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Developing Effective Methods to Monitor, Track & Assess T-Cell Efficacy *In Vivo & In Vitro*

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Medigene AG

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Differentiated Approach Addressing Current TCR-T Therapy Challenges

Key Challenges

Suboptimal Target Interaction

Low specificity, low/high affinity, low avidity

➢ ***Reduced efficacy & safety***

Immunosuppressive TME

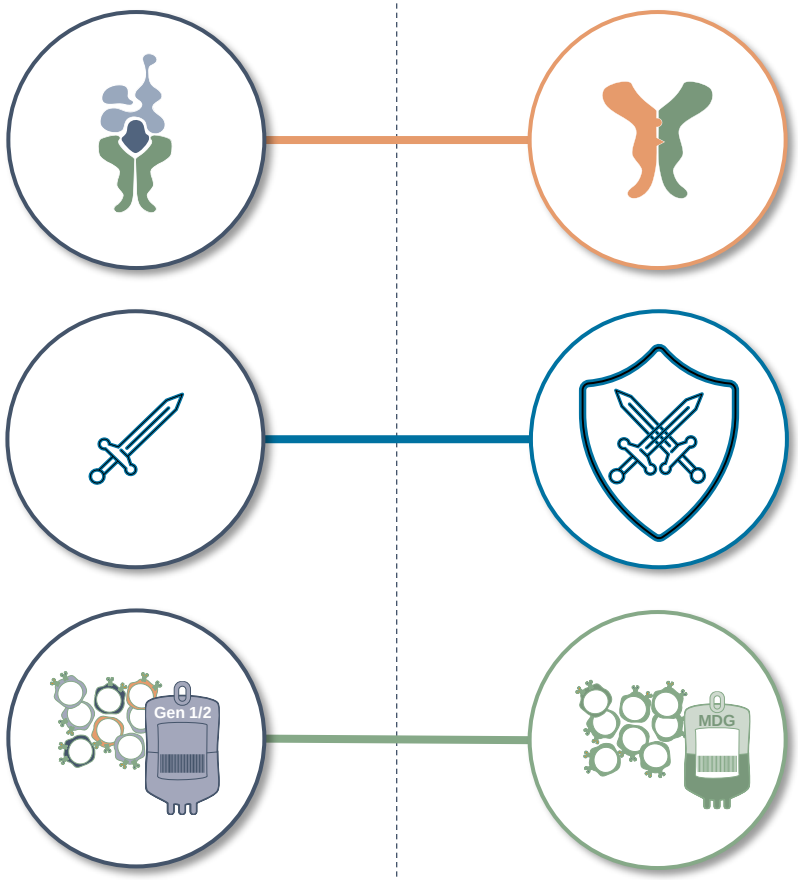
Poor penetration, persistence of T cells, lack of proliferation

➢ ***Reduced efficacy & durability***

Inadequate DP Composition

Lack of proliferation, functionality and sub-optimal cell composition

➢ ***Reduced efficacy, safety & durability***



Medigene's Solutions

Optimal Affinity TCRs

- ✓ Young, healthy donors with broad TCR repertoires
- ✓ Sensitive, specific and safe (3S) attributes for **improved clinical safety & efficacy**

CSP Armoring & Enhancement

- ✓ Improved TME penetration
- ✓ Enhanced proliferation / persistence overcome TME immunosuppression to **enhance clinical efficacy**

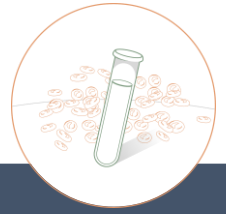
Tailored DP Composition

- ✓ Accelerated 6-day automated GMP manufacturing
- ✓ ~20-day vein-to-vein time
- ✓ $CD8^+$ DP characteristics with high proportion of T_{scm} / T_{cm} to **improve clinical efficacy & safety and durability**

TME; Tumor microenvironment, CSP: Costimulatory switch protein, DP; Drug Product

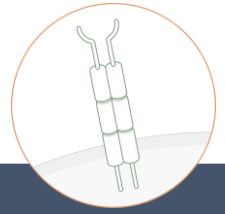
Medigene's End-to-End Platform

Multiple combinable, exclusive & proprietary technologies create highly differentiated, best-in-class TCR-T therapies



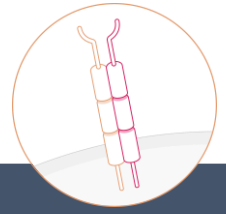
TARGET SCREENING

- Expitope
- Tailored Mass Spectrometry



TCR GENERATION & OPTIMIZATION

- Healthy Donor DC-TCR Priming
- Precision Pairing
- CrossTAg Vector System
- JOVI Tag Enrichment Technology
- Robotic Functional HTS



TCR-T THERAPY ARMORING & ENHANCEMENT

- PD1-41BB CSP
- CD40L-CD28 CSP
- Inducible iM-TCR

TCR-T DRUG PRODUCT MANUFACTURING

- 6-Day Automated Cell Production Process
- Optimal Drug Product Cell Composition
- SIN-γ- Retroviral Gene Transfer System
- Drug Product Immune Assessment

CLINICAL DEVELOPMENT

- Patient Immune Monitoring

- Safety Enhancements
- Efficacy Enhancements
- Development Optimization

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Select E2E Platform Technologies

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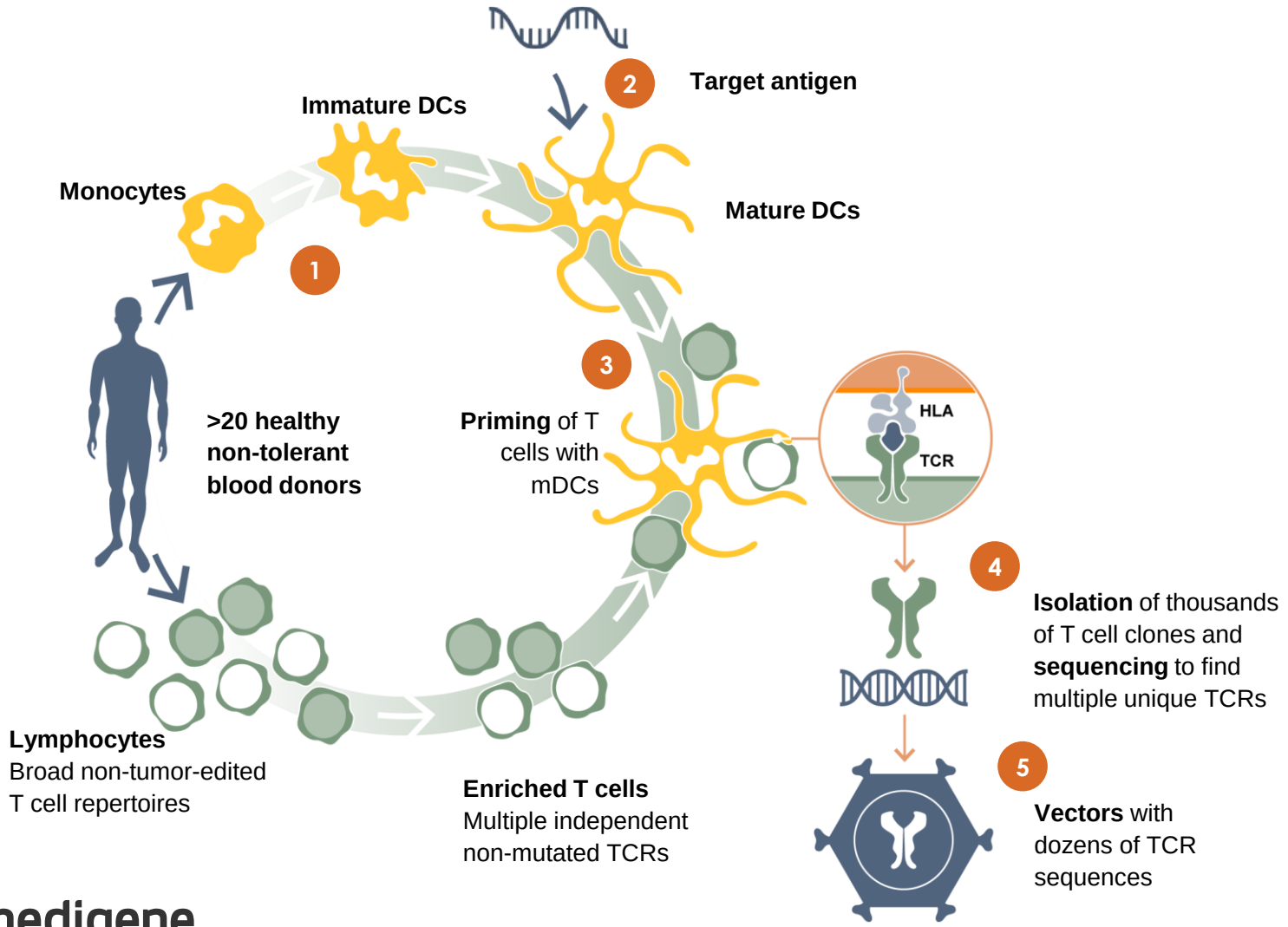
TCR Generation – DC-T Cell Priming Using Healthy Donors

