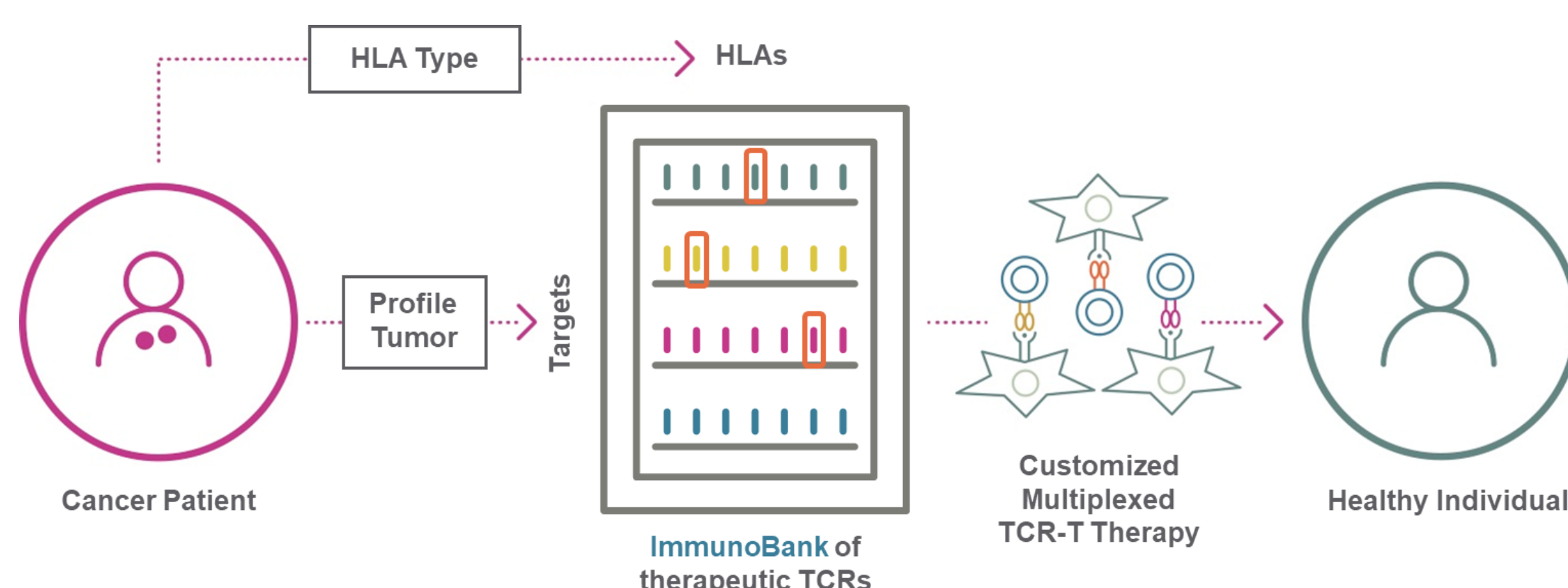


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Abstract # 709

Background and Rationale

- Most patients fail checkpoint immunotherapy due to lack of sufficient endogenous anti-tumor T cells
- A potential solution is to engineer T cells with exogenous T cell receptors (TCRs) that target tumor antigens
- However solid tumors are notoriously heterogenous with heterogenous target antigen expression
- Solid tumors have also been recently recognized to have HLA loss of heterozygosity (LOH) in up to 40% of tumors
- First generation TCR-Ts targeting single antigens had limited response rates (30-50%) and short durations of response (3-4 months)
- TScan's solution is to develop multiplexed TCR-Ts targeting different antigens on different HLA types
- TCR-T cells also have genetic enhancements to enable potent tumor killing and long-term persistence.

