Unleash Immunity

Solid Tumor Strategy

May 2022

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Reprogramming T cells with proven, highly effective TCRs addresses patients with insufficient *endogenous* T cells

Checkpoint therapy works by unleashing *endogenous* T cells

But… >50% of patients don't have potent *endogenous* T cells

Solution: reprogram T cells with proven, highly effective *exogenous* TCRs

Challenge 1: Solid tumors have a hostile tumor microenvironment, leading to short duration of response

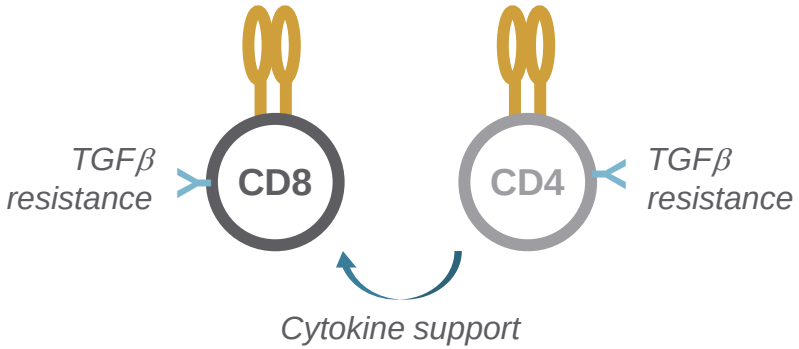
Challenge 1: Short Duration of Response
~3-4 months
Poor T cell persistence

- Most products only include cytotoxic ($CD8^+$) T cells
- Helper ($CD4^+$) T cells not present to provide cytokine support for the cytotoxic T cells
- T cells suppressed by TGFβ in tumor microenvironment

→ Poor T cell persistence → poor duration of response

1st gen TCR-T	ORR of ~30-50% but short duration of response

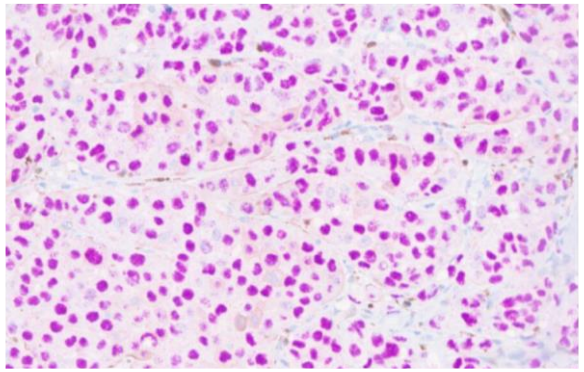
Solution: Enhanced TCR-Ts
Engage $CD4^+$ T cells (add CD8 co-receptors)
Make T cells resistant to TGFβ



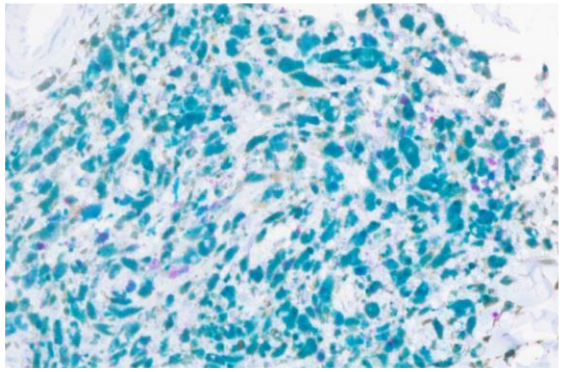
DN-TGFβRII	TCR-T cells resistant to TGFβ
CD8α/β	Engage both cytotoxic and helper T cells
1st gen TCR-T	ORR of ~30-50% but short duration of response

Challenge 2: Solid tumors are heterogeneous, leading to relatively few complete responses

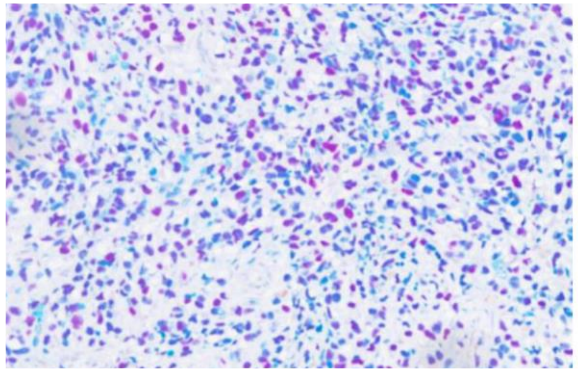
PRAME



MAGE-C2

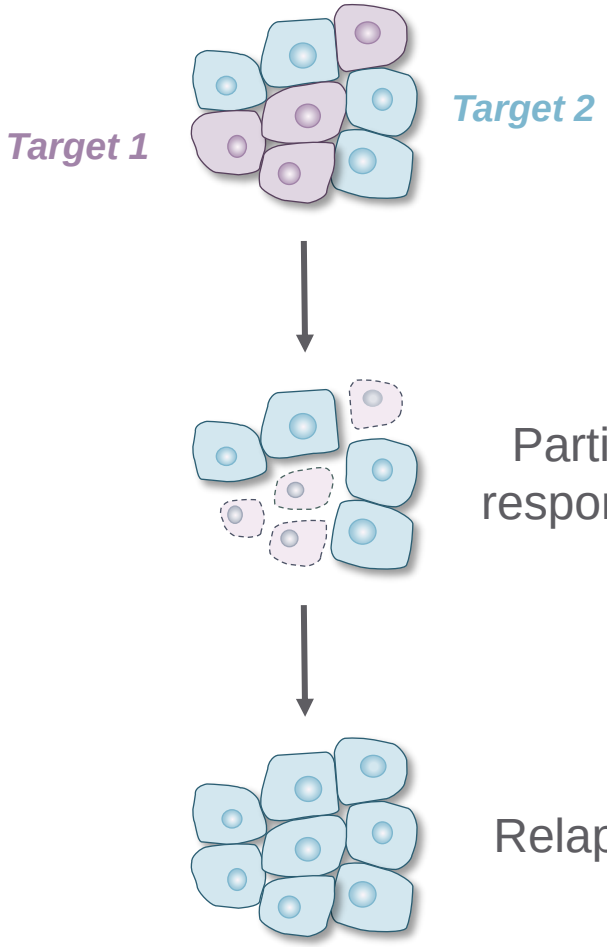


PRAME + MAGE-C2



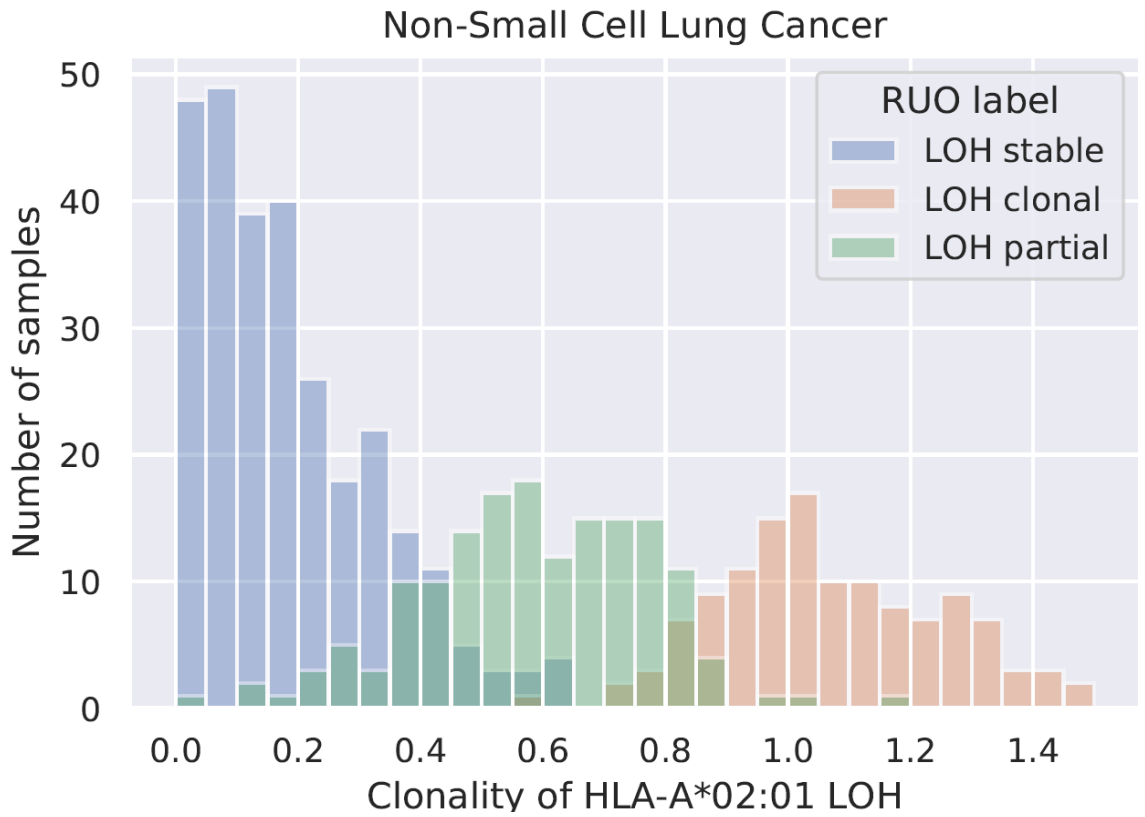
PRAME and MAGE-C2 are often expressed in distinct cells

SOLID TUMOR



Solid tumors also exhibit heterogeneity with respect to HLA loss of heterozygosity (LOH)

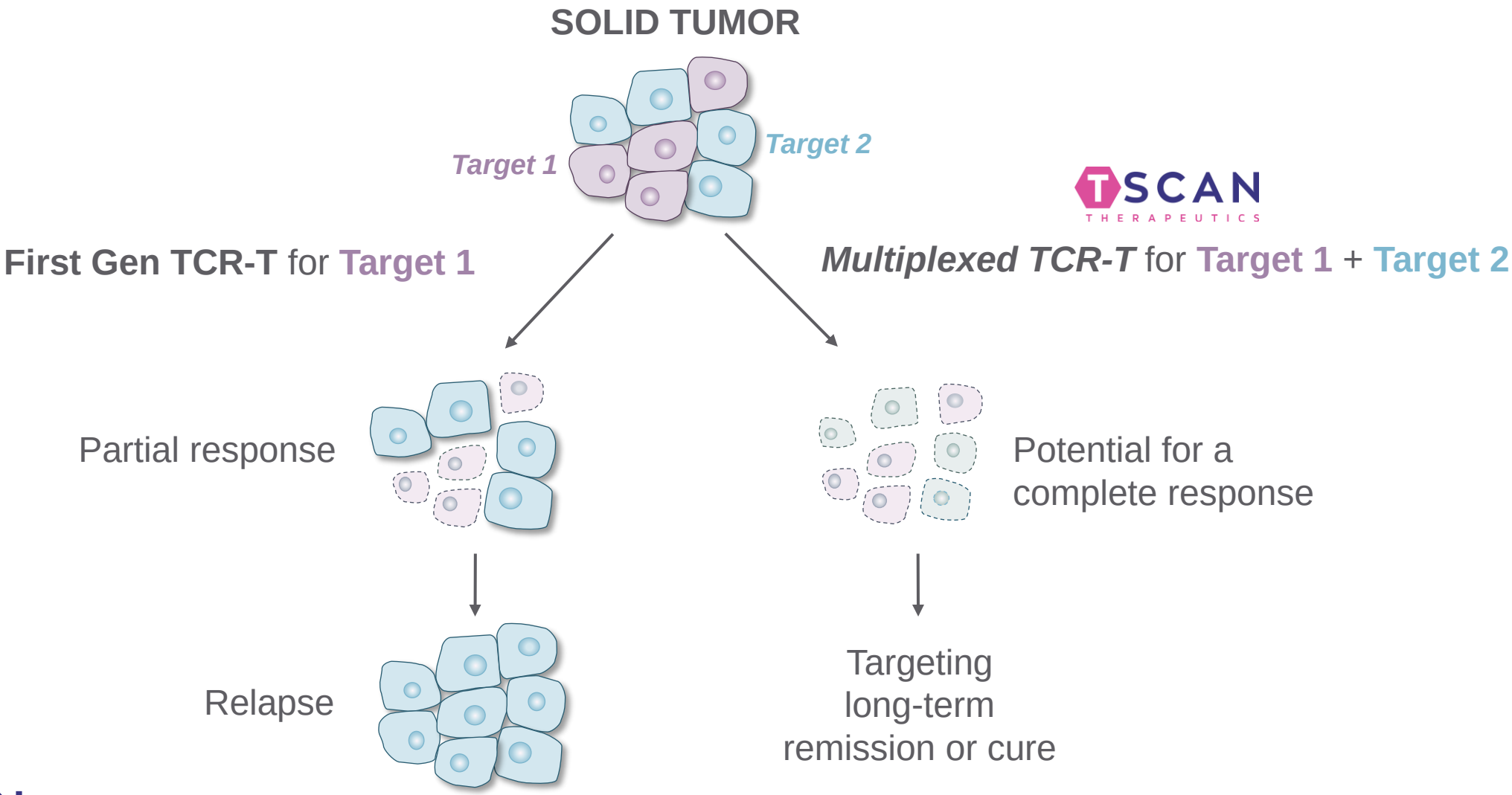
- Most genomic analysis tools are focused on point mutations
- Point mutations in HLA genes are rare (<5% of tumors)
- New genomic methods enable detection of clonal and subclonal HLA loss
- ***17% of all solid tumors*** have clonal HLA loss
- ***Up to 40% of NSCLC*** samples have clonal (~15%) or subclonal (~25%) HLA loss



