Trial in progress: A phase 1 trial of TSC-100 and TSC-101, engineered T cell therapies that target minor histocompatibility antigens to eliminate residual disease after hematopoietic cell transplantation

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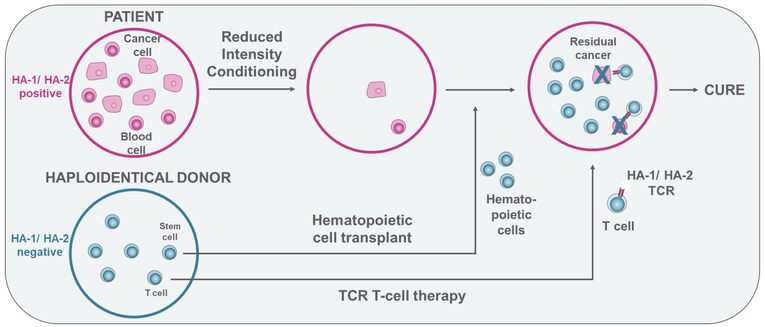
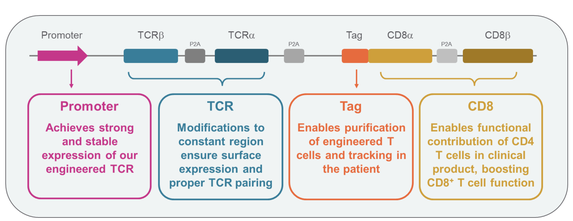
Abstract # CT151

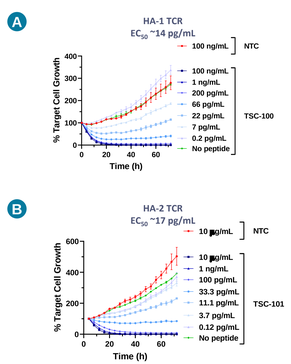
Background and rationale

- Engineered T cell therapies have been transformative for lymphoid malignancies because depleting normal B cells or plasma cells can be tolerated. Other hematologic malignancies have not benefited because depleting other normal blood cells like myeloid cells cannot be tolerated.
- Allogeneic hematopoietic cell transplantation (HCT) remains the best curative option for most hematologic malignancies, yet relapses occur in ~40% of patients post-HCT and are associated with high mortality.
- A potential solution is targeting hematopoietic-lineage specific minor histocompatibility antigens (MiHAs) mismatched between transplant recipients and their donors.
- TScan has developed the engineered T cell products TSC-100 and TSC-101 that express TCRs targeting MiHAs HA-1 and HA-2 respectively, both presented by HLA-A*02:01 and expressed only in hematologic cells.
- By choosing HCT patients who are HLA-A*02:01 positive and either HA-1 or HA-2 positive, and donors who are mismatched on either MiHA or HLA-A*02:01, TSC-100 and TSC-101 can eliminate all residual recipient hematologic cells while leaving donor hematologic cells untouched.



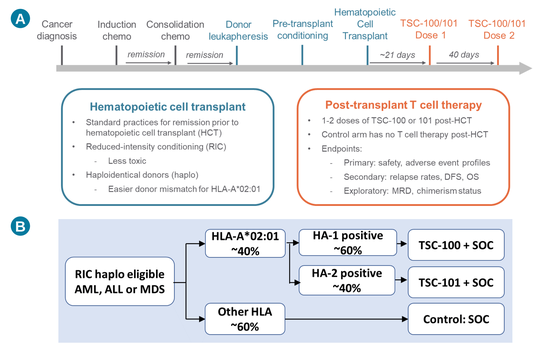
TSC-100 and TSC-101 target HA-1 and HA-2