Healthy donors provide high TCR sequence diversity for better choice of lead TCRs



Advantages of priming approach

- ✓ Ready access to healthy donors
  - ✓ autologous DCs
  - ✓ autologous T cells
- ✓ ivtRNA is versatile source of antigen
- ✓ HTS yields thousands of specific T cell clones for lead TCR selection
- ✓ RV TCR transfer vector is efficient and fast

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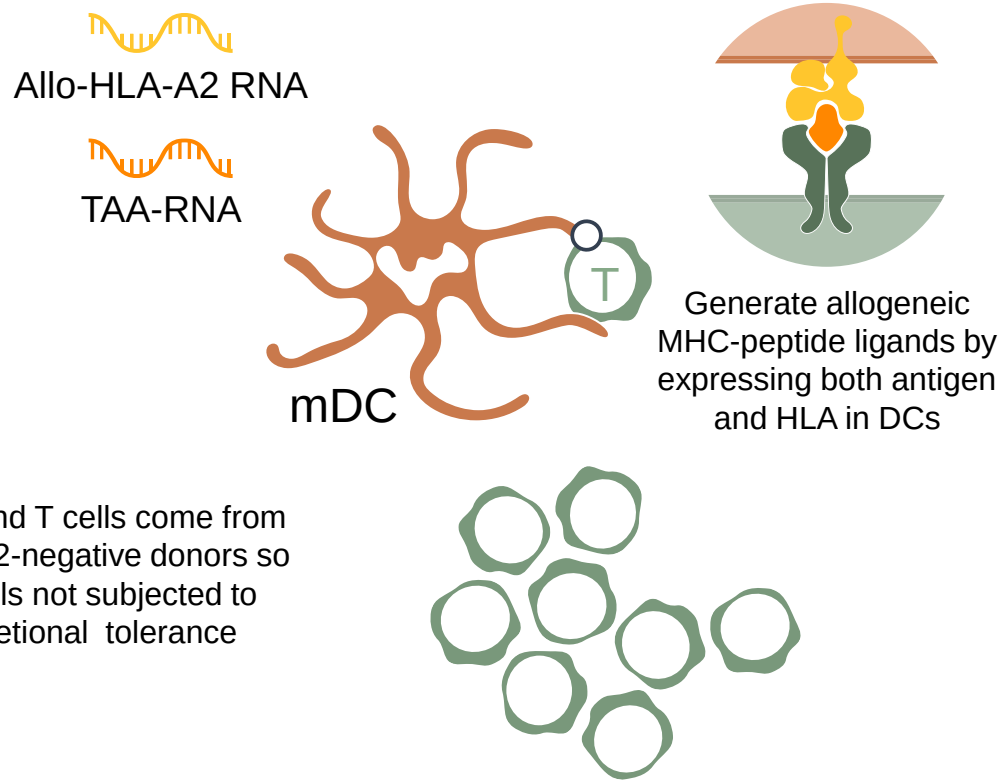
Allo-HLA TCR Priming Helps Find Optimal TCRs for Self-Antigens

Bypasses *Central Tolerance* that limits TCR affinities to self-antigens like CGAs

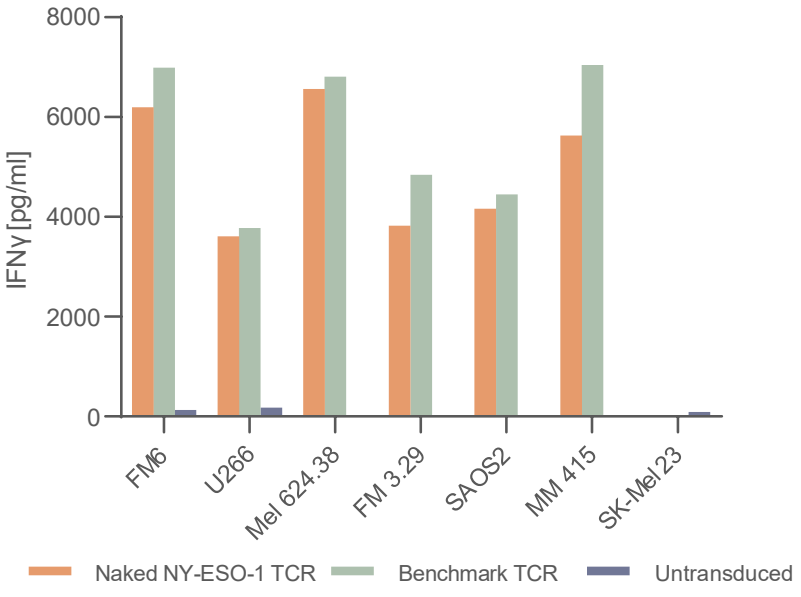


Advantages of Allo-HLA-Priming to Discover TCRs

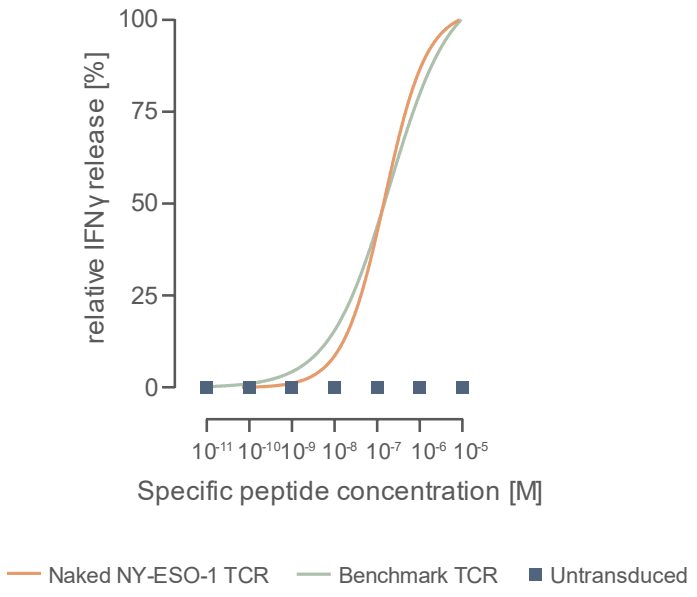
- ✓ Higher-affinity TCRs
- ✓ Any HLA allotype
- ✓ Any target antigen
- ✓ No patient samples
- ✓ No need for affinity maturation

