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PATIENT-DERIVED TAC01-HER2 TAC T CELLS PRODUCED IN COCOON® PLATFORM ARE HIGHLY FUNCTIONAL IN MODELS OF SOLID TUMORS

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ABSTRACT

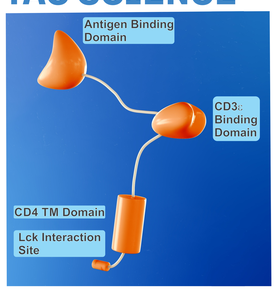
Background
The T cell antigen coupler (TAC) is a novel, proprietary chimeric receptor that facilitates the re-direction of T cells to tumor cells and activates T cells by co-opting the endogenous T cell receptor complex with the goal to elicit a safe and durable anti-tumor response. TAC01-HER2, a first-in-class TAC T product targeting HER2 (ERBB2), has entered a Phase I/II clinical trial in patients with HER2-positive solid tumors. Here, we characterized the TAC T cell phenotypes and anti-tumor activity of TAC01-HER2 manufactured using leukocytes from Phase I/II patients in nonclinical in vitro and in vivo assays.

Materials and Methods
TAC T cell proliferation, activation, and phenotype of patient-derived TAC01-HER2 were assessed by flow cytometric analysis. In vitro anti-tumor cytotoxicity was assessed via a real-time microscopy-based co-culture assay, and in vivo anti-tumor activity of TAC01-HER2 was assessed in mice engrafted with established solid HER2-expressing human tumors.

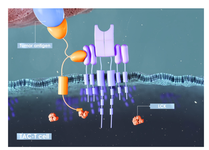
Results
Complex phenotype analysis showed that patient-derived TAC01-HER2 products consisted of a high percentage of memory T cells similar to products generated from healthy donors. Patient-derived products had significant proportions of CD4 and CD8 T cells, with CD4 being the predominant population in several of these. In a 5-day in vitro potency assay, patient-derived products showed effective tumor cell killing at low E:T ratios (1:1 to 1:20) which was comparable to product generated from healthy donors. Similarly, intravenous administration of patient-derived TAC01-HER2 in mice carrying HER2-positive tumors xenografts led to a complete and sustained tumor clearance.

Conclusions
The in vitro and in vivo data confirm the potency of patient-derived TAC01-HER2 against HER2-expressing solid tumor models. This work combined with other biomarkers may help correlate nonclinical potency with clinical outcomes.

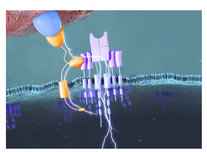
TAC SCIENCE



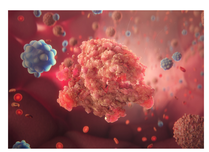
The membrane-bound TAC receptor interacts directly with the TCR-CD3 epsilon domain and...



...binds directly to the targeted tumor antigen. Clustering of TAC-TCR complexes leads to recruitment of kinases (Lck) via the cytoplasmic co-receptor domain and...



... initiates T cell activation via the endogenous CD3-TCR complex.



This results in effective cell lysis of multiple tumor cells during multiple killing events.

Watch a short animation to understand the TAC mechanism

Key features of TAC technology:

- TAC functions independently of MHC
- TAC activates T cells via the endogenous TCR
- TAC incorporates the co-receptor and recruits the TCR complex, mimicking natural TCR activation

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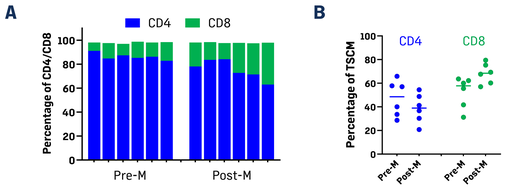
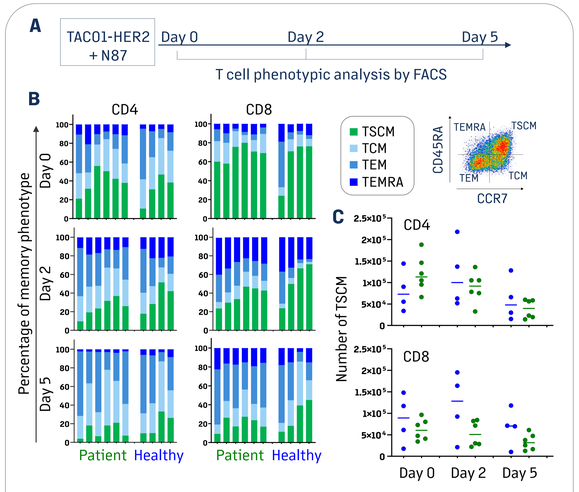
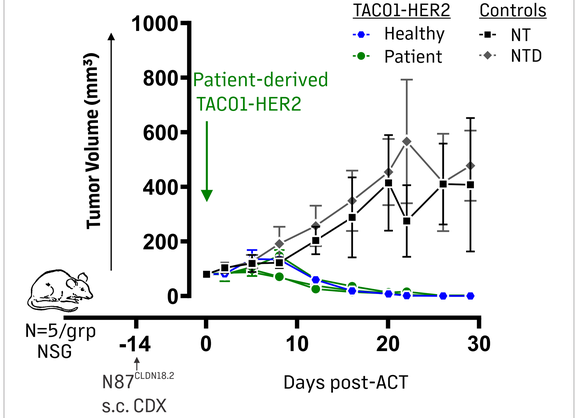


