Trial in Progress: A Phase 1 Umbrella Study of TCR-Engineered T Cells That Target HA-1 (TSC-100) and HA-2 (TSC-101) to Treat Residual Leukemia after Hematopoietic Cell Transplantation

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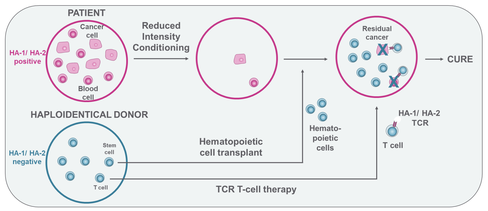
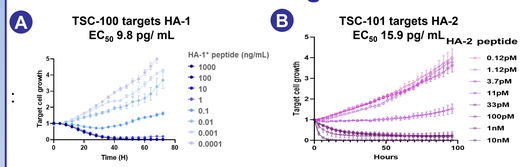
Introduction

Engineered T cell therapies targeting the lineage-specific antigens CD19 (B cells) or BCMA (plasma cells) are highly effective in patients with lymphoid malignancies and feasible because depleting normal B cells or plasma cells can be tolerated by patients. Targeting lineage antigens in myeloid malignancies is not feasible, however, since depleting normal myeloid cells like neutrophils would lead to serious complications such as febrile neutropenia. To address myeloid malignancies with T cell therapies, one solution is to target antigens that are expressed on the hematopoietic cells of patients undergoing allogeneic hematopoietic cell transplantation (HCT), but not expressed on their donor's cells. Hematopoietic lineage-specific minor histocompatibility antigens (MiHAs) can be targeted by T cell receptors (TCRs), but not chimeric antigen receptors, because they most frequently represent single-amino acid changes in intracellular proteins that are presented on the cell surface by human leukocyte antigens (HLA). 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. By choosing HCT patients who are 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 can eliminate all recipient hematopoietic cells while leaving donor hematopoietic cells untouched. These products are being developed in patients with AML, ALL and MDS undergoing HCT to eliminate any residual hematopoietic cells after HCT and prevent disease relapse that affects ~40% of patients. We describe the clinical trial design and translational assays to generate early evidence of biological activity.



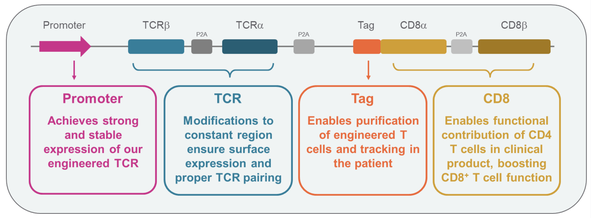
TSC-100 or TSC-101 target HA-1 or HA-2



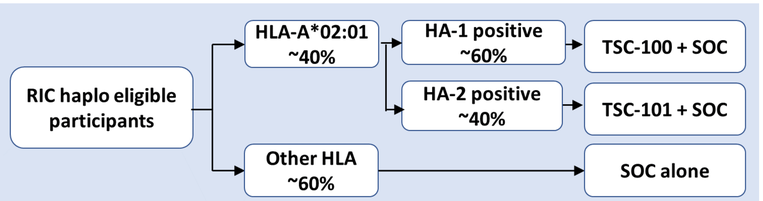
Potency of TSC-100 or TSC-101 targeting HA-1 (**A**) or HA-2 (**B**) was measured using peptide –pulsed T2 cells.

Product characteristics: TCR modifications, CD34 tag, CD8α/β coreceptors

The common vector used to manufacture TSC-100 or TSC-101 includes a strong promoter, modifications to ensure correct TCR pairing, a CD34 tag to purify and track the engineered T cells and CD8α/β coreceptors to allow CD4+ helper T cells to participate in target recognition and cytotoxicity. The manufacturing platform uses a transposon/ transposase system enabling the introduction of larger vectors with an increased number of functional elements.