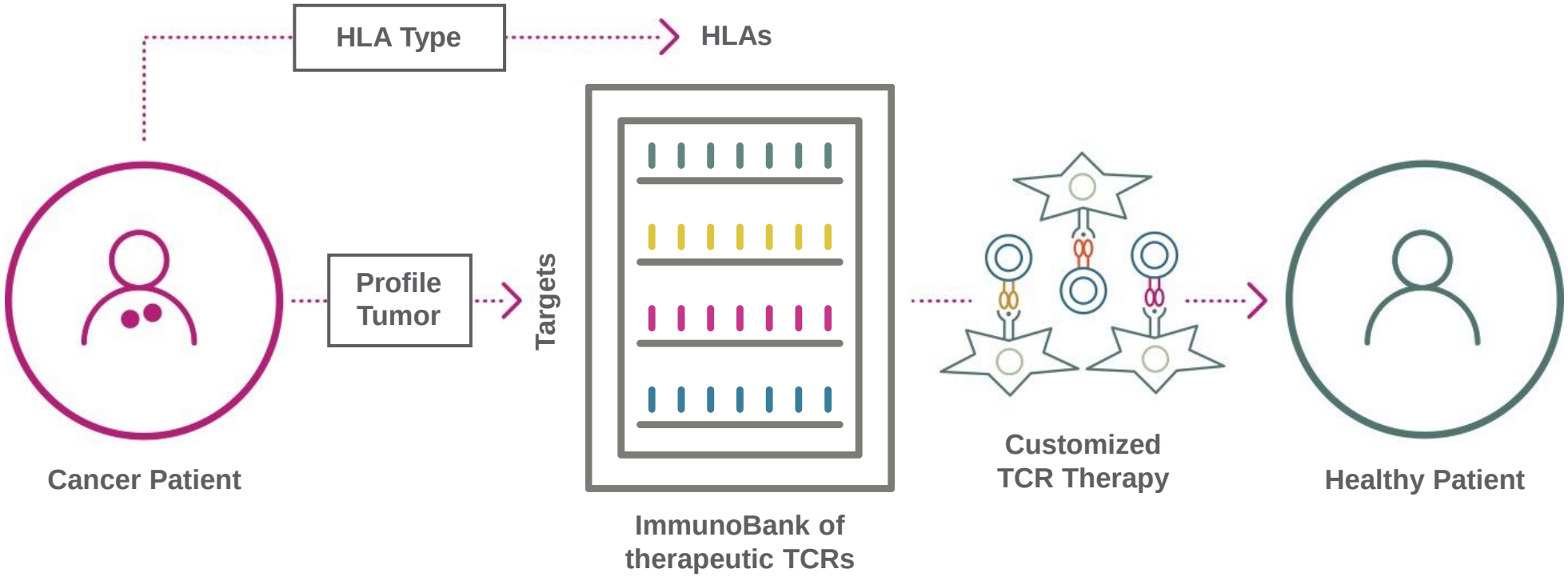
McGranahan, 2017, *Cell*
Montesion, 2021, *Cancer Disc*

Data generated at Tempus

Solution: Multiplexed TCR-T cell therapy is designed to overcome the problem of solid tumor heterogeneity

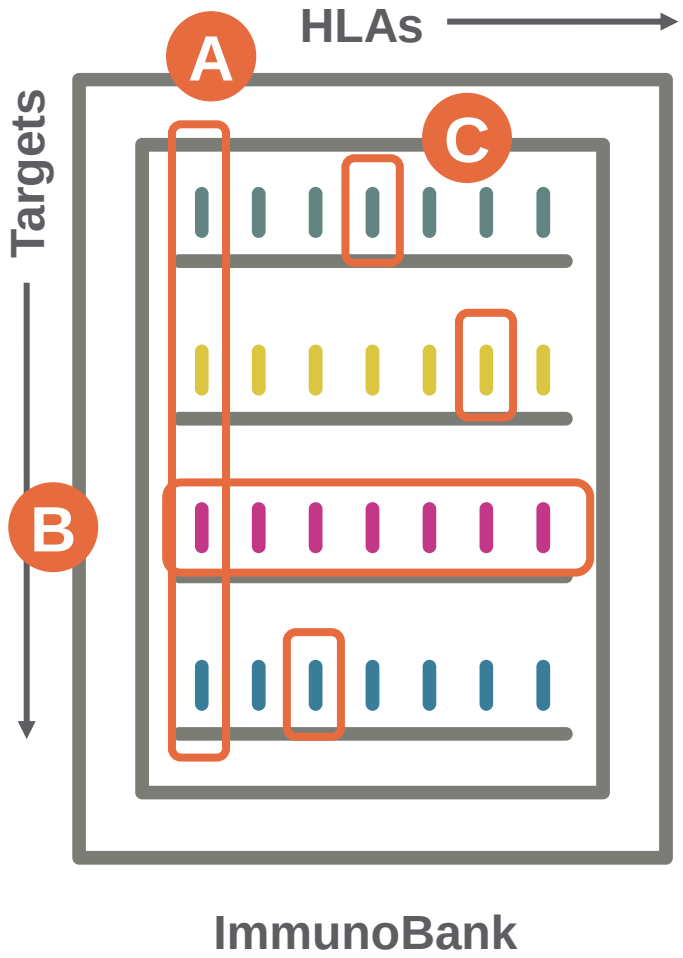


ImmunoBank of TCRs enables customized, off-the-shelf, multiplexed TCR-T



Multiplexed TCR-T may overcome **heterogeneity of target expression** and **HLA loss of heterozygosity**

TScan is addressing tumor heterogeneity by populating the ImmunoBank with proven, highly active TCRs

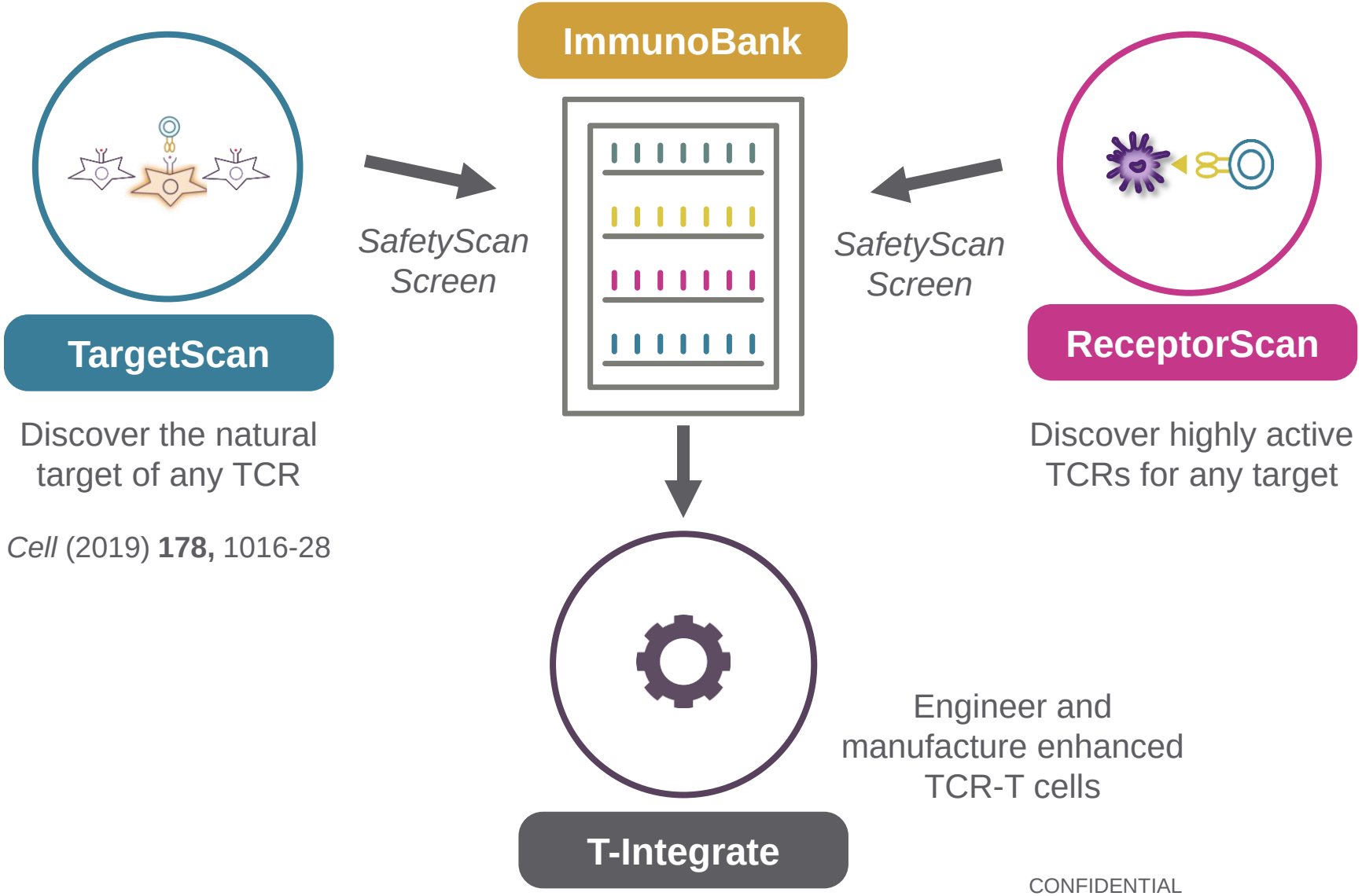


A Multiplexing across targets addresses the problem of tumor target heterogeneity

B Multiplexing across HLAs prevents resistance due to HLA loss of heterozygosity

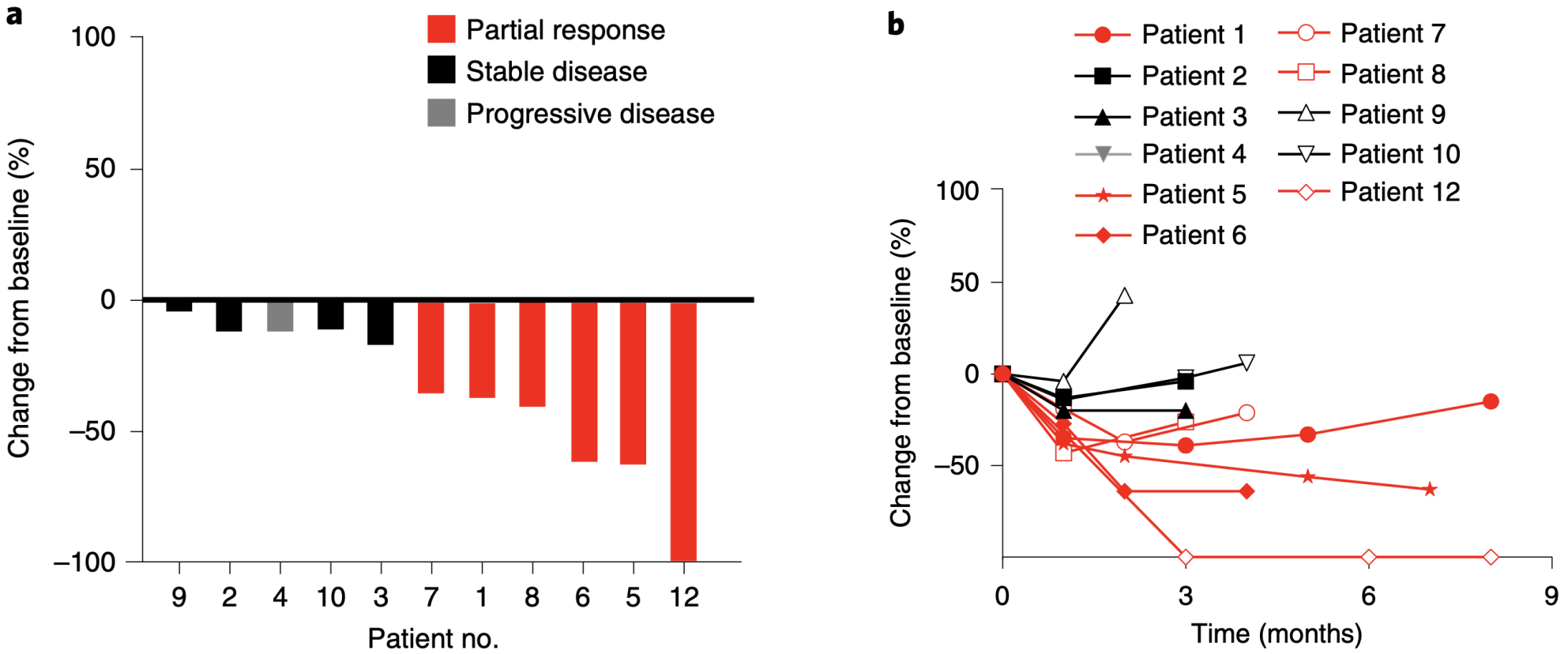
C Multiplexing across both targets and HLAs provides a potential solution to both problems

