Multiplexed TCR-T cell therapy for solid tumors

November 14, 2022

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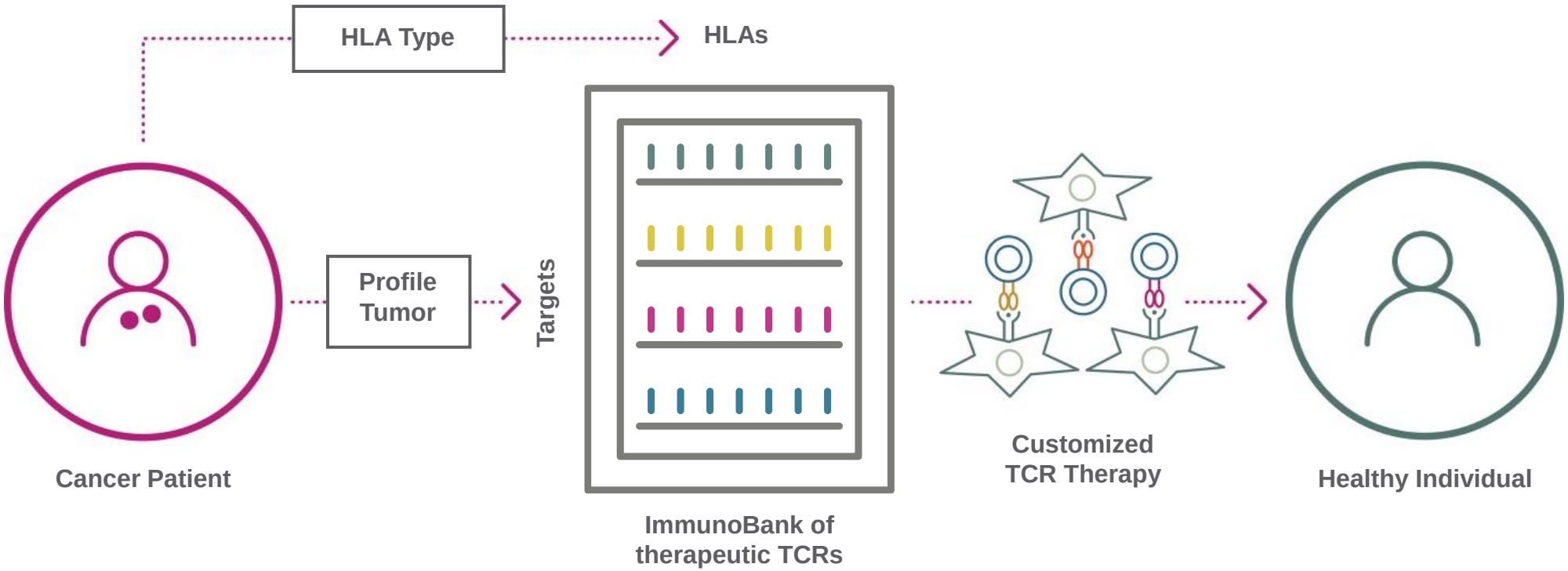
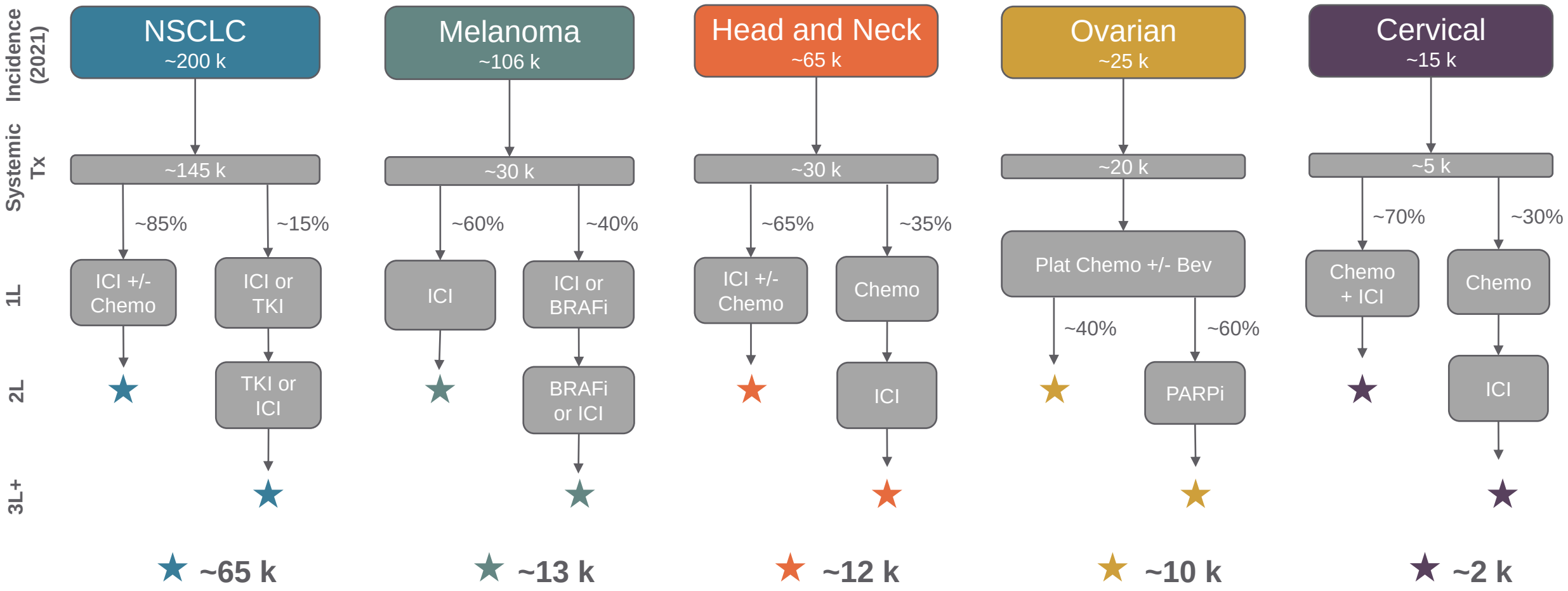
TScan's solid tumor strategy



Prioritized indications provide significant market opportunity



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

ICI: Immune Checkpoint Inhibitors; TKI: Tyrosine Kinase Inhibitors/Targeted Therapies
Sources: SEER, Kantar Report, Chao et al.

Engineering T cells with effective TCRs provides a solution for patients with inadequate endogenous T cells

T Cell Therapies for Cancer

Endogenous T cells

- Checkpoint inhibitors
- TIL therapy
- Cancer vaccines

Reactivate defective T cells

Expand existing T cells

Reprogrammed T cells

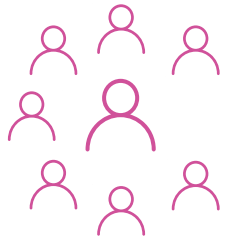
- T cell engaging bispecific Abs

Redirected T cells (temporary; no memory)

- CAR-T
- TCR-T

Engineered T cells (permanent; with memory)

Reactivate, expand, and arm



Solution

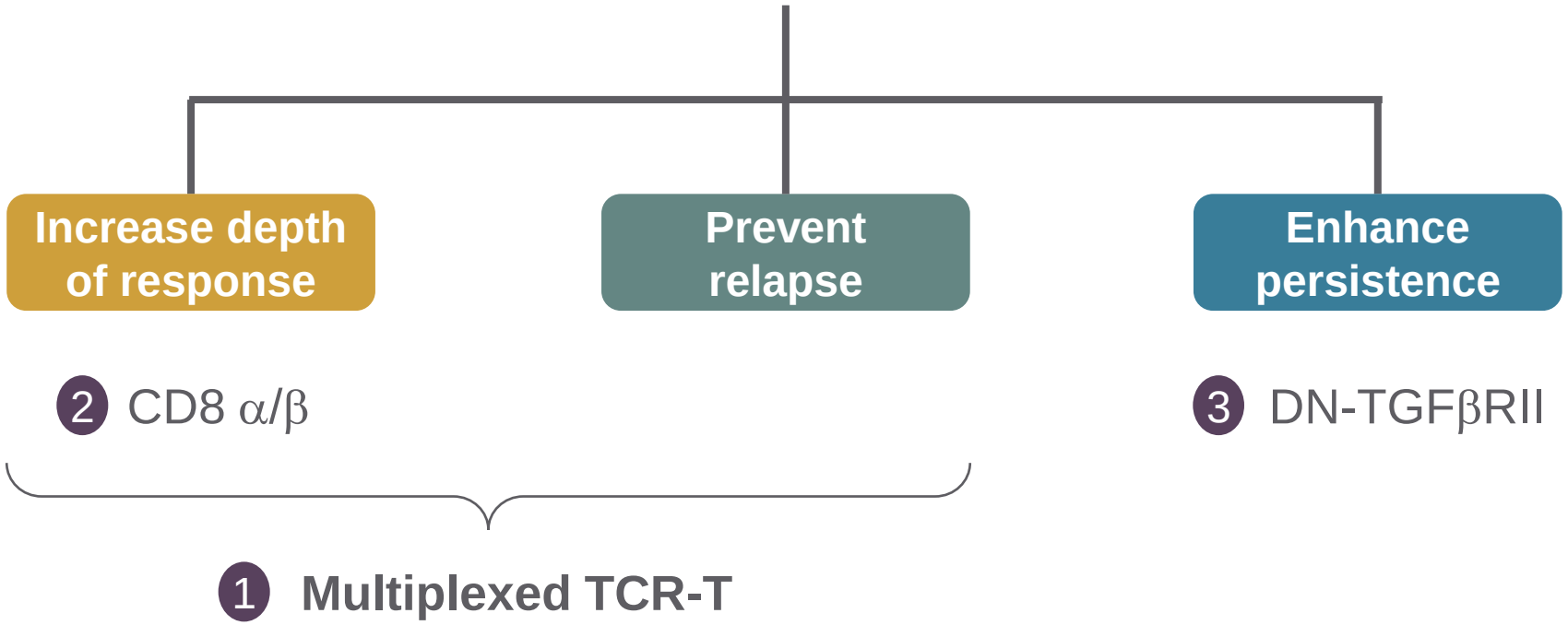
- Reprogram with proven, highly effective TCRs
- Reactivate, expand, & arm T cells

TScan is building on the success of first-generation TCR-T to address the problem of limited duration of response

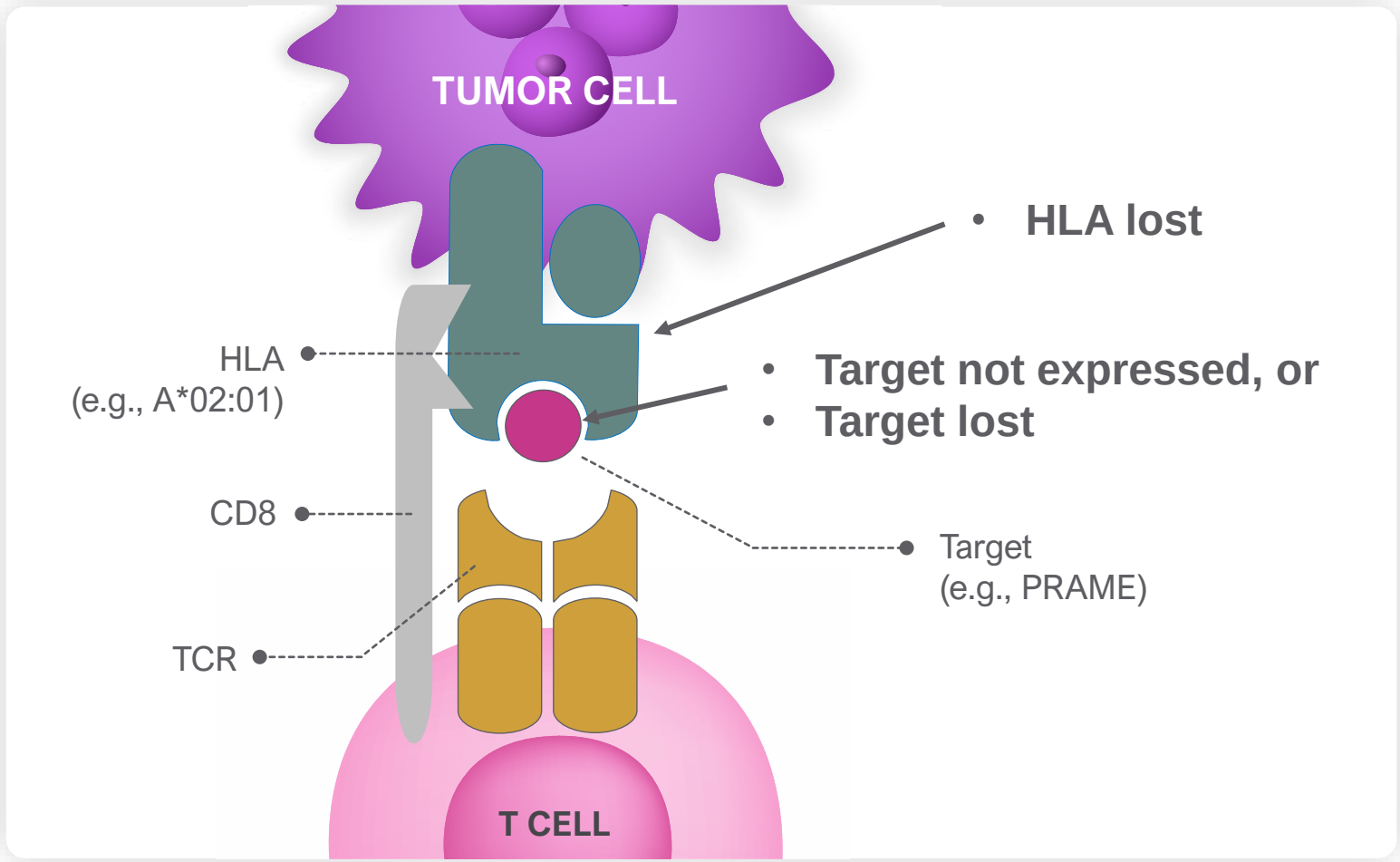
First-generation TCR-T

ORR: 30-50% DOR: 3-4 months

TScan's solution for enhancing durability



Solid tumors do not respond to TCR-T or become resistant if either the target is missing or the HLA is lost

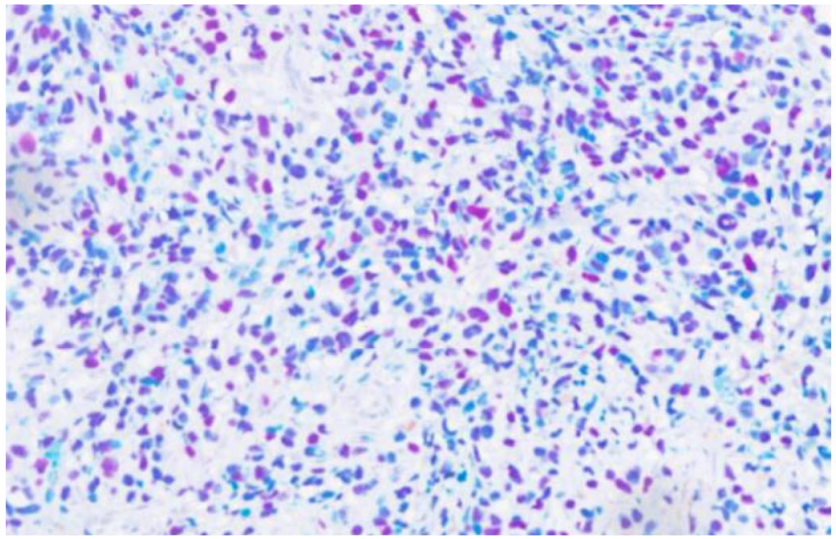


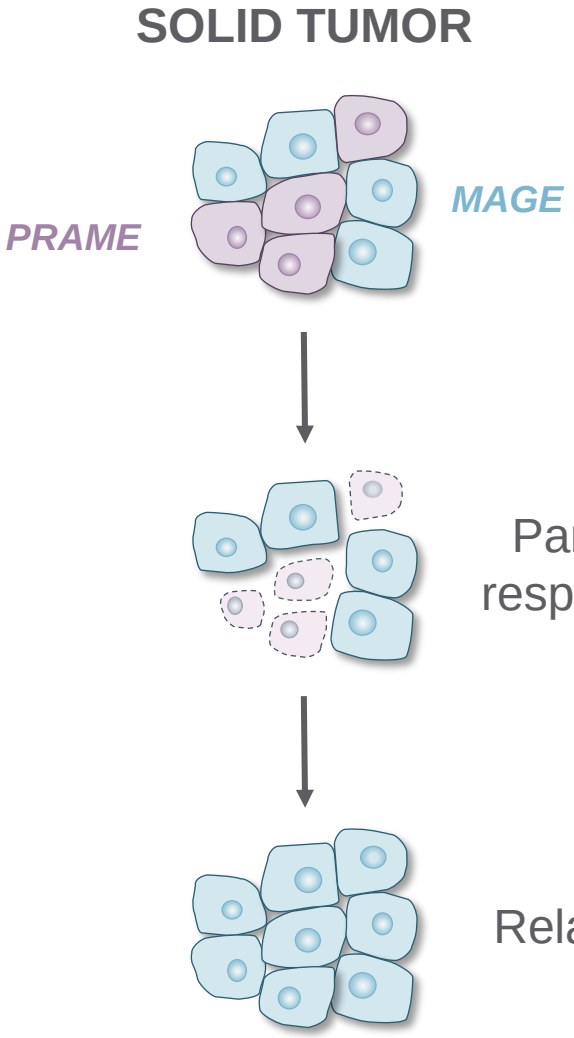
Solid tumors are heterogeneous, resulting in partial responses and rapid relapse

