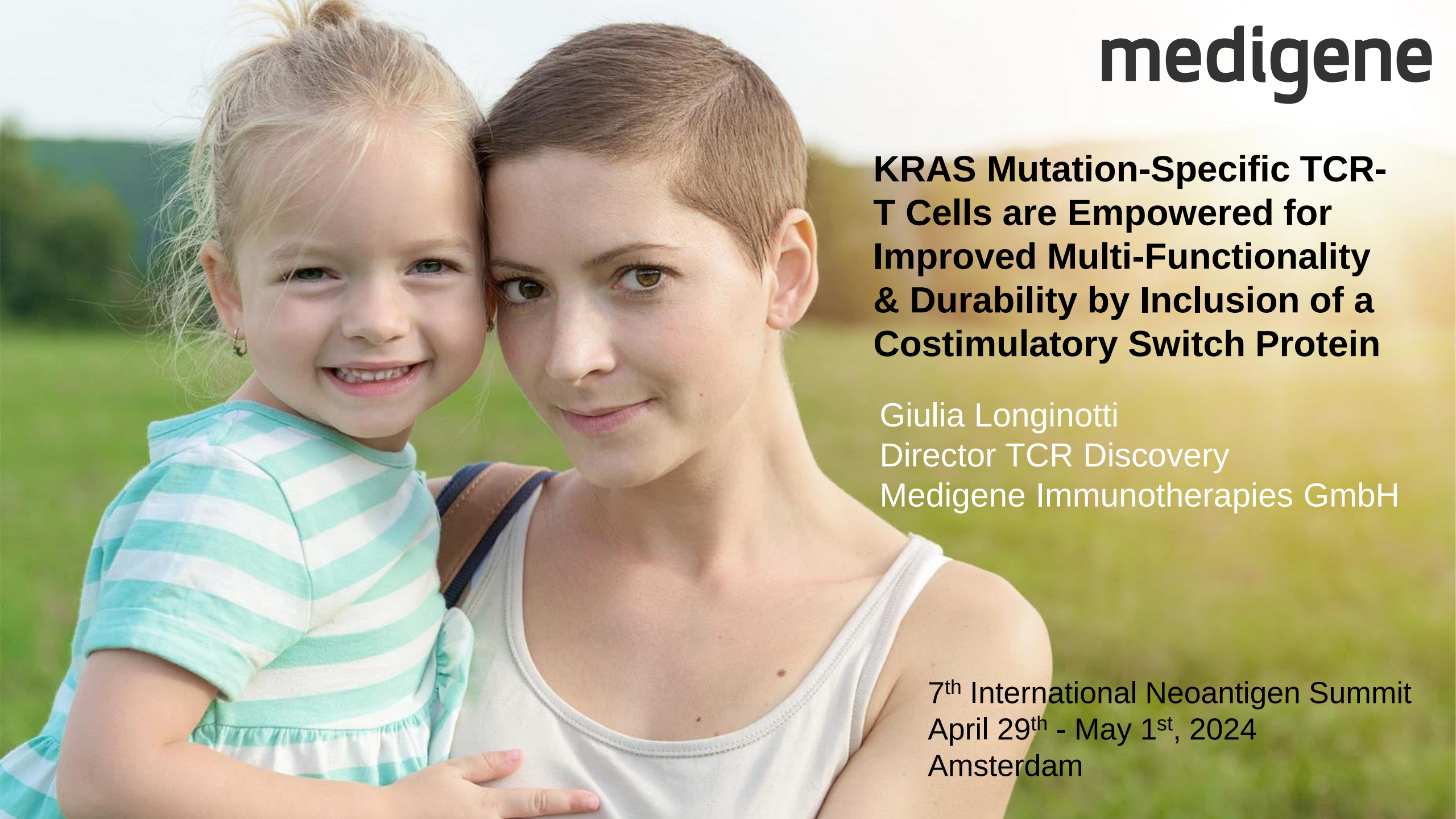

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KRAS Mutation-Specific TCR-T Cells are Empowered for Improved Multi-Functionality & Durability by Inclusion of a Costimulatory Switch Protein

Giulia Longinotti
Director TCR Discovery
Medigene Immunotherapies GmbH

7th International Neoantigen Summit
April 29th - May 1st, 2024
Amsterdam

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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

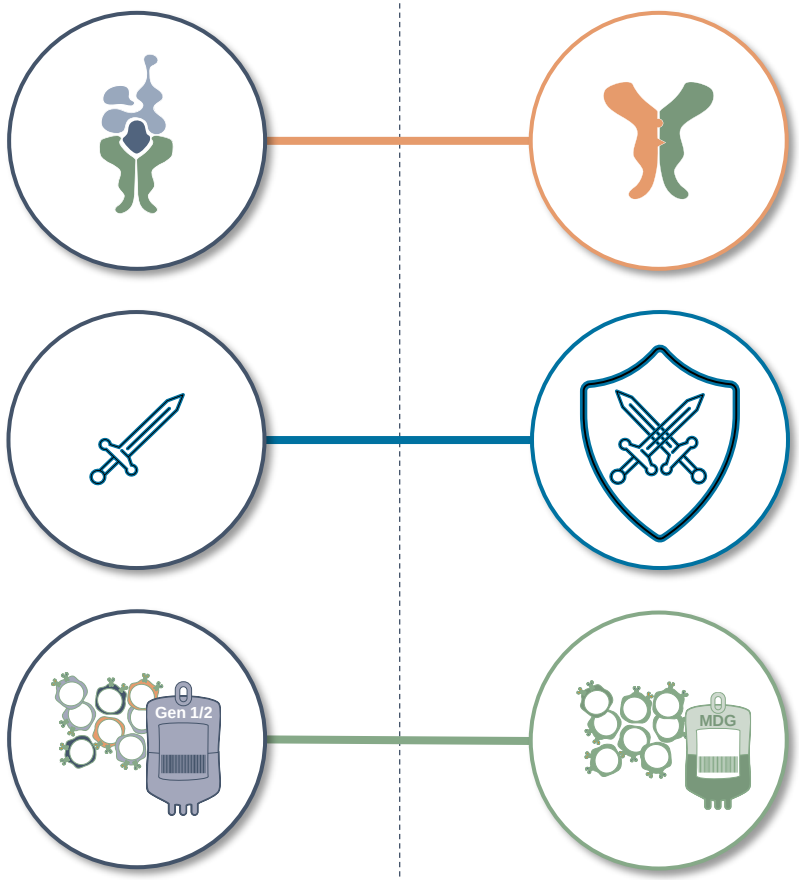
Poor penetration, persistence of T cells, lack of proliferation