Overall trial design for TSC-100/ TSC-101 in patients undergoing HCT



Patients with AML, MDS and ALL planned for HCT with reduced intensity conditioning (RIC) from a haploidentical donor (haplo) are assigned to treatment or control arms depending on their HLA and minor antigen type. All patients with HLA-A*02:01 (~40% prevalence) are genotyped to assign treatment arms. If they are HA-1 positive (~60% prevalence), they receive TSC-100 with standard of care (SOC) transplantation. If HA-2 positive (~40% chance) they receive TSC-101 +SOC. Donors would need to be mismatched for either HLA or minor antigen type. Patients without HLA-A*02:01 (~60%) or without mismatched donors will be assigned to the SOC control arm.

Inclusion/ exclusion criteria and key protocol restrictions

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 Restrictions

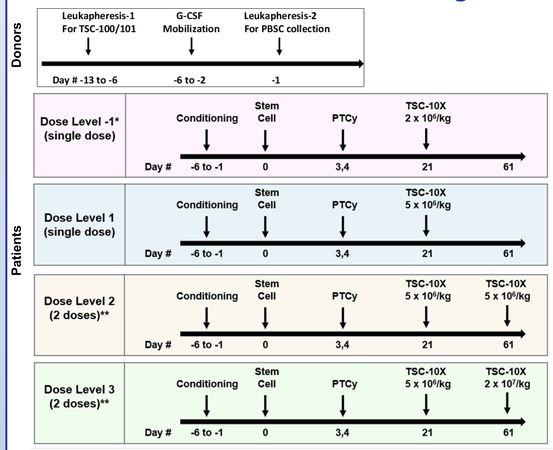
RIC regimens:
- Fludarabine/ cyclophosphamide/ total body irradiation (200 or 400 cGy)
- Fludarabine/ melphalan +/- / total body irradiation (200 cGy)
- Thiotepa/ busulfan/ fludarabine

GvHD prophylaxis:
- Post-transplant cyclophosphamide
- Mycophenolate
- Tacrolimus

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

Dose cohorts and treatment regimen for donors & patients in treatment arms



*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.

Donors for patients in treatment arms will undergo 2 rounds of leukapheresis. The first is before G-CSF mobilization and is used to manufacture TSC-100/ 101. The second is after G-CSF mobilization and is for standard peripheral blood stem cell (PBSC) collection.

Patients will undergo standard RIC conditioning followed by stem cell infusion then post-transplant cyclophosphamide (PTCy). Upon count recovery (around Day 21), they will receive a single dose of TSC-100 or TSC-101 (TSC-10X) in Dose Level 1. In Dose Level 2, patients receive 2 doses of TSC-10X, the first around Day 21 and the second 40 days after the first dose (around Day 61). In Dose Level 3, the second dose will be escalated to 4X the initial dose. Dose escalation will follow interval 3+3 design[1] (i3+3) with 3-12 patients per cohort.

Endpoints: Primary endpoints include adverse event profile and dose limiting toxicities. Secondary endpoints include relapse rates at 1 year. Exploratory endpoints include donor chimerism kinetics, MRD+ rates & TSC-10X persistence.

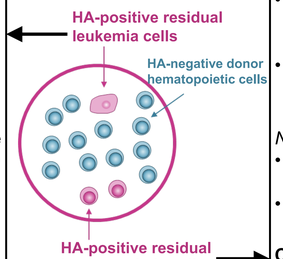
Early markers of efficacy and biological activity in translational labs

Minimal Residual Disease (MRD)

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].

MRD detection approach:
- 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 will be early indicator of efficacy



Mixed donor cell chimerism

Standard STR-based assay
- Pros: clinically validated; measurable in all patients; mixed chimerism predicts ~60% risk of relapse[6,7]
- Cons: Poor limit of detection (~1%); PTCy causes high donor chimerism > 98% by Day 30[8]

Novel NGS-based assay (Alloheme)
- Pros: NGS of ~400 SNPs improves limit of detection of 0.04%.
- Cons: Predictive value of NGS assay unknown, trial ongoing (NCT04635384)

Chimerism detection approach:
- Chimerism will be detected in bone marrow, whole blood, CD3 and CD33 subsets using standard STR and novel NGS assays
- Higher donor chimerism and faster kinetics will indicate biological activity

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