Tumor exhibiting target heterogeneity

PRAME

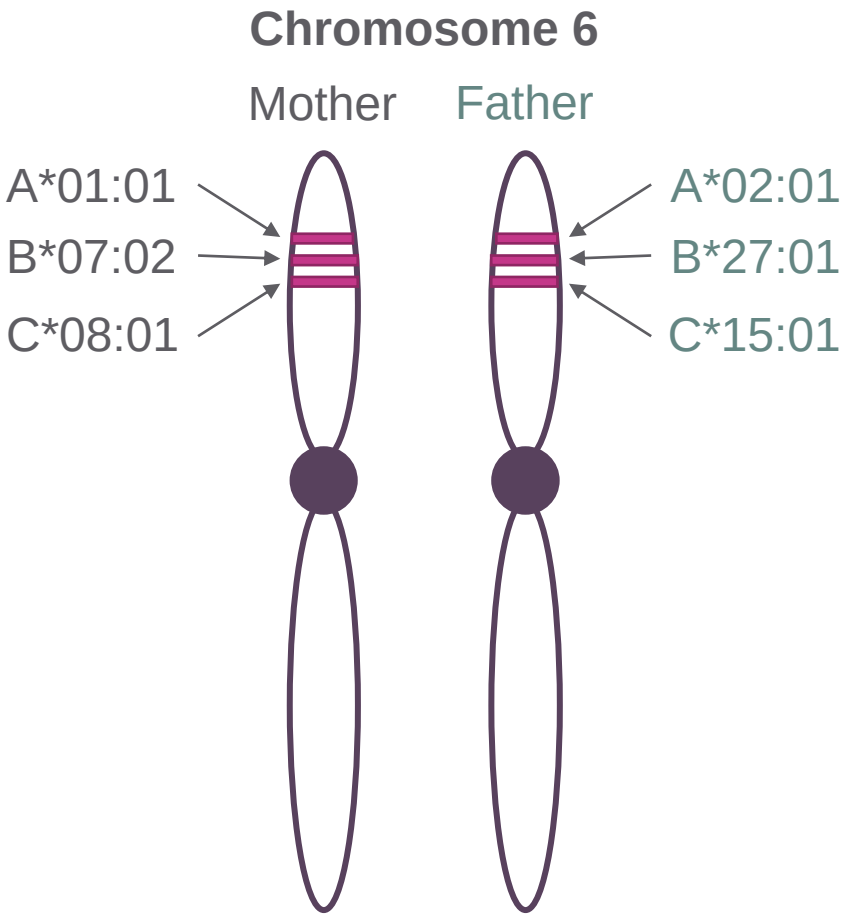
MAGE



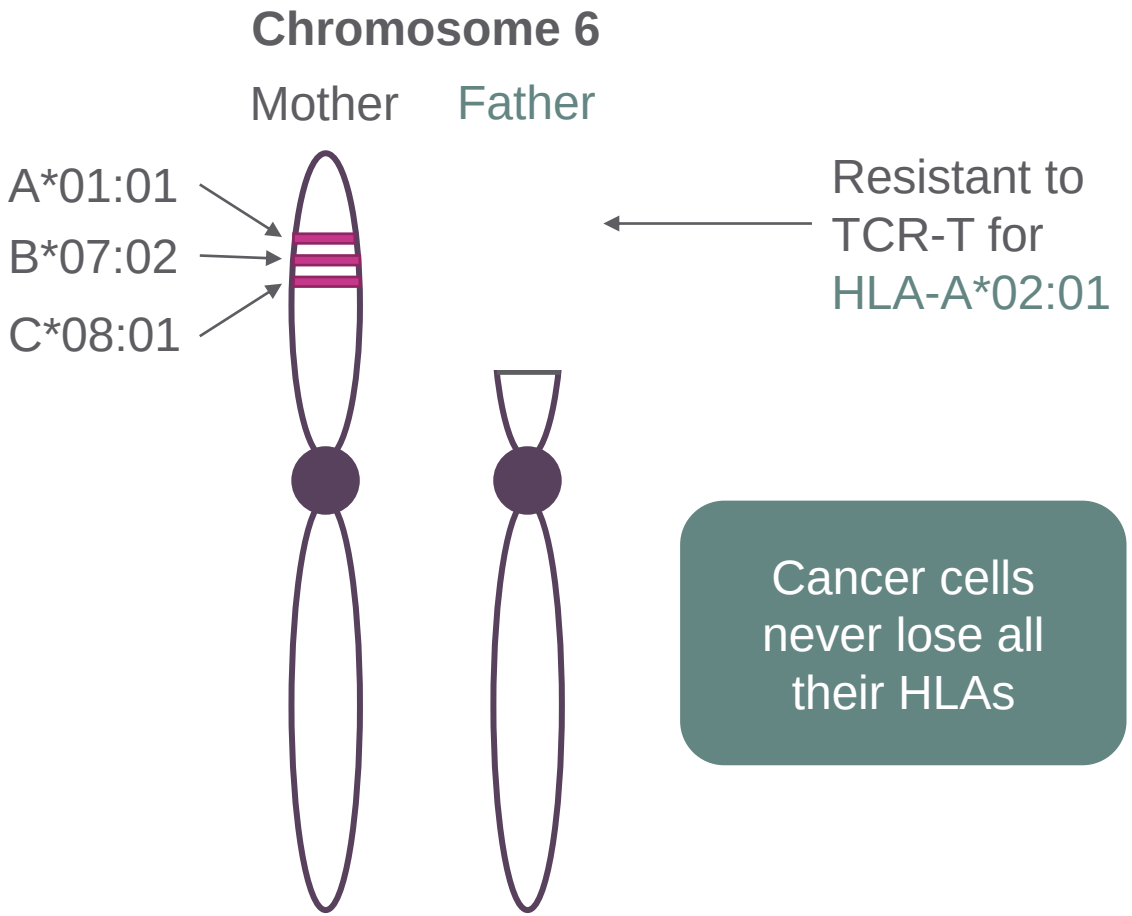


Cancer cells often lose half their HLA genes, becoming resistant to immunotherapy

Normal cells



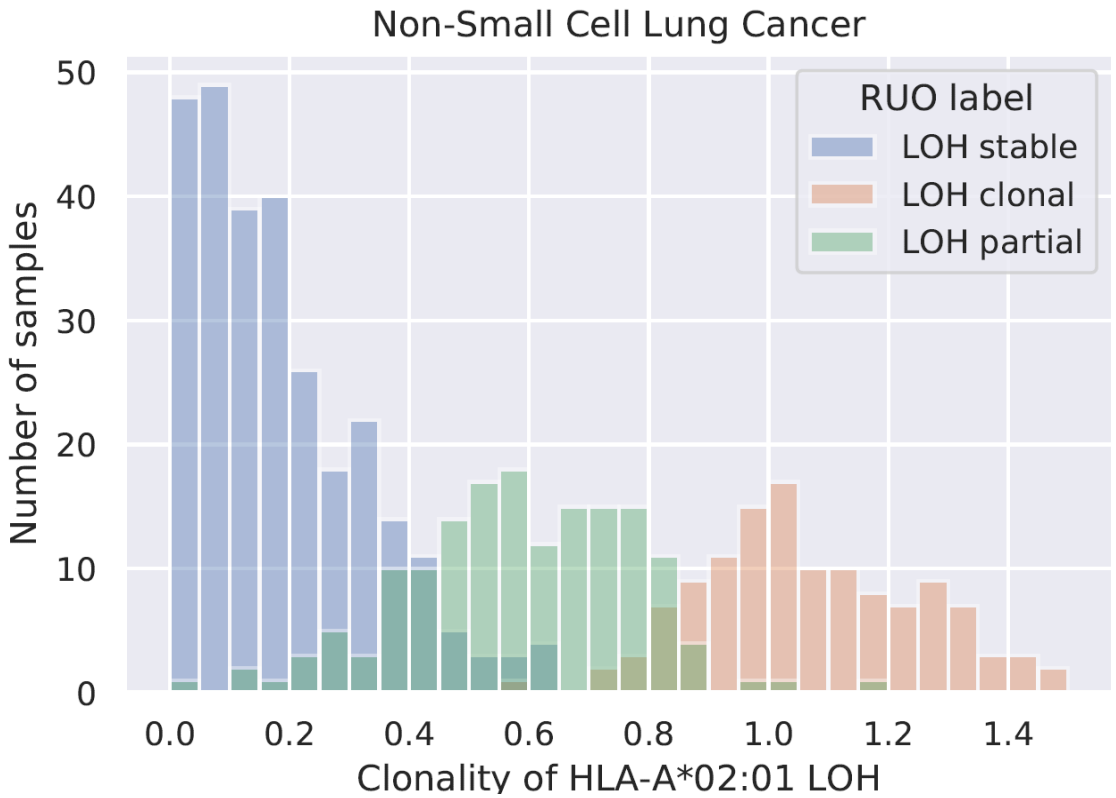
Cancer cells



Cancer cells never lose all their HLAs

HLA loss of heterozygosity (LOH) is a prevalent and overlooked mechanism of immunotherapy resistance

- ***17% of all solid tumors*** have clonal HLA loss
- ***Up to 40% of NSCLC*** samples have clonal (~15%) or subclonal (~25%) HLA loss

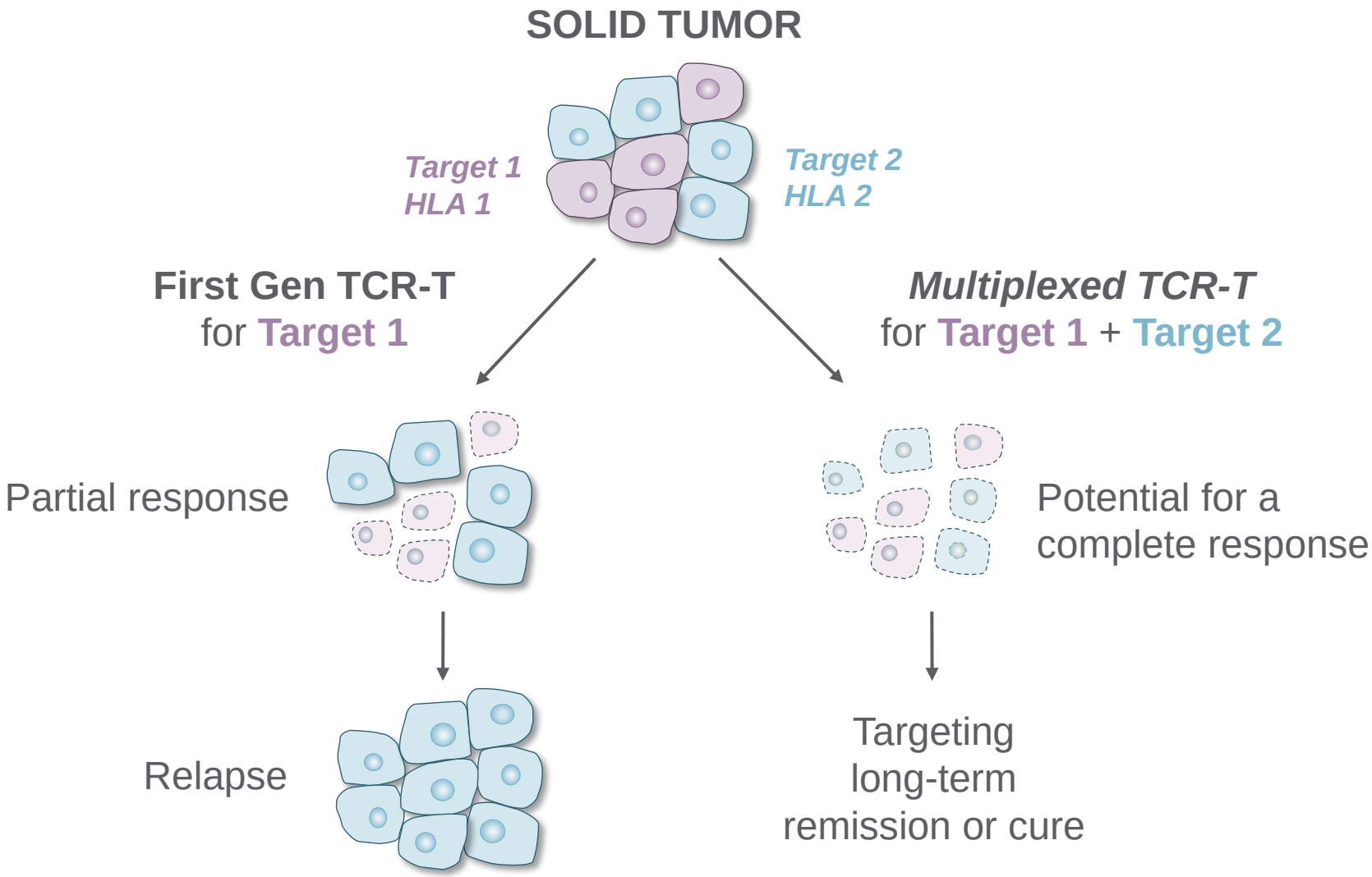


McGranahan, 2017, *Cell*
Montesion, 2021, *Cancer Disc*
Tempus internal analysis

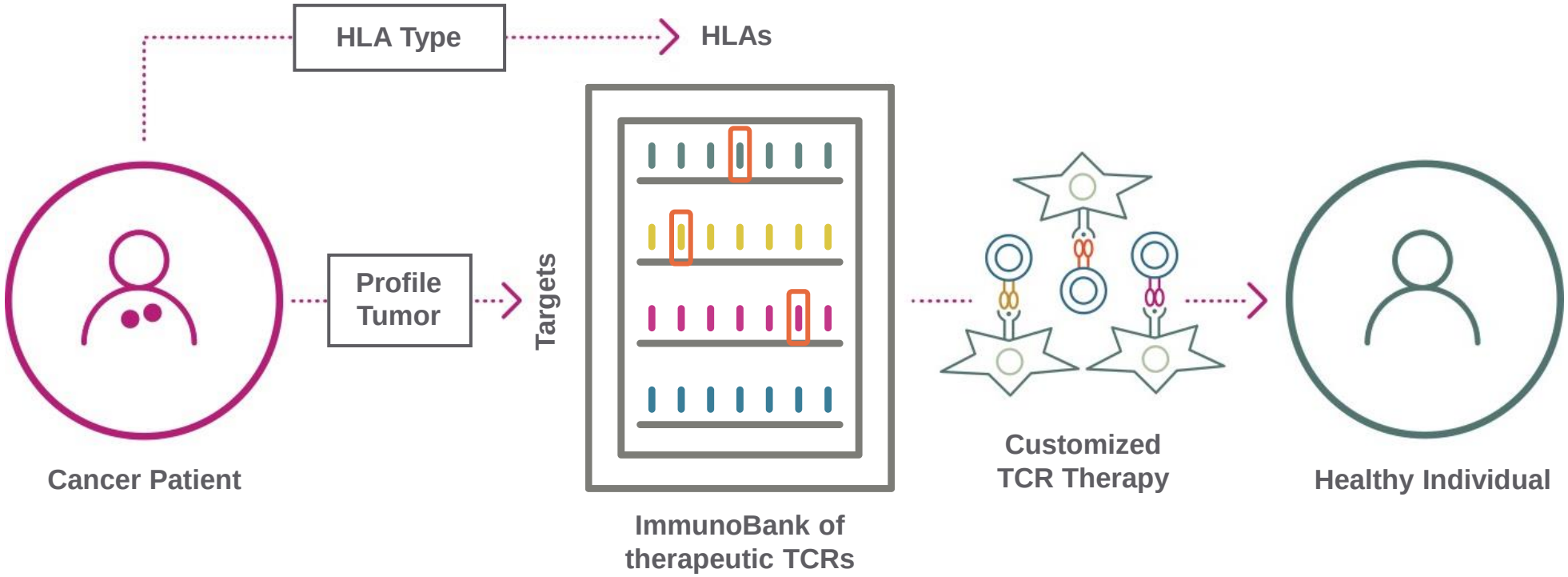
Multiplexed TCR-T is designed to overcome the problem of target heterogeneity and HLA loss