Platform enables discovery and manufacturing of a broad range of enhanced TCR-T cell therapy candidates



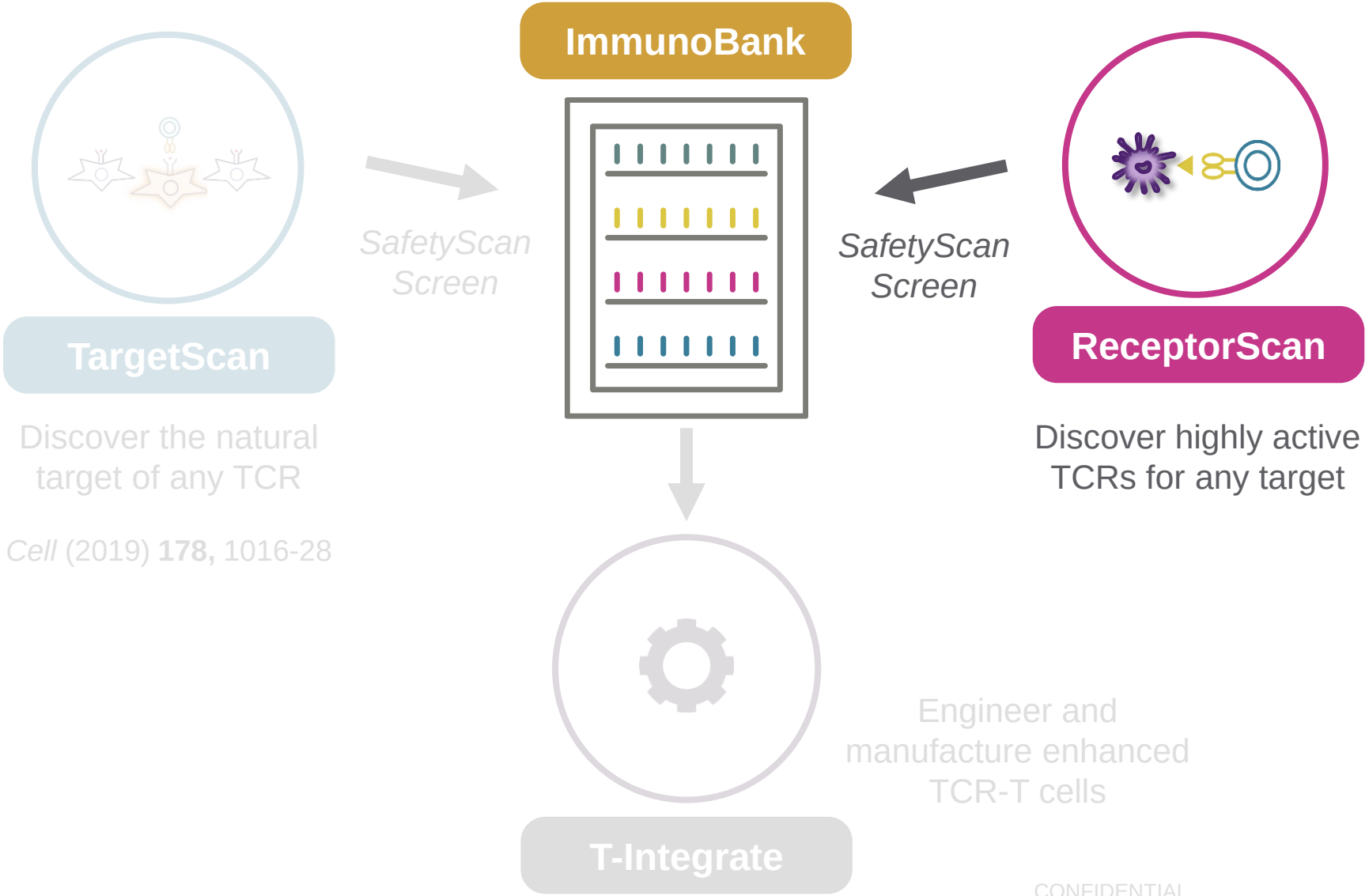
Discovery of TSC-200-A02: A natural HPV16 E7-specific TCR-T cell therapy candidate for the treatment of HPV-positive solid tumors

To date, the most impressive TCR-T results in solid tumors were achieved by targeting E7 of HPV16

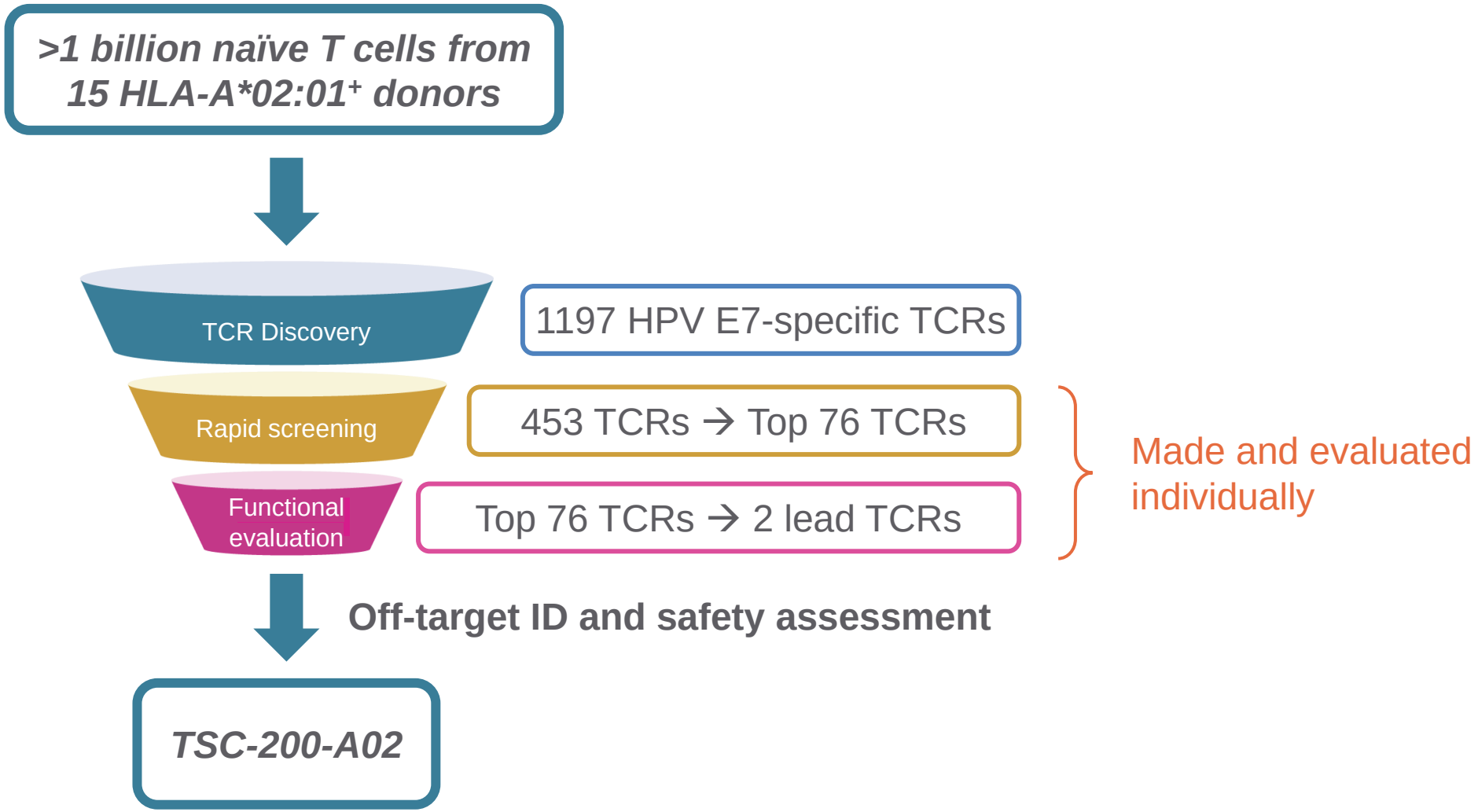


Nagarsheth NB, …, Hinrichs CS (2021) *Nature Medicine,* **27**, 419-425.

TSC-200-A02 was discovered using TScan's ReceptorScan platform



TSC-200-A02 was identified from >1 billion T cells using ReceptorScan platform

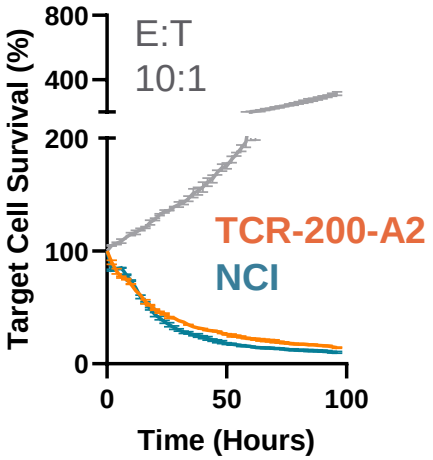


TScan's TCR-200-A02 shows comparable activity to NCI TCR

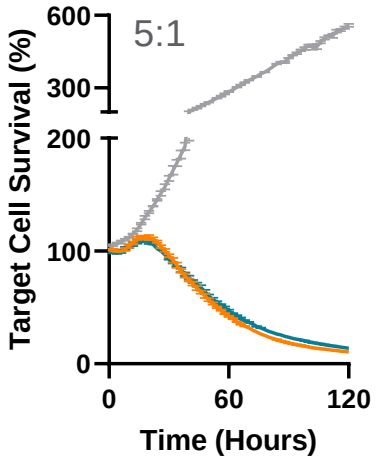
HPV16+, HLA-A*02:01-positive

NEGATIVE CONTROLS

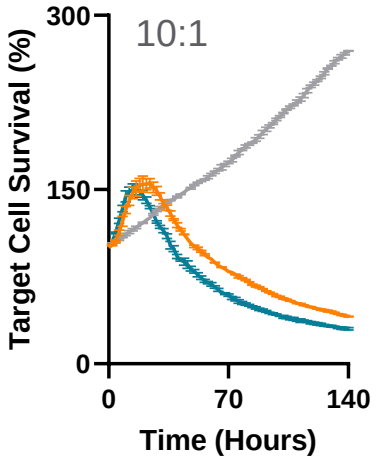
CaSki



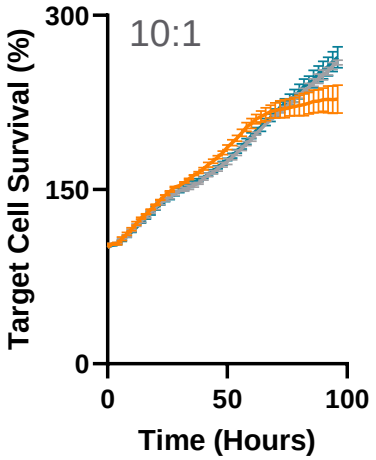
SCC152



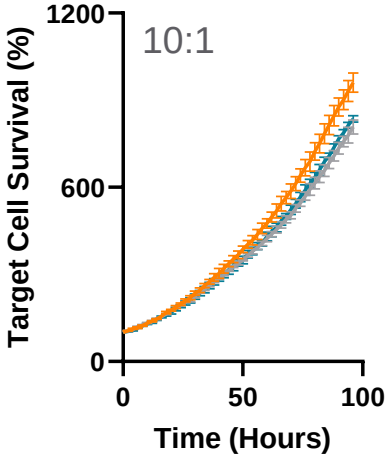
SCC090



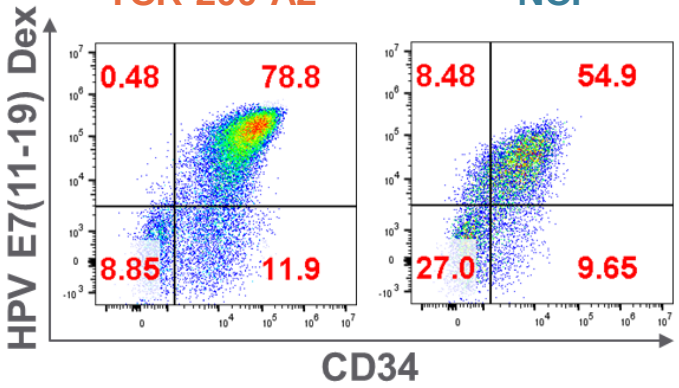
SiHa
(HLA-A*02:01-neg)