➢ ***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**

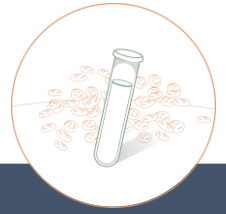
Tailored DP Composition

- ✓ 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

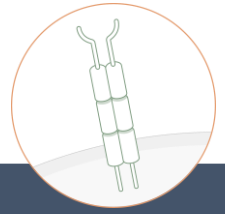
Medigene's End-to-End Platform

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



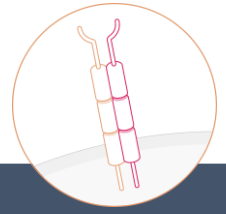
1 TARGET SCREENING

- Expitope
- Tailored Mass Spectrometry



2 TCR DISCOVERY & OPTIMIZATION

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



3 TCR-T THERAPY ARMORING & ENHANCEMENT

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

4 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

5 CLINICAL DEVELOPMENT

- Patient Immune Monitoring

- Safety Enhancements
- Efficacy Enhancements
- Development Optimization

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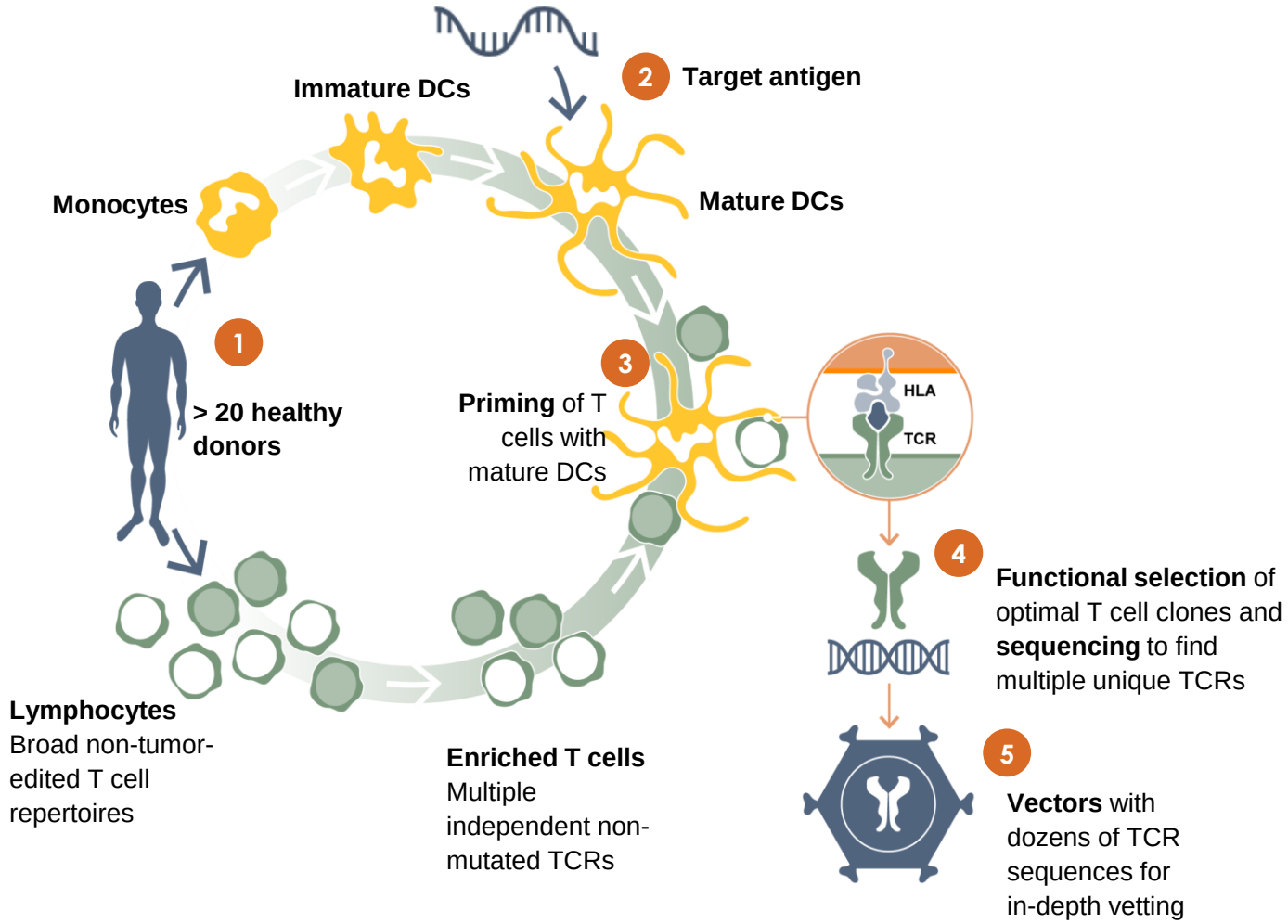
Schendel Front Immunol 2023

TCR Discovery: DC-T Cell Priming Using Healthy Donors

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



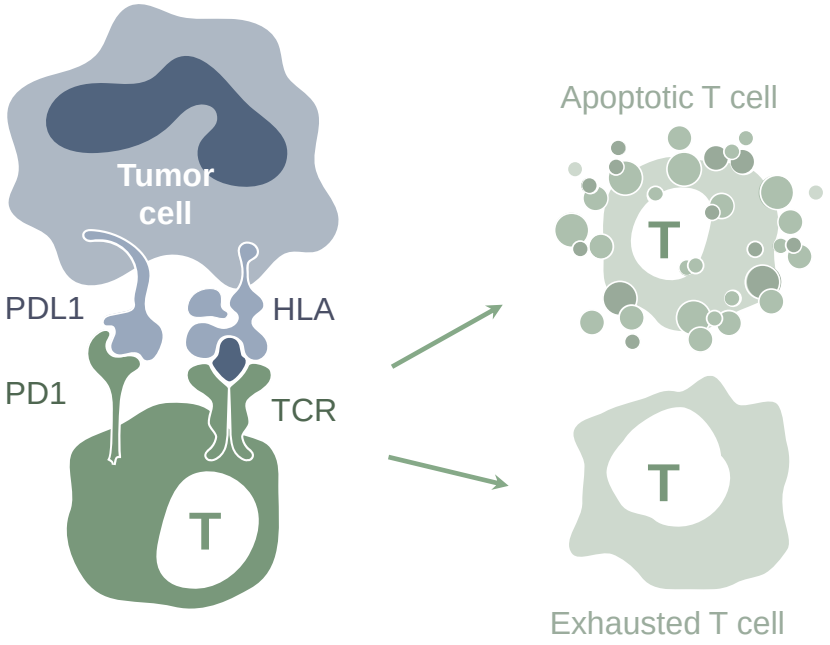
Key Advantages

- Ready access to **multiple healthy donors**
- **Auto-HLA** or **Allo-HLA approach**
- ***ivt*RNA** as **source of antigen** (and HLA in Allo-HLA approach)
- **High-throughput process** with **early functional screens** allow identification of rare multiple unique TCRs

Armoring and Enhancing TCR-T Cells: PD1-41BB CSP

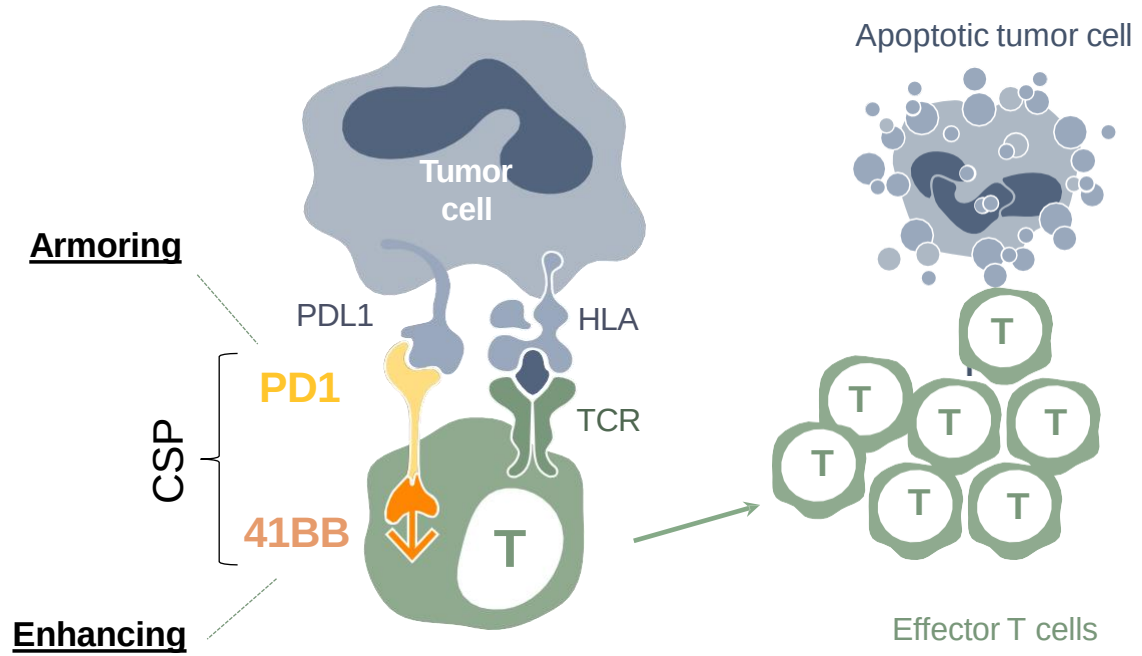
PD1-41BB costimulatory switch protein (CSP) addresses immunosuppressive PD1-PDL1 signals

TME challenge: PD1-PDL1 signals



- Inhibits T cell activity
- Induces T cell exhaustion
- Drives T cell apoptosis

Medigene's solution: PD1-41BB CSP



- Blocks PDL1-mediated inhibition
- Provides T cell costimulation via 41BB pathway
- Enhances and sustains TCR-T activity and survival