Increase depth of response

Prevent relapse



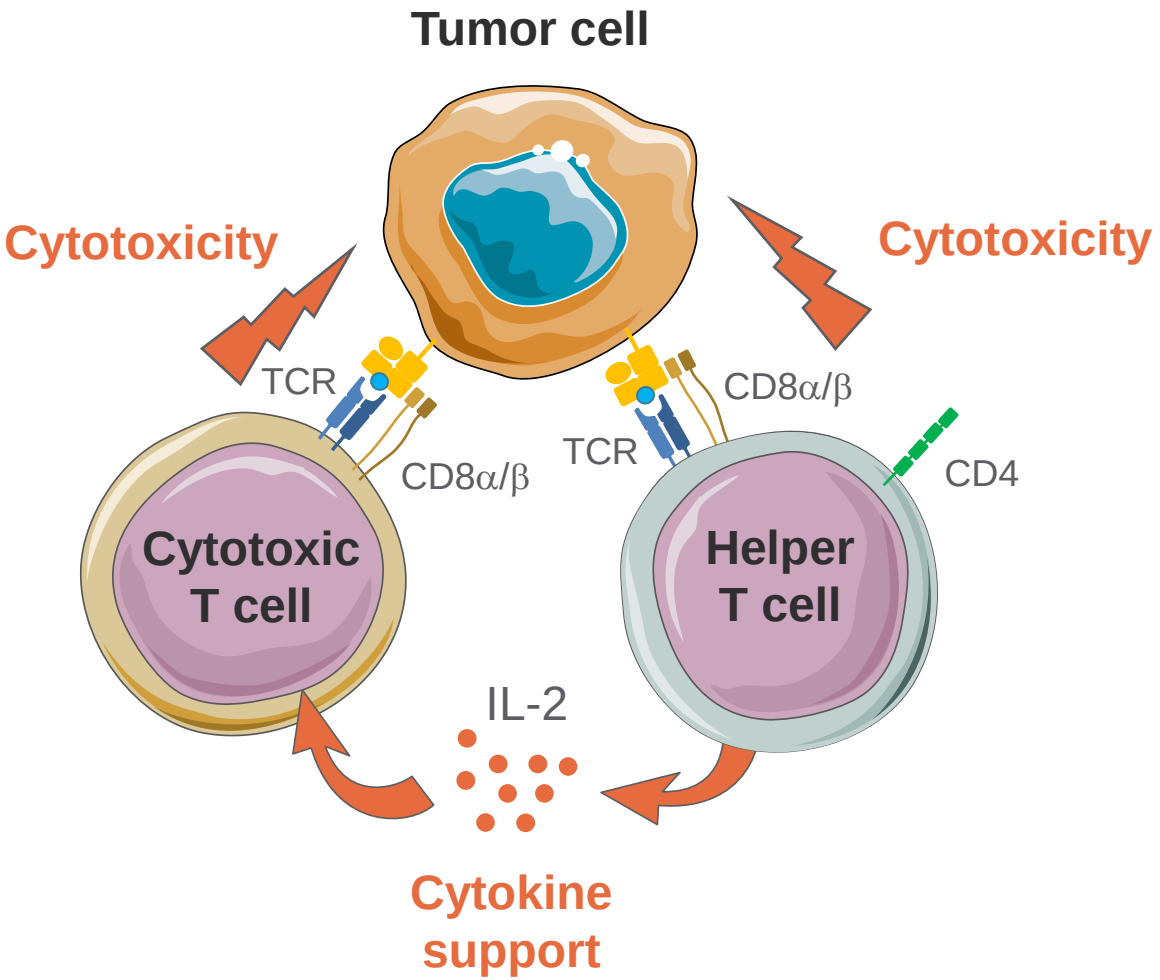
ImmunoBank of TCRs provides customized, off-the-shelf, multiplexed TCR-T



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

Helper T cells provide support for cytotoxic T cells and directly contribute to cytotoxicity

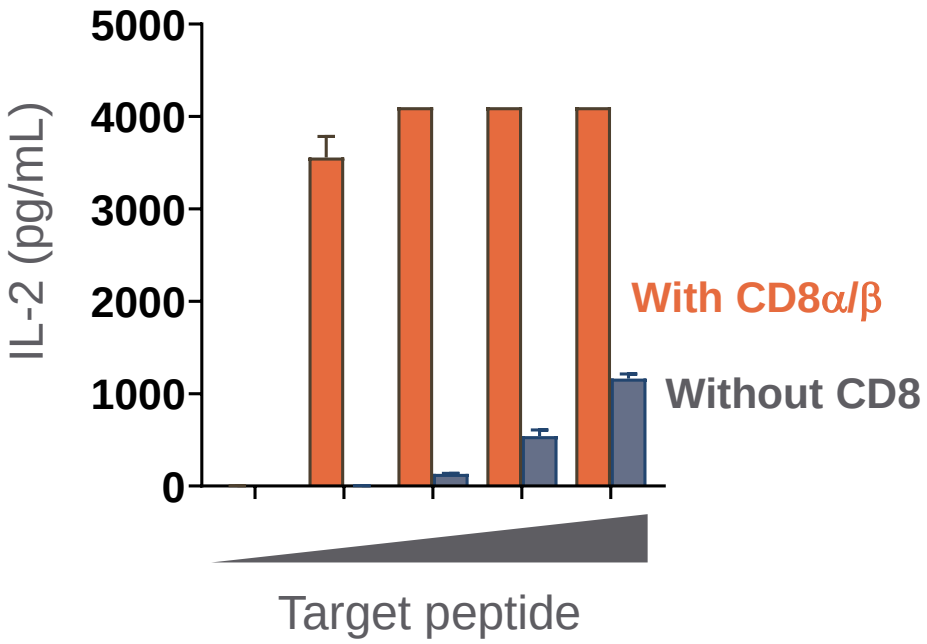
Increase depth of response



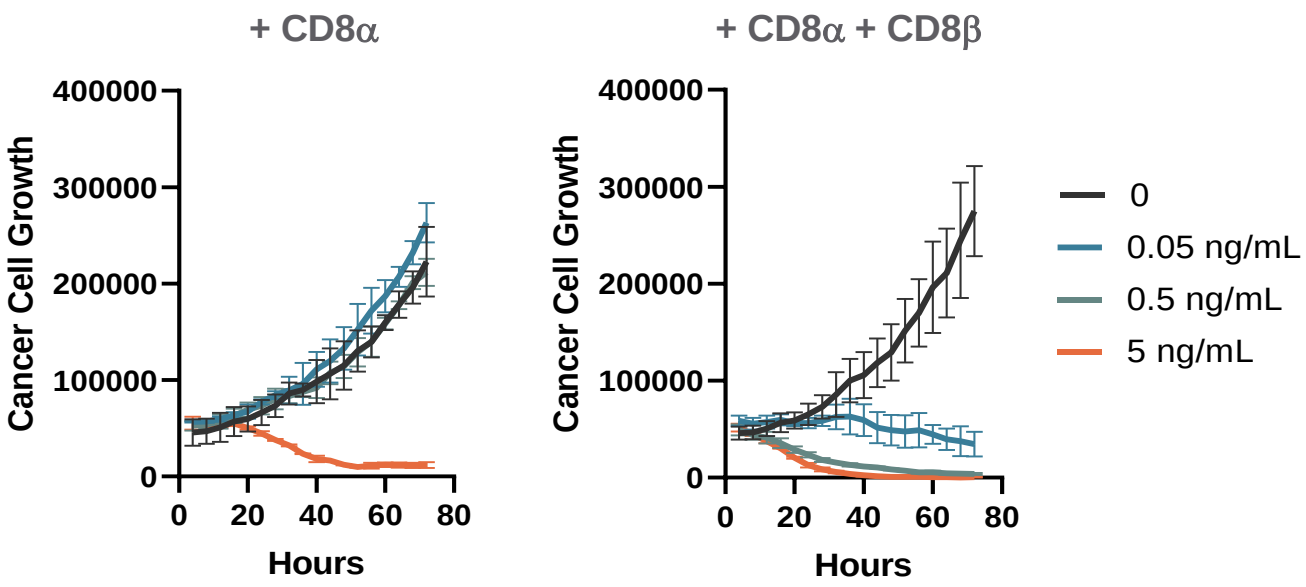
Addition of CD8 α/β to TScan's TCR-T cells engages helper T cells and results in greater anti-cancer activity

Helper T cells engineered with CD8α/β

Cytokine production (IL-2)



Cytotoxicity



Including helper T cells result in greater depth of response in clinical trials

Adaptimmune's data with non-sarcoma patients treated with MAGE-A4 TCR-T

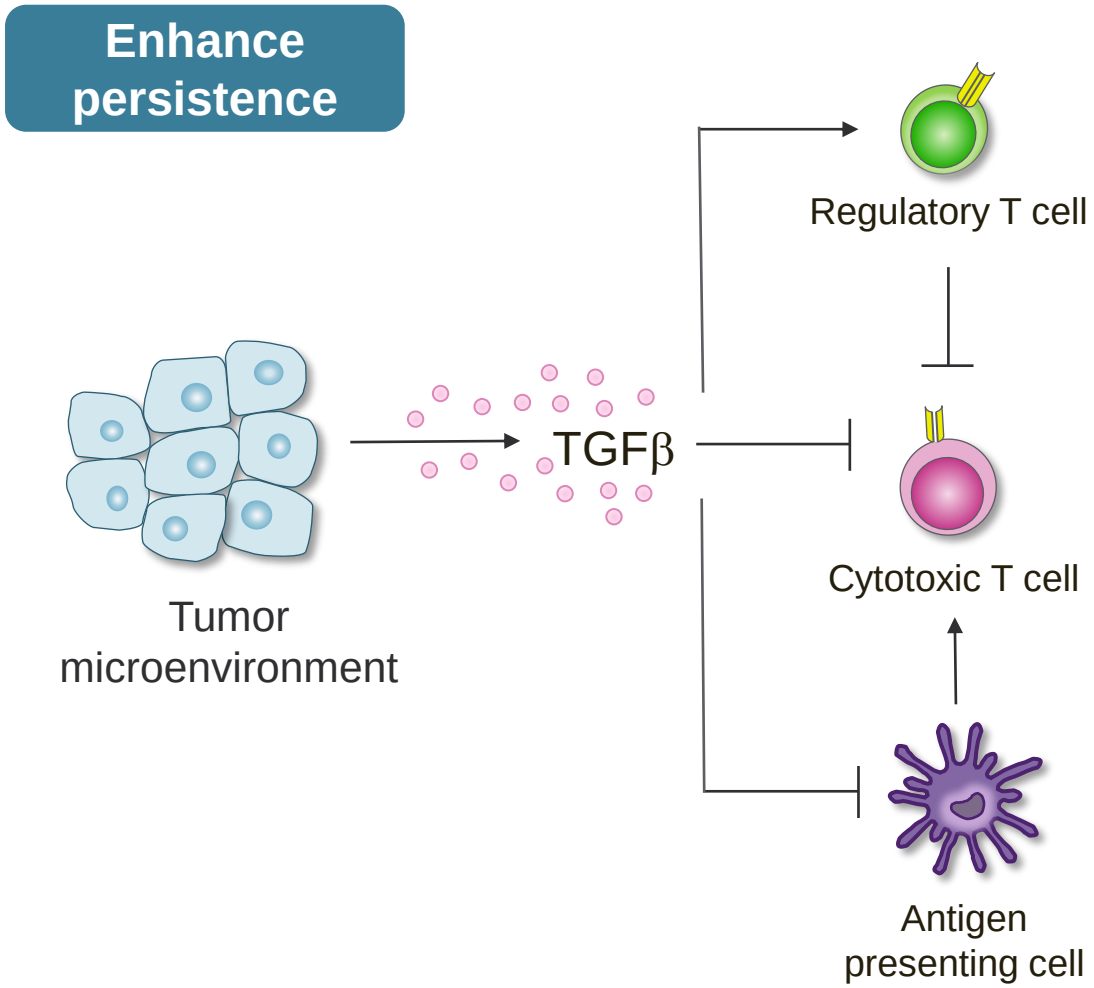
MAGE-A4 TCR alone (afami-cel)	
Number of non-sarcoma patients	22
Complete response (%)	0
Partial response (%)	2 (9.1%)
Stable disease (%)	11 (50%)
Overall response rate (%)	**9.1%**

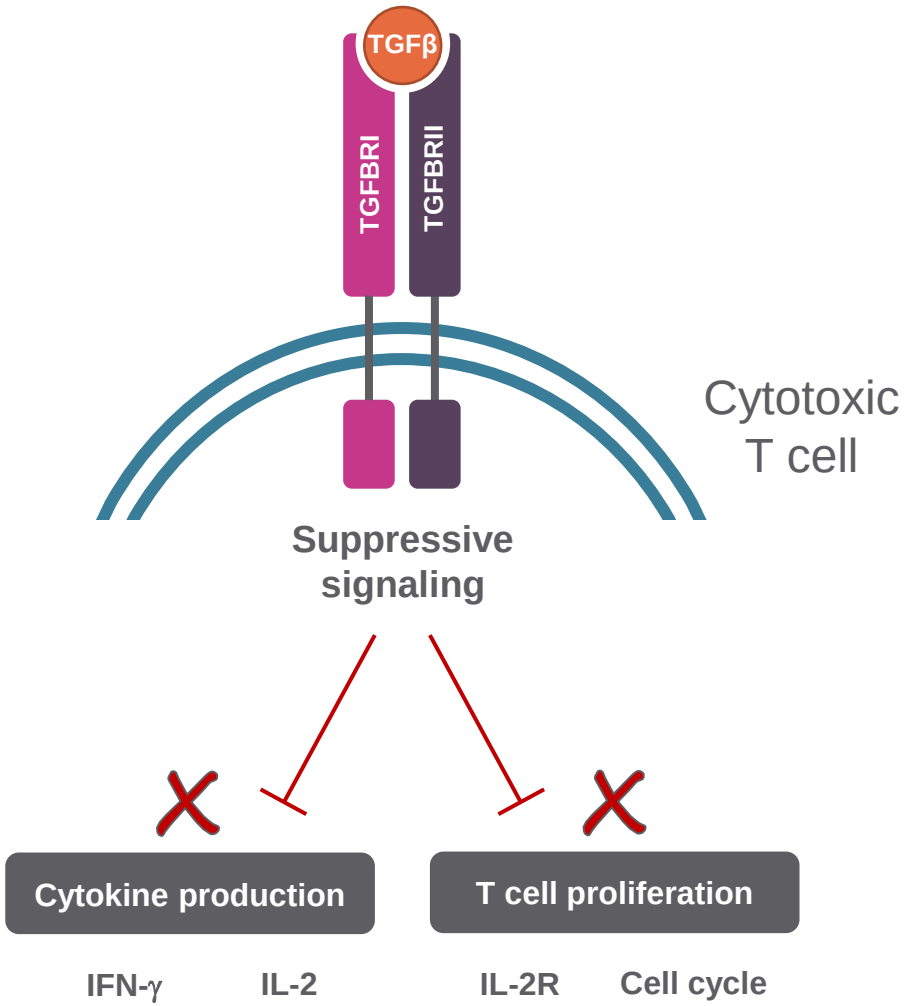
Hong, ASCO 2020

MAGE-A4 TCR + CD8α (ADP-A2M4CD8)	
Number of patients	44
Complete response (%)	1 (2%)
Partial response (%)	13 (29.5%)
Stable disease (%)	21 (48%)
Overall response rate (%)	**32%**