NCI-H1792
(HPV16-neg)



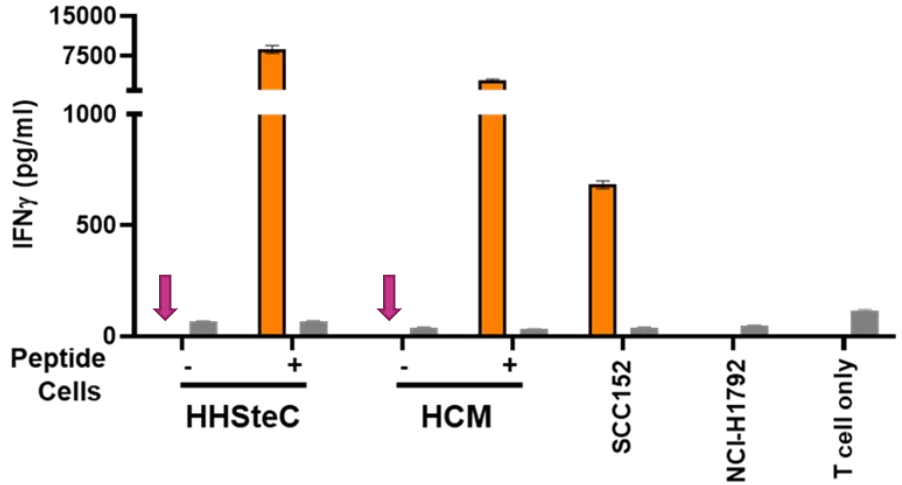
TCR-200-A2 NCI

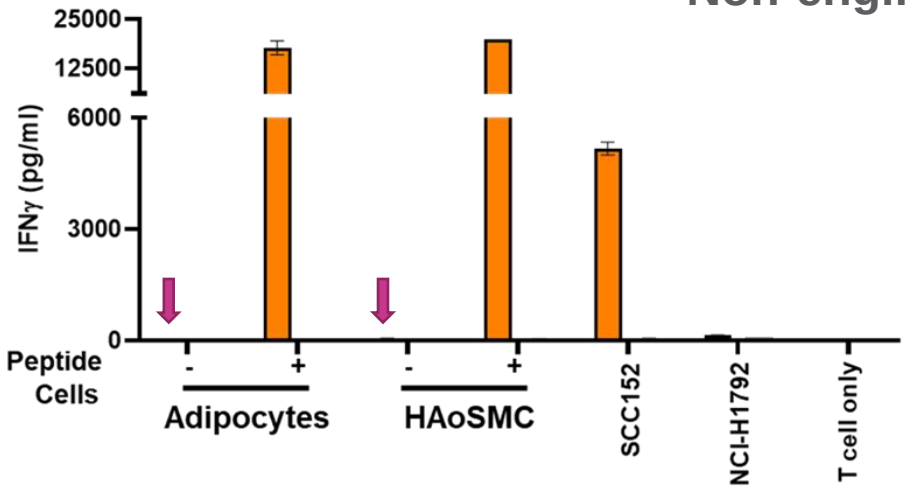


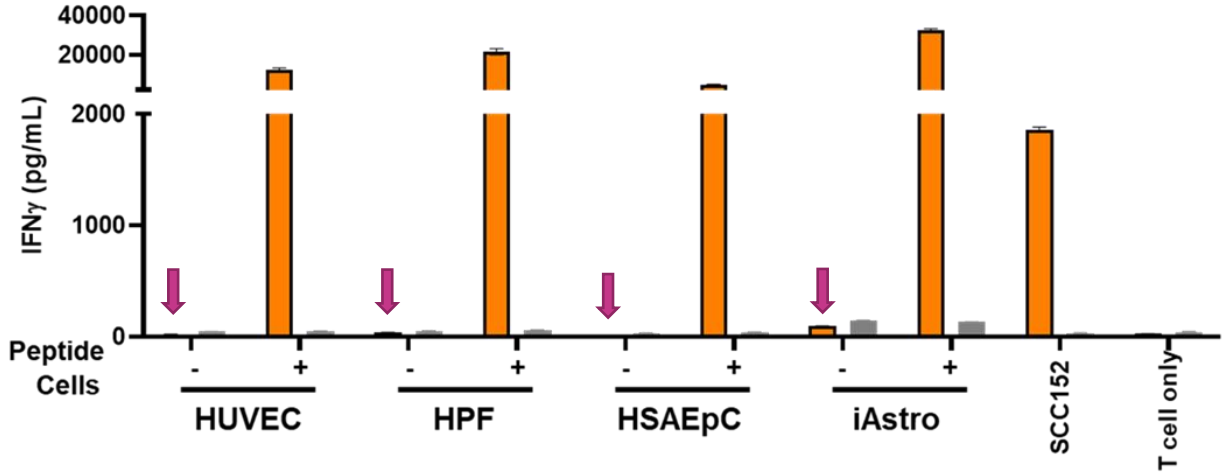
TSC-200-A2 is efficiently expressed in T cells

TCR-200-A02 shows *no reactivity* to any normal human cells

TSC-200-A2
Non-engineered T cells

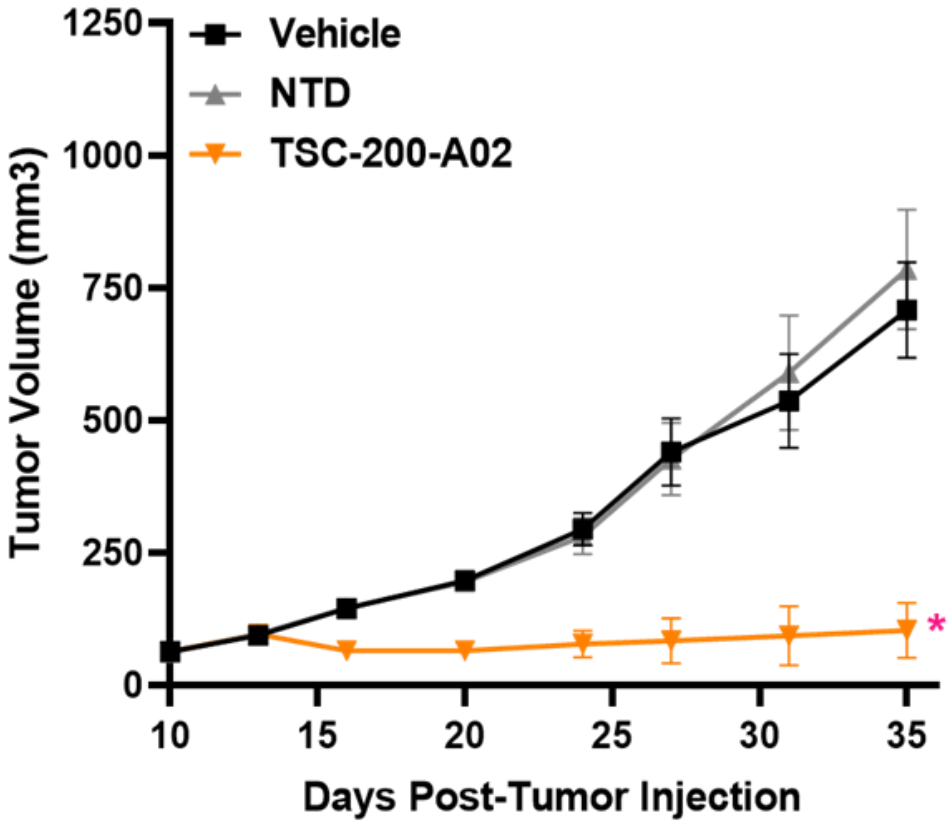


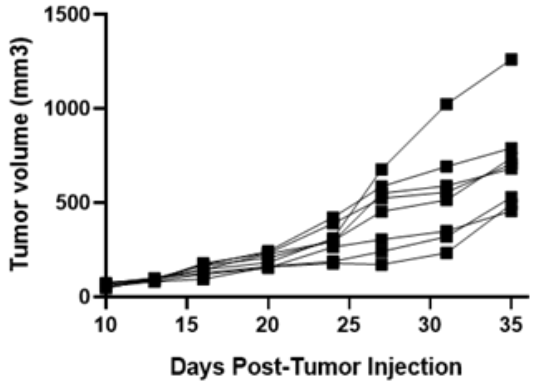


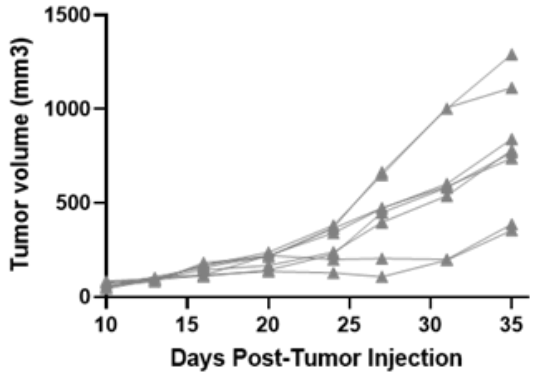


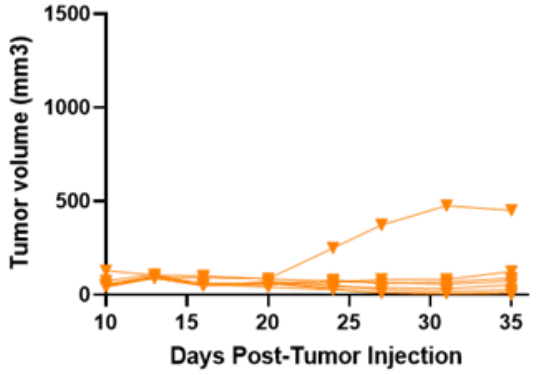
Abbreviation	Cell Type
HHSteC	Human Hepatic Stellate Cells
HCM	Human Cardiac Myocytes
HAoSMC	Human Aortic Smooth Muscle Cells
HUVEC	Human Umbilical Vein Endothelial Cells
HPF	Human Pulmonary Fibroblasts
HSAEpC	Human Small Airway Epithelial Cells
iAstro	iPS cell-derived Astrocytes

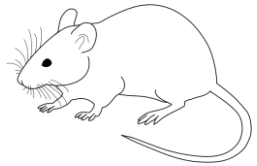
TSC-200-A02 eliminates established tumors in a mouse model of HPV-positive cancer





