medicine and Cell Therapy Process Development at Medigene

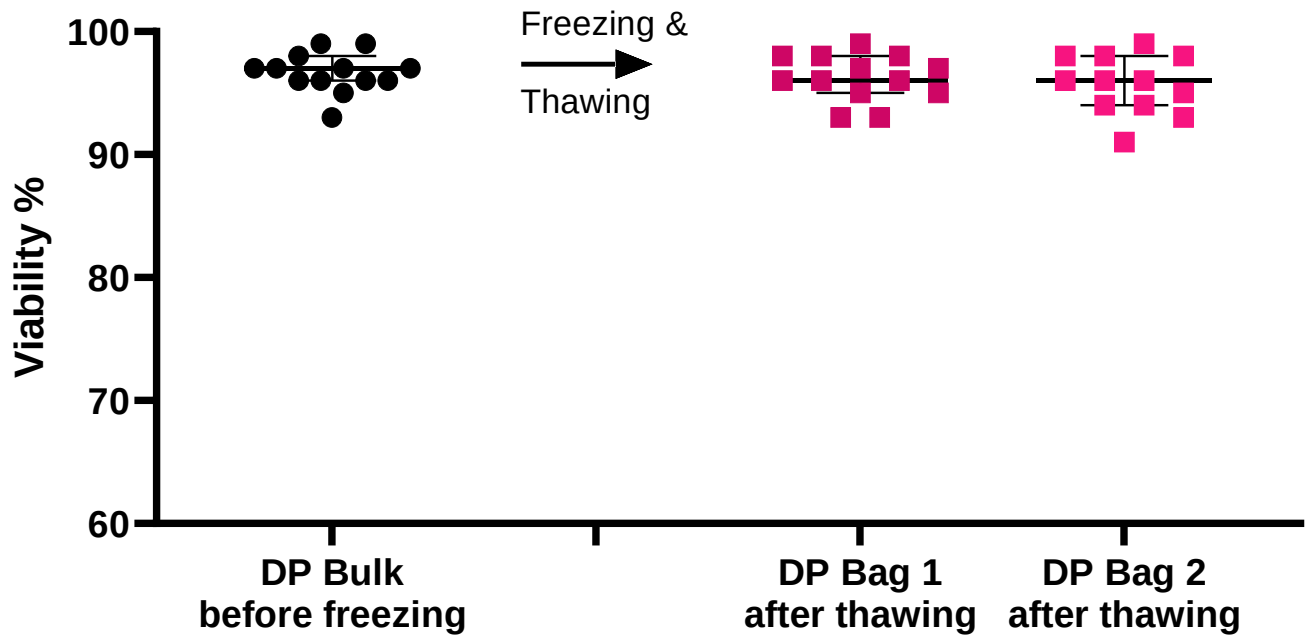
MDG1011: Consistent CD8+ TCR-T cell Drug Products generated from variable patient leukapheresis starting materials



MDG1011: Production of required TCR-T cell numbers expressing specific TCR was feasible for Dose Cohorts 1 - 3



MDG1011: Drug Products with excellent cell viability before and after freezing and thawing were manufactured for all patients

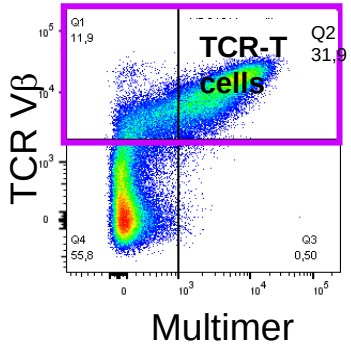


n = 13 batches, for one batch only one bag was filled

MDG1011: Drug Product characterization encompassed multiple molecular and cellular technologies