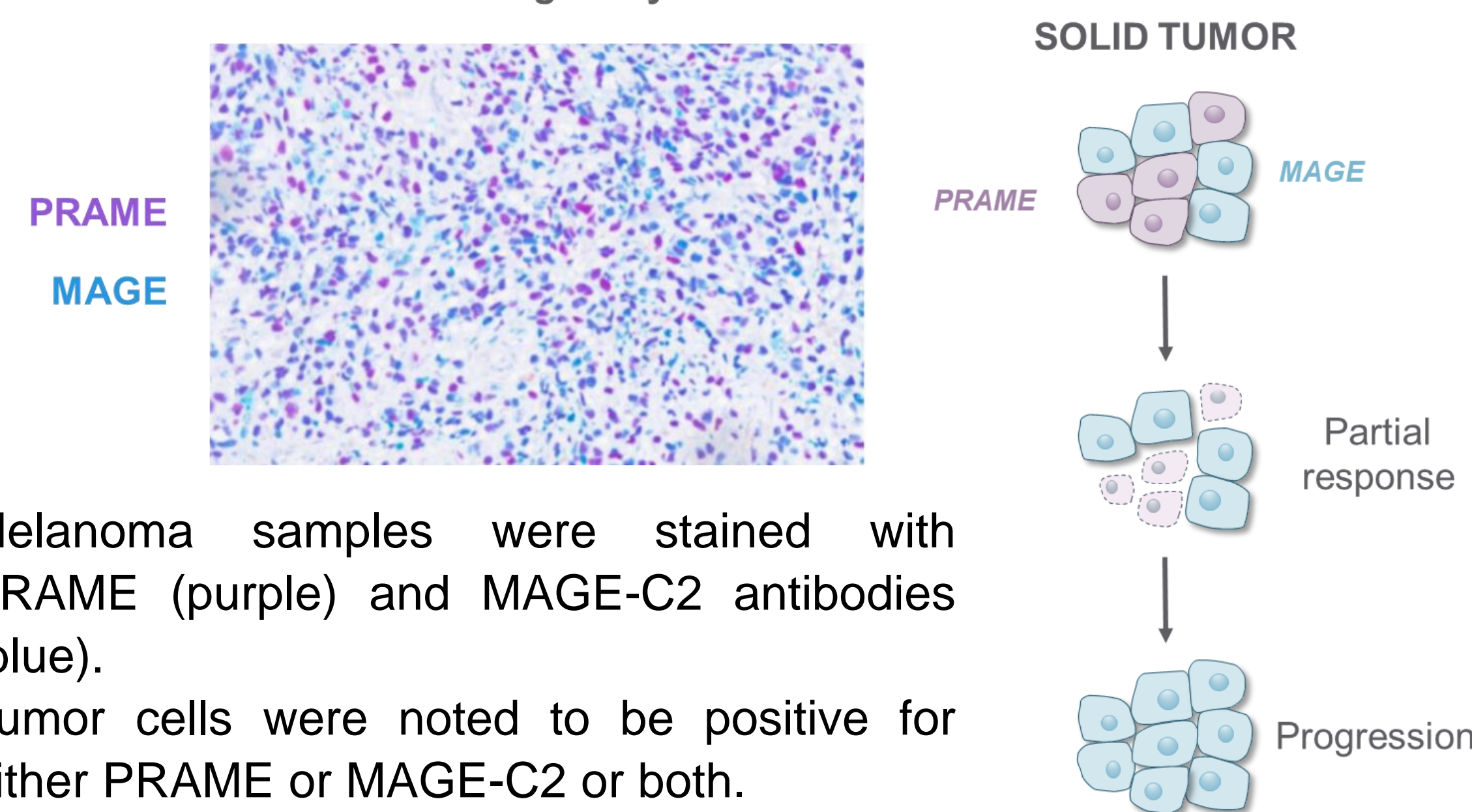


TScan's solution for increasing duration of response



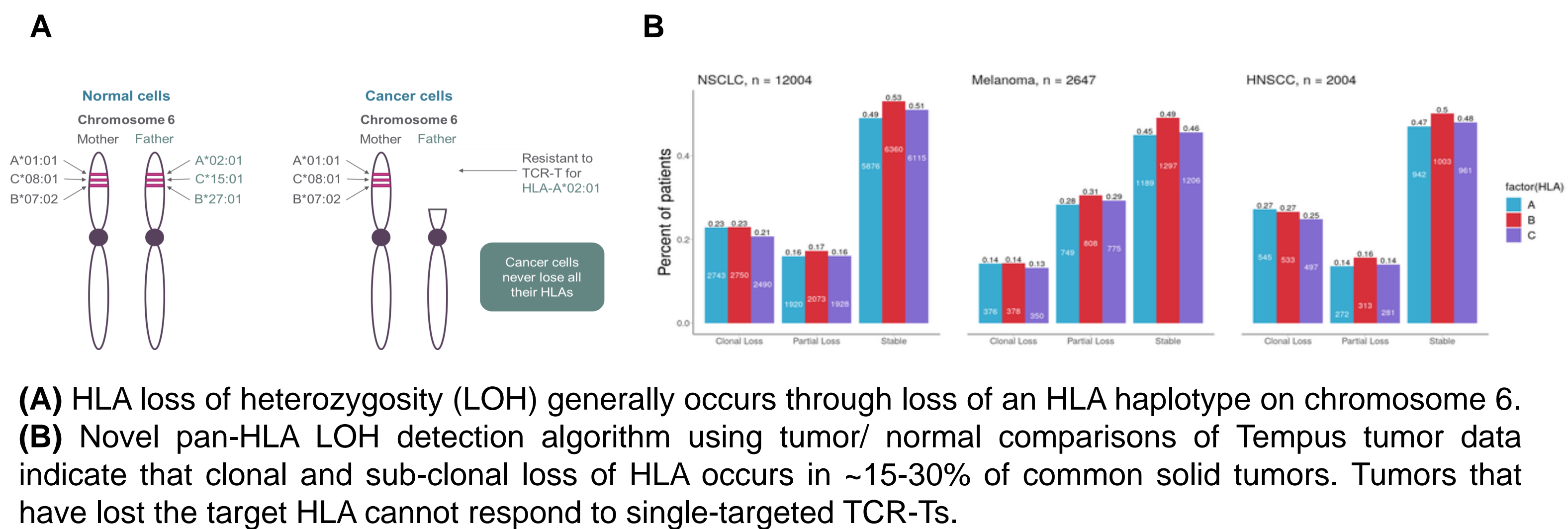
Target Heterogeneity in Solid Tumors

Tumor exhibiting target heterogeneity

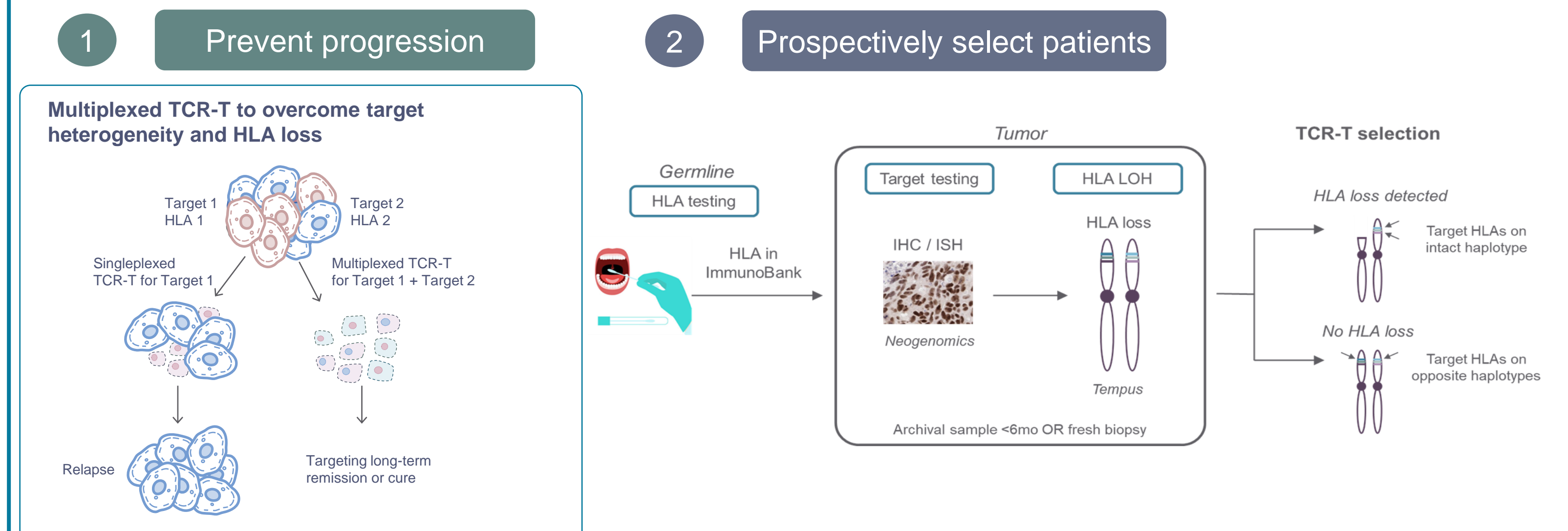


- Melanoma samples were stained with PRAME (purple) and MAGE-C2 antibodies (blue).
- Tumor cells were noted to be positive for either PRAME or MAGE-C2 or both.
- Targeting single antigens is expected to result in partial responses in these tumors with rapid progression.