Natural TCR Generation & Optimization Through DC Priming

Tumor Cell Panel Sensitivity



TCR-T Cell Functional Avidity



Advantages of Allo-HLA Priming to Generate TCRs

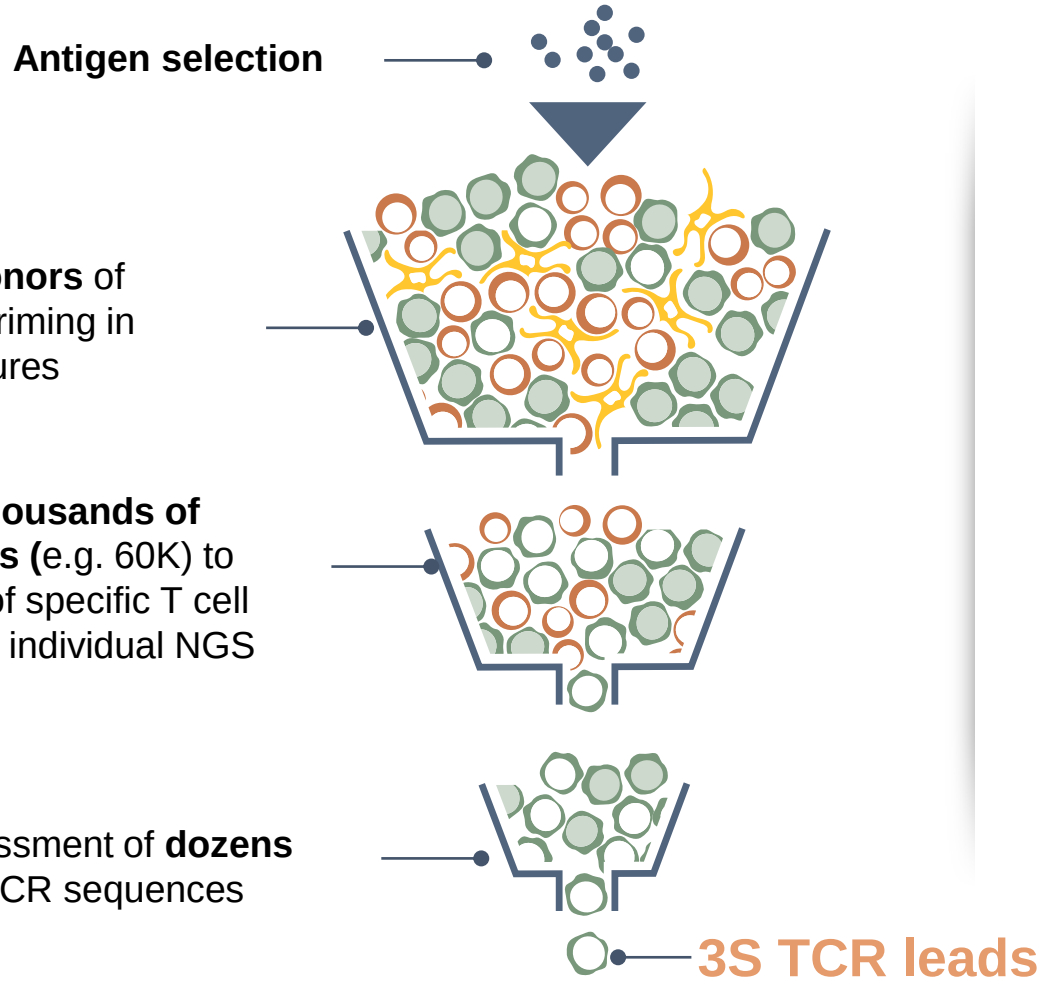
- ✓ Higher-affinity TCRs
- ✓ Any HLA allotype
- ✓ Any target antigen
- ✓ No patient samples
- ✓ No need for affinity maturation
- ✓ Safety benefits

Medigene's natural TCRs do not require affinity maturation to enhance sensitivity

DC; Dendritic cell, Untransduced; T cells lacking TCR-encoding viral vector

TCR Generation – High-Throughput Approach to TCR Discovery

Automated high-throughput TCR discovery rapidly delivers multiple, unique TCR candidates



High-throughput automation

- ✓ Standardization and reproducibility
- ✓ Functional screen of thousands of T cell clones
- ✓ Fast isolation of high-affinity TCRs

3S TCR selection for Specificity, Sensitivity & Safety

- ✓ TCRs developed from healthy donor T cells
- ✓ Assay algorithm to select optimal target-specific TCRs
  - ✓ *Potency / efficacy* — high-affinity TCRs with optimal tumor cell cytotoxicity and highest peptide sensitivity
  - ✓ *Safety / specificity* — exhaustive assessment to minimize potential cross-reactivity

JOVI-Tag

Standardizing enrichment and tracking of rTCR-expressing T cells to select superior TCRs

Unmet need

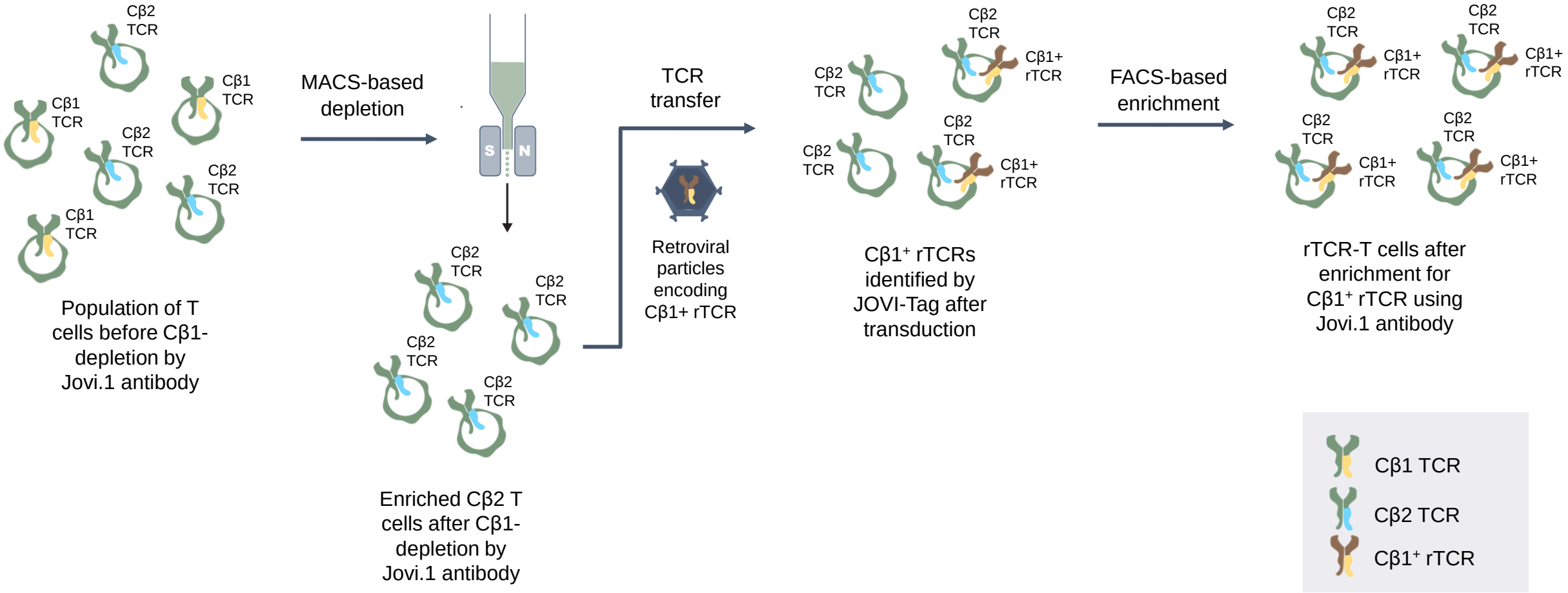
High-throughput screening and characterization of multiple TCRs requires a reliable and standardized method for enrichment and tracking of recombinant (r)TCR-expressing T cells

Medigene' solution: JOVI-Tag

- JOVI-Tag utilizes a "natural tag", a polymorphism that distinguishes the two human TCR β chain constant regions (TRBC1 vs. TRBC2). An antibody (Jovi.1) binds rTCRs reconstructed using TRBC1 domains.
- Jovi.1 antibody depletes recipient cell populations of Cβ1-positive T cells and tracks and enriches JOVI-Tag rTCR-positive T cells.
- The Jovi.1 selection system ensures rTCR-T cells expressing different rTCRs to be easily compared for specificity, sensitivity and safety using enriched rTCR-T cells.