Hong, ESMO 2022

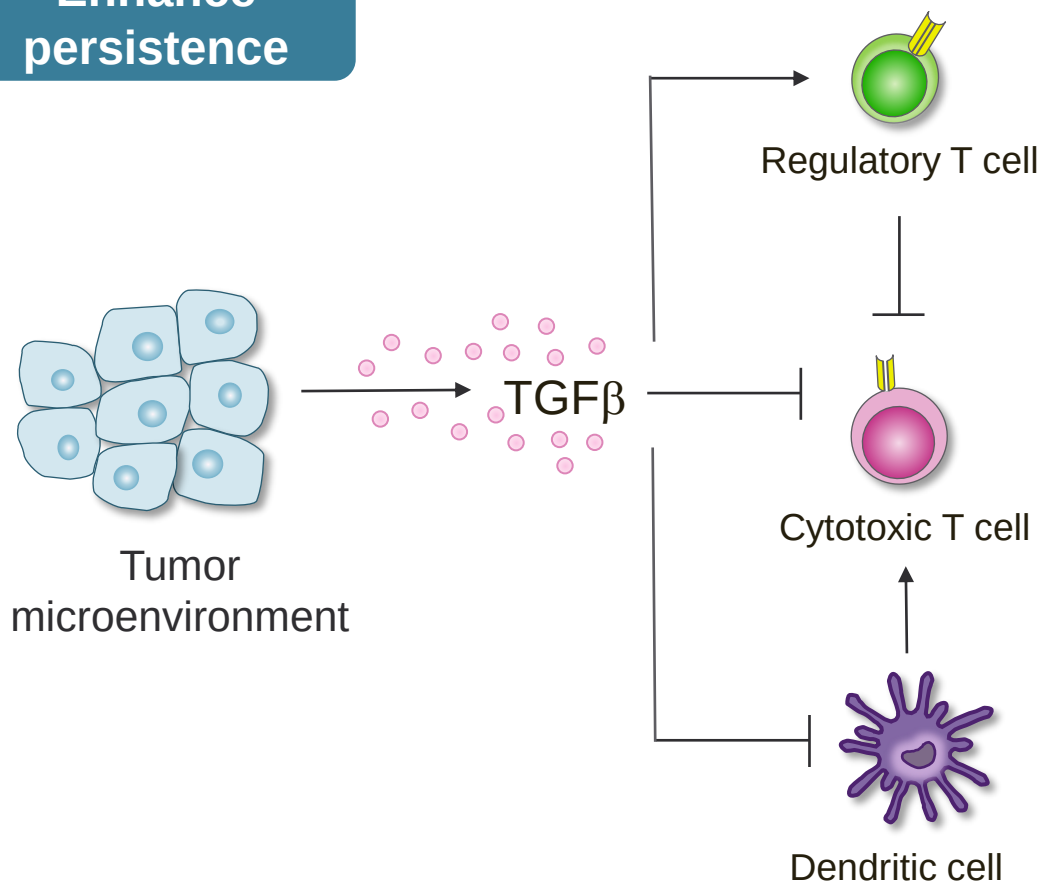
TGFβ is the key immune suppressor in the hostile tumor microenvironment

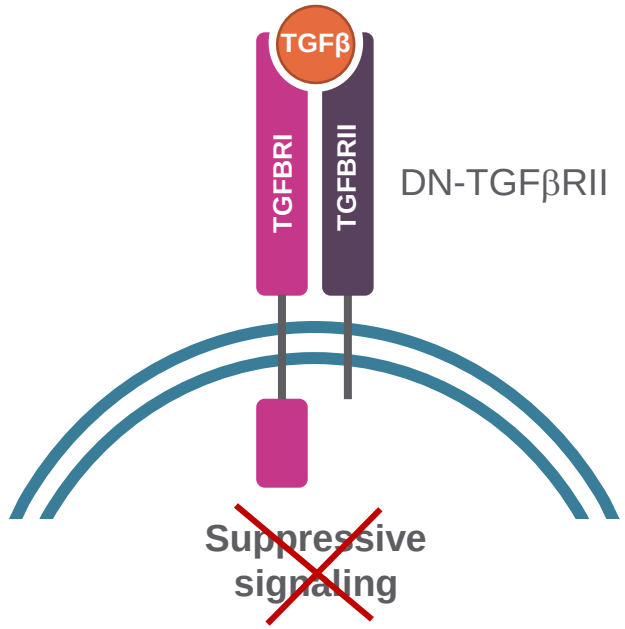




Dominant negative TGFβRII makes cells resistant to the effects of TGFβ

Enhance persistence



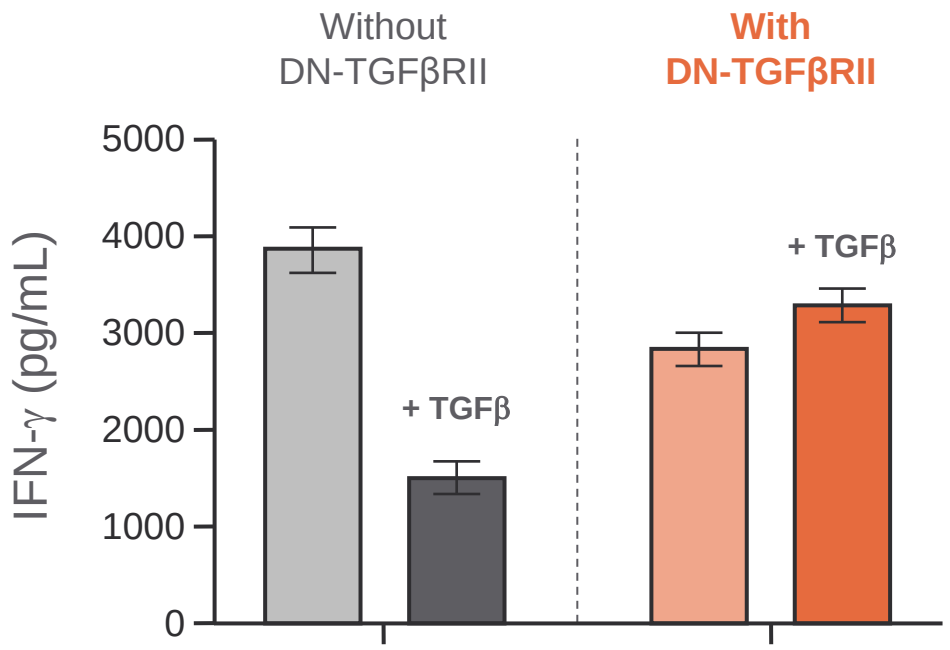


✓ **Cytokine production** — IFN-γ, IL-2

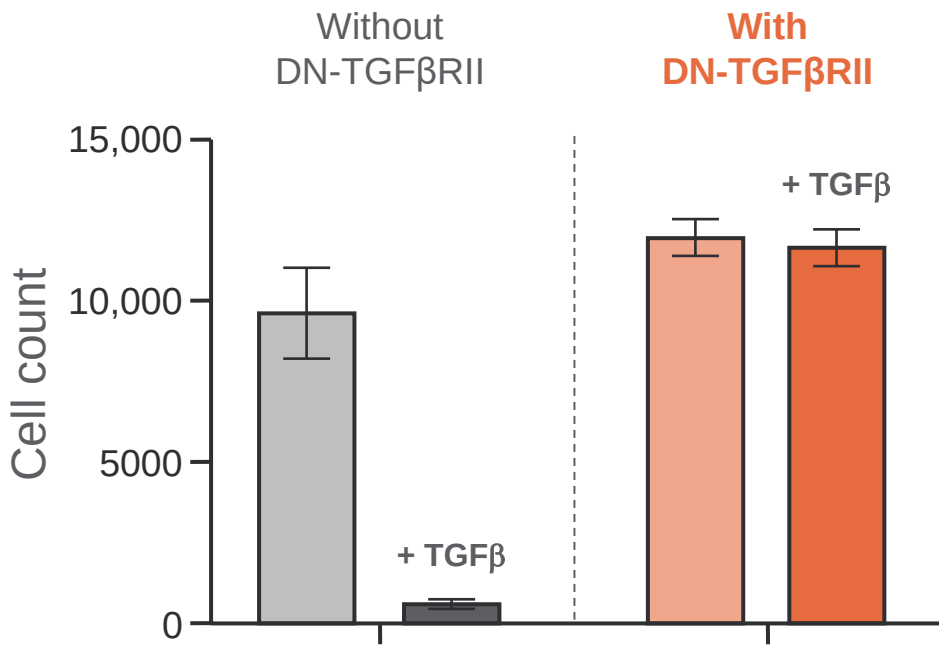
✓ **T cell proliferation** — IL-2R, Cell cycle

Adding DN-TGFβRII to TScan's TCR-T cells enables proliferation in the presence of TGFβ

Cytokine production



Proliferation



Clinical trials of T cells engineered with DN-TGFβRII show increased T cell expansion and persistence in patients

EBV-targeted T cells expressing DN-TGFβRII

- 8 Hodgkins lymphoma patients treated with 2-12 doses without lymphodepletion
- T cells expanded up to 100-fold and persisted for 4 years
- 4 out of 7 patients had responses lasting >2 years

J Clin Oncol (2018) **36**, 1128-1139.

PSMA-targeted CAR-T cells expressing DN-TGFβRII

- 13 metastatic prostate cancer patients treated with 1 dose +/- lymphodepletion
- T cells expanded >100,000-fold and persisted >200 days
- 2 patients developed grade 3 CRS, 1 grade 3 ICANS, 1 patient died of CRS
  - Death believed not to be linked to DN-TGFβRII as expanded T cells were clonally expanded

Nat Med (2022) **28**, 724-734.

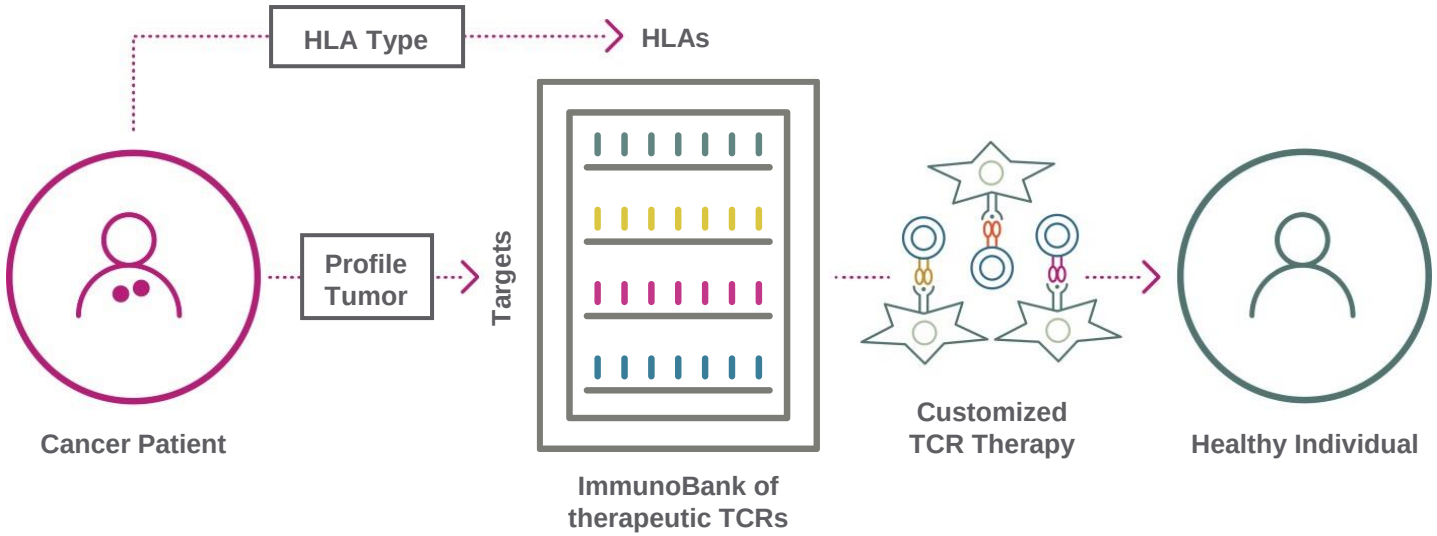
The key to success is building the ImmunoBank to enable *enhanced, multiplexed TCR-T*

TScan's solution for enhancing durability

Increase depth of response

Prevent relapse

Enhance persistence

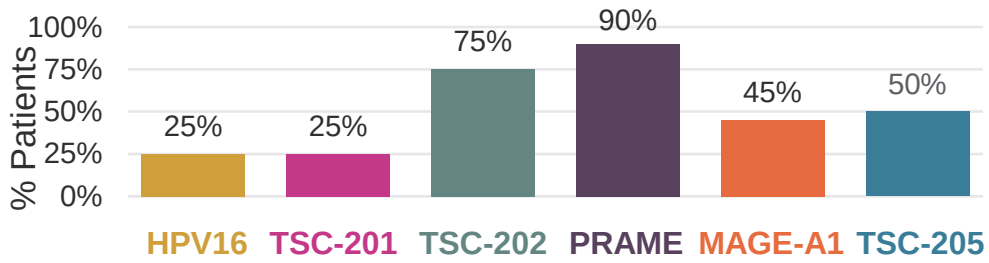


Building the ImmunoBank

ImmunoBank is being built with validated targets that exhibit high prevalence in immune-rich cancers with high unmet need

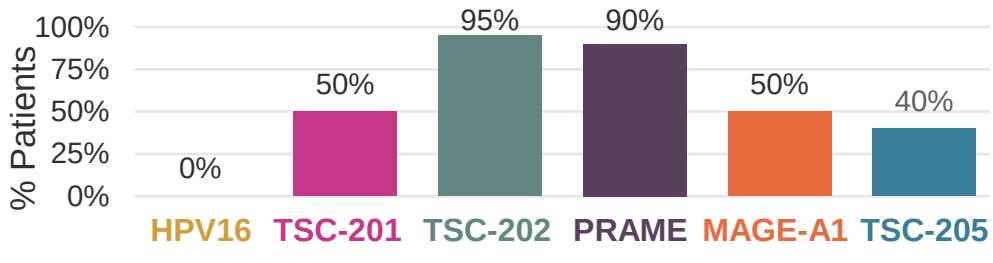
Head & Neck

66 K Incident Patients in U.S.



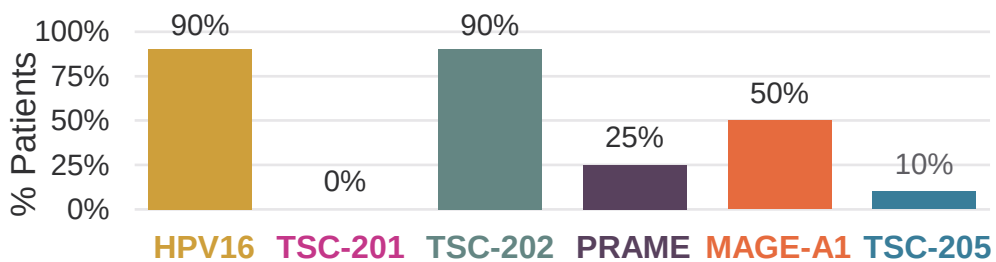
Melanoma

100 K Incident Patients in U.S.



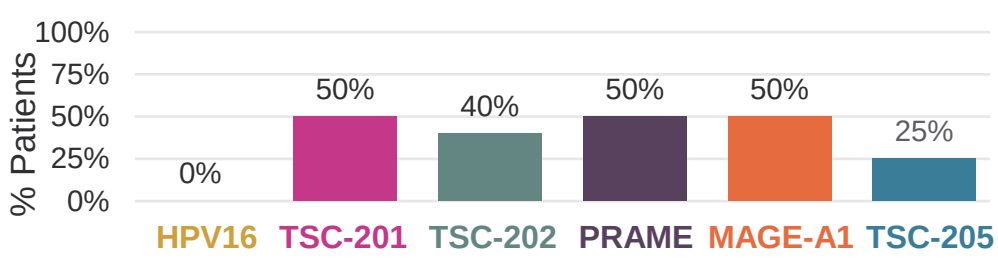
Cervical (Uterine cervix)