HLA loss of heterozygosity (LOH) is prevalent and overlooked in solid tumors



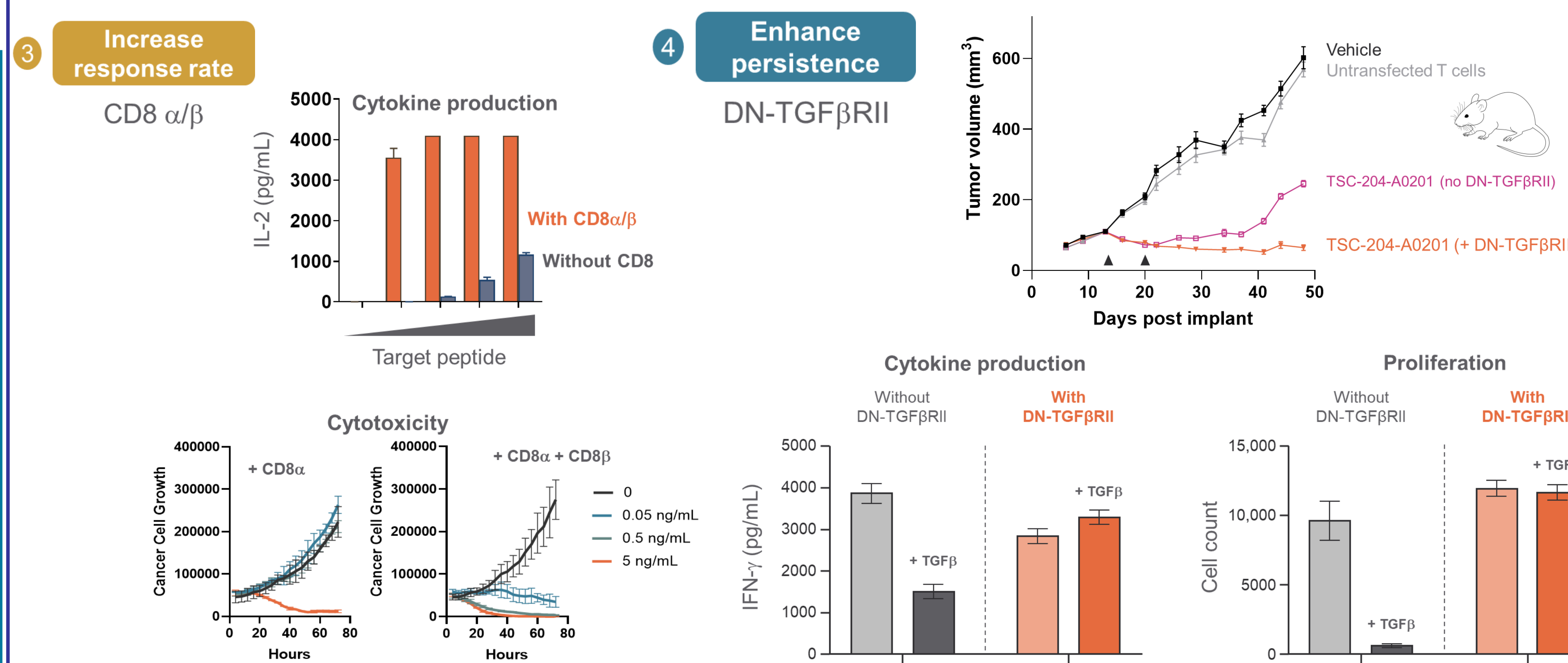
Multiplexed TCR-T cell therapy (T-Plex) can effectively address tumor heterogeneity and HLA LOH



(A) **Prevent Relapse:** First-generation TCR-Ts targeting single antigens on single HLA types often result in partial responses and rapid progression. Multiplexed TCR-T targeting different target antigens on different HLA types has the potential to induce more durable or even complete responses

(B) **Prospectively select patients:** Germline HLA typing is followed by testing tumors for target antigens and HLA LOH. TCR-T selection can be used to overcome HLA LOH.