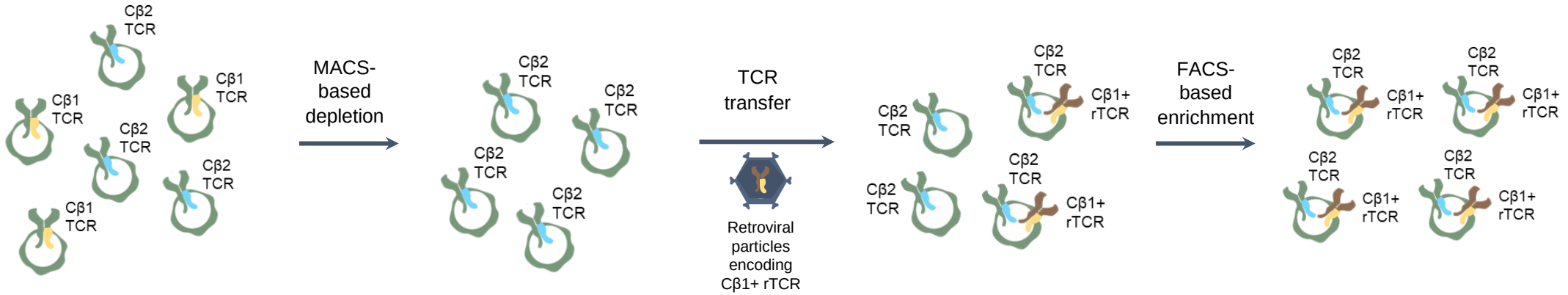
JOVI-Tag

Standardizing enrichment and tracking of rTCR-expressing T cells to select superior TCRs

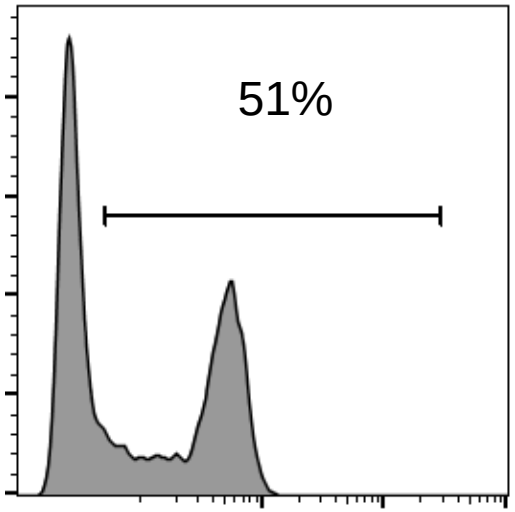


JOVI-Tag

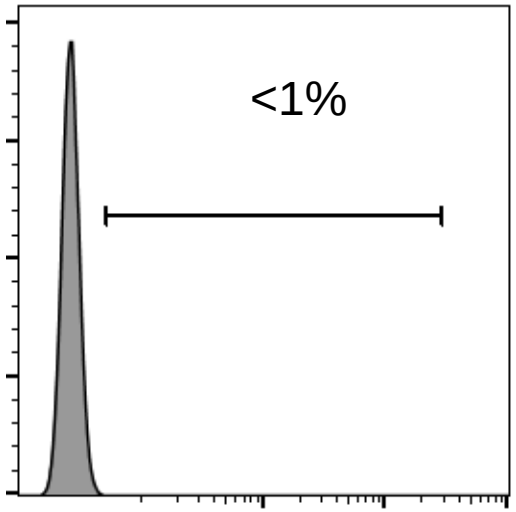
JOVI-Tag creates highly homogenous population of T cells using Jovi.1 antibody