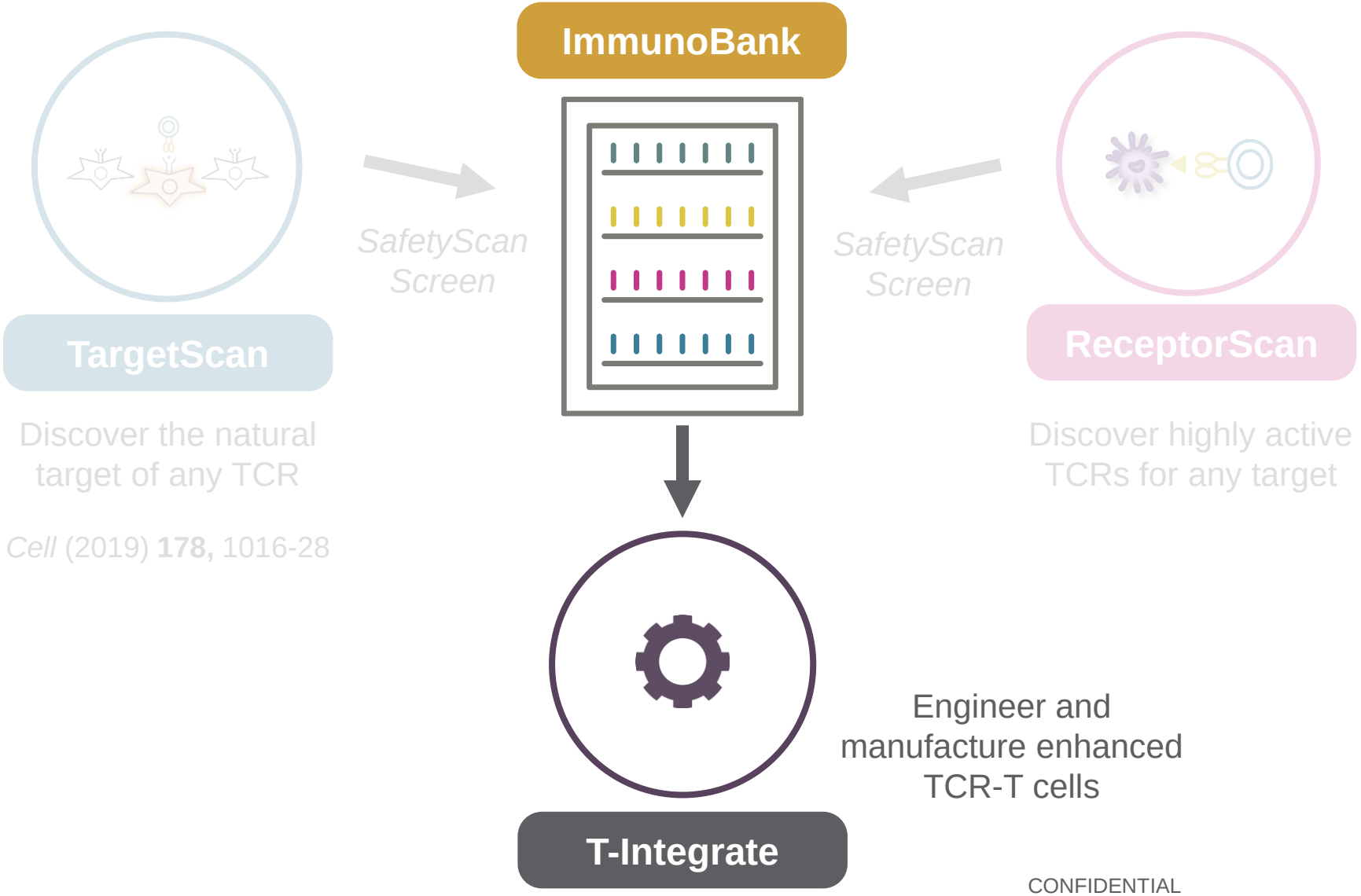




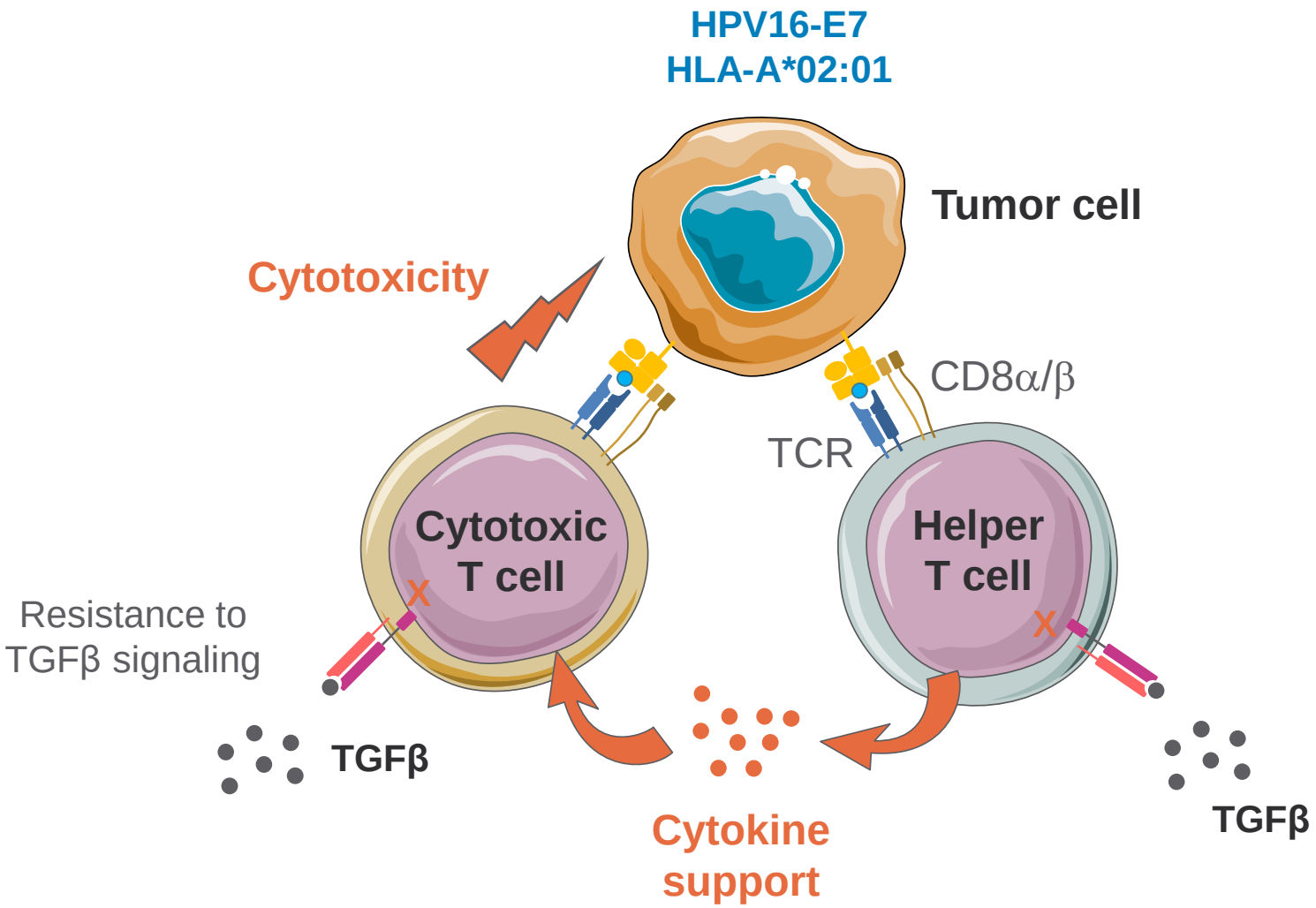


SCC152 (HPV16+, HLA-A*02:01+)

TScan's T-Integrate platform enables manufacturing *enhanced* TCR-T cell products



TSC-200-A02 is an enhanced TCR-T cell product designed to increase durability of response

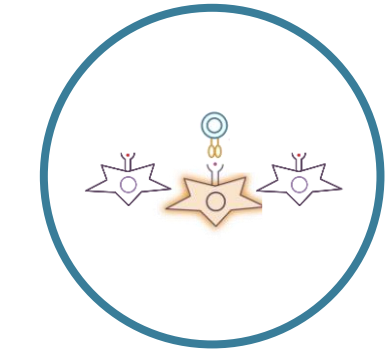


Building on 1st generation TCR-T

DN-TGFβRII	TCR-T cells resistant to TGFβ
CD8α/β	Engage both cytotoxic and helper T cells
1st gen TCR-T	ORR of ~30-50% but short duration of response

Discovery of a novel C*07:02-restricted epitope on MAGEA1 and preclinical development of an enhanced TCR-T cell therapy candidate for the treatment of solid tumors

TSC-204-C07 was discovered using TScan's TargetScan platform



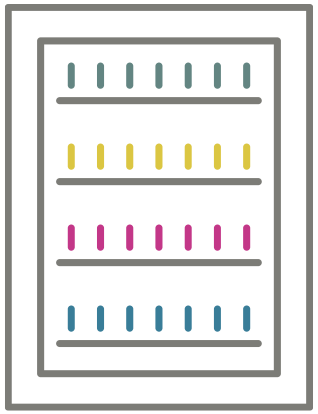
TargetScan

Discover the natural target of any TCR

Cell (2019) **178,** 1016-28

SafetyScan Screen

ImmunoBank



SafetyScan Screen

ReceptorScan

Discover highly active TCRs for any target

Engineer and manufacture enhanced TCR-T cells

T-Integrate

Clinically active TCRs were identified from Head & Neck cancer patients responding to immunotherapy

