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

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Abstract # 1901

Background and Rationale

- Engineered chimeric antigen receptor T cells (CAR-T) have transformed cell therapy for lymphoid malignancies because depletion of normal B cells or plasma cells can be tolerated and medically managed. Other hematologic malignancies have not benefited as depletion of other normal cells, like myeloid cells, can be life-threatening.
- Allogeneic hematopoietic cell transplantation (HCT) remains the best curative option for most hematologic malignancies, yet relapses occur in ~40% of patients post-HCT and relapses are associated with significant mortality.
- A potential solution to preventing relapse after HCT is targeting hematopoietic-lineage specific minor histocompatibility antigens (MiHAs) mismatched between transplant recipients and their donors.
- Unlike CAR-Ts, T cell receptor engineered T cells (TCR-T), can recognize both intracellular and extracellular tumor antigens and therefore provide a better T cell platform for designing adoptive cell therapies that target MiHAs.
- TScan has developed the engineered TCR-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 the MiHA or HLA-A*02:01, TSC-100 and TSC-101 are designed to eliminate all residual recipient hematologic cells while leaving donor hematologic cells untouched (Figure 1).

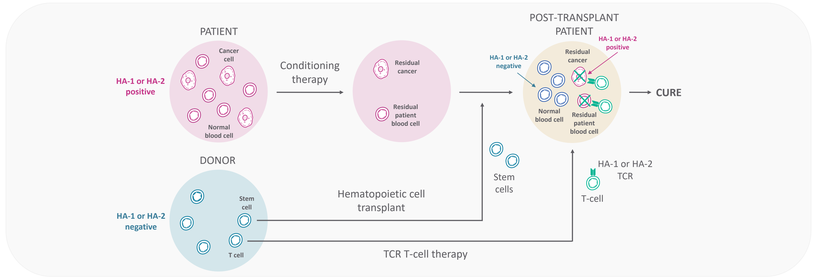
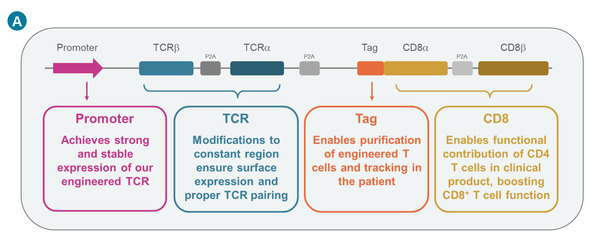
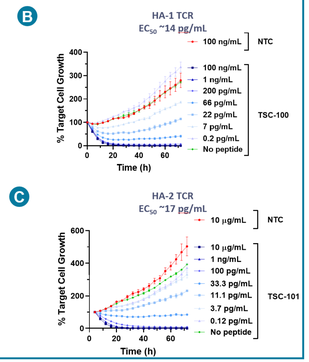


Figure 1: Depiction of differences in MiHAs between patients and donors allowing for selective targeting of residual cancer and patient-derived blood cells by TCR-T cells

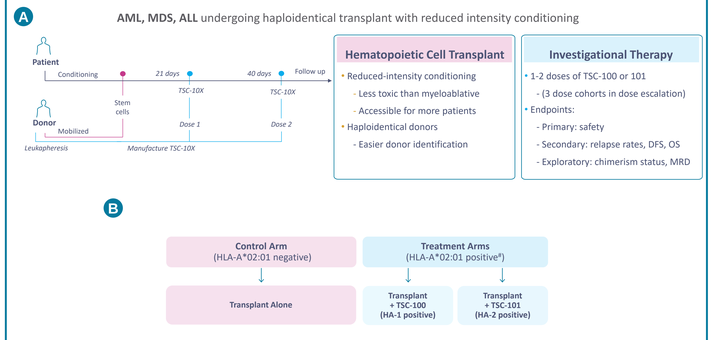
TSC-100 and TSC-101 Target HA-1 and HA-2





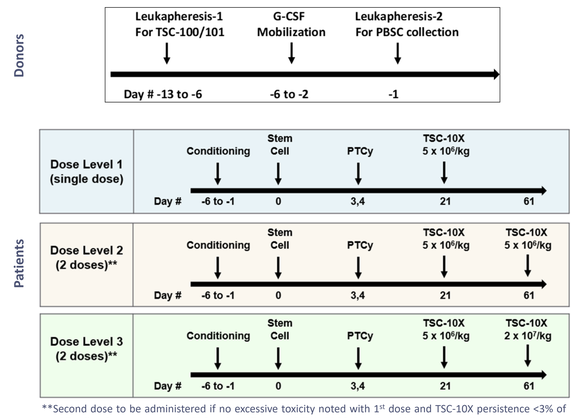
Common vector used to manufacture both TSC-100 and TSC-101 (A). Potencies of TSC-100 (B) and TSC-101 (C) were measured using peptide-pulsed T2 cells vs. non-targeted control (NTC) TCRs.

Treatment Plans and Assignment to Treatment Arms



(A) All participants receive standard of care HCT transplant (pink) and treatment arm participants receive investigational (blue) 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+ transplant or transplant alone. # ~42% of the U.S. population is A*02:01 positive.

Investigational Treatment Plans and Dose Escalation Cohorts



**Second 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. PBSC: Peripheral blood stem cells

Investigational treatment plans for donors (top) or patients (bottom). Donors undergo two rounds of leukapheresis, first before granulocyte-colony stimulating factor (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. Dose escalation rules follow the interval 3+3 design[1] with 1-12 patients per cohort. **The study is currently enrolling patients at Dose Level 3.**

Key Inclusion/Exclusion Criteria and 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:

- Per institutional guidelines, if required

Maintenance Therapies:

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

Exploratory Endpoints of Minimal Residual Disease (MRD) and Donor Chimerism can Indicate Biological Activity and Early Efficacy

Minimal Residual Disease

Pre-transplant

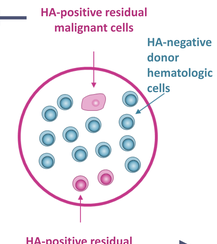
- Pre-transplant MRD+ patients have ~67% risk of relapse with RIC[3].
- Combination of next-generation sequencing (NGS) with flow cytometry detects MRD in 40% of AML patients[2].

Post-transplant

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

<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 is associated with high donor chimerism (> 98%) by Day +30, therefore residual recipient cells may be below detection limit after PTCy[7] is used for GvHD prophylaxis

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 could 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 could 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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