15 K Incident Patients in U.S.



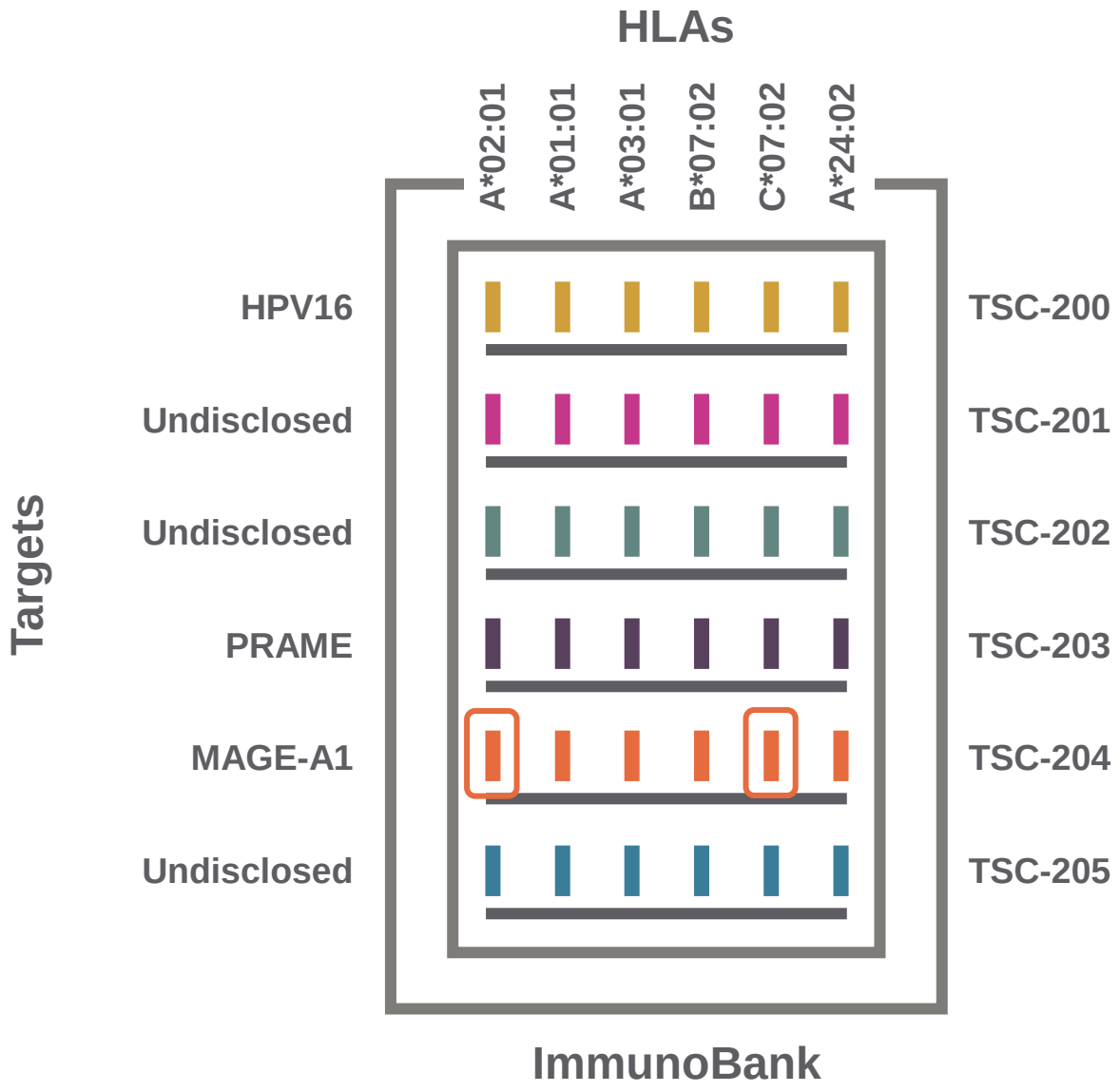
NSCLC

230 K Incident Patients in U.S.



*Denotes broad lung cancer expression.
Source: American Cancer Society

TScan is planning to file INDs for the first two TCRs this year



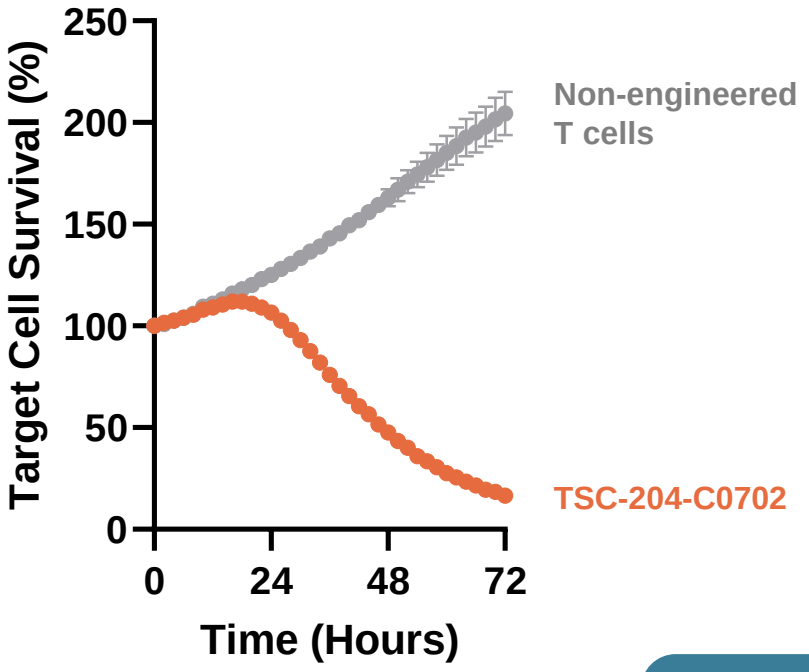
INDs

Q4, 2022 — 2 INDs

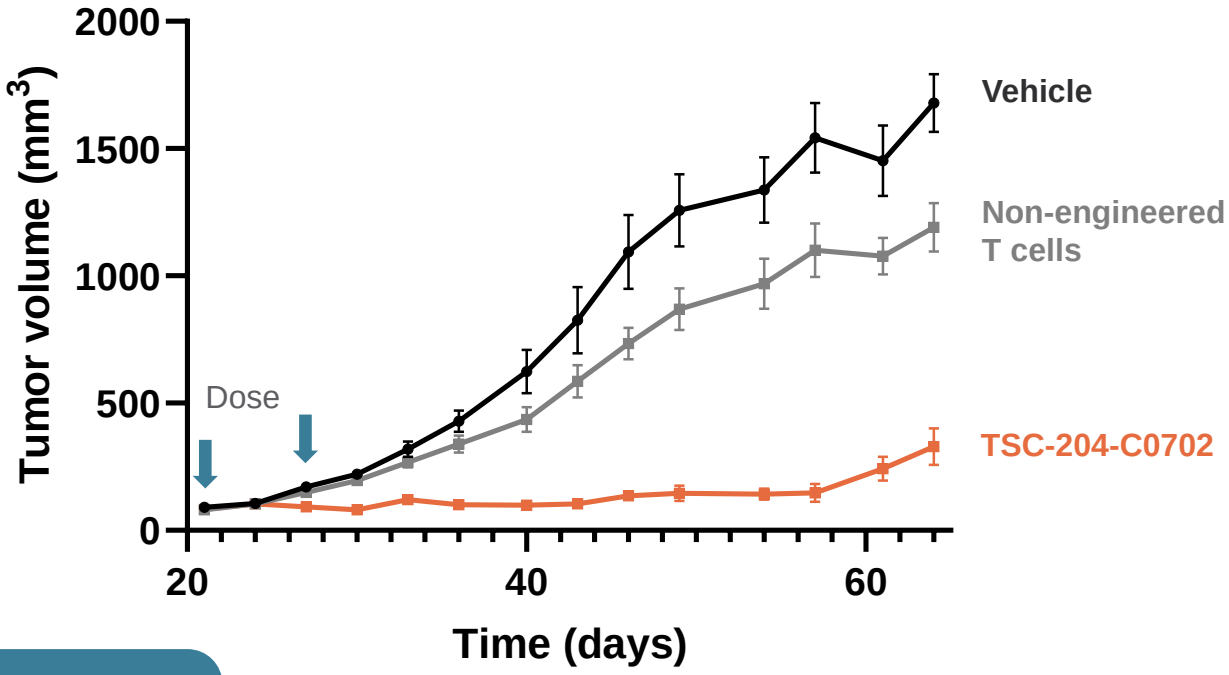
TSC-204-C0702 is an enhanced TCR-T that targets MAGE-A1 on HLA-C*07:02

Discovered from a patient with head & neck cancer using **TargetScan**

HS936T
MAGE-A1⁺ melanoma



U266B1
MAGE-A1⁺ mouse model



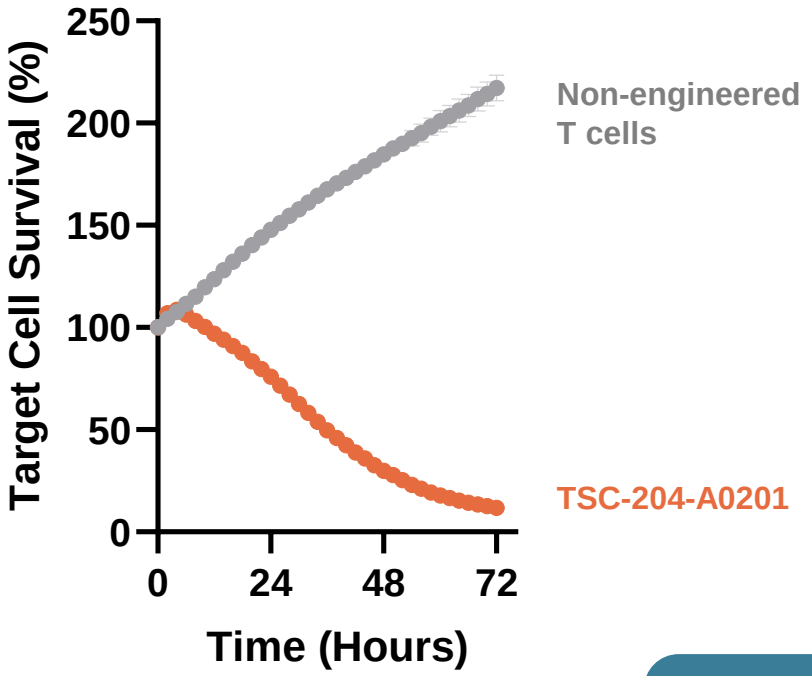
Discovery published in *Cell*

Luoma AM *et al.* (2022) *Cell*, **185**, 2918-2935.e29

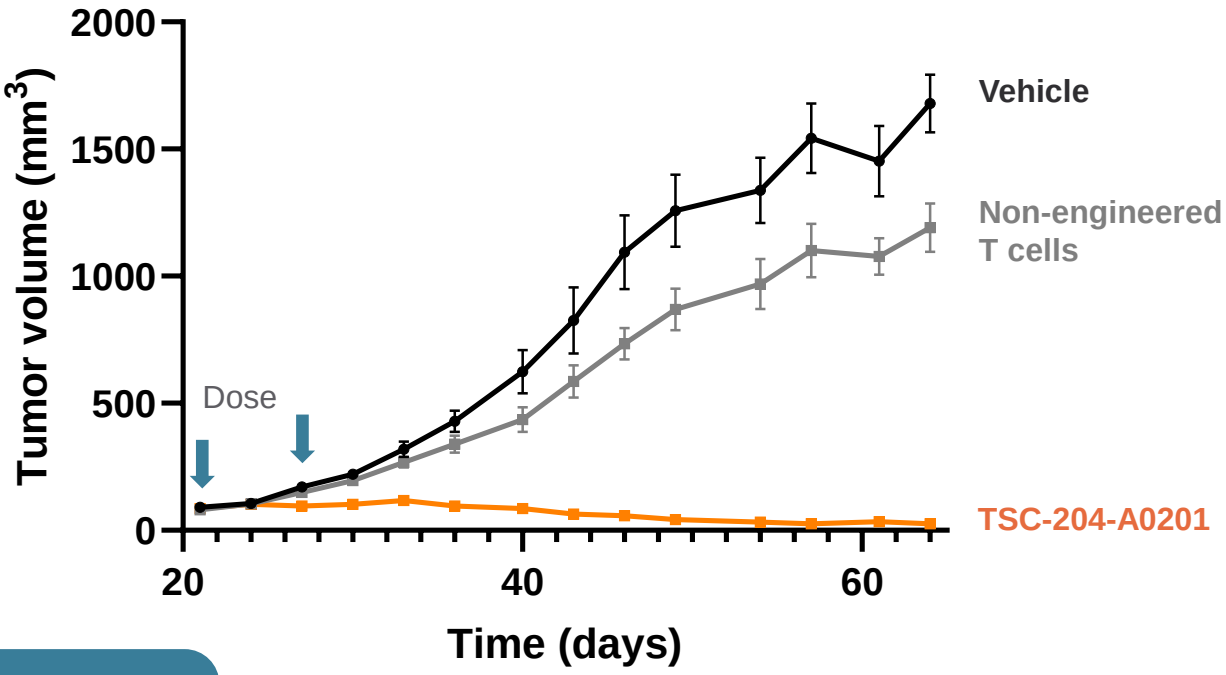
Initial T-Plex IND will also include TSC-204-A0201, which targets MAGE-A1 on HLA-A*02:01

Discovered from a healthy donor using **ReceptorScan**

NCI H1702
MAGE-A1^{+} melanoma

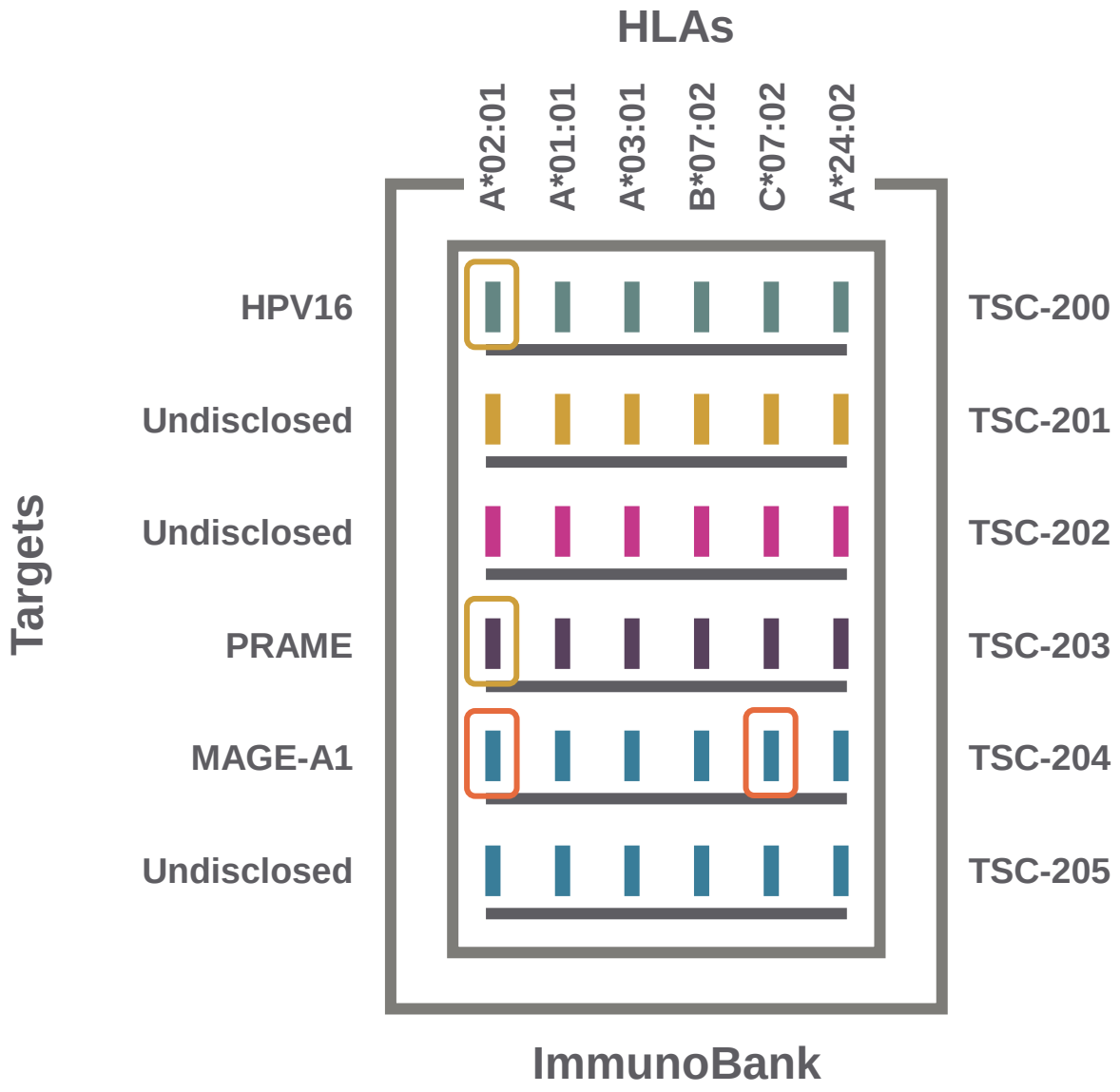


U266B1
MAGE-A1^{+} mouse model



SITC Annual Meeting
2022

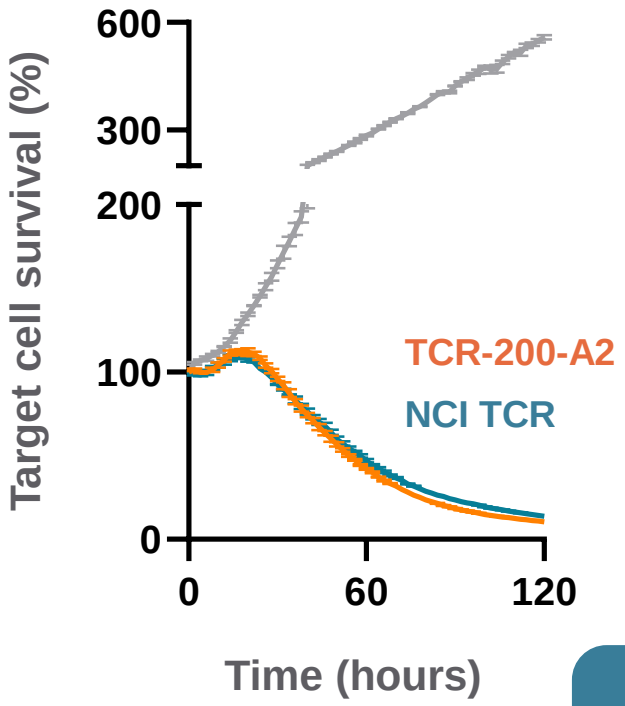
TScan is planning to file 2 additional INDs in H1, 2023