Focus on patients with exceptional responses to immunotherapy

Ipilimumab
+ Nivolumab

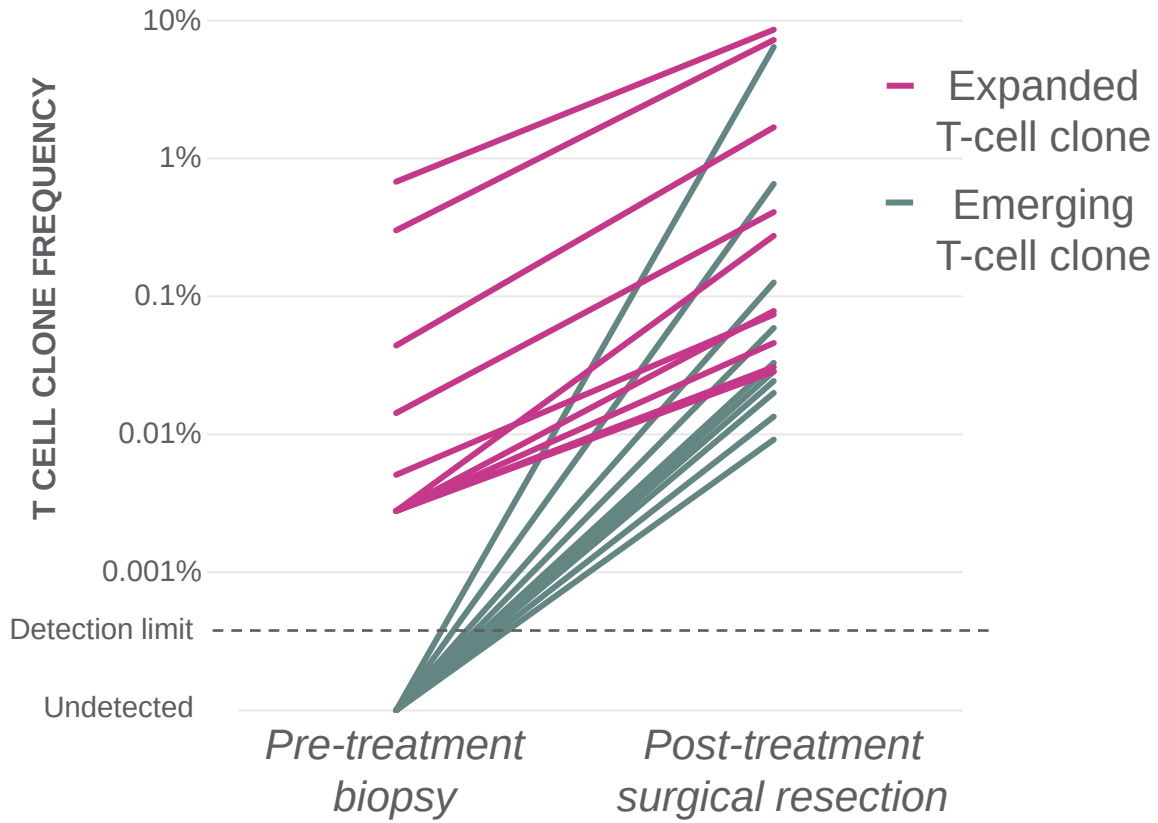
Pathological Response

Pre-treatment biopsy

Post-treatment surgical resection

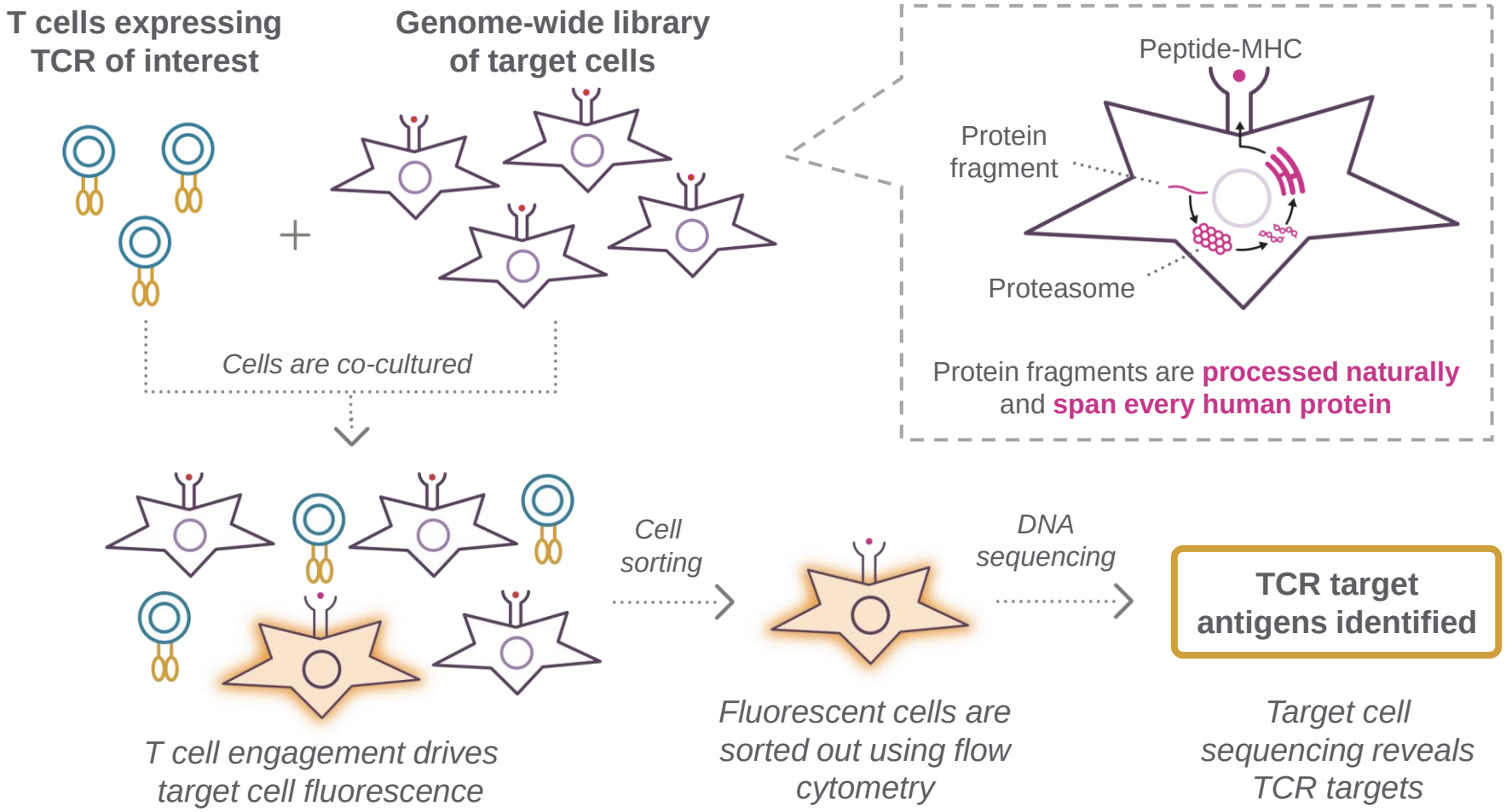
Single cell TCR sequencing

Patient with a complete response



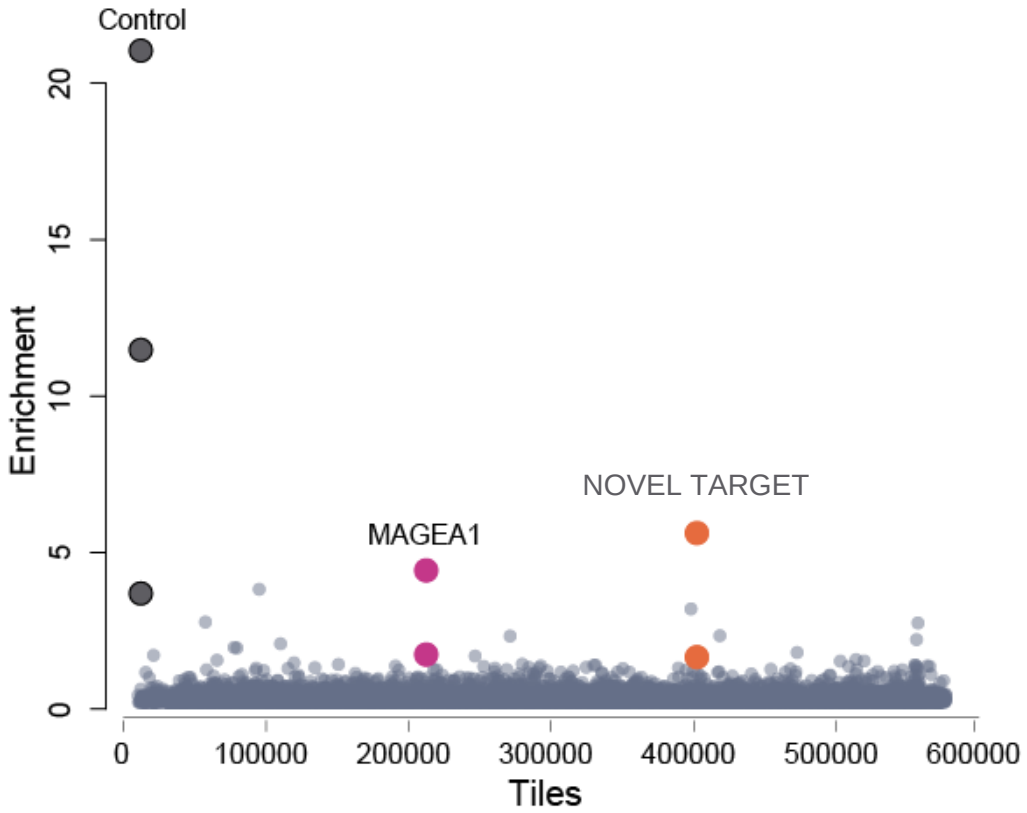
Schoenfeld J et al (2020) *JAMA Oncol*, **6**, 1563

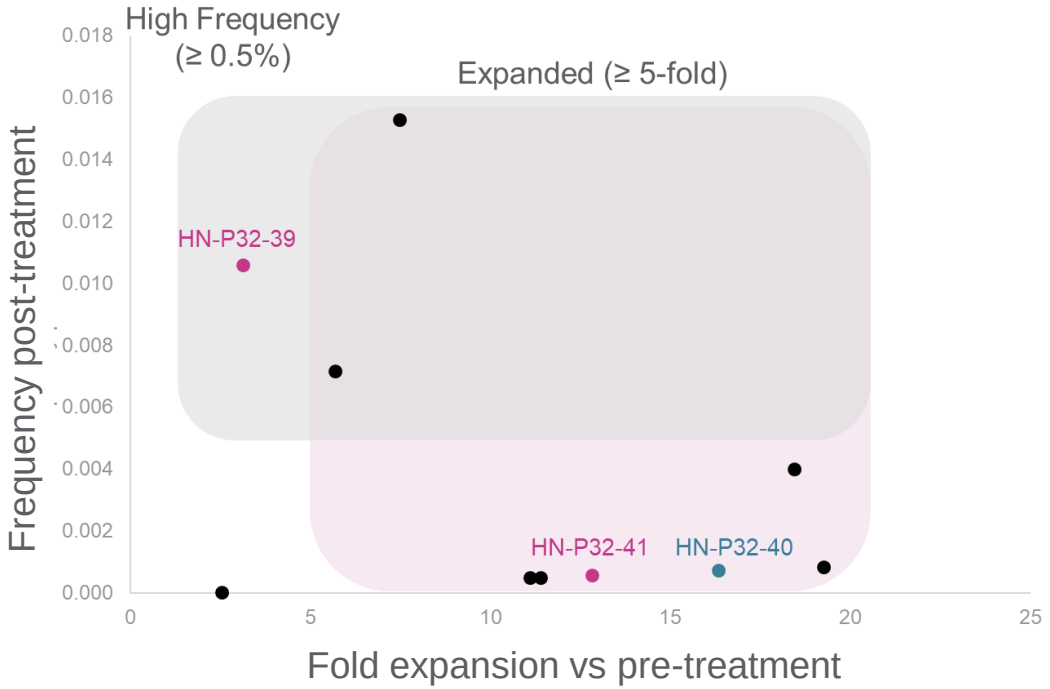
TScan's proprietary platform – TargetScan – enables identification of the natural targets of any T cell receptor



Multiplexed screen shows convergent recognition of a novel C*07:02-restricted epitope on MAGE-A1

- Patient 32 had 60% reduction in primary tumor size following anti-PD1 and anti-CTLA4 therapy

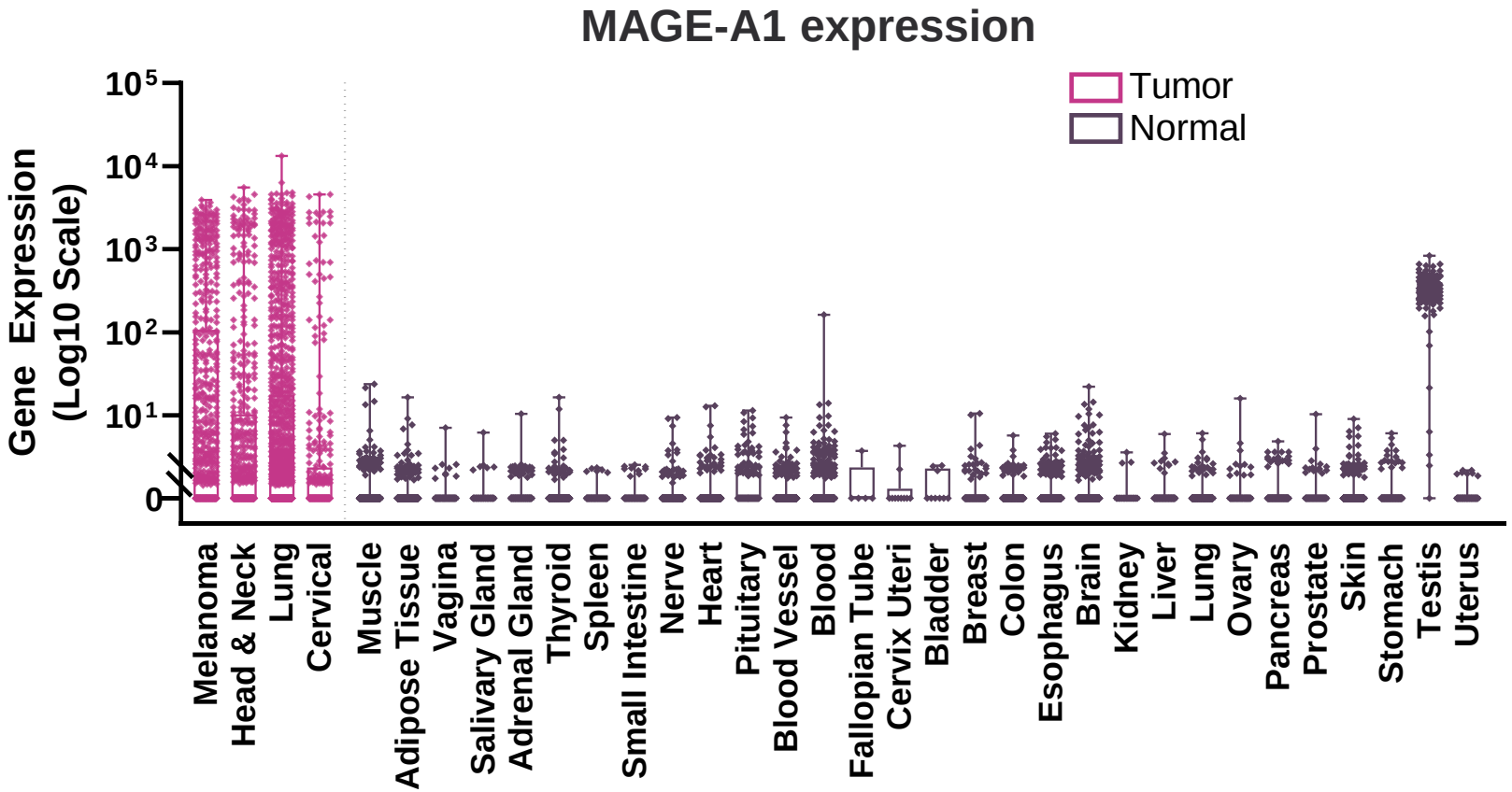




TCR	Target	HLA
HN-P32-39	MAGEA1	C*07:02
HN-P32-41		

MAGE-A1 is specifically expressed in cancer tissue

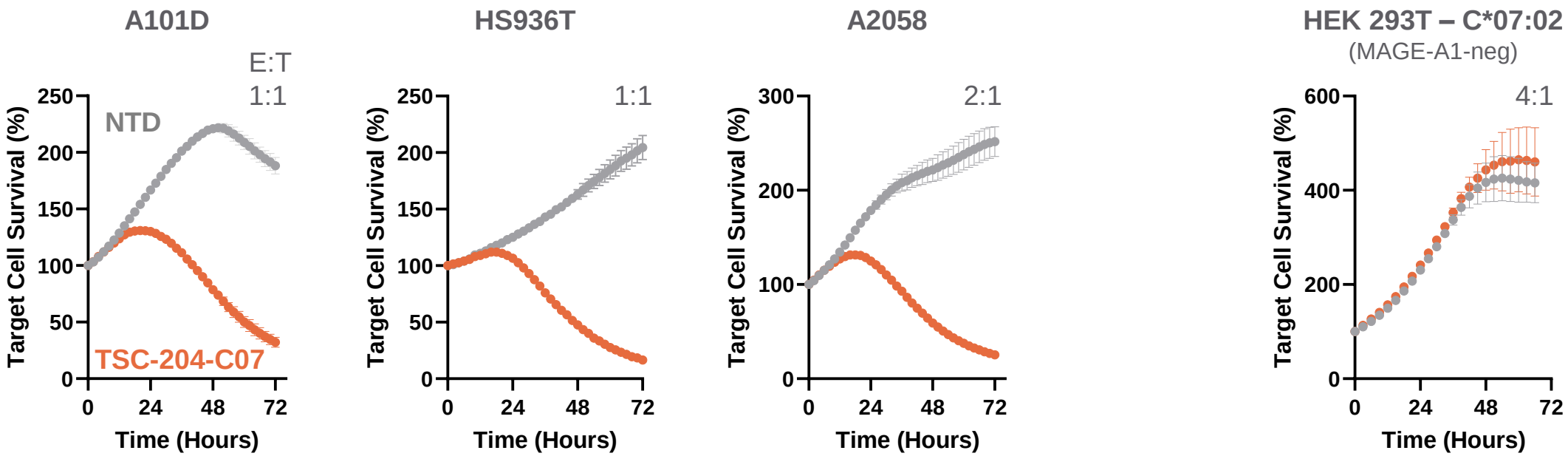
- Melanoma-associated antigen A1 is a member of the MAGE-A gene family
- Not expressed in normal tissues, except testis, and selectively expressed in multiple tumor types
  - 50% of metastatic melanomas, 46% of NSCLC
  - High expression correlated with shorter patient survival