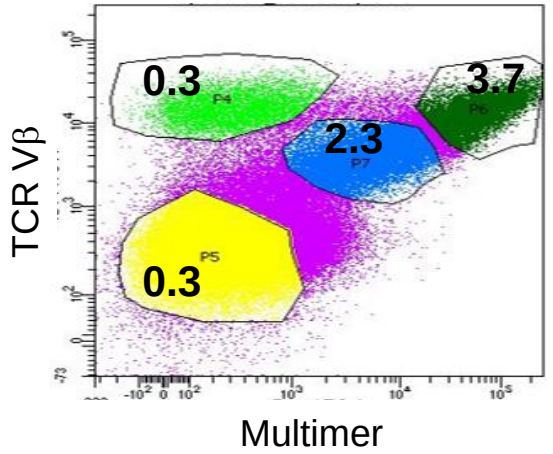
Surface Expression

Double staining of TCR Vβ chain and pHLA-specific multimer measured by flow cytometry



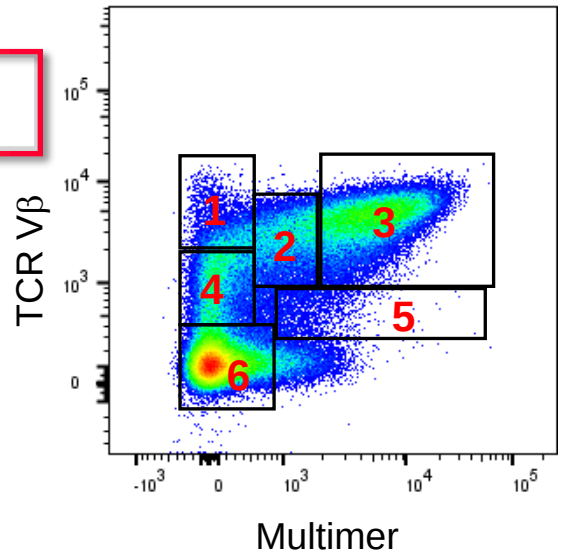
Molecular Expression

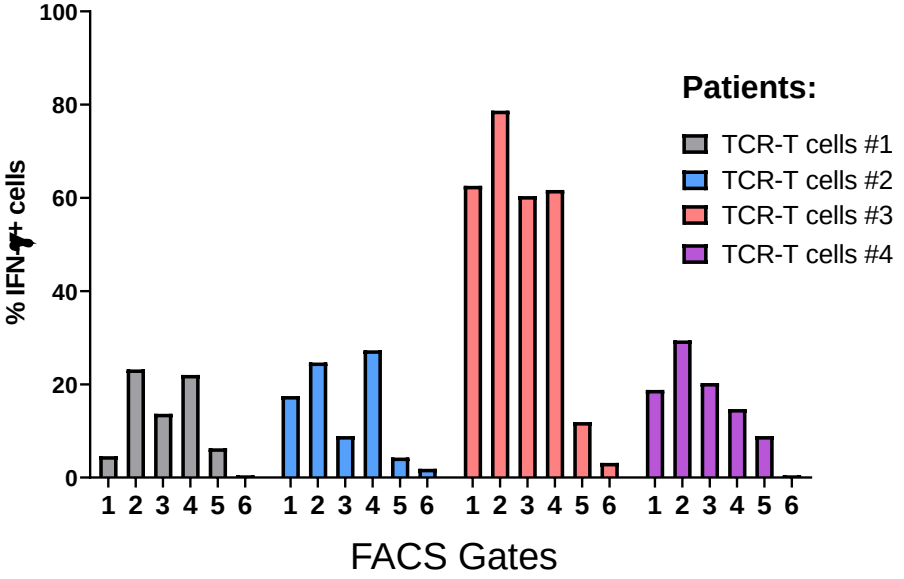
Vector copy number measured in sorted TCR-T cell populations by dPCR