TSC-200-A0201 (HPV16) is on-track to an IND in H1, 2023

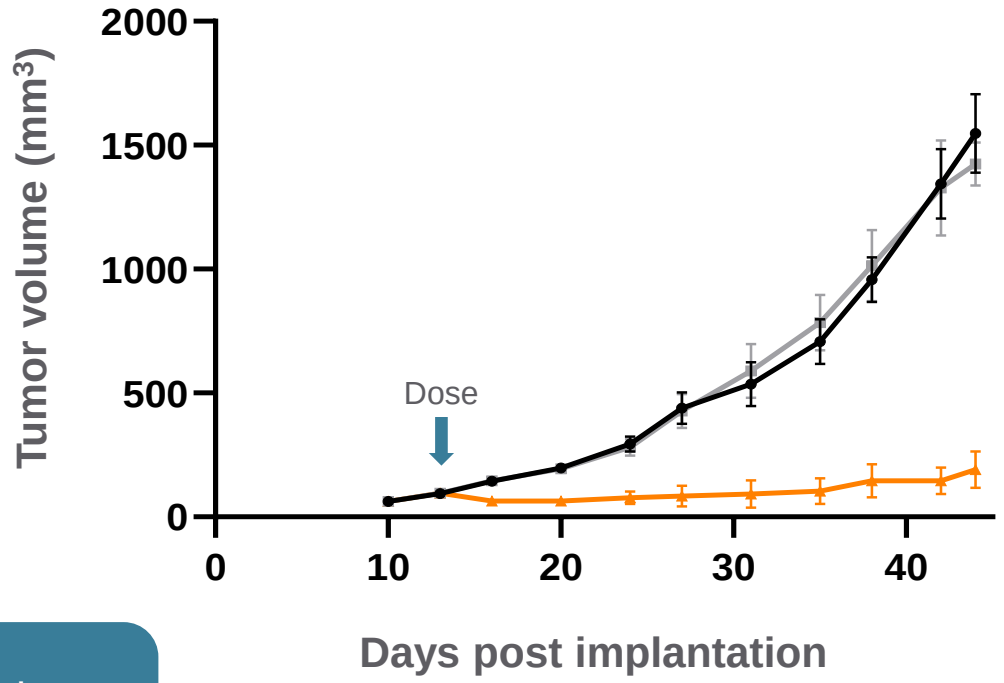
In vitro

SCC152
(head & neck)



In vivo

SCC152
(head & neck)



ASGCT Annual Meeting
2022

TScan presented two posters at SITC in support of the planned solid tumor program

Society for Immunotherapy of Cancer

SITC 2022 NOVEMBER 8-12 BOSTON MASSACHUSETTS

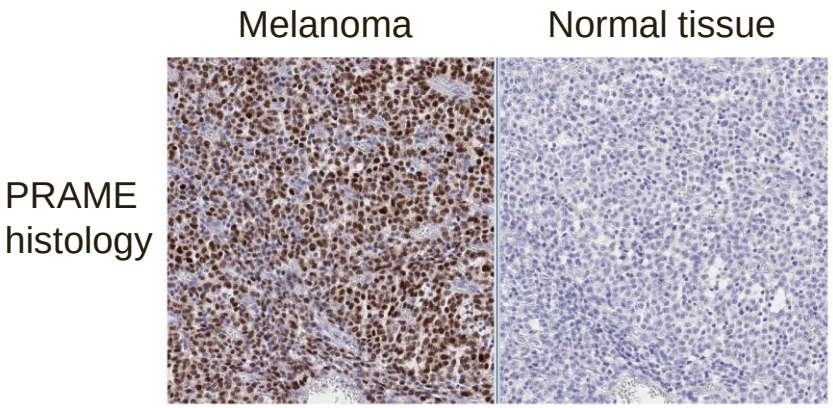
Discovery of PRAME-specific TCR-T cell therapy candidates for the treatment of solid tumors

Mollie M Jurewicz, Elizabeth M Hall, Alexandra L Luther, Kimberly M Cirelli, Vivin Karthik, Kenneth L Jahan, Tary Traore, Maytal Bowman, Victor Ospina, Sonal Jangalwe, Shubhangi Kamalia, Sadie Lee, Daniel C Pollacksmith, Sida Liao, Amy Virbasius, Kristen Murray, Jillian L Oliveira, Lisa Nip, Christina E Lam, Livio Dukaj, Danielle Ramsdell, Jin He, Joel W Sher, Ribhu Nayar, Qikai Xu, Yifan Wang, Antoine Boudot, Cagan Gurer, Gavin MacBeath

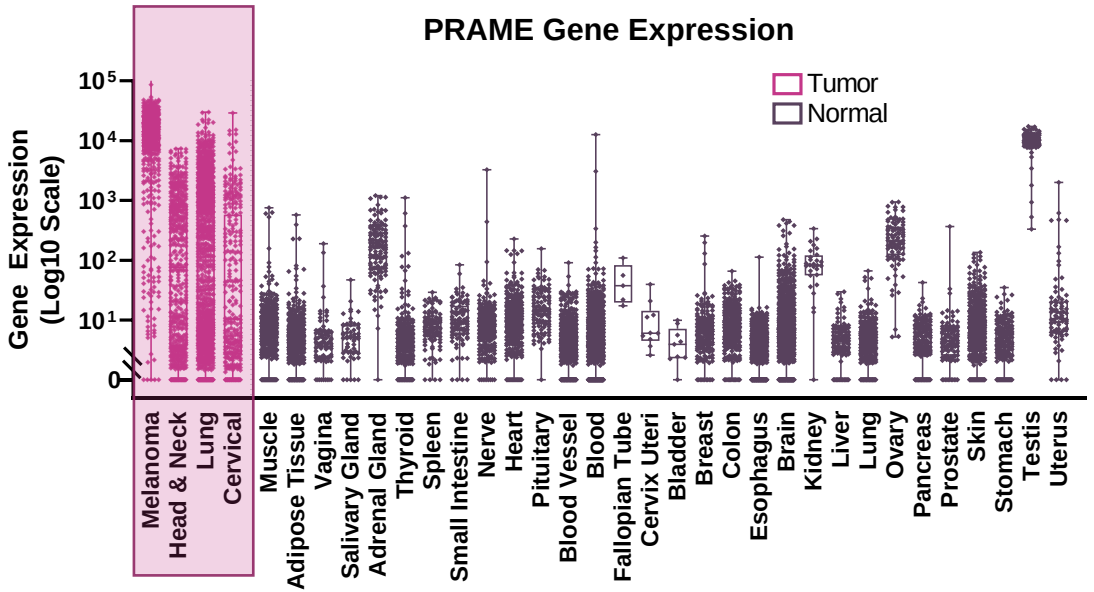
Multiplexed TCR-T cell therapy targeting MAGE-A1 and PRAME enhances the activity of adoptive T cell therapy in pre-clinical models

Antoine J. Boudot, Jenny Tadros, Tary Traore, Maytal Bowman, Victor Ospina, Nancy Nabilsi, Mollie M Jurewicz, Elizabeth M Hall, Qikai Xu, Yifan Wang, Cagan Gurer, Gavin MacBeath

PRAME is a clinically validated target with prevalent expression in melanoma, head & neck, and NSCLC



- Inhibits growth arrest and apoptosis, leading to oncogenic transformation
- High expression correlates with increased metastasis and poor prognosis
- High and often homogeneous expression in 90% of melanomas, 90% head & neck, and 50% NSCLC

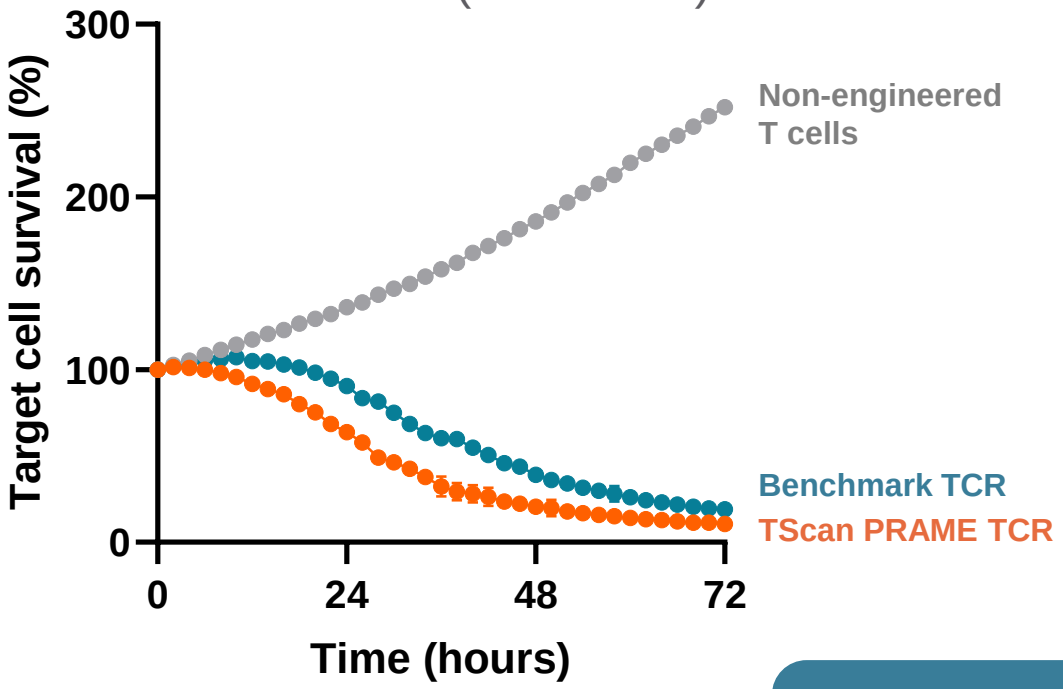


PRAME TCRs display cytotoxicity similarly to comparator TCR

Discovered from a healthy donor using **ReceptorScan**

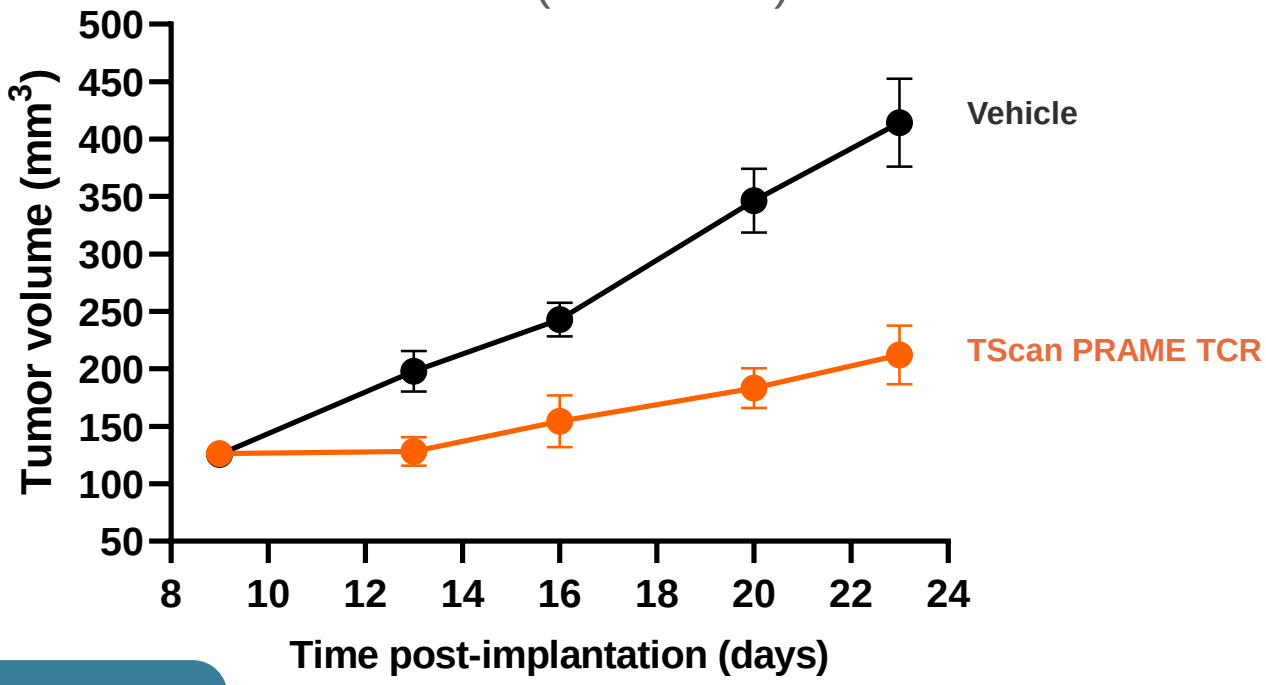
In vitro

Hs695T
(melanoma)



In vivo

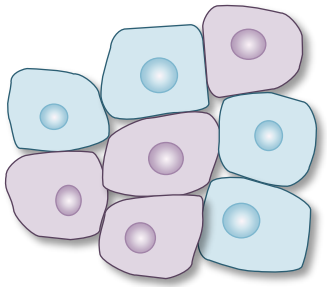
Hs695T
(melanoma)



SITC Annual Meeting
2022

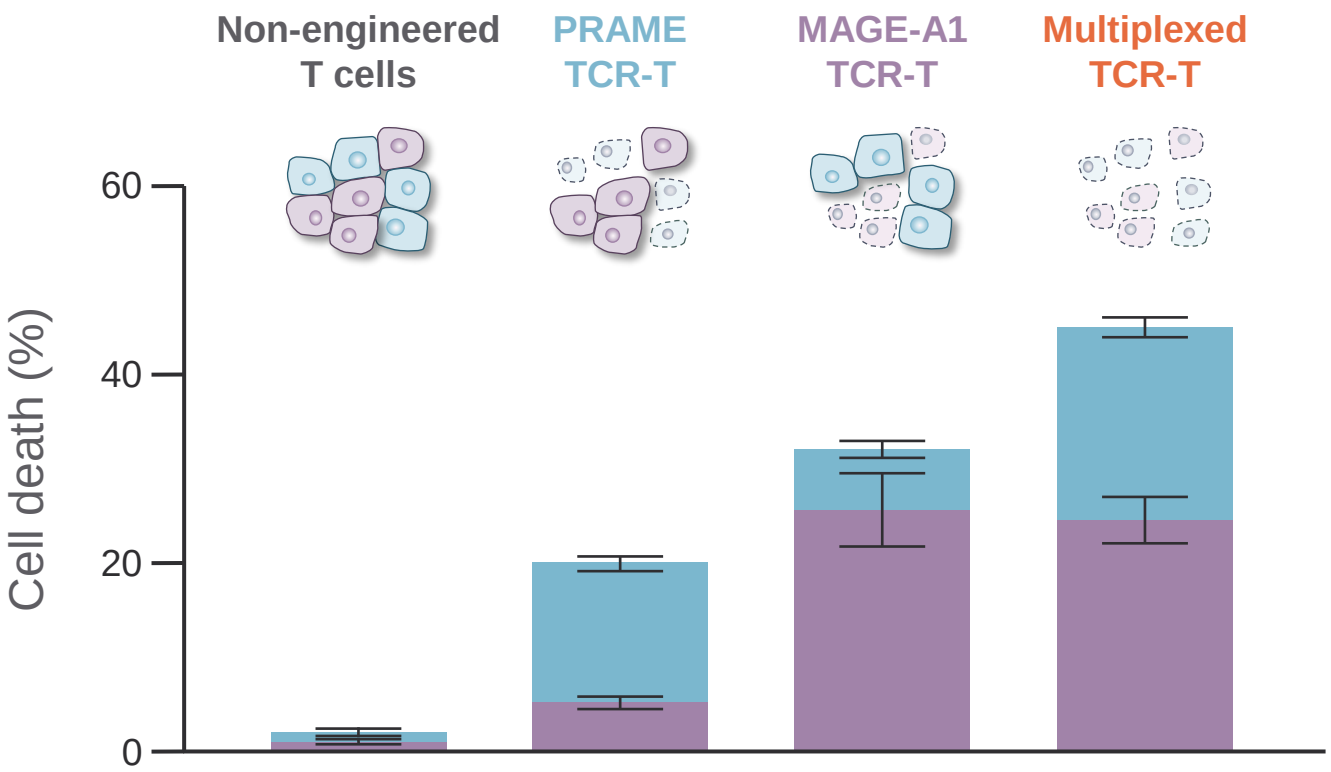
Multiplexed TCR-T addresses the problem of target heterogeneity