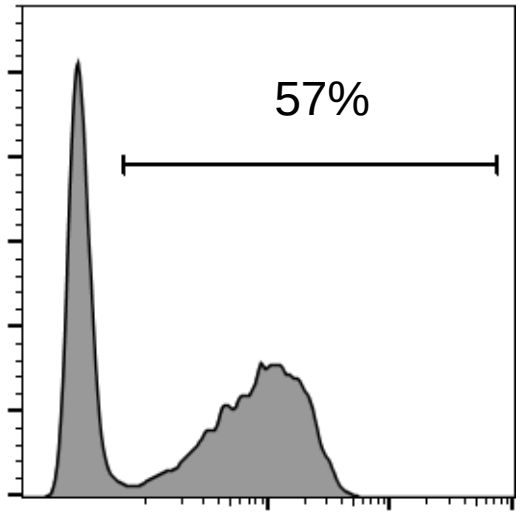
T cells before Cβ1-depletion



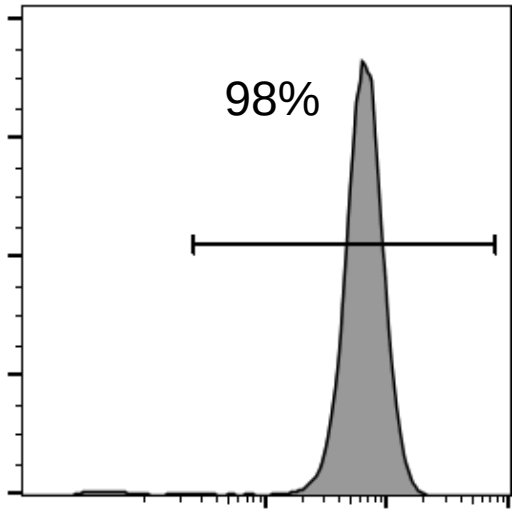
after Cβ1-depletion



after Cβ1⁺ rTCR transduction



rTCR-T product after Cβ1-enrichment and expansion



→ Jovi.1

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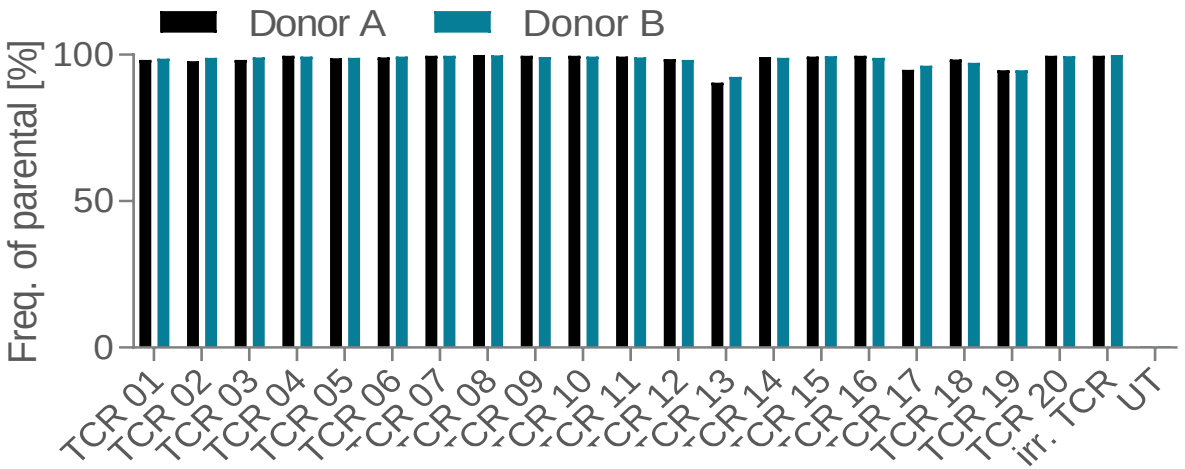
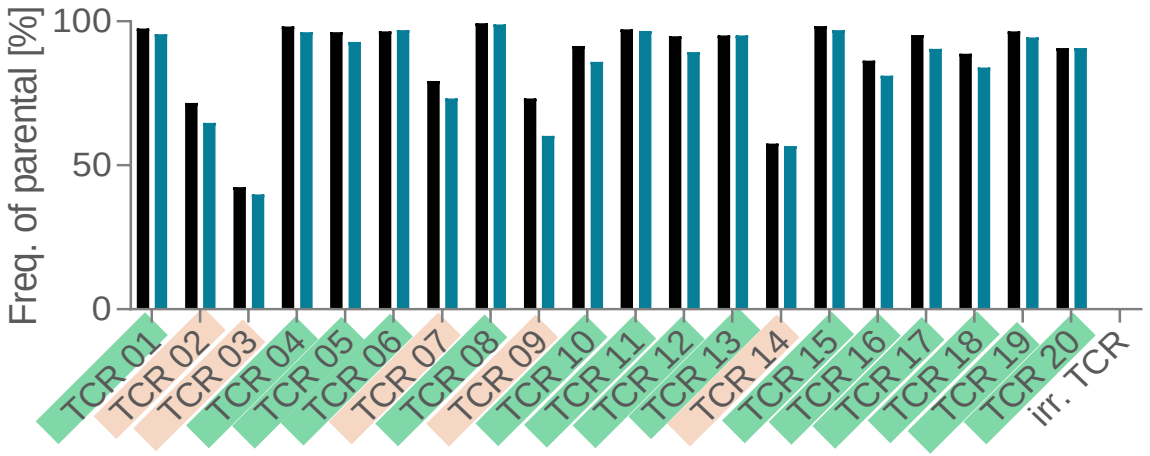
JOVI-Tag

High-throughput comparison of multiple rTCRs in parallel allows selection of superior TCRs

% Cβ1⁺ cells



% multimer⁺ cells on Cβ1⁺ cells



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Medigene TCR Generation – Selecting Optimal Affinity 3S TCRs

Refined and robust workflows established

Selected Target Antigen

Selected Lead TCR

High Specificity

pHLA recognition reaches pre-defined thresholds

High Sensitivity

Optimal affinity to recognize and kill tumor cells with low levels of antigen / epitope

Safety

Clear differentiation between tumor and healthy cells

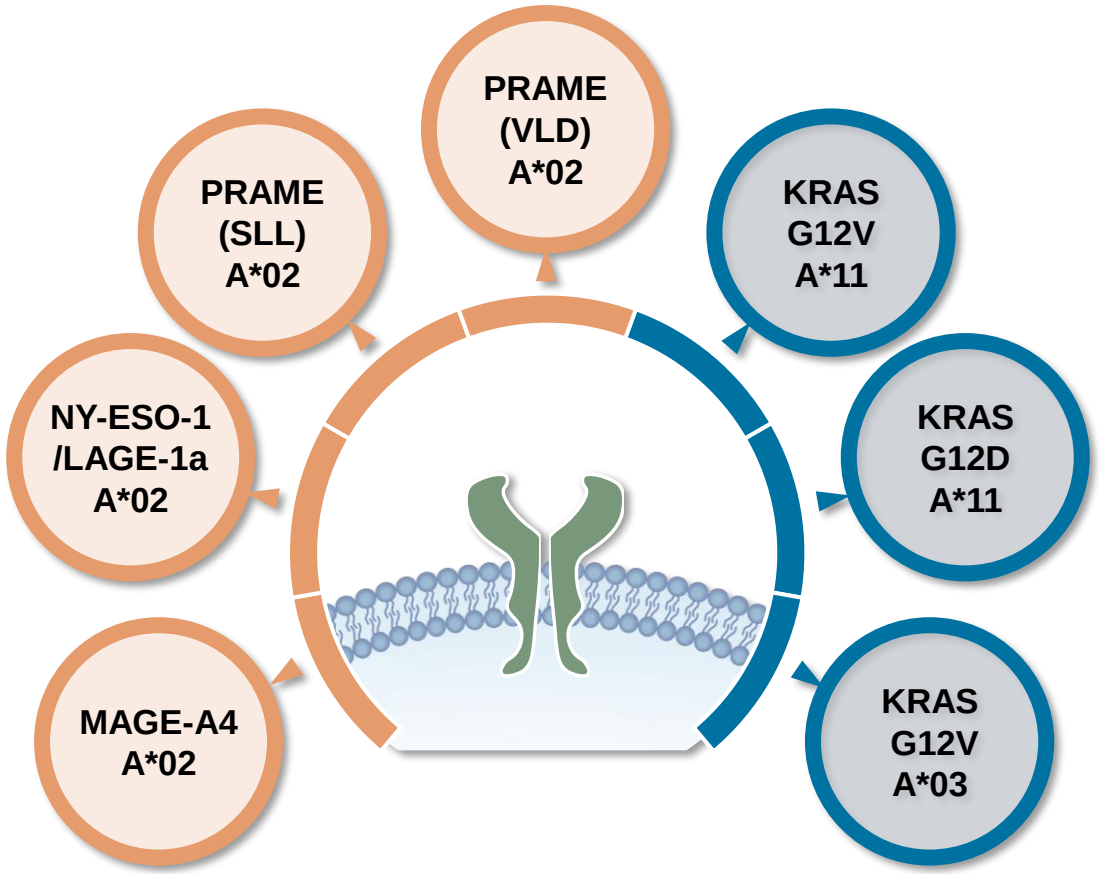
No recognition of allogeneic HLAs

Additional Attributes

Natural high heterodimer pairing → High avidity through high surface expression on recipient T cells

CD8 co-receptor independency → Strong TCR-mediated functions in both CD4 and CD8 T cells

Medigene – An Established Leader in Developing Optimal TCRs



Multi-decade experience of optimal TCRs directed at CTAs, neoantigens & other targets

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CTA; cancer-testis antigen

Armoring & Enhancing TCR-T Cells

Modification of recipient T cells

- ✓ Efficient methods available to transfer and express genes in T cells
- ✓ Recipient cell preparation and high transgene expression with consequent functionality
- ✓ Functional activities of TCR-T cells analyzed in great detail

+

- PD1-41BB CSP#
- CD40L-CD28 CSP#
- Inducible iM-TCR*

Costimulatory Switch Proteins (CSPs)

- ✓ Enhance TCR-T cell functions and overcome an immunosuppressive TME
- ✓ Engineer TCRs to control TCR surface expression

CSPs allow TCR-T cells to thrive within the TME leading to enhanced functionality and persistence of cells