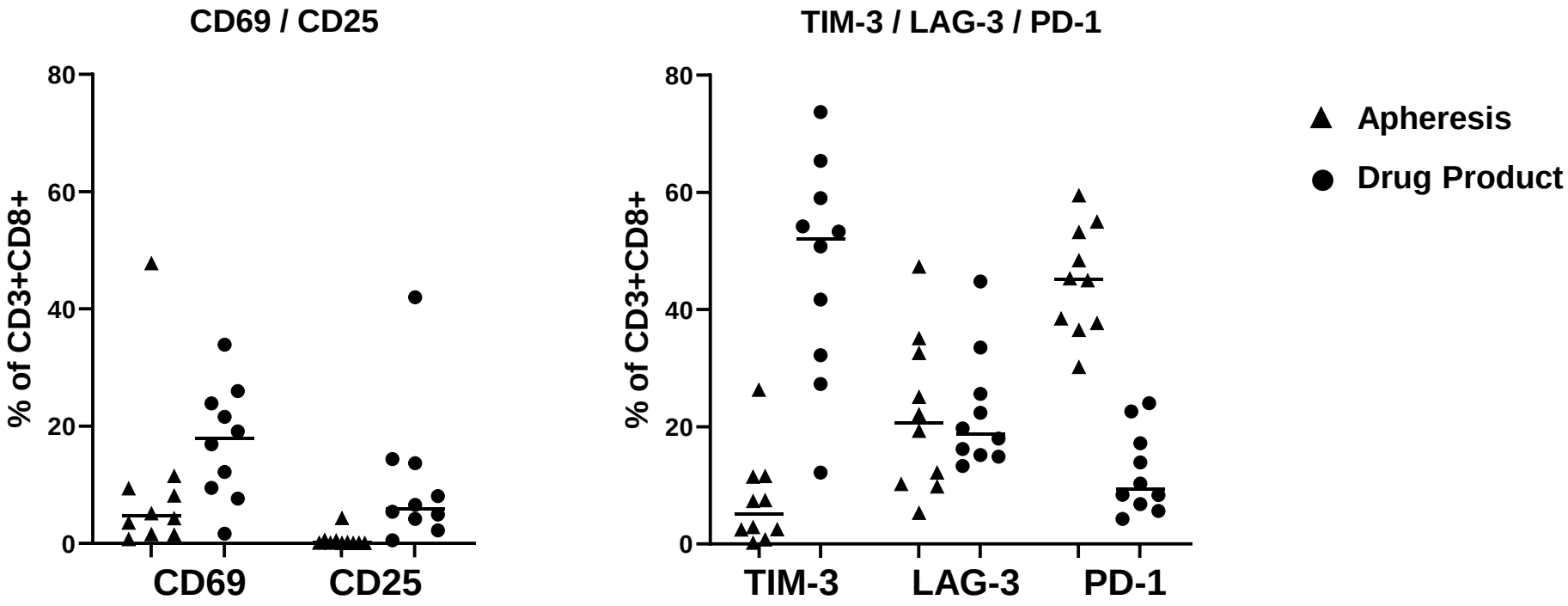
Antigen-Specific Cytokine Responses

Intracellular IFN-γ-staining of TCR-T cell populations after stimulation with T2 cells + specific peptide; T2 cells + ctrl peptide are IFN-γ negative (not shown)
Multiple cytokines/cytotoxins can be studied