Mixed cell culture
50:50

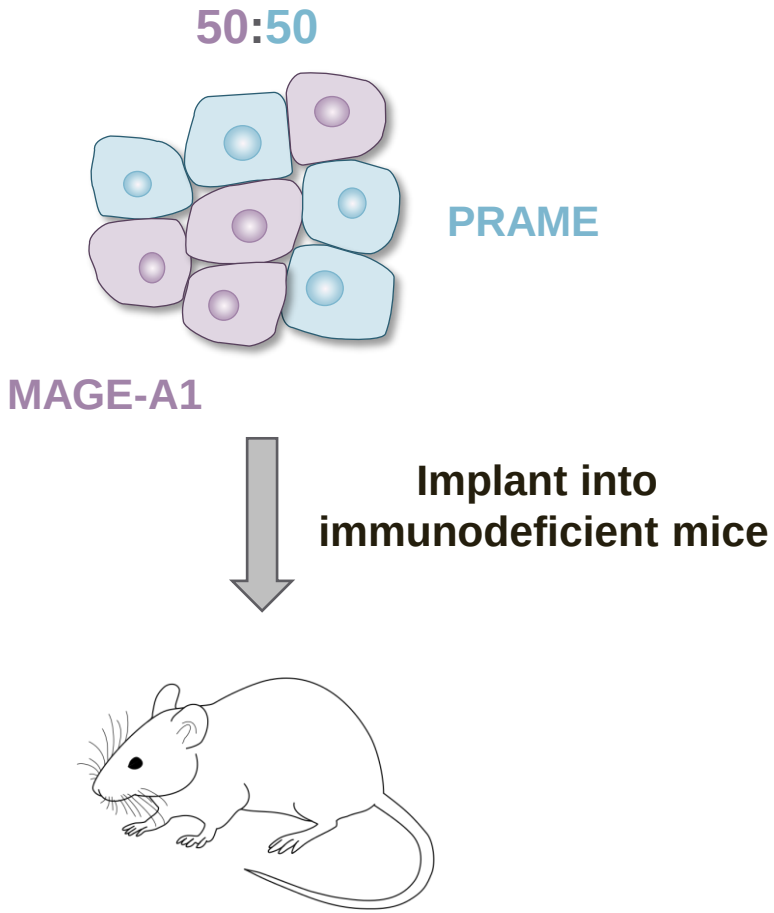


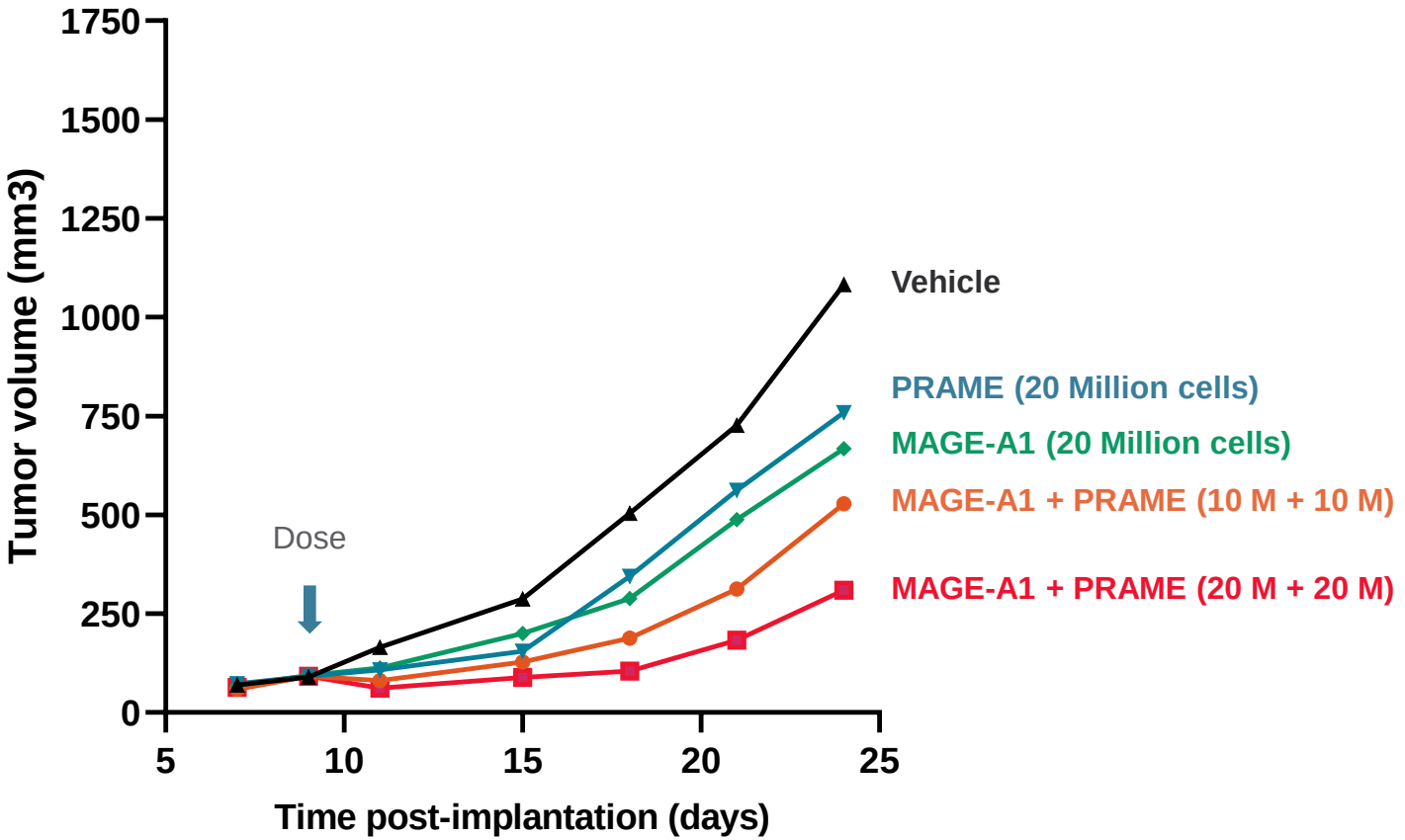
PRAME

MAGE-A1



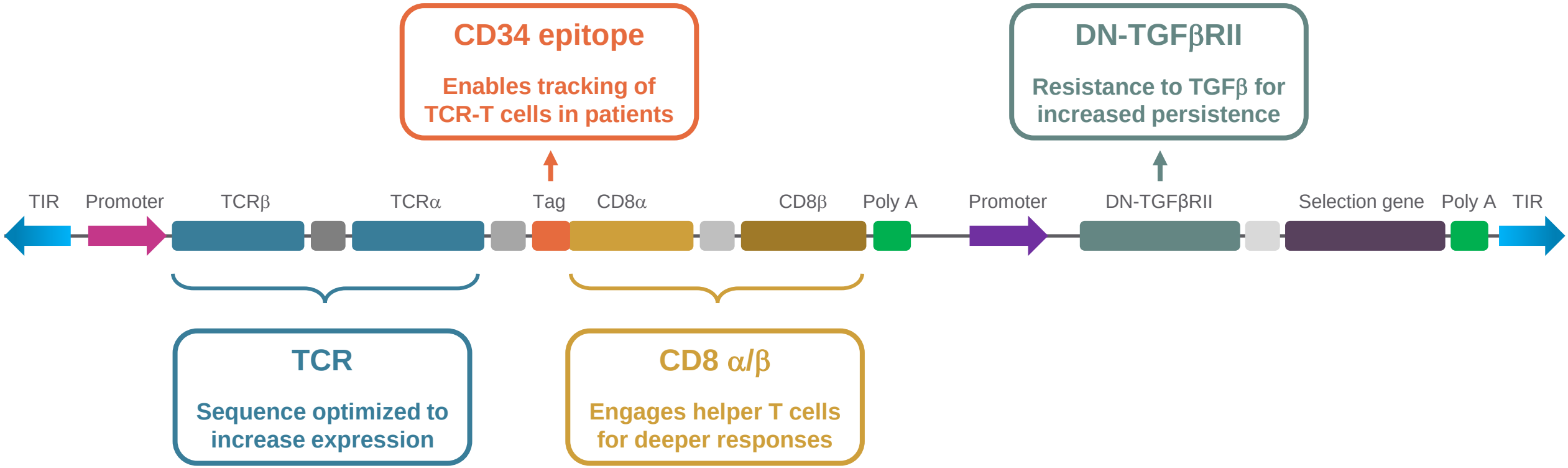
Multiplexed TCR-T controls *in vivo* heterogenous tumor growth better than singleplex therapy



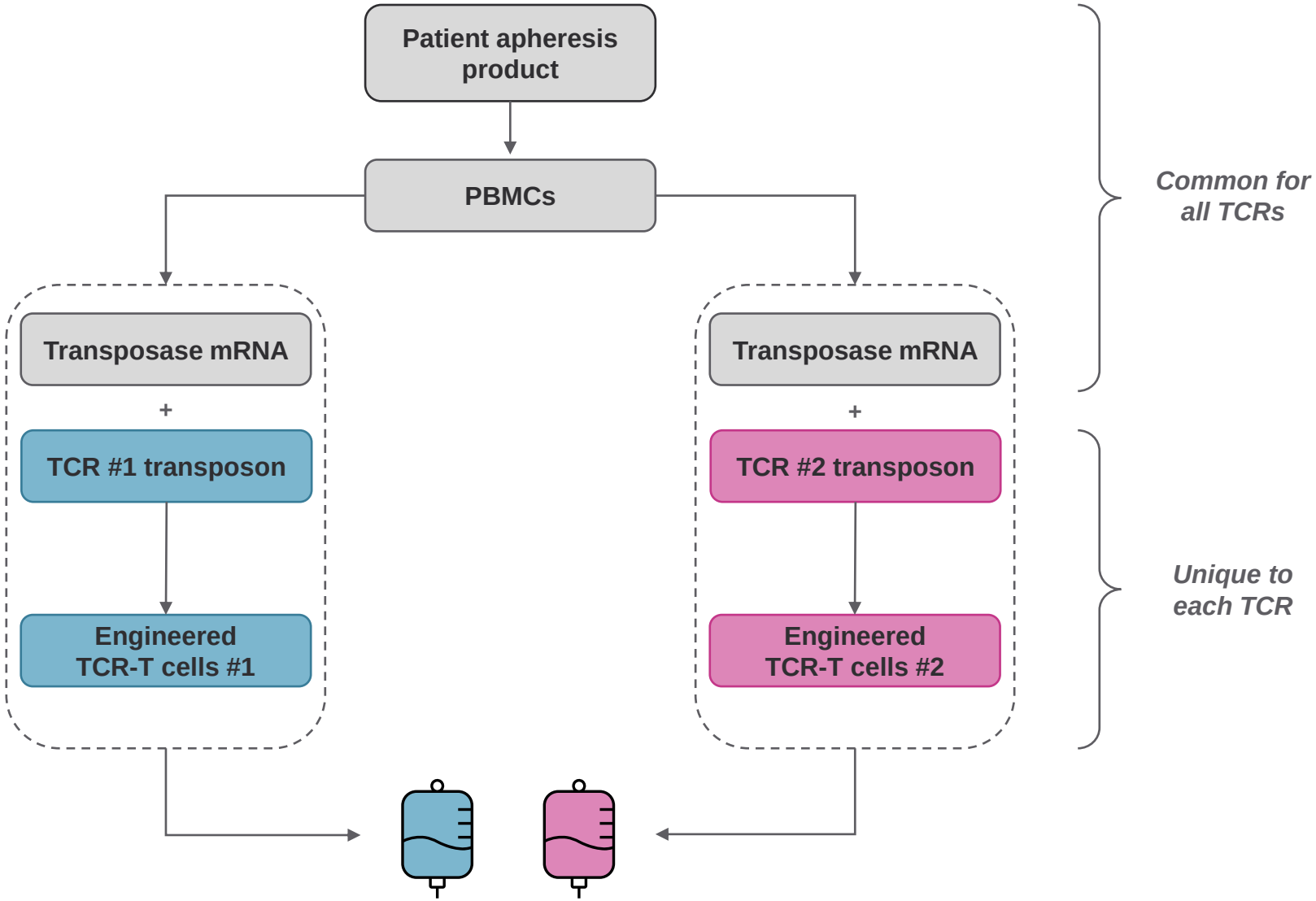


Bringing multiplexed TCR-T to patients

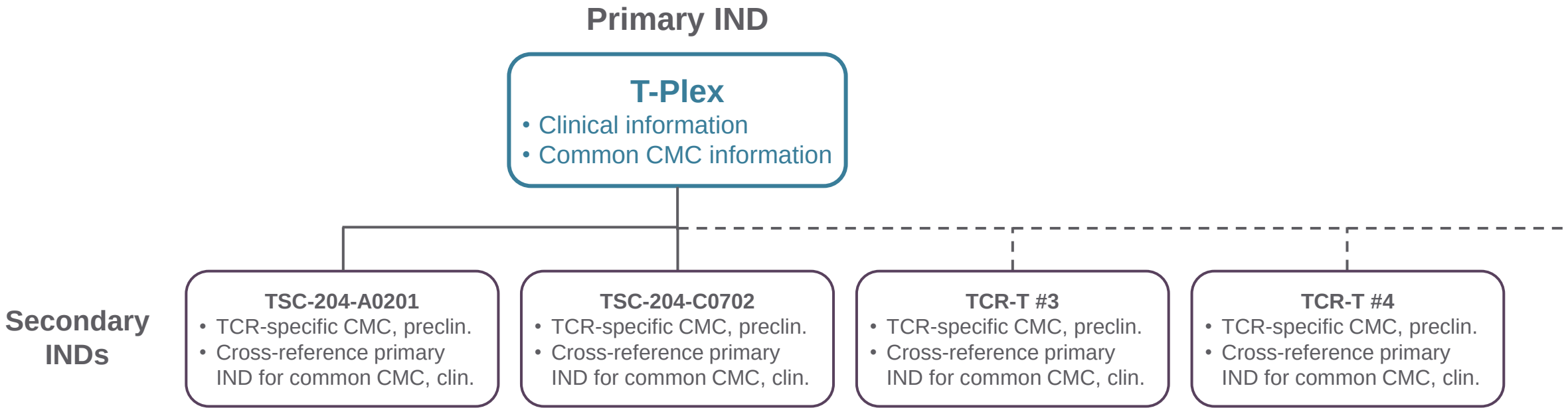
The same transposon vector will be used to engineer every *enhanced* TCR-T cell product in the ImmunoBank



Process enables facile manufacturing for multiplexed TCR-T

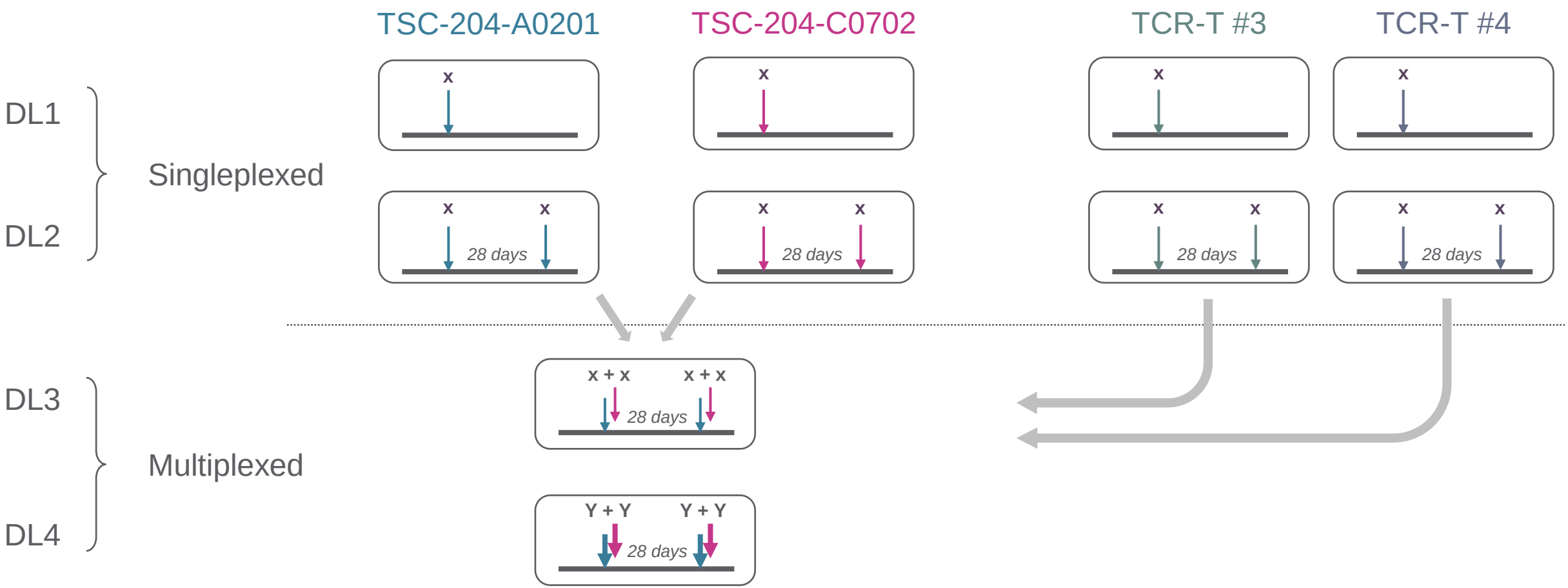


Based on feedback from the FDA, TScan has a clear path to building the ImmunoBank and developing multiplexed TCR-T