CSP PD1-41BB Addresses Immunosuppressive PD1-PDL1 Signals

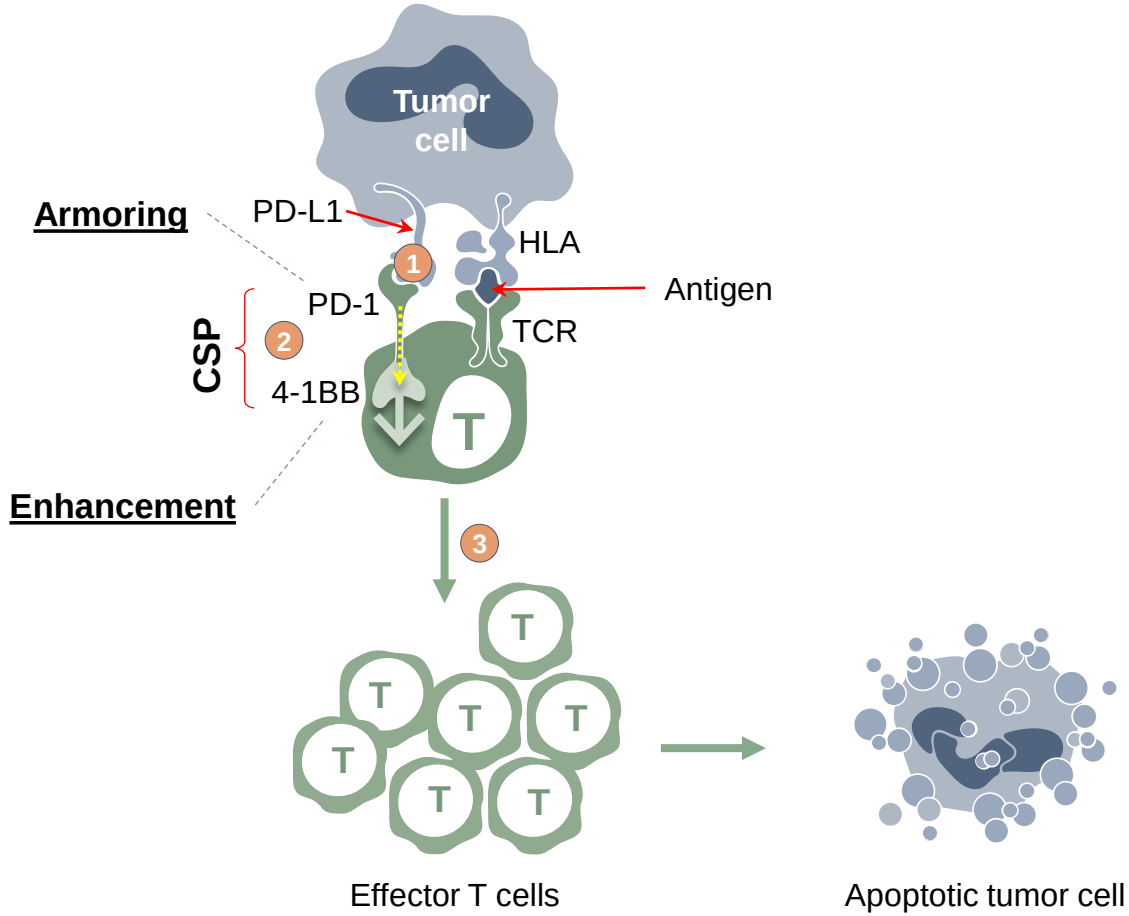
Sub-optimal TCRs and unarmored T cells:

1. PD1-PDL1 interaction reduces anti-tumor response through T cell inhibition, exhaustion and apoptosis

3rd Gen. TCR-T therapy armored & enhanced with PD1-41BB CSP:

2. PD1-PDL1 interaction activates the 4-1BB costimulatory pathway

3. 4-1BB costimulation leads to enhanced anti-tumor response through:
   - ✓ Increased T cell proliferation
   - ✓ Enhanced effector T cell function
   - ✓ Sustained tumor cell killing



CSP CD40L-CD28 Fosters Tumor Penetration & T Cell Costimulation

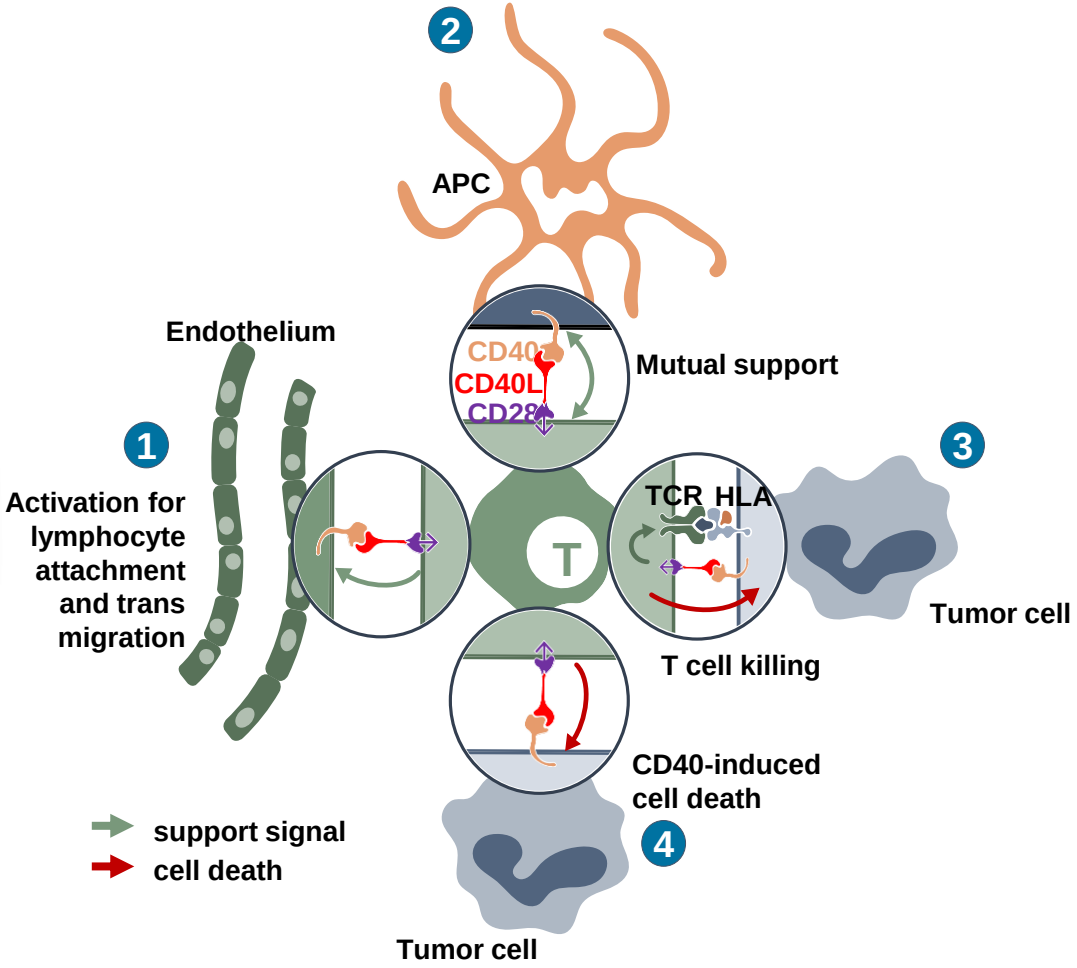
3rd Gen. TCR-T therapy with dual enhancement by CD40L-CD28 CSP:

CD40L Enhancement

1. Improves T cell tumor penetration via modulating the endothelium
2. Supports APC activation in the TME
3. Supports enhanced tumor killing by T cells in the TME
4. Can trigger HLA independent tumor killing via CD40

CD28 Enhancement

Activates costimulatory pathway in TCR-T cells to improve T cell proliferation and limit T cell exhaustion



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Adapted from https://www.frontiersin.org/articles/10.3389/fimmu.2021.750478/full