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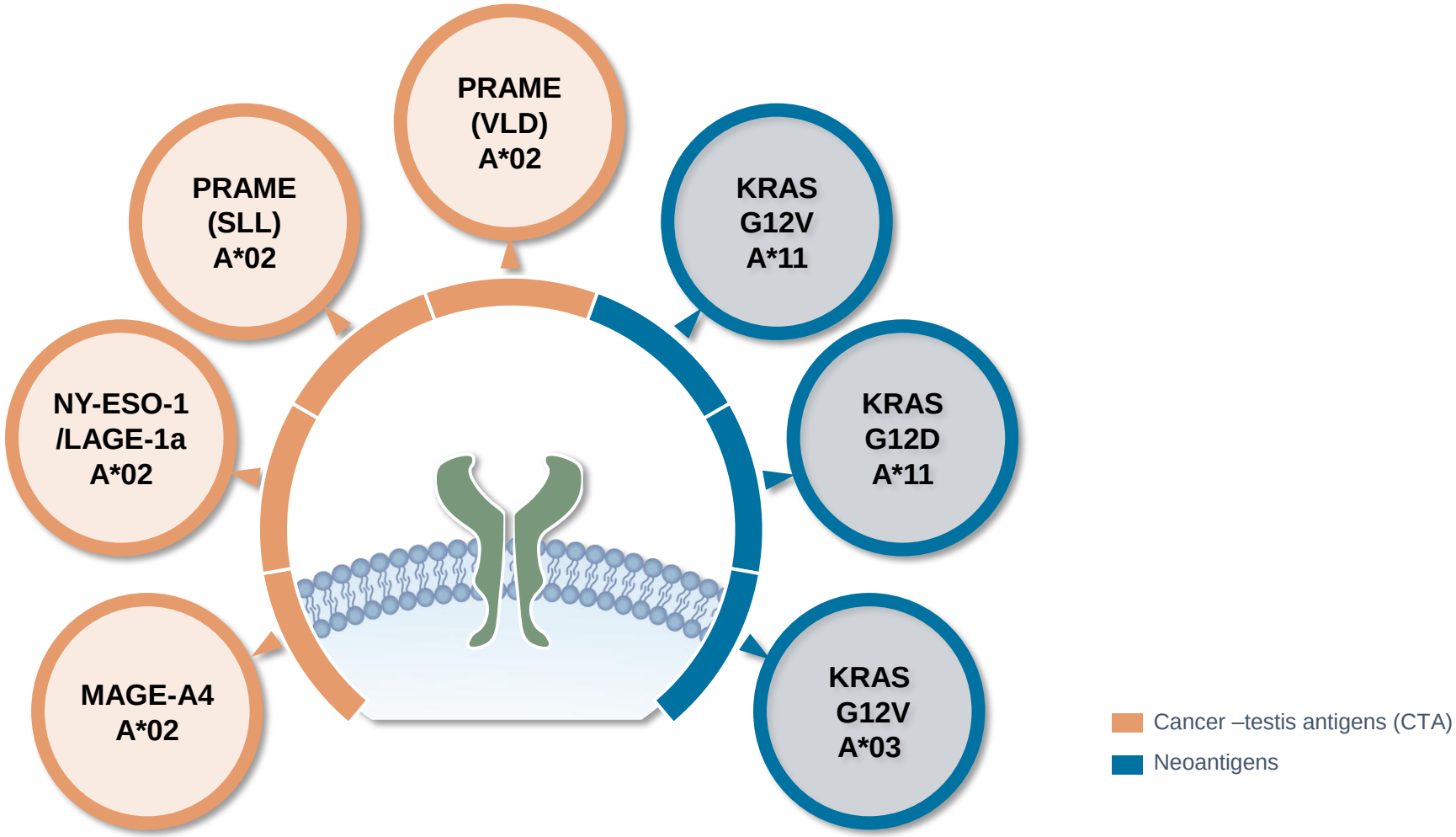
Medigene – An Established Leader in Developing Optimal TCRs

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



Medigene's Own Programs: Advancing mKRAS TCR-T Library

Multiple KRAS mutations and HLA allotypes to address large global patient populations

Indications	Program	Target	Armoring & Enhancement	Discovery	Lead Candidate Selection	CTA / IND enabling	Clinical Studies	Next Milestone
	Medigene Programs							
Multiple Solid Tumor Types	**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

Cancer Testis Antigens

Neoantigens

Undisclosed targets

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FIH; First-in-human

1. MDG20XX – Medigene exploring multiple, additional HLAs and/or G12 mutations

KRAS – A Well Validated Neoantigen Target

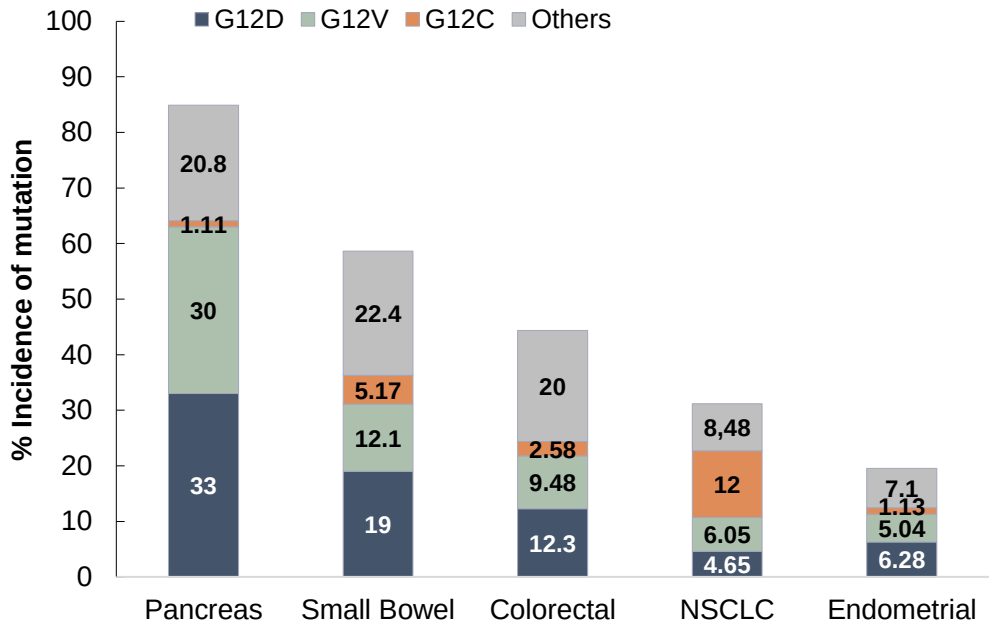
Robust expression in multiple tumors results in large potential patient populations

KRAS mutations widely recognized as the most common oncogene mutations in difficult-to-treat solid tumors existing in ~30% of solid tumors[2]

Small molecule KRAS therapies are now approved but unmet need remains for improved efficacy and safety[3]

KRAS TCR-T therapies with enhancing and armoring may address the challenges of the TME and improve patient outcomes

Incidence of KRAS mutations across tumor indications[1]



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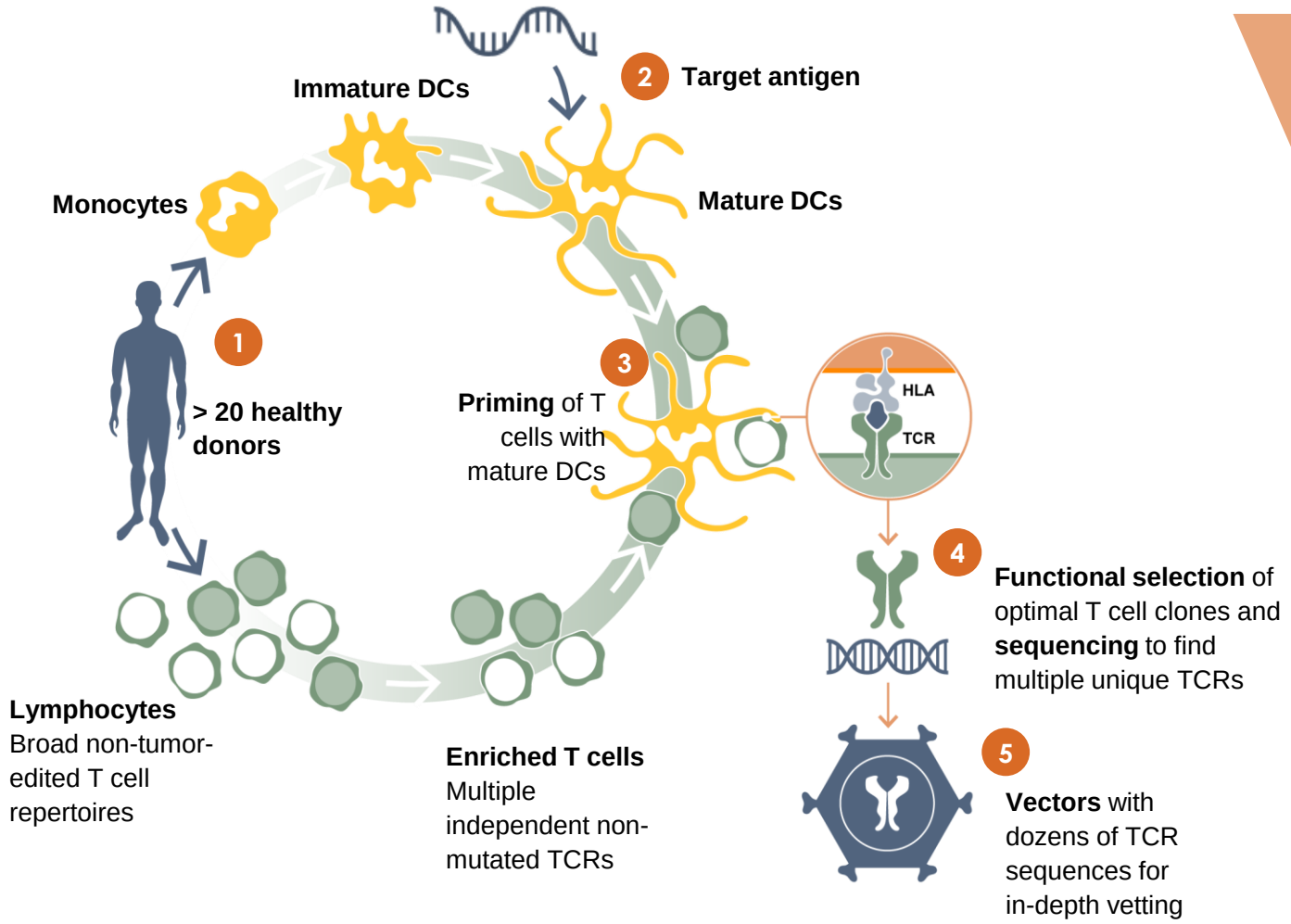
1. ECIS - European Cancer Information System, 2. Stephen Cancer Cell 2014, 3. FDA Approved Lumakras /Sotorasib and Krazati/Adagrasib G12C inhibitor package inserts