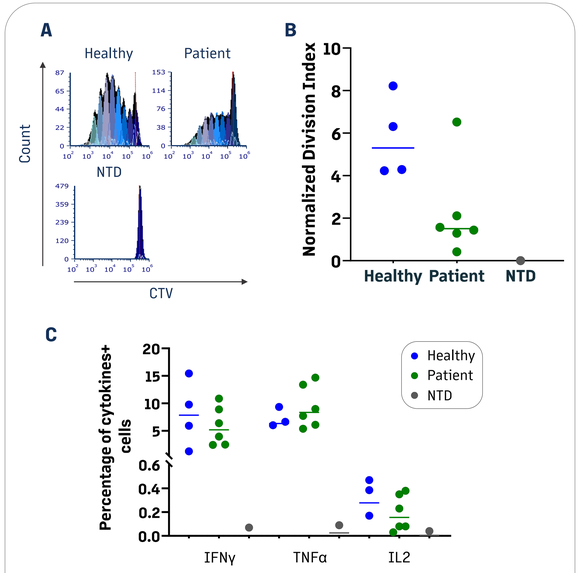
Manufacturing Increases the CD8 TSCM Population in TAC01-HER2 Products
T cells from six patients were characterized by flow cytometry analysis before and after manufacturing with TAC. **A.** Percentage of CD4/CD8 T cells. Each bar represents one patient product. **B**. Percentage of TSCM (CD45RA+, CCR7+) within CD4 and CD8 T cells.



Antigen-Exposure Induces Similar Memory-phenotype, Activation and Exhaustion in Patient-Derived TAC01-HER2 and Healthy Donor-Derived Products
A. TAC01-HER2 derived from patient or healthy donor was co-cultured with N87 for 5 days. The phenotype of T cells were analyzed on day 0, 2 and 5 by FACS analysis. **B.** Memory phenotype - Stacked bar chart of the percentages of TSCM, TCM, TEM and TEMRA. **C.** Absolute counts of TSCM within CD4 and CD8 T cells. **D.** Surface expression of T cell activation markers. **E.** Expression of exhaustion markers.



Patient-Derived TAC01-HER2 Products Eradicate Tumors in Mice
NSG mice were inoculated subcutaneously with $N87^{CLDN18.2}$ tumor cells, then treated with a single dose of 3×10^6 TAC01-HER2 or NTD control once tumors reached ~80 mm^3. A no treatment (NT) group was included as the negative control. Mean tumor volumes are shown ± SEM.



Patient-Derived TAC01-HER2 Products Show Robust Proliferation and Cytokine Production
A. TAC01-HER2 derived from patient / healthy donor or NTD control was stained with CTV dye before co-culturing with N87 for 4 days. Proliferation was measured by the proportion of CTV dye remaining in the T cells. **B.** The normalized division indices are shown. **C.** TAC01-HER2 was co-cultured with N87 for 4h, followed by intracellular staining for IFNγ, TNFα and IL2. Percentage of cytokine positive cells are shown.

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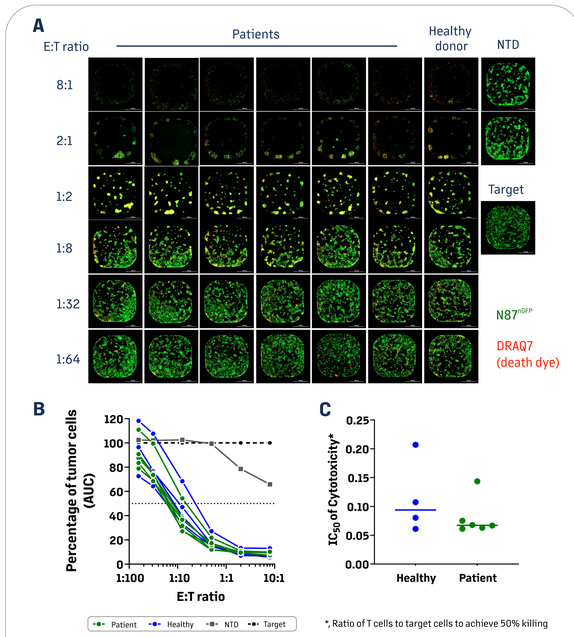

Patient-Derived TAC01-HER2 Products are as Potent as Healthy Donor Products in vitro
A. TAC01-HER2 derived from patient or healthy donor or NTD control was co-cultured with $N87^{nGFP}$ for 5 days at different E:T ratios. Co-Cultures were imaged every 8h, representative images at 120h are shown. **B.** The total GFP area was quantified, the area under the curve (AUC) was calculated, normalized to target alone and plotted against E:T ratio. **C.** IC_{50} of cytotoxicity (AUC) was calculated from nonlinear regression curve fit.

Summary

- **Cocoon® manufacturing increases the CD8 TSCM population in TAC01-HER2 products.**
- **Patient-derived TAC01-HER2 products retain a significant TSCM T cell population during antigen exposure in vitro and display activation phenotypes similar to healthy donor-derived products.**
- **Antigen exposure leads to robust proliferation and cytokine production of patient-derived TAC01-HER2.**
- **Patient-derived TAC01-HER2 products are highly potent in vivo and in vitro, comparable to healthy donor-derived products.**