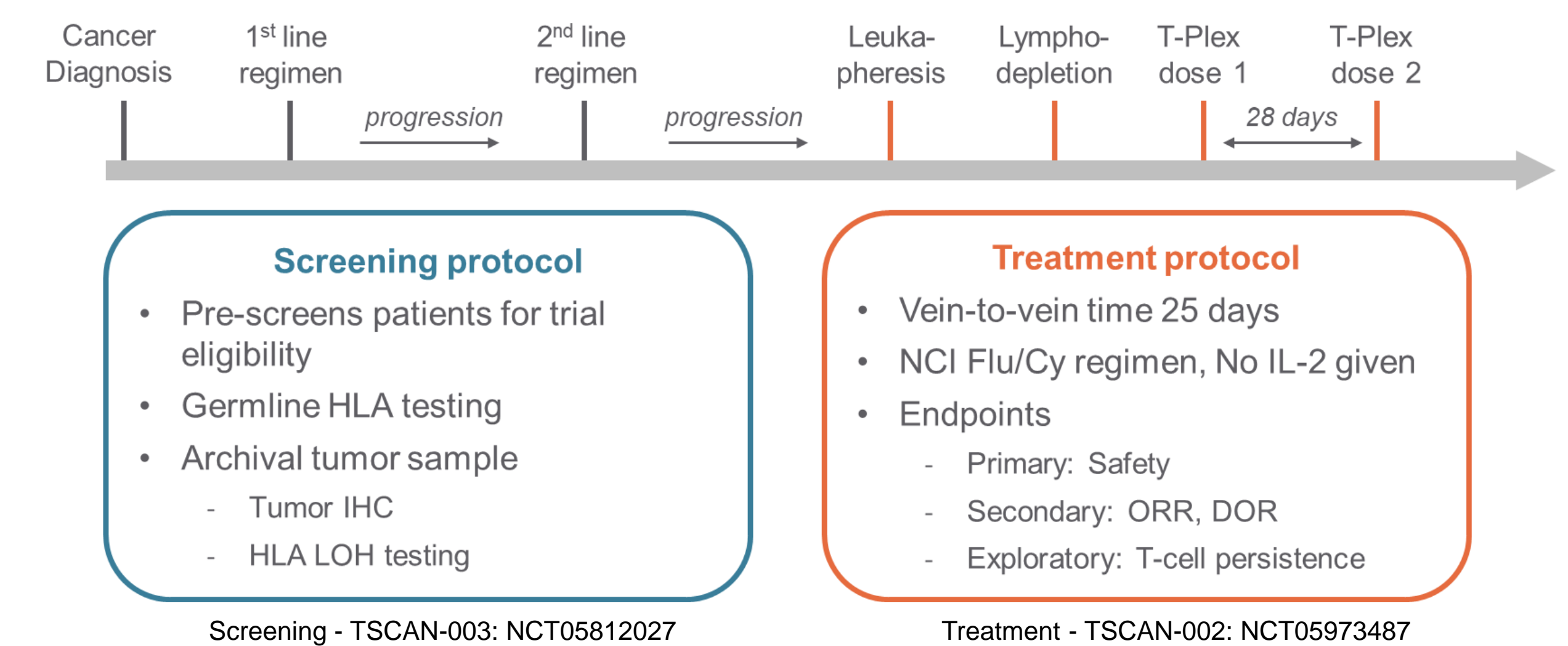
TCR-T cell function is enhanced with CD8α/β coreceptors and DN-TGFβRII



(3) **Increase response rate:** CD4+ T cells engineered to express TCR+CD8α+CD8β coreceptors had ~100-fold higher cytokine production (top) and cytotoxicity (bottom) versus CD4+ cells expressing TCR alone or TCR+CD8α.

(4) **Enhance persistence:** Expression of dominant-negative TGFβRII (DN-TGFβRII) results in durable responses of tumors *in vivo* (top), and ~2-fold higher cytokine production and ~10-fold higher T-cell expansion in the presence of TGFβ *in vitro* (bottom).