TCR Discovery: mKRAS G12V HLA-A*11 Program

High-throughput TCR discovery rapidly delivers multiple, unique mKRAS G12V-specific TCRs



>20 donors screened
(Auto-HLA priming approach)

~20000 sorted clones
(multimer-based sorting)

1434 G12V-reactive clones

15 analyzed TCRs

6 candidate TCRs

Selected for in-depth vetting in a transgenic setting

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Vetting of Candidate TCRs for Specificity, Sensitivity and Safety

Refined and robust workflow established to select 3S TCRs and develop superior TCR-T therapies

Armoring and Enhancing TCR-T cells with PD1-41BB CSP

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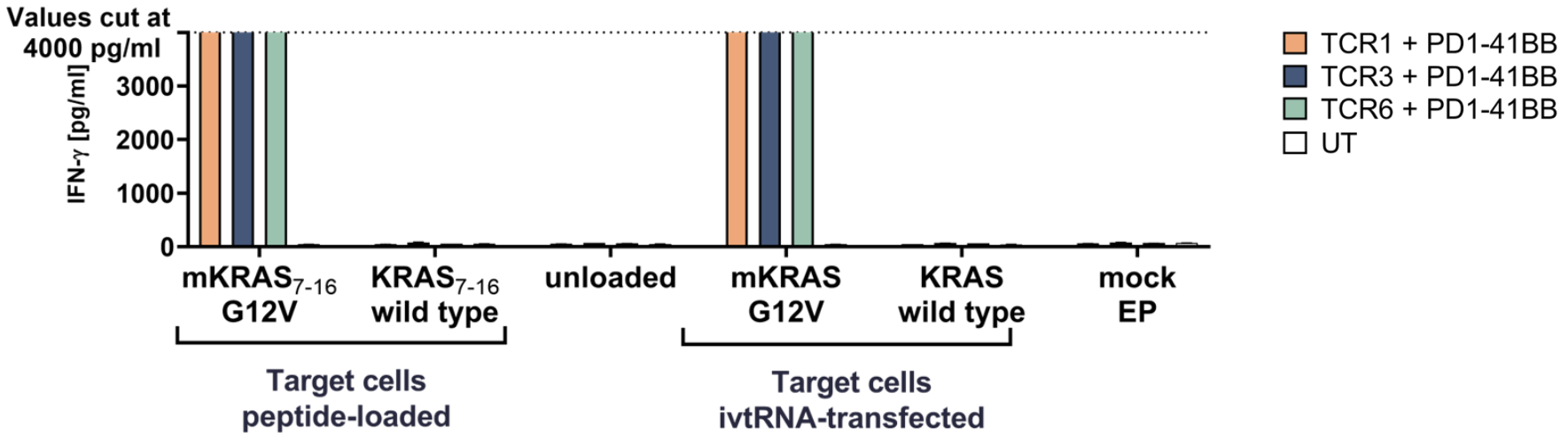
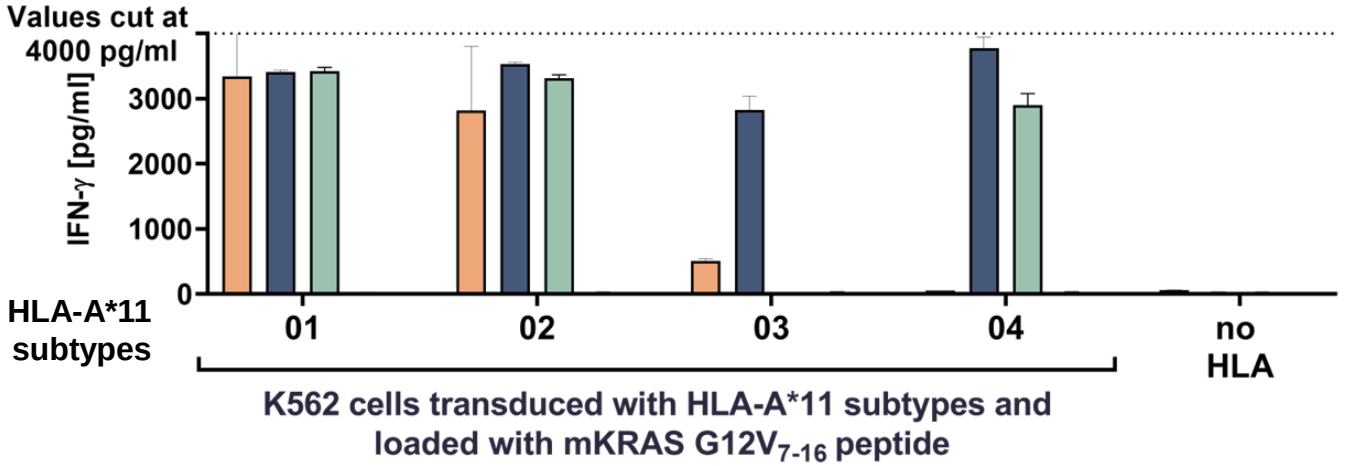
Selecting TCRs with Exquisite Specificity

Exclusive mKRAS G12V mutant specificity with no recognition of KRAS wild type protein

Assessment of mKRAS G12V mutant specificity

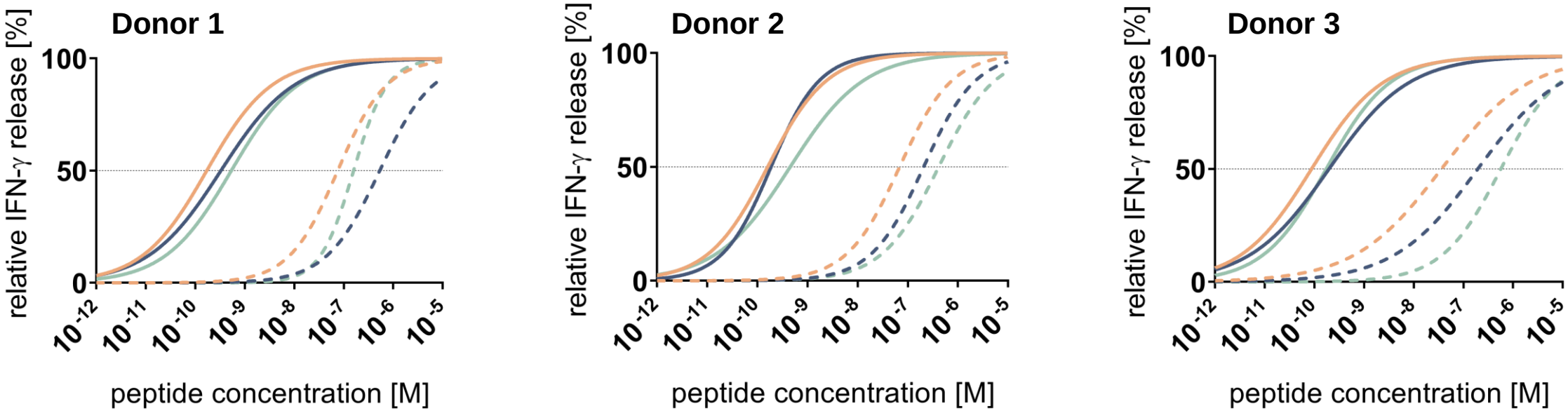


Assessment of HLA-A*11 fine-typing specificity



Selecting TCRs with Optimal Peptide Sensitivity

High peptide sensitivity for mKRAS$_{7-16}$ G12V epitope (10-mer)



- - TCR1 + PD1-41BB
- - TCR3 + PD1-41BB
- - TCR6 + PD1-41BB

mKRAS G12V$_{8-16}$ (**9-mer**)

— TCR1 + PD1-41BB
— TCR3 + PD1-41BB
— TCR6 + PD1-41BB

mKRAS G12V$_{7-16}$ (**10-mer**)

mKRAS G12V$_{7-16}$ (**10-mer**)	**EC50** values*
TCR1+PD1-41BB	0.14 nM
TCR3+PD1-41BB	0.23 nM
TCR6+PD1-41BB	0.38 nM