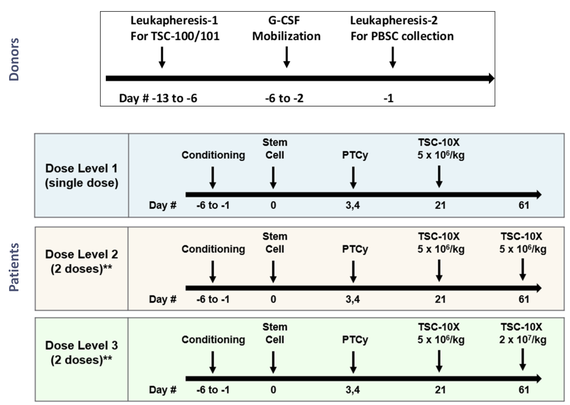
Left: Common vector used to manufacture both TSC-100 and TSC-101. **Right**: potencies of TSC-100 (A) and TSC-101 (B) were measured using peptide-pulsed T2 cells vs. non-targeted control TCRs.

Treatment plans and assignment to treatment arms



(A) All participants receive standard of care (SOC, blue) and treatment arm participants receive investigational (orange) treatment for patients with AML, ALL or MDS undergoing hematopoietic cell transplantation (HCT) following reduced intensity conditioning (RIC) from a haploidentical donor (haplo). (B) RIC-haplo eligible patients are assigned to treatment or control arms depending on their HLA and HA-1/ HA-2 genotypes and receive TSC-100/101+ SOC or SOC alone.

Investigational treatment plans and dose escalation cohorts



*Dose Level -1 reserved if toxicity observed at Dose Level 1 and need to de-escalate
**2nd Dose to be administered if no excessive toxicity noted with 1st dose and TSC-10X persistence <3% of total T cells, after review by the SRC and notification of FDA.

Investigational treatment plans for donors (top) or patients (bottom). Donors undergo two rounds of leukapheresis, first before G-CSF mobilization, to manufacture TSC-100/101, and second after mobilization, for standard peripheral blood stem cell collection. Patients receive conditioning therapy from Days -6 to -1, stem cell infusions on Day 0, post-transplant cyclophosphamide (PTCy) on Days 3,4 then upon count recovery (around Day 21), receive the 1st dose of TSC-100 or 101. In Dose Levels 2 and 3, a second dose is administered at least 40 days after the 1st dose. In Dose Level 3, the 2nd dose is escalated by 4-fold. Dose escalation rules follow the interval 3+3 design1 with 1-12 patients per cohort. **The study is currently enrolling patients at Dose Level 3.**

Inclusion/ exclusion criteria and key specifications for study NCT05473910

Inclusion Criteria

Patients in all arms:

- ≥18 years with AML, ALL or MDS
- ECOG-PS ≤2 any time in screening period
- Eligible for reduced intensity conditioning (RIC)
- Eligible for haploidentical donor HCT
- Treatment arms: HLA-A*02:01 positive
  - TSC-100 arm: HA-1+/- or HA-1+/+
  - TSC-101 arm: HA-2+/- or HA-2+/+
  - Agree with 15-year long term follow up
- Control arm: Any HLA type apart from HLA-A*02:01 or HLA-A*02:01 positive without suitably mismatched donor

Donors in treatment arms:

- ≥ 18 years old
- Able to undergo peripheral blood stem cell (PBSC) collection & 2 rounds of leukapheresis
- Donors matched to TSC-100 participants should be negative for all HLA-A*02 alleles or HA-1-/- (negative)
- Donors matched to TSC-101 participants should be negative for all HLA-A*02 alleles

Exclusion Criteria

Patients in all arms:

- Levels of donor-specific HLA antibodies high enough to warrant desensitization protocols and who have no alternate donors
- Treatment arms: HLA-A*02:07 positive
- Patients with evidence of clinically significant infection or uncontrolled viral reactivation of cytomegalovirus (CMV), Epstein-Barr virus (EBV), Adenovirus, BK virus (BKV), or human herpesvirus 6 (HHV-6)
- Prior allogeneic HCT

Donors in treatment arms:

- Donors for TSC-100 positive for any HLA-A*02 allele, unless they are HA-1 negative.
- Donors for TSC-101 positive for any HLA-A*02 allele regardless of HA-2 status.
- Donors who test positive for: HIV-1, HIV-2, HTLV-1, HTLV-2 or with active hepatitis B or hepatitis C, syphilis, West Nile virus infection or screen positive for risk of Creutzfeldt-Jakob disease or Zika virus with questionnaires.