- Master clinical protocol resides in one Primary IND
- IND filing structure enables adding new TCRs as they become available
- Each secondary IND cross-references common CMC and clinical information in the Primary IND

Dose escalation scheme provides a rapid path to testing and expanding multiplexed TCR-T in Phase 1



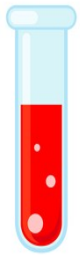
Patients will be prospectively selected in Phase 1 based on target expression and HLA loss

1 Germline HLA typing

2 Tumor target testing

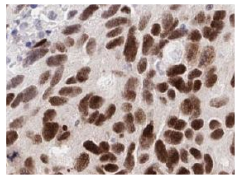
3 Tumor genomics

4 TCR-T selection



HLA in ImmunoBank

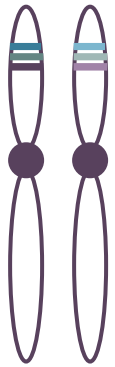
IHC / ISH



Neogenomics

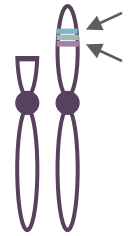
Targets present

HLA loss



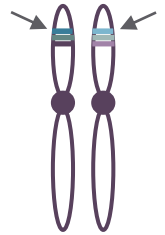
Tempus

HLA loss detected



Target HLAs on intact haplotype

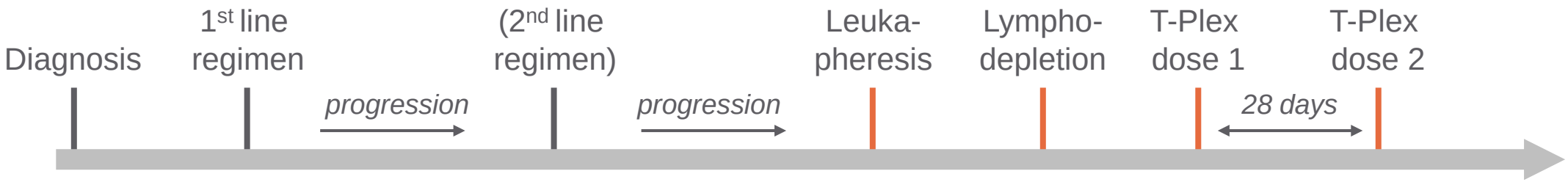
No HLA loss



Target HLAs on opposite haplotypes

Patients will be pre-identified for clinical trials using a screening protocol initiating in Q1, 2023

Patient journey



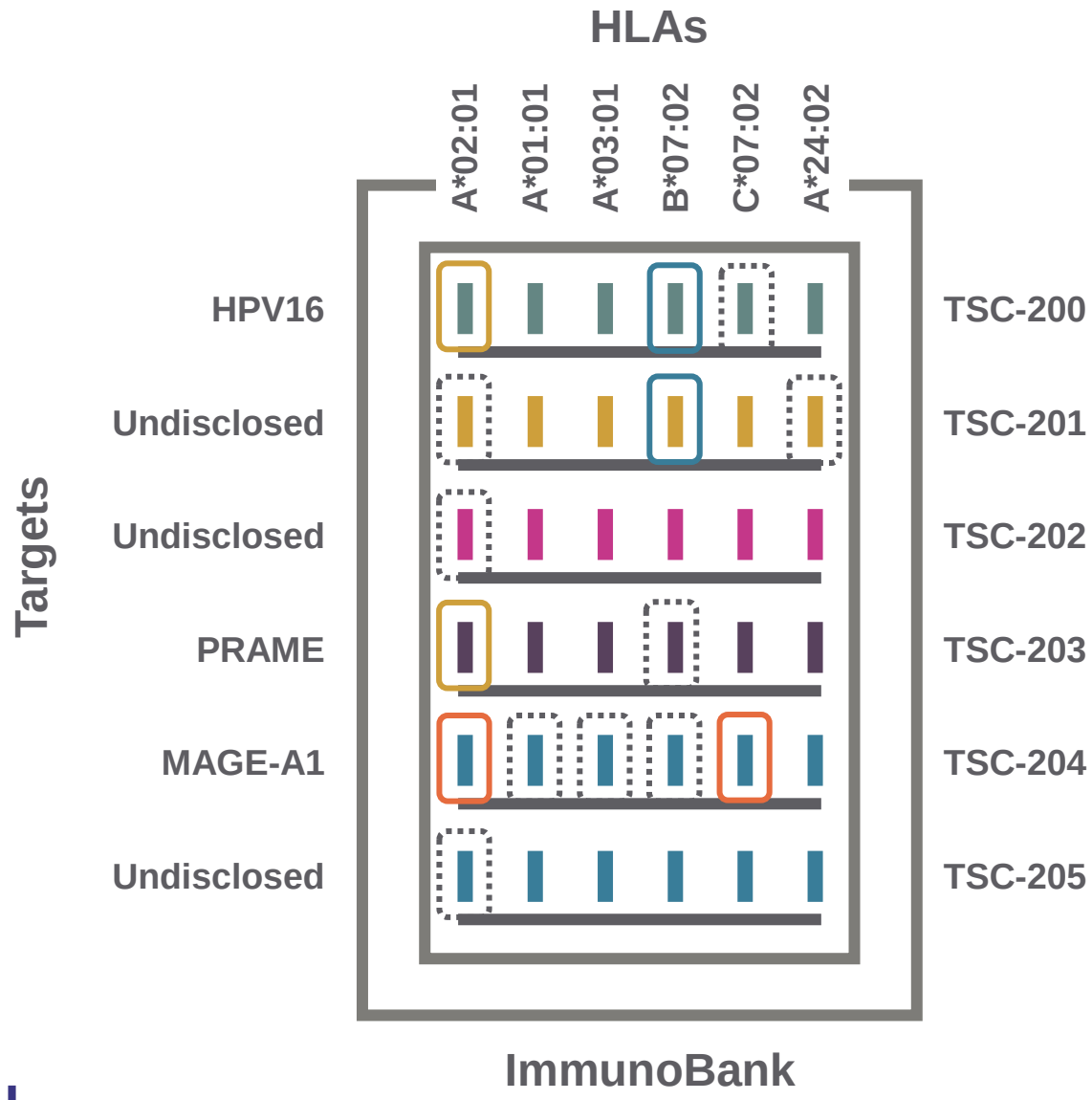
Screening protocol

- Pre-screens patients for trial eligibility
- Germline HLA testing
- Archival tumor sample
  - Tumor IHC
  - HLA LOH testing

Treatment protocol

- Vein-to-vein time 25 days
- No IL-2 given
- Endpoints
  - Primary: Safety
  - Secondary: ORR, DOR
  - Exploratory: T-cell persistence

Multiplexed TCR-T is enabled by a growing ImmunoBank

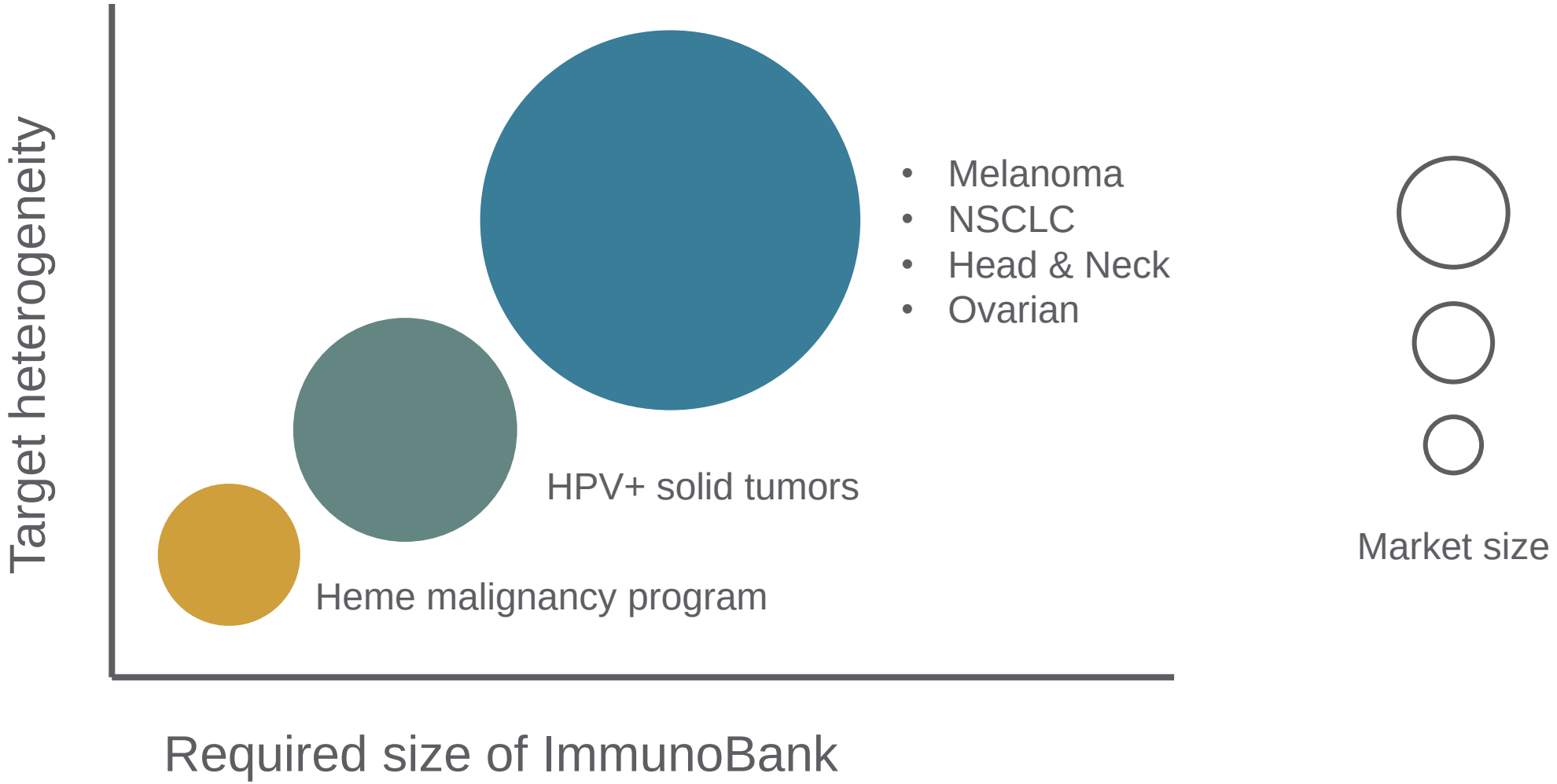


INDs

Q4, 2022	2 INDs
H1, 2023	2 INDs
H2, 2023	2 INDs
Discovery	4+ INDs, 2024

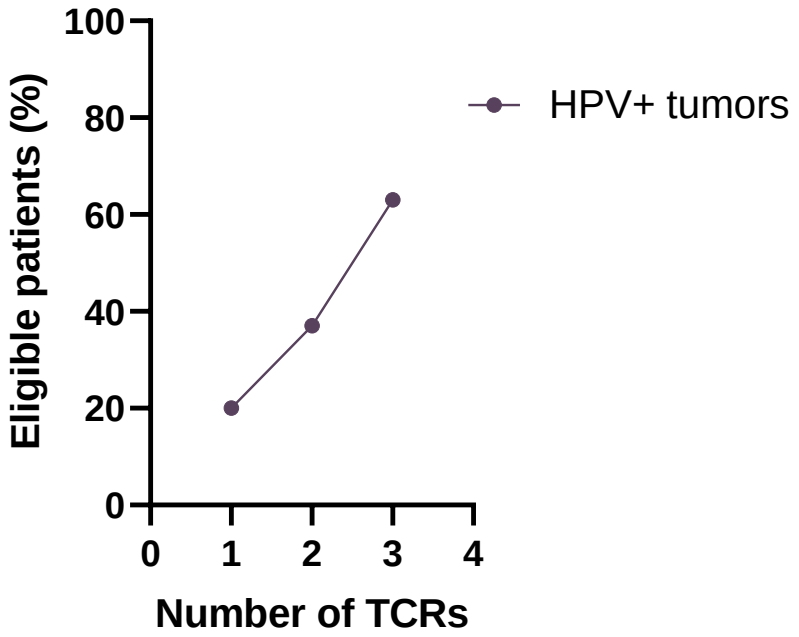
10+ TCRs in the clinic by the end of 2024

TScan's successive programs build layers of value with minimum number of required TCRs



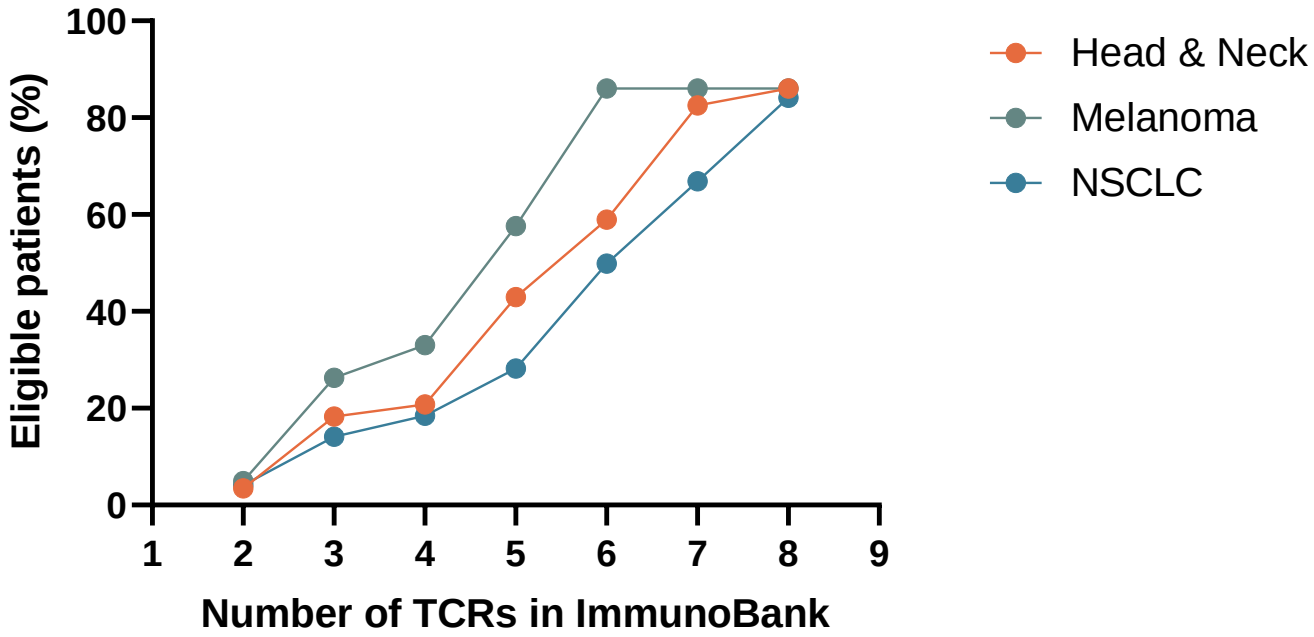
Patient eligibility and market size increases substantially as the ImmunoBank grows

HPV16+ cancers



Eligible patients include patients who do not require multiplexing (homozygous or hemizygous for targeted HLA type) or are eligible for at least 2 HPV16 TCRs

Other solid tumors



Eligible patients include patients who are positive for at least 2 TCRs in the ImmunoBank

Broad Pipeline Enables Multiplexed Therapy in Solid Tumors

	HLA Type	Indications	Discovery	Lead Optimization	IND-Enabling	Phase 1	Phase 2/3	Milestones
PROGRAMS (TARGET)								
Hematologic Malignancies								
TSC-100 (HA-1)	HLA-A*02:01	AML, MDS, ALL						Progress update by year-end 2022
TSC-101 (HA-2)	HLA-A*02:01							
Solid Tumors								
TSC-200 (HPV16)	HLA-A*02:01 HLA-B*07:02 HLA-C*07:02	Head & Neck, Cervical, NSCLC, Melanoma						
TSC-201 (undisclosed)	HLA-B*07:02 HLA-A*02:01 HLA-A*24:02							INDs for two TCRs anticipated by year-end 2022
TSC-202 (undisclosed)								
TSC-203 (PRAME)	HLA-A*02:01 HLA-B*07:02							Clinical data and four additional INDs in 2023
TSC-204 (MAGE-A1)	HLA-A*02:01 HLA-C*07:02 HLA-A*01:01 HLA-A*03:01 HLA-B*07:02