*Average of 3 donors

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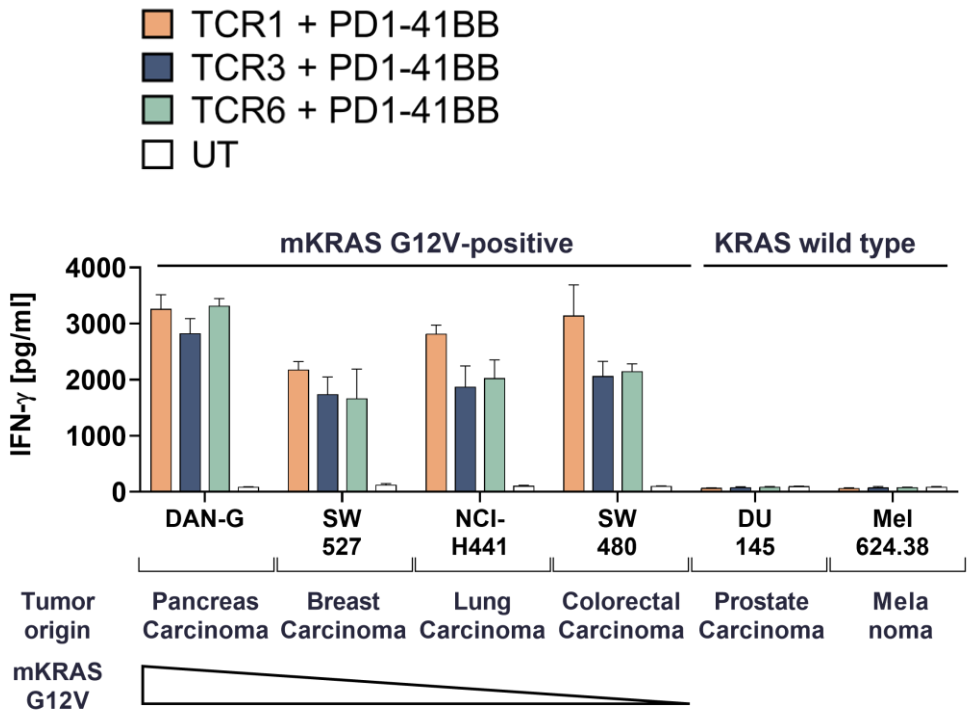
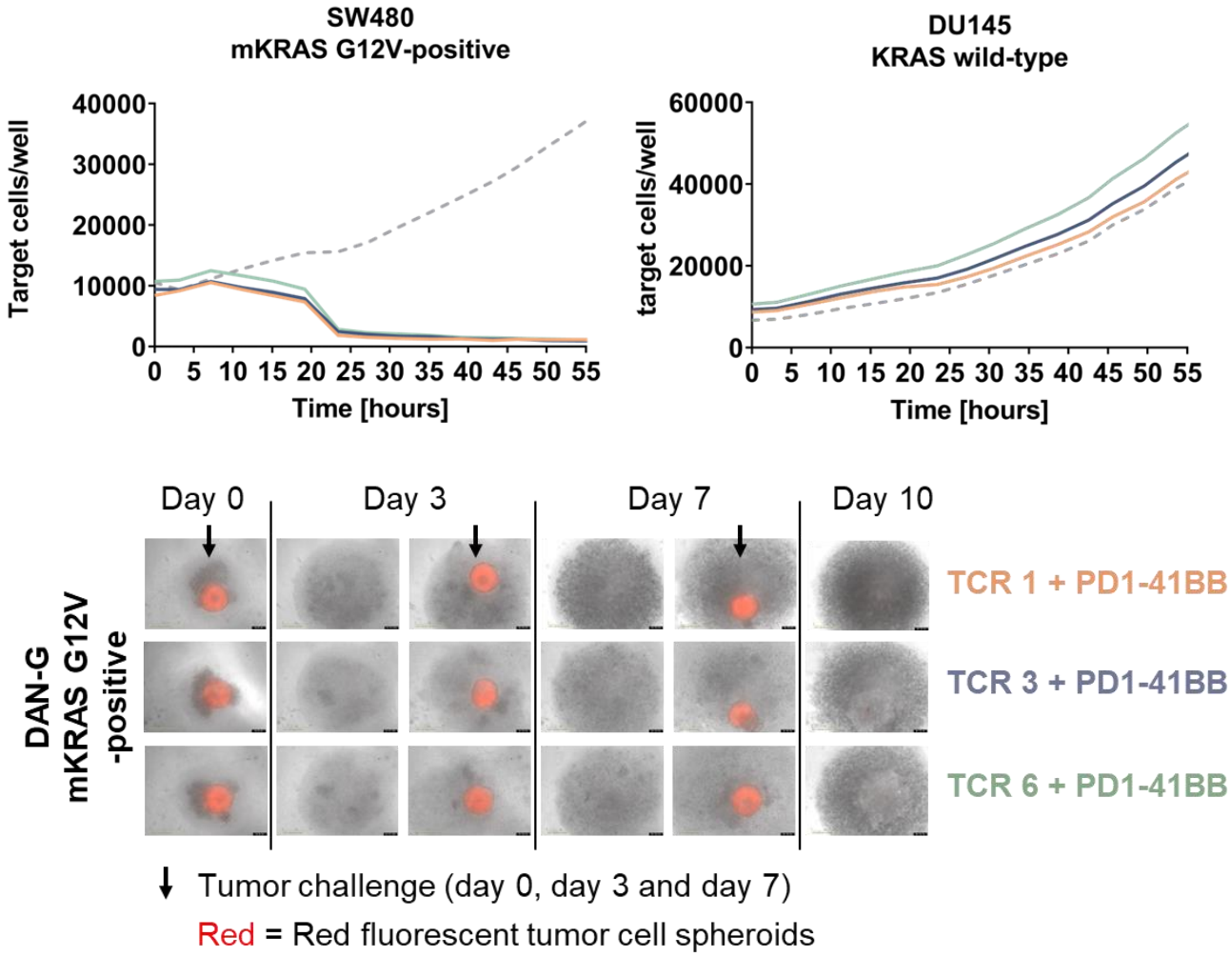
Selecting TCRs with Strong Tumor Recognition

High IFN-γ secretion and strong cytotoxicity in response to mKRAS G12V-positive tumor cells



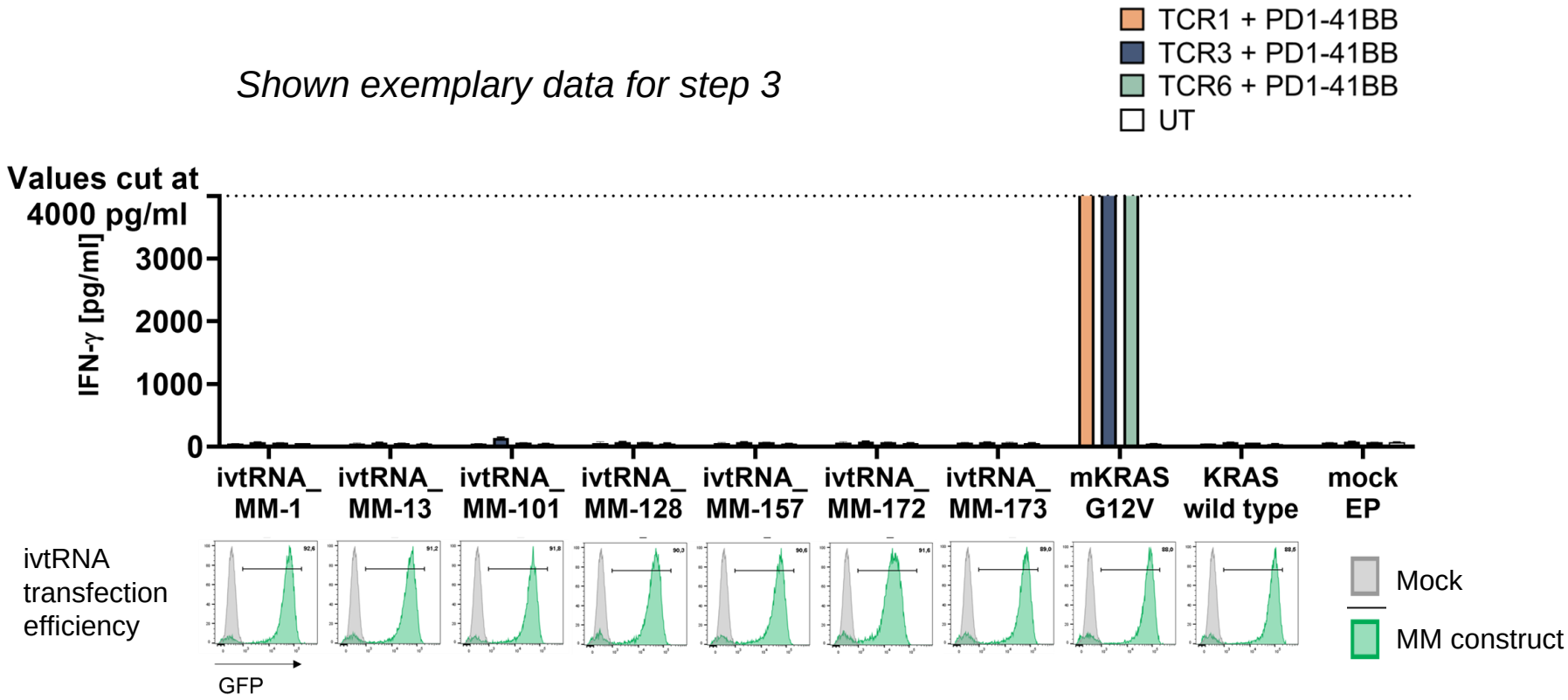


Selecting TCRs with a Favorable Safety Profile

No signs of off-target toxicity by testing a library of self-peptides partially homologous to target epitope