Protocol Specifications

RIC regimens:

- Fludarabine/ cyclophosphamide/ total body irradiation (200 or 400 cGy)
- Fludarabine/ melphalan +/- / total body irradiation (200 cGy)
- Thiotepa/ busulfan/ fludarabine
- Fludarabine/ melphalan/ thiotepa

GvHD prophylaxis:

- Post-transplant cyclophosphamide (Days 3,4)
- Mycophenolate (until >Day 35)
- Tacrolimus (until >Day 90)

Acute or chronic GvHD treatment:

- Any therapy per institutional guidelines

Maintenance therapies:

- FLT3, BCR/Abl, IDH inhibitors- allowed 60 days post TSC-10X or after Day 100
- Other anti-leukemia agents (e.g. oral azacytidine) not allowed

Exploratory endpoints of minimal residual disease (MRD) and donor chimerism can indicate biological activity and early efficacy

Minimal Residual Disease

Pre-transplant

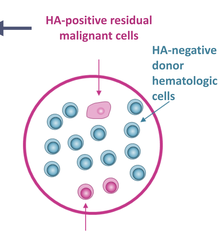
- Combination of next-generation sequencing (NGS) with flow cytometry detects MRD in 40% of AML patients[2].
- Pre-transplant MRD+ patients have ~67% risk of relapse with RIC[3].

Post-transplant

- Post-HCT MRD+ by flow alone tends to be low ~16%[4]. NGS expected to double MRD detection[2].
- Post-HCT MRD+ patients have up to 90% chance of relapse[4,5].

<u>MRD detection approach</u>:

- MRD will be detected in pre- and post-transplant bone marrow biopsies with a combination of flow (local sites) and NGS (central lab)
- **Conversion from MRD positive to negative can be an early indicator of biological activity and an early surrogate of efficacy**



Mixed donor cell chimerism

Standard STR-based assay

- <u>Pros</u>: clinically validated; measurable in all patients; mixed chimerism predicts ~60% risk of relapse[6]
- <u>Cons</u>: Poor limit of detection (~1%); PTCy causes high donor chimerism > 98% by Day 30[7]

Novel NGS-based assay (AlloHeme)

- <u>Pros</u>: NGS of ~400 SNPs improves limit of detection to 0.13%.
- <u>Cons</u>: Predictive value of NGS assay unknown, trial ongoing (NCT04635384)

<u>Chimerism detection approach</u>:

- Chimerism will be detected in bone marrow, whole blood, CD3 and CD33 subsets using standard STR and novel NGS assays
- **Complete donor chimerism and faster kinetics can indicate biological activity and early efficacy**

Endpoints: <u>Primary endpoints</u> include adverse event profile and dose limiting toxicities. <u>Secondary endpoints</u> include relapse rates at 1 year, disease-free-survival and overall survival. <u>Exploratory endpoints</u> include complete or mixed donor chimerism rates and kinetics, MRD+ rates before and after HCT and TSC-100/101 persistence in the treatment arms. Following transplantation, residual HA-positive patient-derived malignant cells are measured with high-sensitivity MRD assays (left) whereas residual HA-positive patient-derived hematologic cells, malignant, pre-malignant or normal, are measured using standard and high-sensitivity chimerism assays (left). **Clearance of MRD or mixed donor cell chimerism can be early indicators of biological activity and early surrogates of efficacy**. Preliminary results were presented at ASH, Dec 2023[8] and the Best Abstracts session at the Tandem Transplantation and Cellular Therapy Meeting, Feb 2024 with abstract available at: https://tandem.confex.com/tandem/2024/meetingapp.cgi/Paper/23846

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