Screening protocol pre-identifies patients eligible for treatment



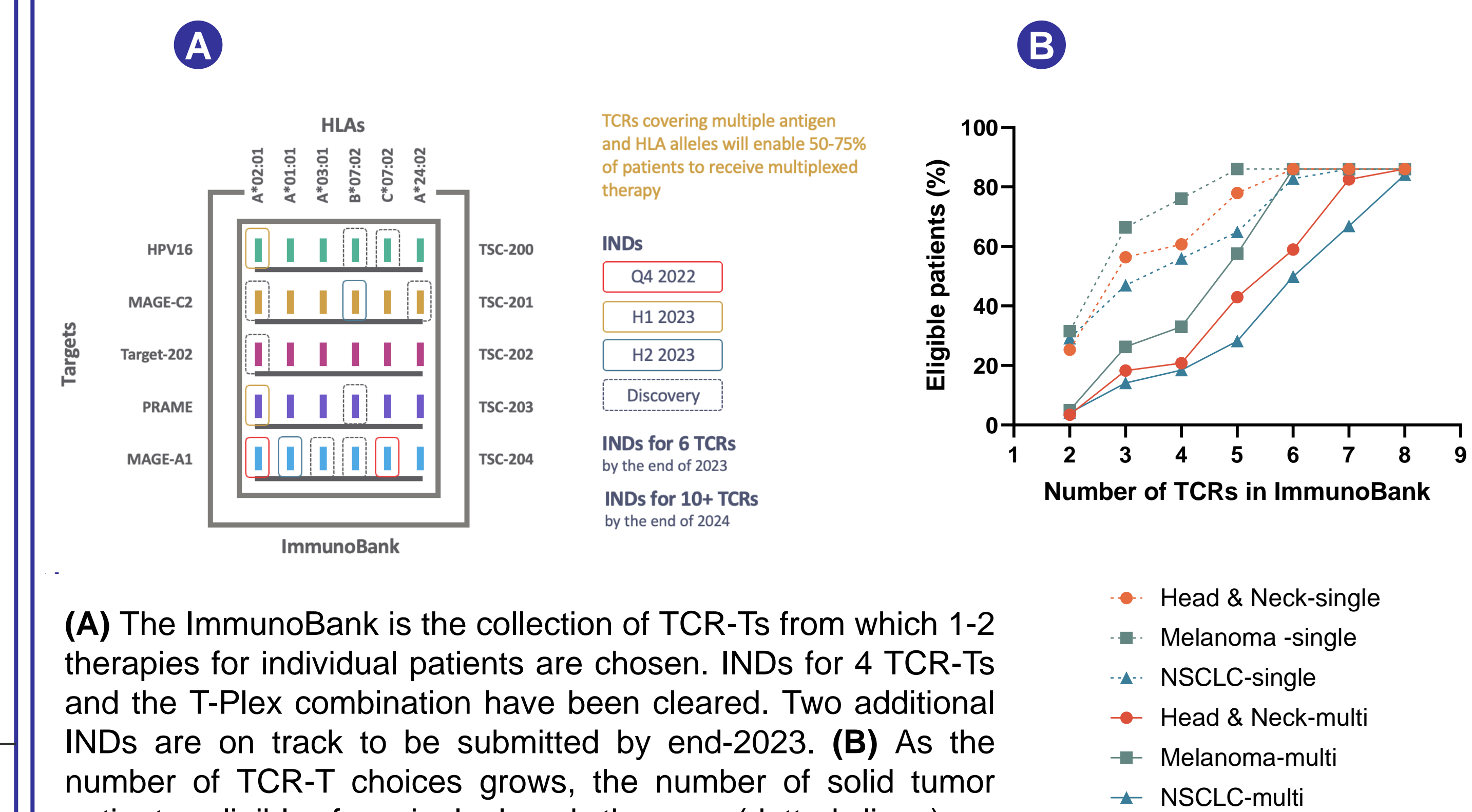
Patients with melanoma, NSCLC, head and neck cancer, cervical cancer, ovarian cancer or anogenital cancers are eligible. Screening includes germline HLA typing then archival tumor testing for antigens and HLA LOH any time during standard cancer treatment. Treatment involves 1-2 doses of TCR-T cell therapy after lymphodepletion.

Rapid dose escalation path to multiplexing from dose level 3



INDs have been cleared for 4 TCR-Ts: targeting MAGE-A1 on HLA-A*02:01 (TSC-204-A0201) and on HLA-C*07:02 (TSC-204-C0702), HPV 16 on HLA-A*02:01 (TSC-200-A0201), and PRAME on HLA-A*02:01 (TSC-203-A0201), as well as their combination (T-Plex). As additional INDs for new TCR-Ts are cleared, they will be incorporated into the same clinical study and follow the same dose escalation scheme.

Eligibility for multiplexed therapy increases with growing collection of TCR-Ts



(A) The ImmunoBank is the collection of TCR-Ts from which 1-2 therapies for individual patients are chosen. INDs for 4 TCR-Ts and the T-Plex combination have been cleared. Two additional INDs are on track to be submitted by end-2023. (B) As the number of TCR-T choices grows, the number of solid tumor patients eligible for singleplexed therapy (dotted lines) or multiplexed therapy (solid lines) increases.

Of the first 33 patients tested under the TSCAN-003 screening protocol, 24 patients (73%) have at least one HLA that matches the first six TCRs in the ImmunoBank: 18 patients match 1 HLA, 5 match 2 HLAs, and 1 matches 3 HLAs.