ABSTRACT

Background
The T cell antigen coupler (TAC) is a novel, proprietary chimeric receptor that facilitates the redirection of T cells to tumor cells, and activates T cells by co-opting the endogenous TCR receptor complex with the goal to elicit safe and durable anti-tumor responses. TAC01-HER2, a first-in-class, autologous TACT cell product targeting HER2 (GDR823), has entered a phase I/II clinical trial in patients with HER2-positive solid tumors. Here, we describe the development of an allogeneic HER2-TAC T cell product based on lyoHER2 (yT) T cells which belong to a subset of T cells that recognize target cells in a human leukocyte antigen (HLA) independent manner. Thus, yT T cells do not cause HVR and have the potential for allogeneic cell therapy applications.

Materials and Methods
A variety of in vitro and in vivo assays were used to evaluate the potency and safety of HER2-TAC γδ T cells generated from multiple donors. In vitro assays included flow cytometric analysis determining the γδ T cell phenotype, intracellular cytokines, CD09 upregulation and T cell proliferation. Anti-tumor cytotoxicity was assessed via real-time microscopy-based co-culture assays. Adoptive lymphocyte reactions (MLR) were performed to measure cytokine production and proliferation of HER2-TAC γδ T cells in response to HLA mismatches between unrelated donors. In vivo studies examined the anti-tumor effect of HER2-TAC γδ T cells against established solid HER2-expressing tumors.

Results
HER2-TAC γδ T cells selectively reacted to HER2 expressing tumor cells in co-culture, as demonstrated by CD09 upregulation, intracellular cytokine production, increase in proliferation, and cytotoxicity. In contrast, HER2-TAC γδ T cells failed to show activity in MLR assays, potentially indicating that HER2-TAC γδ T cells are free of GvH reactivity. These MLR assays comprised dendritic cells that represent the major HLA subtypes found in North America. In addition, HER2-TAC γδ T cells showed strong anti-tumor efficacy in HER2-positive human tumor xenograft mouse models, without signs of toxicity.

Conclusions
The in vitro and in vivo data confirms strong and specific activity of HER2-targeted TAC γδ T cells against HER2-expressing tumor models, and highlights the potential of the TAC platform in the development of an allogeneic product for therapeutic applications in solid tumors.

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

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Summary
- HER2-TAC γδ T cells are selectively activated in the presence of HER2-positive tumor cells
- HER2-TAC γδ T cells display strong cytotoxicity towards HER2-positive tumor cells in co-culture assays
- HER2-TAC γδ T cells effectively eradicate HER2-expressing tumors in vivo