ACTallo®: Using Allogeneic Gamma-Delta T cells to Treat Cancer

Melinda Mata1, Mamta Kalra1, Nina Pawlowski2, Zoe Coughlin3, Shaunte Expo-Otu1, Frank Schwoebel2, Leonie Alten1, Aleksandra Nowicka1, Sarah Missel2, Sabrina Kutruff-Cooqui2, Norbert Hilt3, Toni Weinschenk2, Harpreet Singh-Jasuja2, Ali Mohamed1, Mo Dao1, Yannick Bulliard4, Steffen Walter1
1Immatics US Inc., Houston, TX, USA. 2Immatics Biotechnologies GmbH,Tuebingen, Germany.

Introduction
Adaptive therapy (ACT) has changed the landscape of cancer immunotherapy; however, the complex manufacture of individualized products from late-stage, heavily pre-treated cancer patients, together with high cost-of-good, encourages the development of simpler ‘off-the-shelf’ alternatives. The unique properties of γδ (gamma-delta) T cells make them an attractive candidate for effective allogeneic ACT. In contrast to γT cells, γδ T cells are endowed with intrinsic antitumor activity while unable to induce graft-versus-host disease. γδ T cells have a high proliferative potential before exhibiting exhaustion. Moreover, in the context of γδ TCR-engineered ACT, γδ T cells pose a low risk of off-target toxicity, due to the absence of expression of endogenous αβ TCR and hence, no possibility of mispairing with the engineered αβ TCR.

The ACTallo® strategy

ACTallo®: Allogeneic T Cells Transduced TCR

Figure 1: Overview of the ACTallo® Strategy

ACTallo® is based on the genetically engineered allogeneic γδ T cells to express novel and xenogenous TCRs. In addition to the specific tumor recognition via the ectopic (“placed”) TCR, gamma-delta T cells may demonstrate inherent activity against numerous tumor types.

✓ γδ TCR chains do not mispair with αβ TCR chains
✓ γδ T cells recognize antigens independent of HLA (no allo-reactivity)
✓ γδ T cells express high levels of CD3
✓ Off-the-shelf ACT with γδ TCR transgenic allogeneic γδ T cells

Overview: The XPRESIDENT® platform

The ACTallo® approach can be combined with Immatics’ XPRESIDENT® platform for discovering specific targets, enabling the generation of donor derived tumor specific T cells against a variety of tumor antigens.

ACTallo® γδ T cells can be transduced ex vivo

Figure 5: γδ T cell transduction of γδ T cells

ACTallo® γδ T cells were transduced with viral vectors expressing a TCR specific for an antigen discovered by the XPRESIDENT® platform and human CD8. γδ T cells transduced with IMA201 TCR (A) or IMA203 TCR (B) were photoregulated for TCR expression via flow cytometry using an antibody specific for TCR chain. Cells were gated on CD3+γδ+T-cells and are representative of n=3 donors. Expansion of transduced ACTallo® γδ T cells was assessed during culture and showed comparable expansion rates to non-transduced (NT) cells [1]. Peak expansion is donor dependent and high dose-to-donor variability for ex vivo expansion of γδ T cells is well documented (Tenaka et al., Cancer Science (2018) 109: 176-189).

ACTallo® γδ T cells effectively recognize and kill tumor cells in vitro

Figure 6: γδ T cells engineered with IMA201 or IMA203 TCRs

ACTallo® γδ T cells expressing IMA201 or IMA203 TCR and CD8 were expanded and co-cultured with tumor cells expressing the target antigen. Cytotoxic potential was assessed using either a fluorescent microscopy-based cytotoxicity assay or a FACS-based cytotoxicity assay. Results are presented as mean ± SD of triplicates and are representative of n=3 donors. IFNγ release was assessed after 24 Hour in vitro co-culture with solid tumor (n=3 donors) or liquid tumor (n=1 donor) cell lines via ELISA.

ACTallo® drug product displays a preferential TCR/TCR phenotype

Figure 7: Phenotype of in vitro expanded ACTallo® γδ T cells

ACTallo® γδ T cells were transduced and expanded ex vivo for 24 days and then phenotypified for CD27 and CD45RA expression via flow cytometry to determine memory phenotype.

Summary and Conclusion

Here, we present the ACTallo® platform, which combines the unique properties of γδ T cells with Immatics’ XPRESIDENT® target/XCLEPTOR® TCR development platform. The ACTallo® process selectively expands γδ/γδ T cells that are transduced to co-express CD8β together with a tumor-specific γδ TCR. Over a period of 21 days or less, ACTallo® γδ T cells can expand >10,000 fold. γδ T cells obtained this way recognize tumor cells, express high-levels of cytokines, degrade and kill tumor cells specifically. In addition, ACTallo® γδ T cells show no signs of exhaustion after expansion, as evidenced by the lack of expression of checkpoint regulators (not shown). ACTallo® is intended to overcome the limitation of autologous cellular therapies, by combining the large-scale expansion potential of allogeneic γδ T cells with novel TCRs against XPRESIDENT® mass-spectrometry guided tumor-specific targets.

Immatics Biotechnologies GmbH
Immatics US, Inc.
www.immatics.com
info@immatics.com
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