TSC-204-C07 shows strong cytotoxic activity *in vitro*

MAGE-A1, HLA-C*07:02

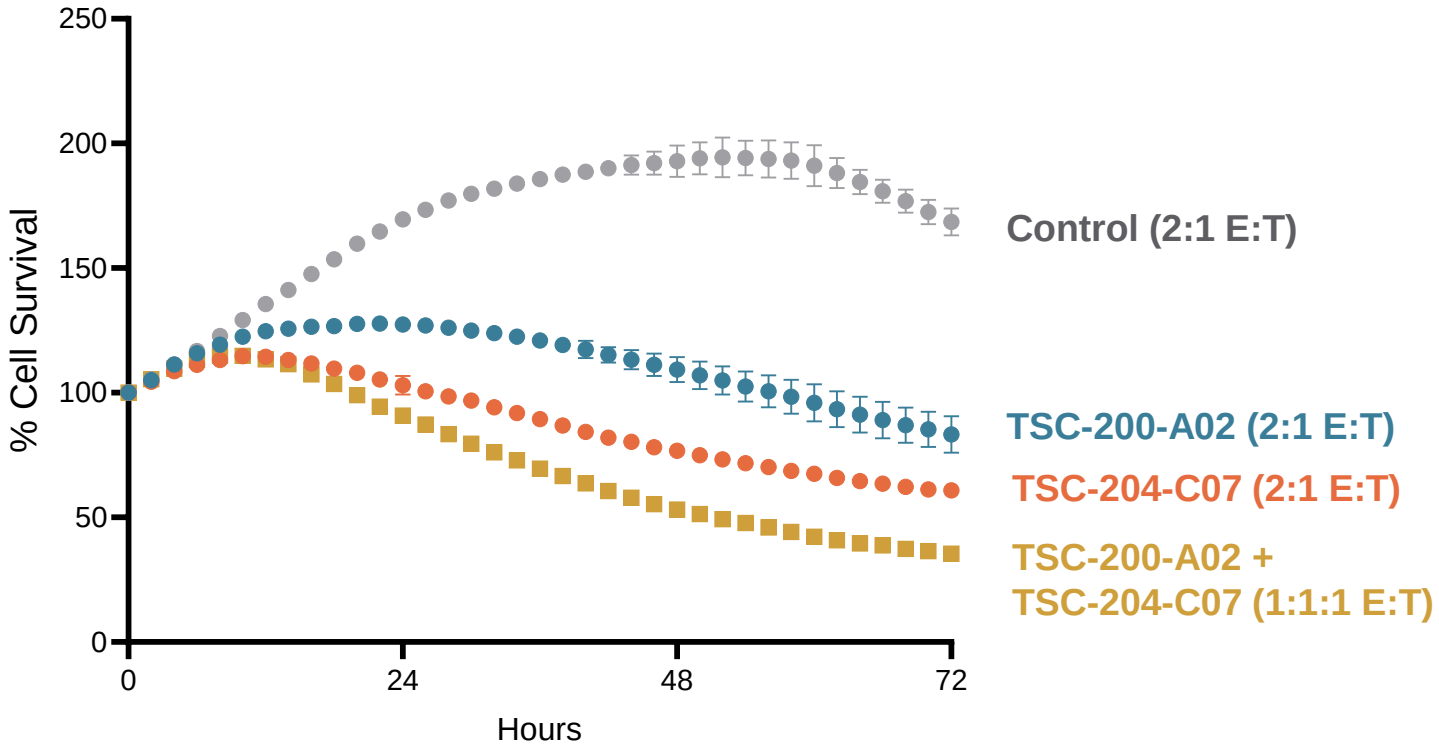
NEGATIVE CONTROL

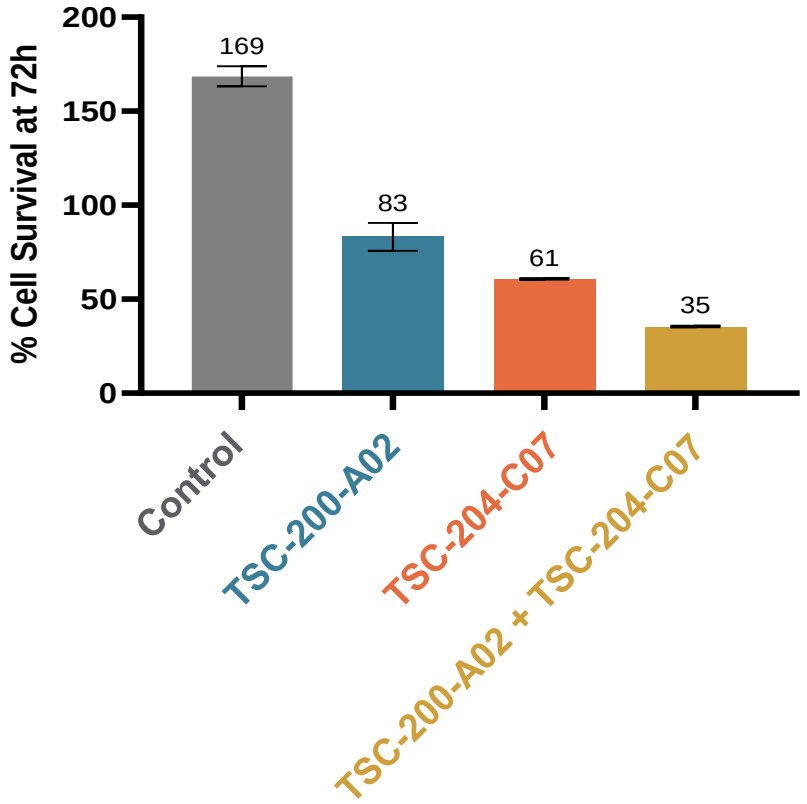


MAGE-A1

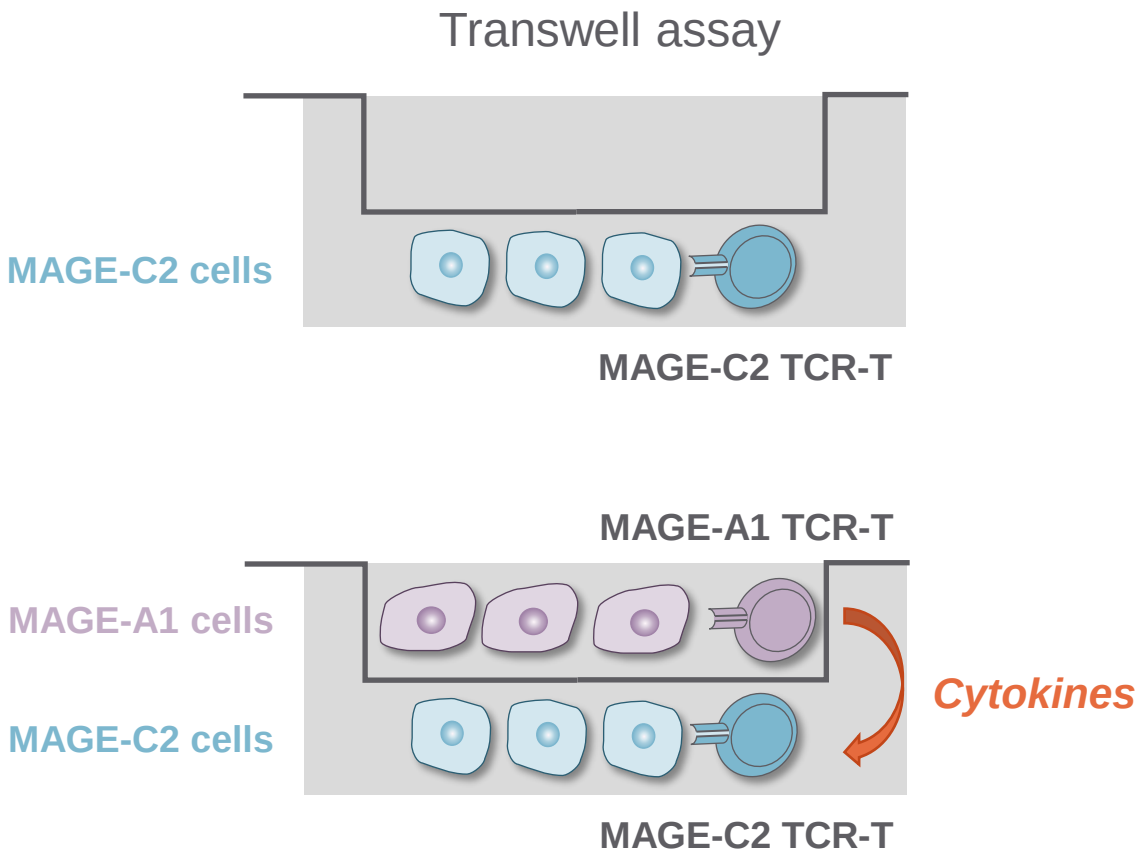
Multiplexed TCR-T Therapy: A Strategy to Enhance the Efficacy of Engineered Adoptive Cell Therapy

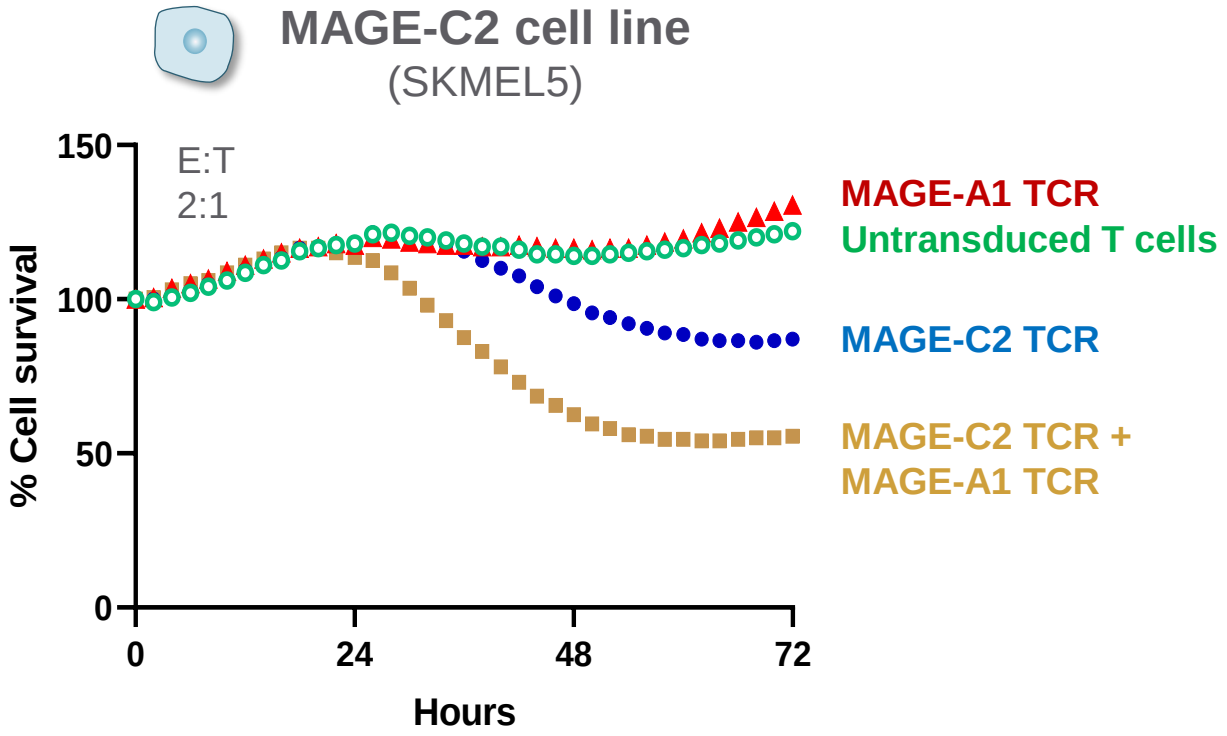
Multiplexed TCR-T shows unexpected synergy against a heterogeneous population of target cells





Multiplexing TCR-Ts has synergistic anti-tumor activity due to cytokine-mediated enhancement





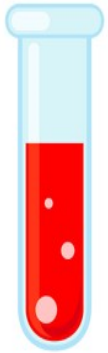
Patients will be selected based on target expression and HLA loss of heterozygosity (LOH)

