Development of a CD8 co-receptor-independent T cell receptor specific for tumor-associated antigen MAGE-A4 for next generation T cell-based immunotherapy

Davari K1, Holland T1, Prassmayer L1, Longinotti G1, Ganley K2, Pechilis LJ2, Diacomu I2,3, Nambiar PR2, Magee MS2, Schendel DJ1, Sommermeyer D1 and Ellinger C1

Authors contributed equally
1Medigene Immunotherapies GmbH, a subsidiary of Medigene AG, Planegg, Germany, 2bluebird bio Inc., Cambridge, MA, USA; 3present address: ElevateBio, Cambridge, MA, USA

For further information and questions please contact Davari Kavet or Daniel Sommermeyer. k.davari@medigene.com or d.sommermeyer@medigene.com

Abstract

Background. The cancer-testis antigen MAGE-A4 is an attractive target for T cell-based immunotherapy, especially for indications with unmet clinical need like non-small lung cancer or triple-negative breast cancer. Overcoming both T cell dysfunction using adoptive transfer of T cells modified to express a transgenic T cell receptor (TCR) demands optimal recognition of the tumor target antigen by tumor cells. The tumor target antigen was selected in an in vitro screen by examining the expression of a human cancer lines (HCL) containing the MAGE-A4-specific epitope. The MAGE-A4-derived TCR was shown to be cytokine-dependent, killing tumor cells displaying the MAGE-A4 epitope, and was used for the development of a TCR-based immunotherapy. The ability of this co-receptor-independent TCR to activate all transduced T cells (independent of CD4 or CD8 co-expression) could provide enhanced cellular responses in the clinical setting through the induction of functionally diverse T cell subtypes that goes beyond what is currently tested in the clinic.

Figure 1. Tumor associated antigen MAGE-A4 harbors an immunogenic cancer cell T cell epitope

Figure 2. MAGE-A4-derived TCRs expressing an all-co-receptor TCR exhibit superior epitope binding characteristics compared to bbT476 expressing the auto-receptor TCR

Figure 3. bbT476 and bbT485 TCRs both display excellent safety profiles for adoptive cell therapy

Figure 4. bbT476 TCR-Ts are more efficacious than bbT476 TCR-Ts in vitro and in vivo

Figure 5. α4β7-independent TCR independence of the all-co-receptor TCR enables CD4+ cell-mediated anti-tumor response

Summary for bbT476 TCRs

- MAGE-A4-specific HLA-A2-restricted TCR (T cell product: bbT476 TCR-Ts)
- Original TCR was isolated from a non-KLED-sorted T cell repertoire (all-co-receptor TCR)
- bbT476 TCRs perform well in vitro (affinity maturation needed)
- bbT476 TCR-Ts show excellent safety profiles
- Highly efficacious TCRs are shown in vitro and in vivo experiments
- CD8 co-receptor-independent
- CD4+ TCRs support anti-tumor response by direct killing
- Strong immunosuppressive-capacity by fully functional HLA repertoire

Graphs showing different read-out of activation of CD8+ and CD4+ T cells expressing transgenic TCRs (data from 4 experiments in A and B, or 5 experiments in C) with or without MAGE-A4. A: Bar graphs depicting the proliferation of T cells in response to MAGE-A4 peptide with different concentrations of MAGE-A4 peptide in CD8+ (left panel) and CD4+ T cells (right panel). B: Flow cytometry showing the expression of CD69 marker on T cells cultured with MAGE-A4 peptide. C: Flow cytometry showing the expression of IFN-γ in T cells cultured with MAGE-A4 peptide.