Medigene TCR-T Therapy Optimization

Two unique CSPs provide complementary mitigation of the immunosuppressive TME

PD1-41BB

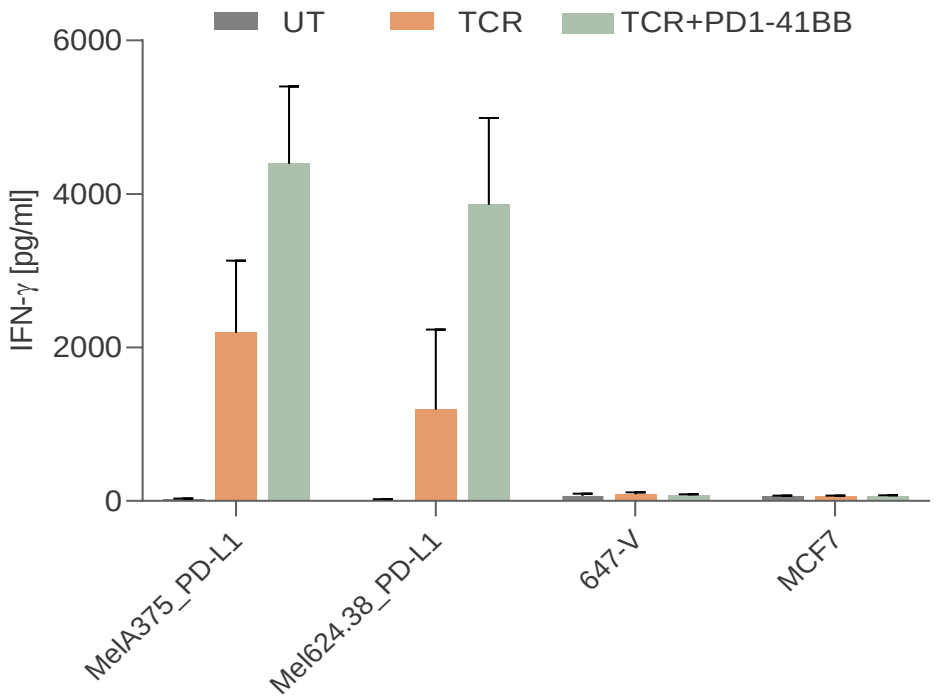
- ✓ Blocks PD1-PDL1 inhibitory axis
- ✓ Improves T cell persistence in TME

CD40L-CD28

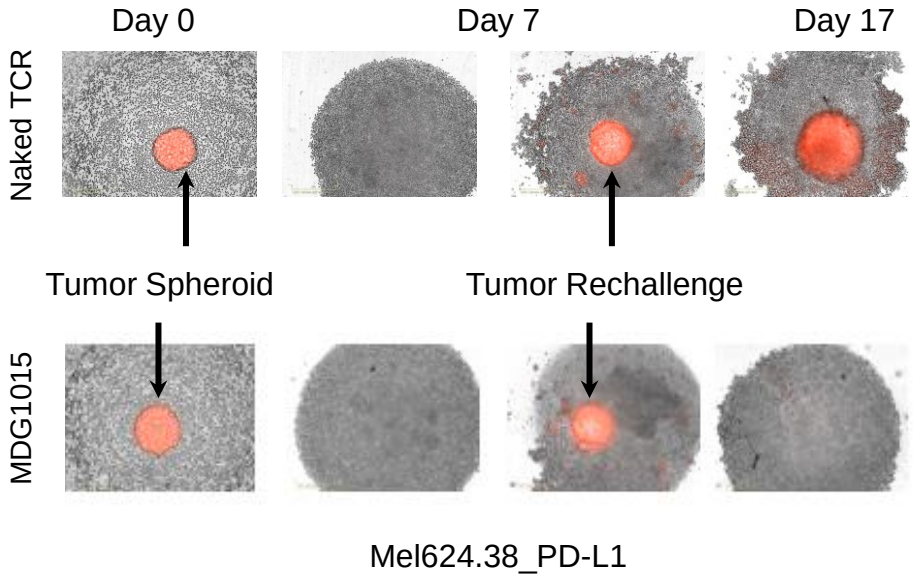
- ✓ Enhances tumor penetration
- ✓ Broadens immune system activation

- ✓ Increases cytokine secretion & tumor cell killing
- ✓ Increases T cell proliferation

MDG1015: Preclinical Superiority of 3rd Generation TCR-T Therapy



Expression*	MelA375_ PD-L1	Mel624.38_ PD-L1	647-V Control	MCF7 Control
NY-ESO-1	+++(305.87)	- (33.76)	- (28.26)	- (40.89)
LAGE-1a	- (1.06)	+++ (1979.62)	- (1.11)	- (1.51)
PD-L1	+++	+++	++	-



Demonstrated superiority over 'naked' TCR in multiple preclinical models

- ✓ Over 2x greater target recognition (left)
- ✓ Strict gating of CSP through TCR ensuring safety (left)
- ✓ Rapid and sustained *in vitro* tumor cell killing upon serial rechallenges (multiple rechallenges not depicted above)

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** Based on historical nCounter data (normalized counts) Coluccio AACR 2023*

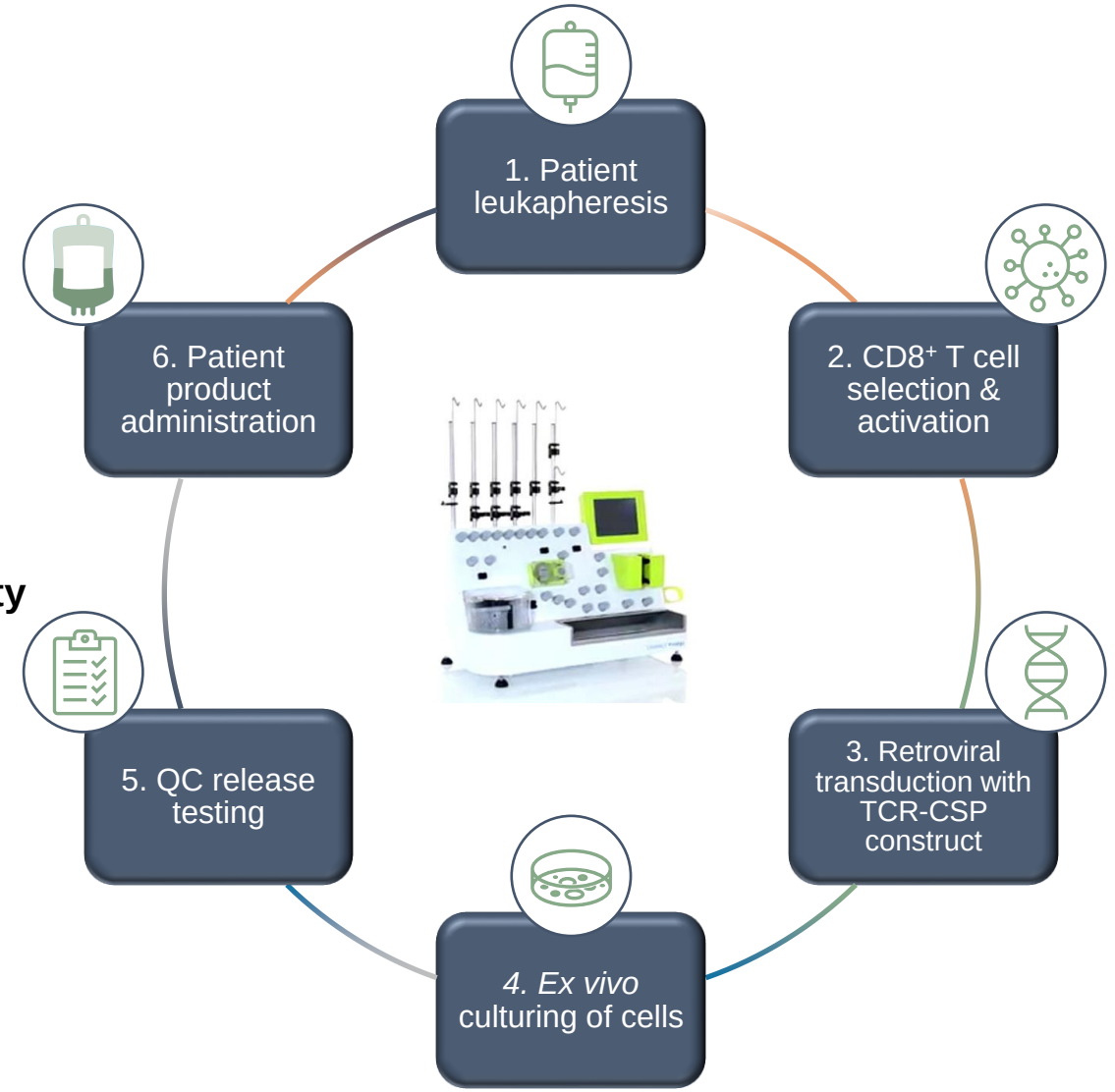
Rapid & Optimal DP Manufacturing Impacts Patient Outcomes