1. Germline HLA genotyping

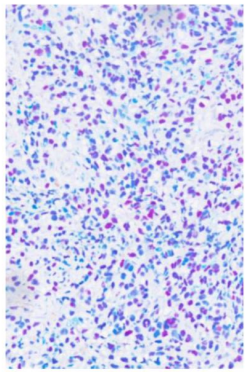
2. Tumor target testing by IHC/ ISH

3. Tumor genomics for HLA LOH

4. TCR-T HLA selection



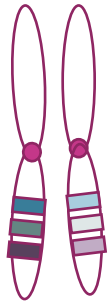
Targeted alleles positive



Targeted alleles negative

Screen failed

Targets present



Targets absent

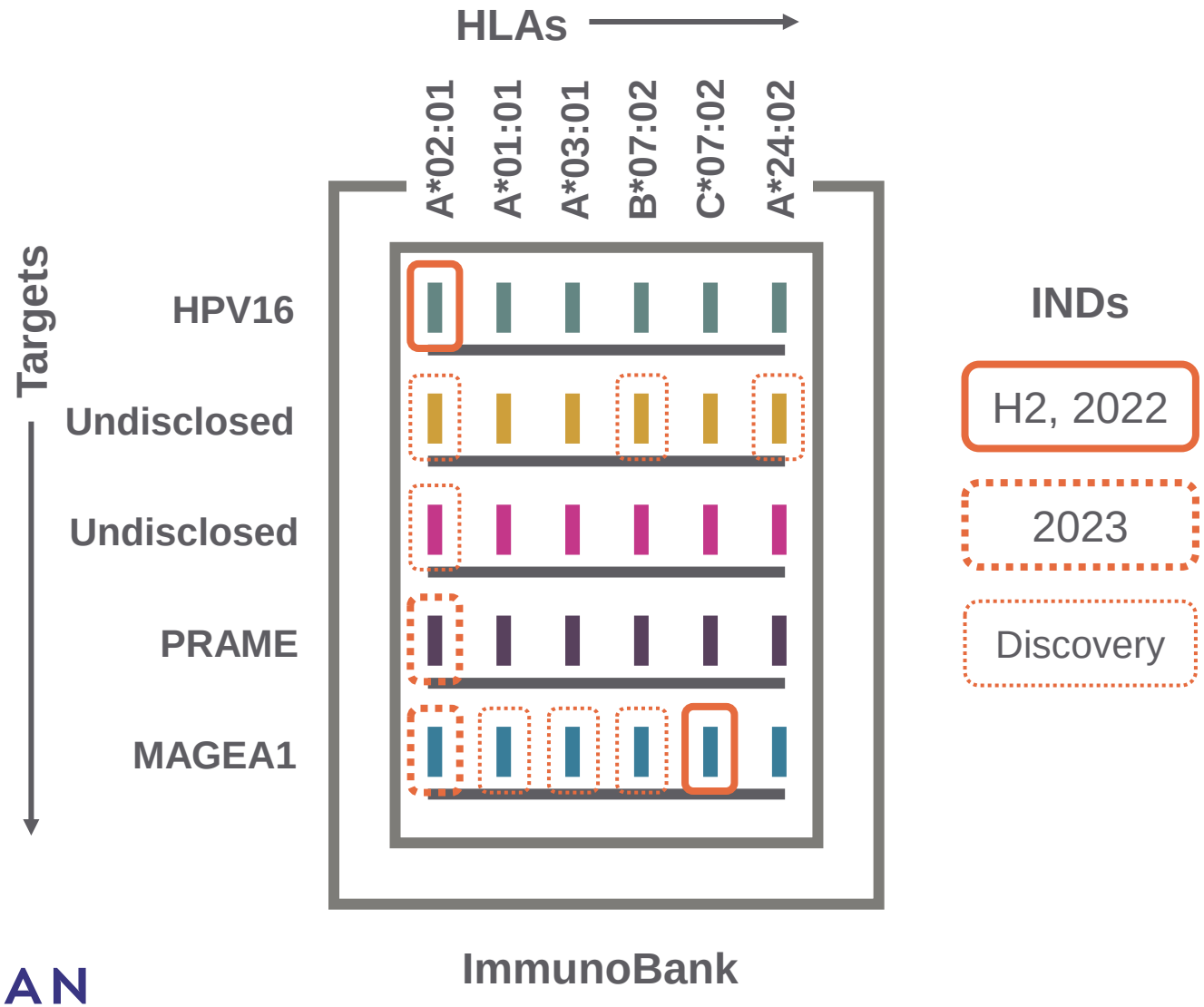
LOH present

Target HLAs on intact haplotype - cannot be lost

LOH absent

Target HLAs on opposite haplotypes - avoid secondary LOH

Expanding TCR-T options substantially increases patients eligible for multiplexed therapy

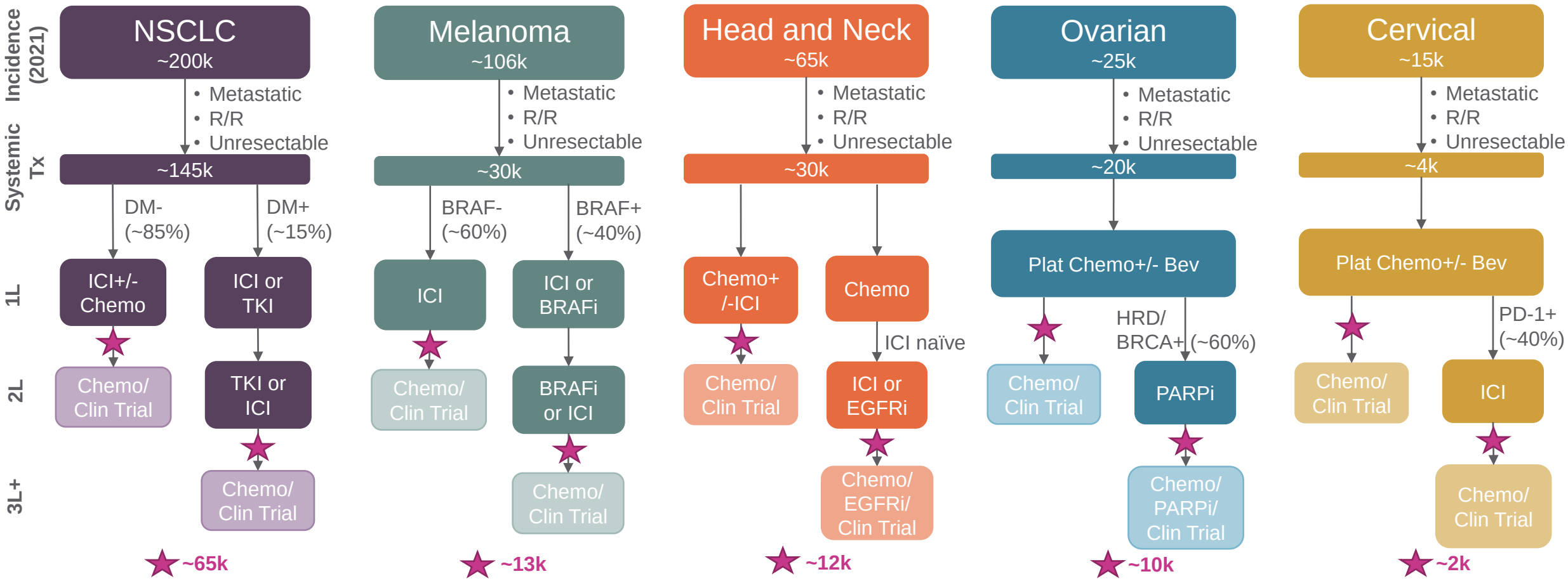


INDs

- H2, 2022
- 2023
- Discovery

TCRs covering multiple antigens and HLA alleles will enable 50-75% of patients in chosen indications to receive multiplexed therapy

Prioritized indications provide significant market opportunity



★ **Potential TCR-T Cell Therapy Entry Point**

~102k currently addressable patient population in selected indications in the US

R/R: Relapsed/Refractory; DM: Driver Mutation; ICI: Immune Checkpoint Inhibitors; TKI: Tyrosine Kinase Inhibitors/Targeted Therapies; HRD: Homologous Repair Deficient
Sources: SEER, Kantar Report, Chao et al.

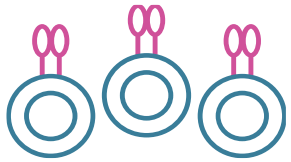
Key Opinion Leader
Kai Wucherpfennig, MD, PhD

TCR-T addresses the limitations of CAR-T and TIL therapy

CAR-T

Engineering T cells with a synthetic receptor

- ✓ Defined target
- ✓ Homogenous cell population for predictable potency
- ✗ Poor solid tumor penetration
- ✗ Limited to cell surface antigens



TCR-T

Engineering T cells to express natural T cell receptors

- ✓ Defined target(s)
- ✓ Mixed, but engineered cell population for predictable potency
- ✓ Promising efficacy in solid tumors
- ✓ Full range of targets seen by immune system

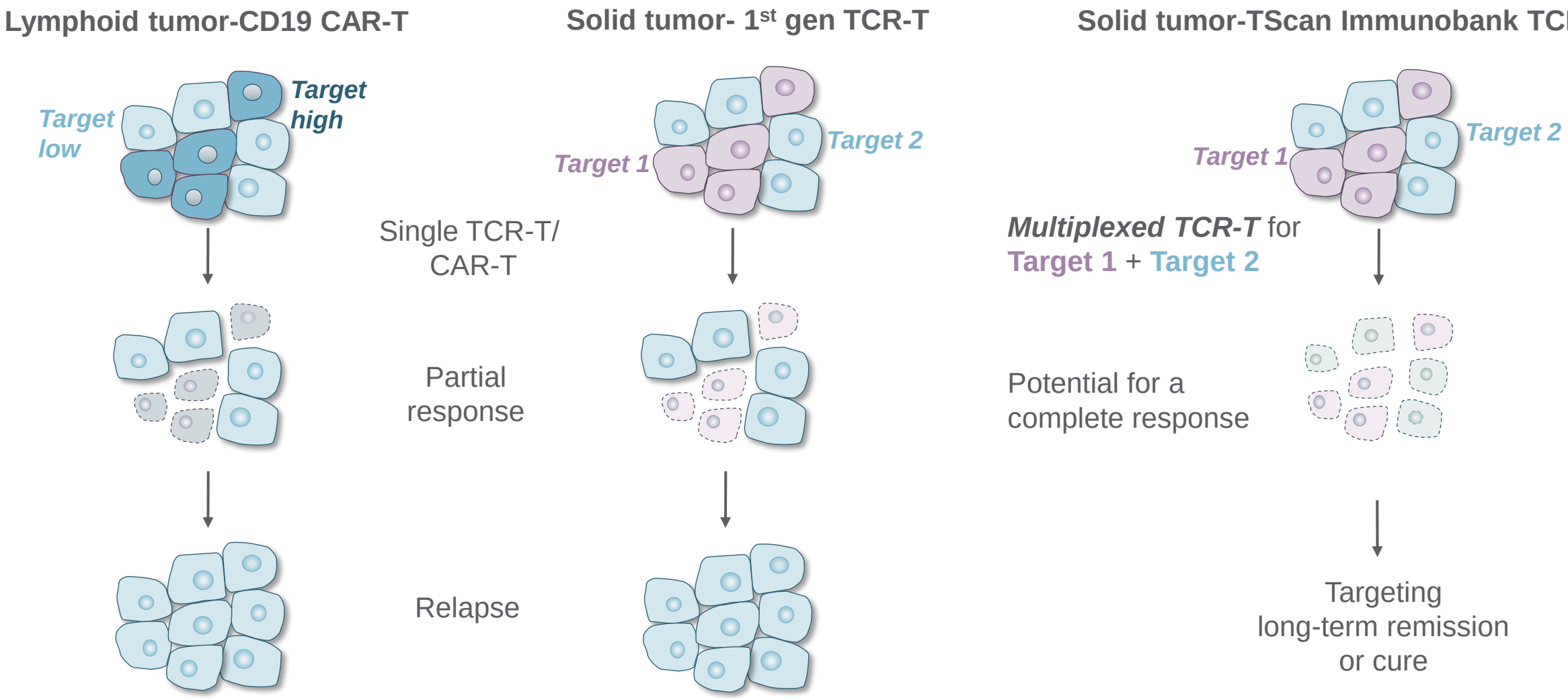
TIL

Expanding and rejuvenating a patient's existing T cells

- ✗ Unpredictable responses due to undefined targets
- ✗ Heterogeneous cell population: variable potency
- ✓ Proven but variable efficacy in solid tumors
- ✓ Full range of targets seen by immune system

TSCAN THERAPEUTICS

Antigen escape is a key limitation of single CAR-Ts or TCR-Ts due to target heterogeneity



Q&A