- **Step 1**: screening of hundreds of peptides at high concentration (10^{-5}M)
- **Step 2**: peptide titration (10^{-6}M, 10^{-7}M)
- **Step 3**: ivtRNA-based expression assay

Shown exemplary data for step 3

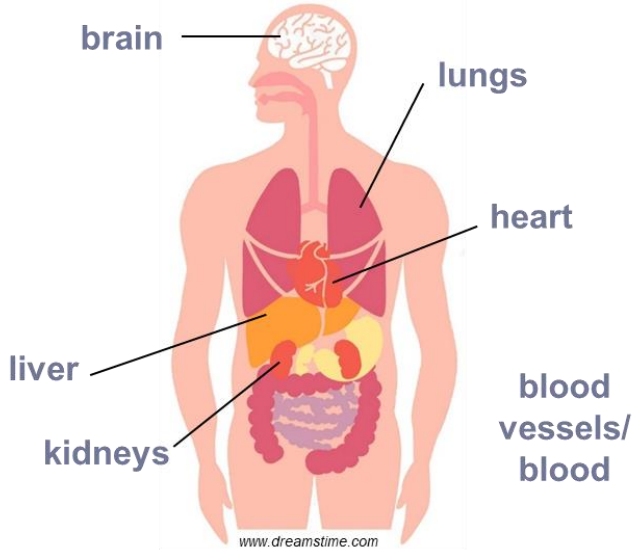


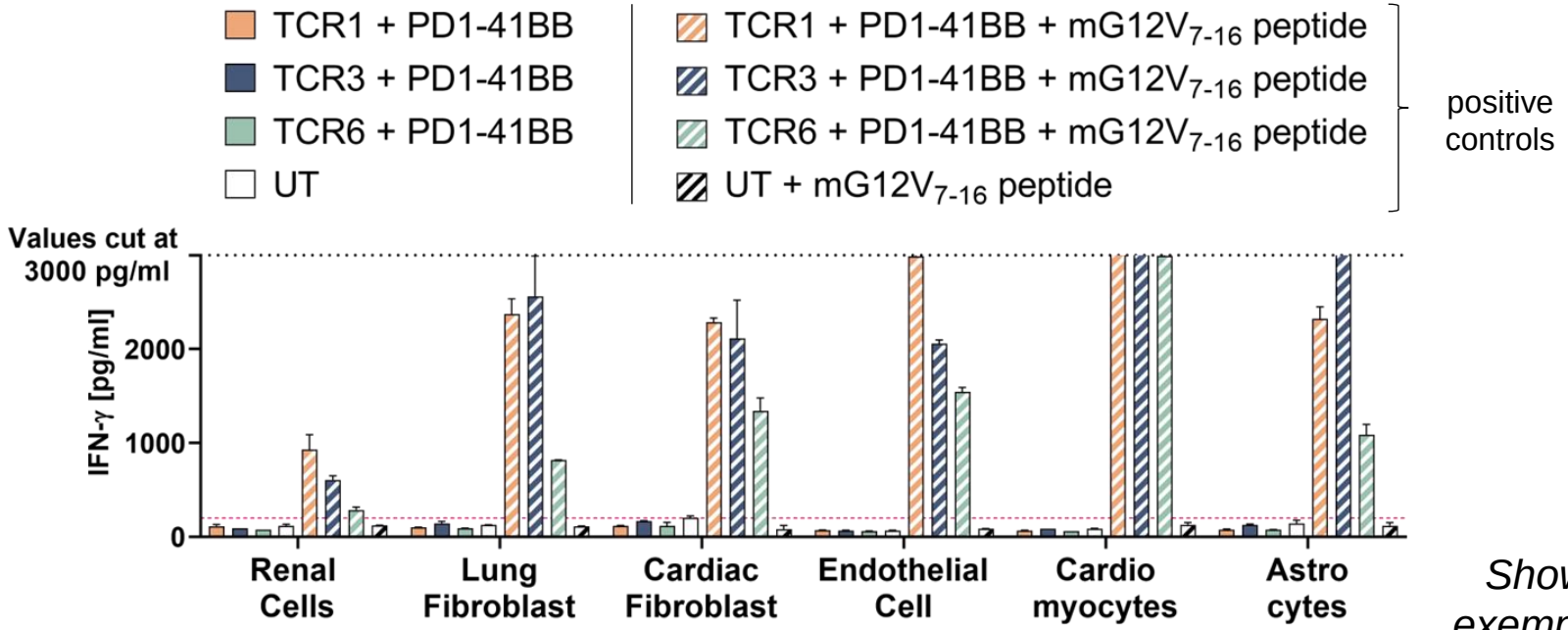
EP = electroporation
MM = mismatched midi-gene antigens

Selecting TCRs with a Favorable Safety Profile

No signs of off-target toxicity by testing a panel of healthy cell types

- Testing of cell types representing **essential healthy tissues or organs**



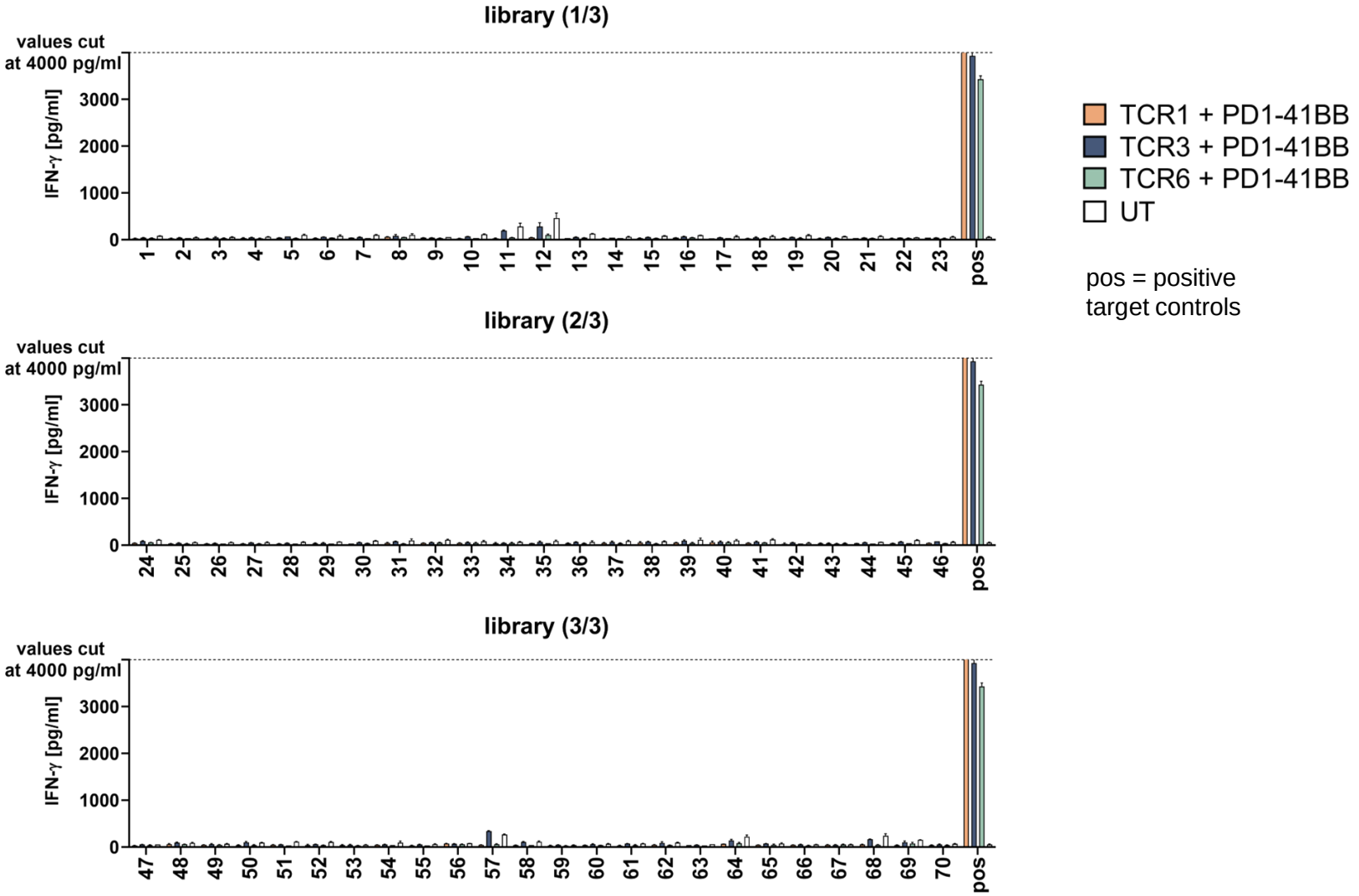


Shown exemplary healthy cell types

Selecting TCRs with a Favorable Safety Profile

No signs of target peptide-independent HLA-allo cross-recognition

- Testing of cellular libraries (~100 samples) covering the **most frequent HLA allotypes worldwide** (HLA frequency > 2%)



pos = positive target controls

Selecting TCRs with Unique Additional Attributes

One candidate TCR exhibits full functionality independently of CD8 co-receptor presence