Short vein-to-vein time (~20 days) reduces need for bridging therapy

- ✓ 6-day GMP manufacturing process
- ✓ Automated, closed manufacturing on Miltenyi Prodigy
- ✓ Rapid 7-day QC release strategy endorsed by US & EU regulators
- ✓ RVV delivery system in place, NVV under assessment

Optimal DP composition enhances clinical safety, efficacy & durability

- ✓ Very high purity of $CD3^+/CD8^+$ T cells in Drug Product (DP)
- ✓ Pure $CD8^+$ T cell selection eliminates potential reduced safety and/or efficacy caused by untransduced $CD4^+$ T cells in DP
- ✓ Very high T_{scm} and T_{cm} fraction in DP



Continuous, ongoing evaluation of all elements of process development to ensure upkeep with state-of-the-art
DP; Drug Product, RVV; Retroviral vector, NVV; Nonviral vector, Tscm; T memory stem cells, Tcm; T central memory cells

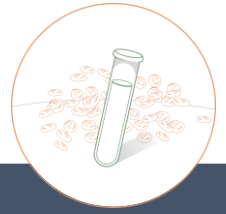
Broad Pipeline with Multiple Value Inflection Points

Indications	Program	Target	Armoring & Enhancement	Discovery	Lead Candidate Selection	CTA / IND-enabling	Clinical Studies	Next Milestone
Multiple Solid Tumor Types	**Medigene Programs**							
	MDG1015	NY-ESO-1 / LAGE-1a	PD1-41BB	HLA-A*02				CTA / IND 2H 2024
	MDG2011	KRAS-G12V	PD1-41BB	HLA-A*11				IND enabling
	MDG2021	KRAS-G12D	PD1-41BB or CD40L-CD28	HLA-A*11				Lead selection 1H 2024
	MDG2012	KRAS-G12V		HLA-A*03				Lead selection 2025
	MDG20XX	KRAS[1]		HLA*				Undisclosed
	MDG10XX	Undisclosed	Undisclosed	HLA*				Undisclosed
	Partnered Programs							
	2seventybio	MAGE-A4	Yes[2]	HLA-A*02				FIH study recruiting[3]
	BIONTECH	PRAME	Yes	HLA-A*02				Undisclosed

Cancer Testis Antigens
Neoantigens
Undisclosed targets

FIH; First-in-human
1. MDG20XX – Medigene exploring multiple, additional HLAs and/or G12 mutations, 2. Enhancement not licensed from Medigene
3. Source: https://www.clinicaltrials.gov/study/NCT06170294?id=NCT06170294&rank=1

Summary of Jovi-Tag Tracking Across Medigene's End-to-End Platform



TARGET SCREENING

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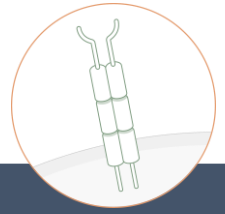
- Tailored Mass Spectrometry

No TCR tracking required



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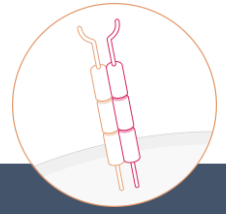
Highly suited to support lead TCR selection



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Well suited to enrich TCR-T cells with CSPs for characterization

TCR-T DRUG PRODUCT MANUFACTURING

- 6-Day Automated Cell Production Process
- Optimal Drug Product Cell Composition
- SIN-γ- Retroviral Gene Transfer System
- Drug Product Immune Assessment

Feasible for early small scale development but not for large scale CMC

CLINICAL DEVELOPMENT

- Patient Immune Monitoring

Not suited as expressed in natural T cell repertoire

- Safety Enhancements
- Efficacy Enhancements
- Development Optimization

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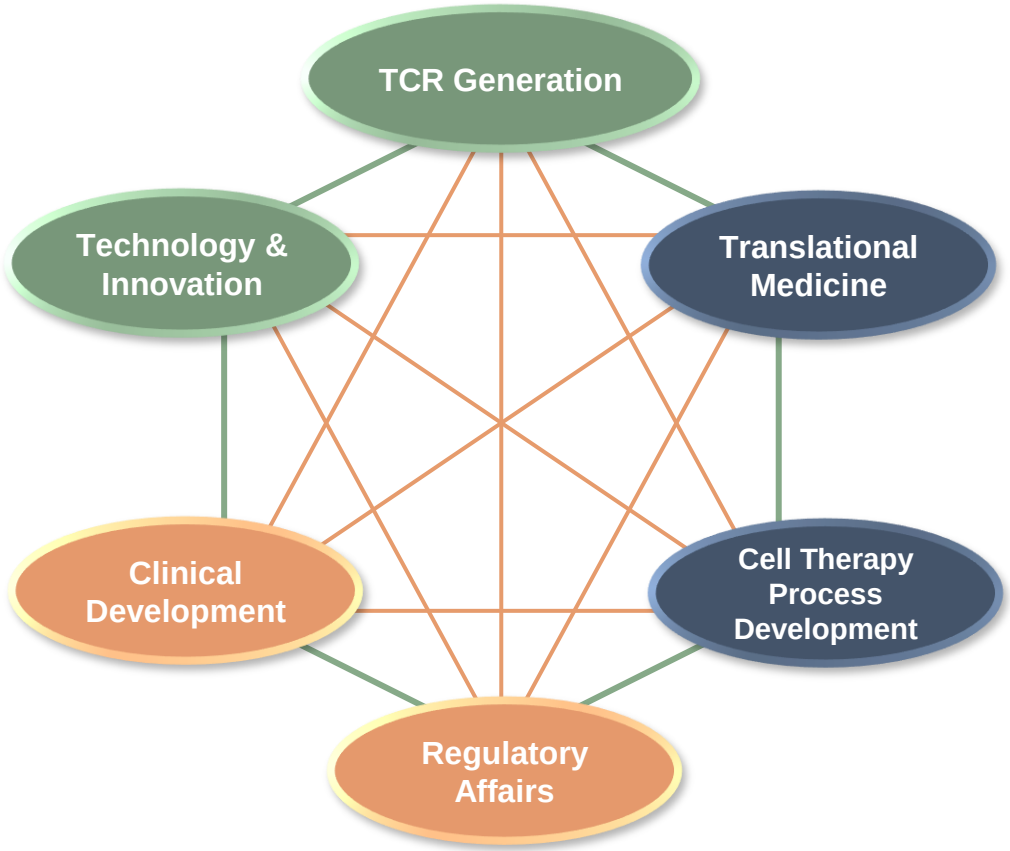

Thank you for your attention