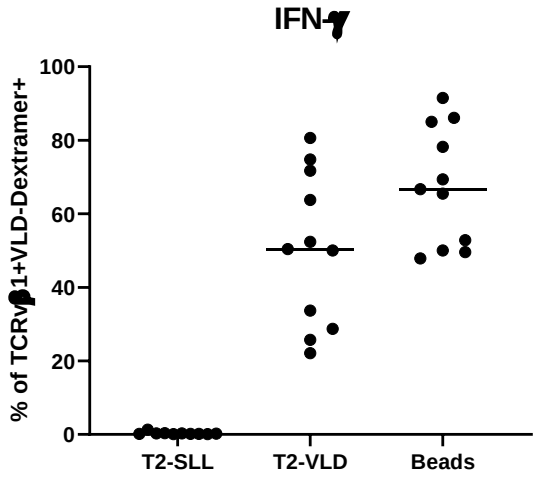


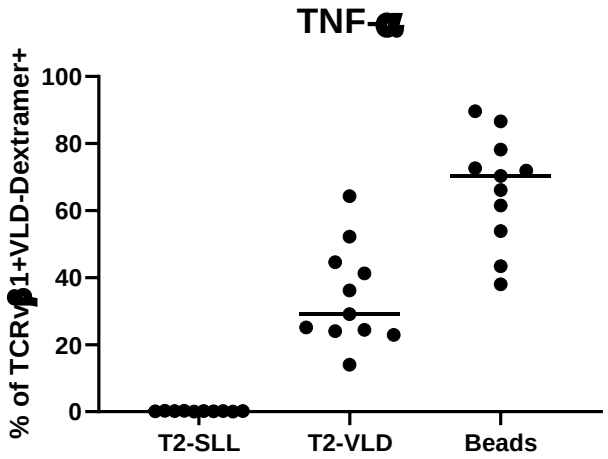


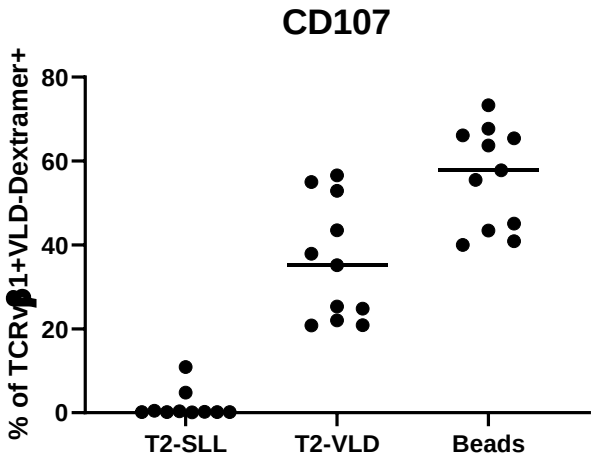
MDG1011: Activation markers and checkpoint receptor expression changed between apheresis starting materials and final Drug Products



MDG1011: Peptide-specific stimulation triggered poly-functional cytokine release in all Drug Products







MDG1011: Analytical methods to assess T cell pharmacokinetics and PRAME mRNA expression in peripheral blood and bone marrow

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- **Pharmacokinetics of TCR-T cells in MDG1011 patients was assessed with validated fit-for-purpose assays using:**
  - **flow cytometry (FC)**
    - TCR-expressing cells were identified with a TCRV-beta antibody + pMHC-specific dextramer
    - Double-positive cells were enumerated in the gated population of $CD45^+$**/** $CD3^+$**/** $CD8^+$ T cells in the peripheral blood **(Limit of quantification (LoQ)= 0.015%)**
  - **Digital droplet PCR (dPCR)**
    - TCR-transduced T cells were identified by the RNA of the viral element Woodchuck Hepatitis Post-transcriptional Regulatory Element (WPRE)
    - Copies of the WPRE element were quantified in bulk RNA of patient peripheral blood samples **(Limit of quantification (LoQ) dPCR = 36 copies/100ng RNA)**
- **Measurement of PRAME mRNA in bone marrow samples and/or peripheral blood and was done using a validated real-time quantitative PCR (qPCR) assay. (Limit of quantification (LoQ) qPCR = 70 copies/25ng RNA)**