CD8 independent TCR

CD8 dependent TCR

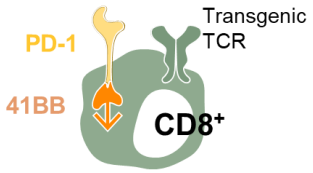
Untransduced cells

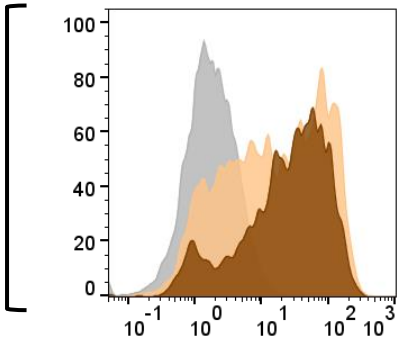
Multimer binding

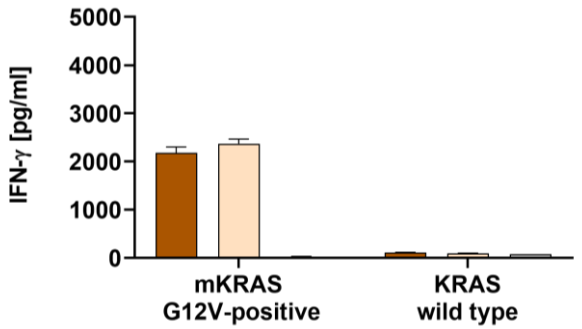
IFN-γ release in response to tumor cells

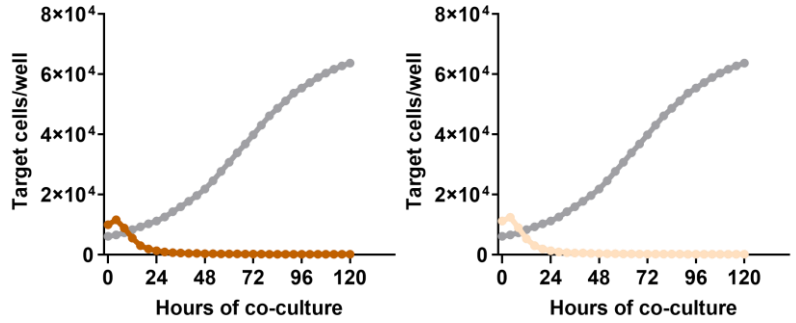
Cytotoxicity in response to tumor cells

CD8⁺ T cells

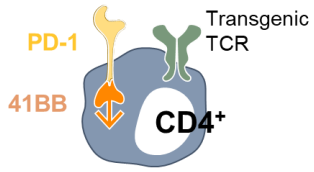


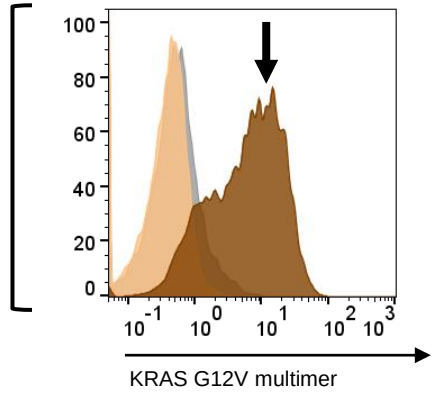


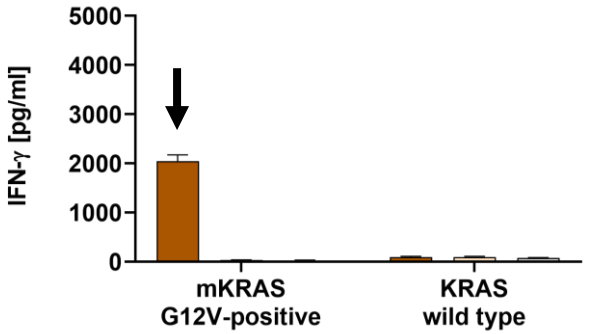


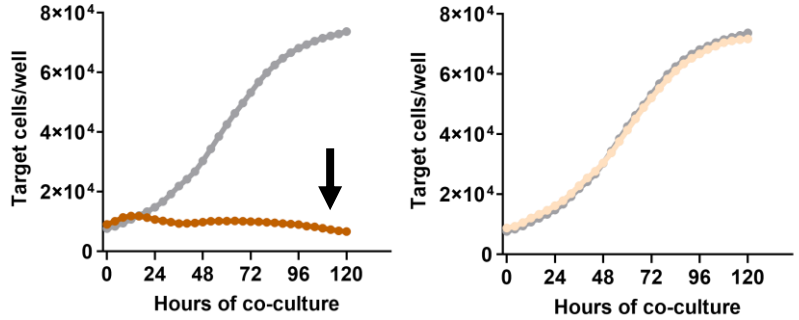


CD4⁺ T cells









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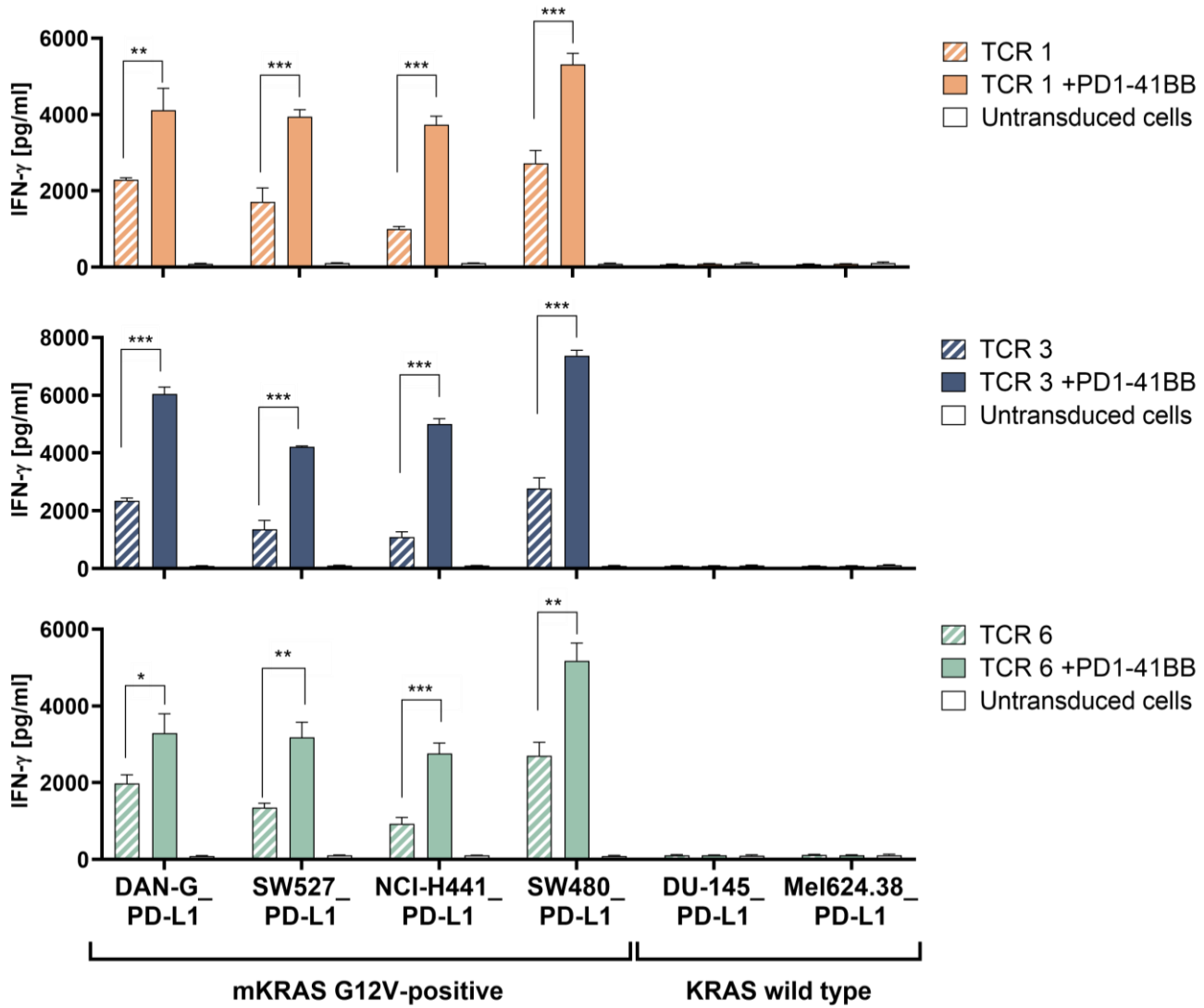
Shown data for two exemplary candidate TCRs