MDG1011: Biological and clinical activity detected in patients *in vivo*

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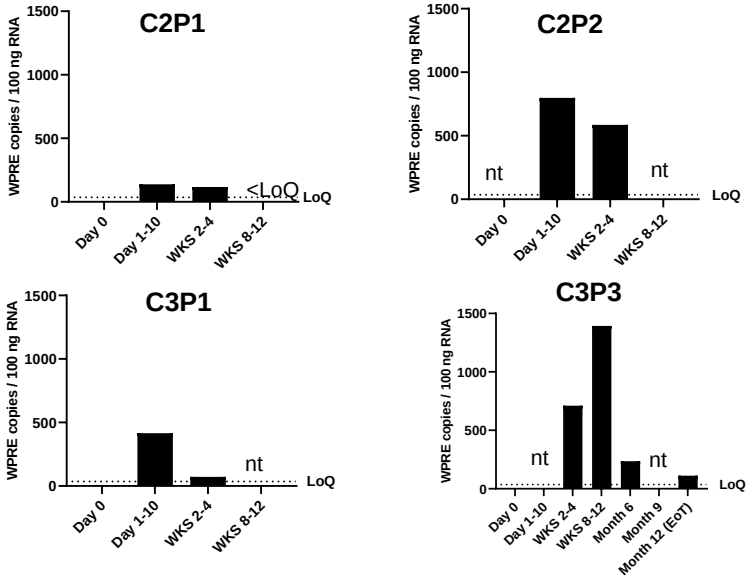
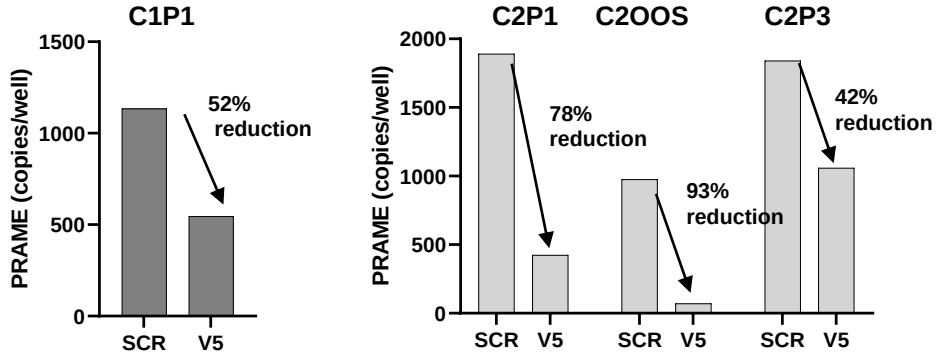
CRS as an indicator for biological activity of MDG1011

- **Grade I Cytokine Release Syndrome seen in C2P1**
- **Grade II Cytokine Release Syndrome seen in C3P1**

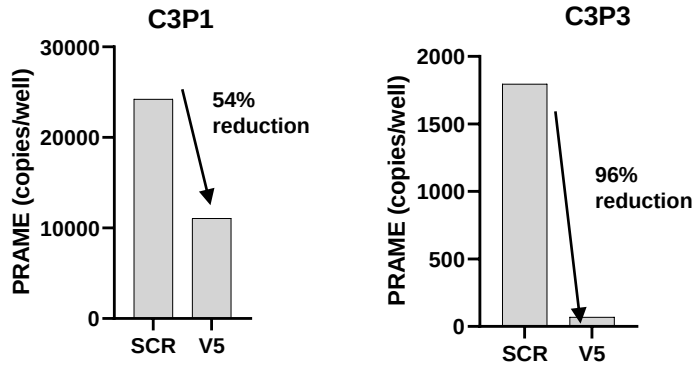
T cell persistence seen in 4 patients treated with the two highest doses of MDG1011



PRAME mRNA was reduced at Week 4 in bone marrow samples of 4 of 5 evaluable patients



PRAME mRNA was reduced at Week 4 in blood of AML/MDS patients treated with highest dose of MDG1011



MDG1011: Benefits of using molecular and cellular Drug Product Immune Assessments and Patient Immune Monitoring

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- Complex characterization of TCR-T Drug Products and immune monitoring of TCR-T cells in patients *in vivo* are critical steps for progressing manufacturing and clinical developments of living immunotherapies
- Deep characterization of Drug Products and correlation with clinical observations in patients:
  - facilitate deeper understanding of immune responses that may yield clinical benefit
  - provide insight into differences between Drug Products associated with CRS and/or clinical response
  - deliver crucial data on effects of TCR-T variations in Drug Product Immune Assessment *in vitro* vs. Patient Immune Monitoring *in vivo*
  - give better insight into parameters needed to define potency of TCR-T cells
- Approaches validated in Phase I study and knowledge gained can be extended in Phase 2 to acquire more data and derive better answers to hypothesis-generated questions from Phase 1

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Thank you