Improving TCR-T Cell Functionality by PD1-41BB CSP

PD1-41BB CSP enhances IFN-γ release in response to PDL1^{+} tumor cells in a strict TCR-gated manner



Multiple unpaired T test, (*): P ≤ 0.05, (**): P ≤ 0.01, (***): P ≤ 0.001

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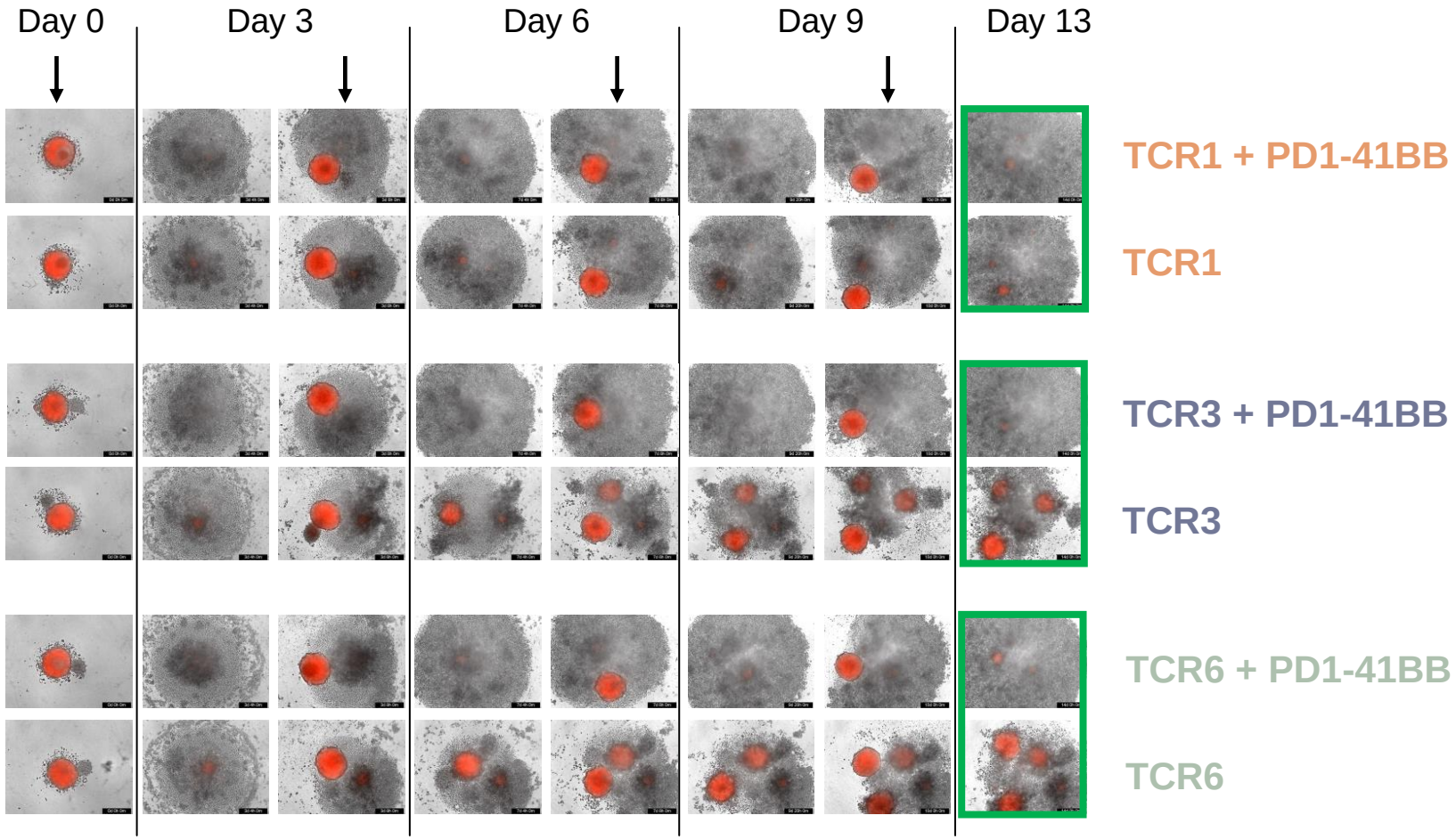
Improving TCR-T Cell Functionality by PD1-41BB CSP

PD1-41BB CSP sustains cytotoxic activity of TCR-T cells in response to serial PDL1^{+} tumor challenges

Red = mKRAS G12V-positive tumor cell spheroids expressing high level of PD-L1

↓ Tumor challenge (four challenges: d0, d3, d6, d9)



3S TCRs with PD1-41BB CSP to Develop Best-in-Class Therapies

Medigene's discovery and vetting processes deliver excellent mKRAS G12V-specific lead 3S TCRs

Candidate TCRs

Lead 3S TCR

Specificity

Exquisite pHLA specific recognition

Sensitivity

Natural optimal sensitivity to recognize tumor cells with low levels of antigen

Safety

Favorable safety profile
No off-target toxicity
No recognition of allogeneic HLAs

Additional Attributes

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

Armoring and Enhancing TCR-T cells with PD1-41BB CSP

Improved T cell effector functions to overcome immunosuppressive TME

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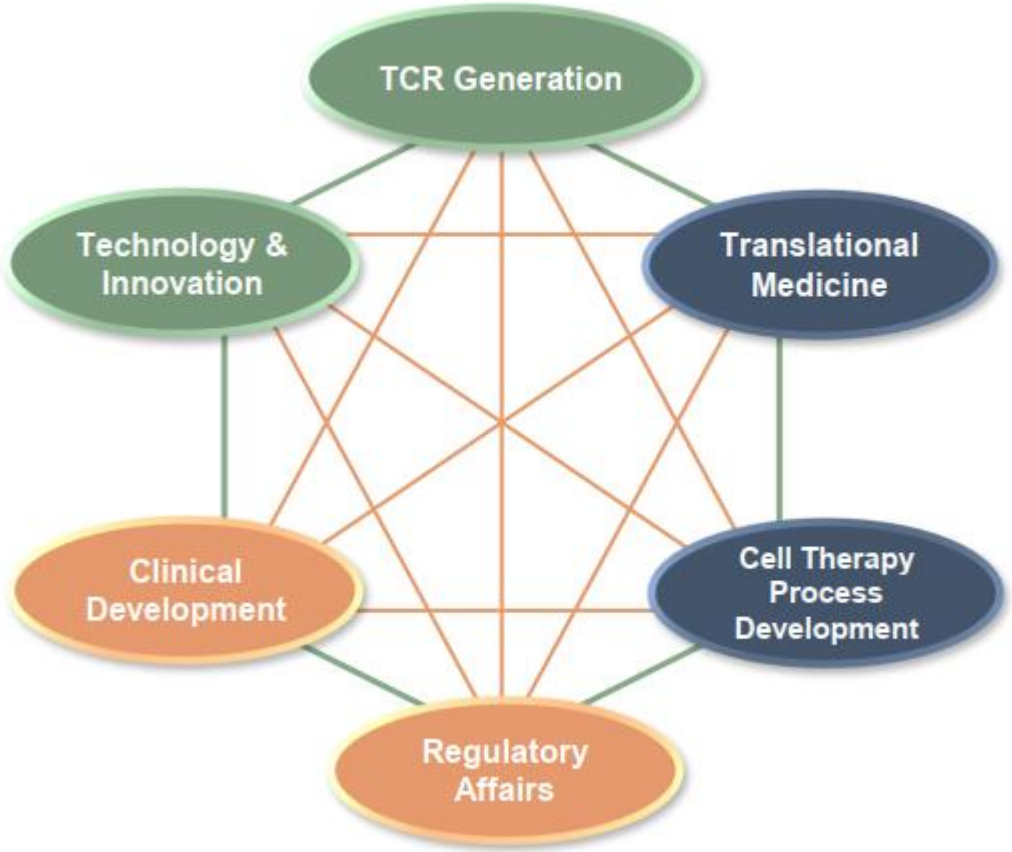

Thank you for your attention