Relevant preclinical models to test T cell engagers: The case of CD28

It would certainly be the understatement of the year to say that immunotherapies have changed oncology. From Immune CheckPoint (ICP) inhibitors to specific immune-cell engagers, this has truly been a revolution for the field, as these new compounds have proved extremely efficient. There is, however, a potentially very costly trade-off to these novel therapies, as some of them have also shown serious adverse effects and immune complications. The regrettable story[1] of CD28 superagonist antibody TGN1412 has changed how compounds are evaluated preclinically, and definitively underscored the absolute need for relevant, physiological preclinical models for compounds' efficacy and safety assessment.

Many compounds, mostly bispecific antibodies and combination therapies, are being developed for the targeting of T cells, with CD3 and CD28 being widely used as targets for such approaches. Considering the differential biology of CD28 in human and mouse, generating a relevant preclinical humanized model has proved challenging. Indeed, CD28 stimulation in humans can lead to the production of various cytokines in absence of TCR ligation,[2] whereas in rodents it produces almost no cytokine and preferentially activates and expands immunosuppressive
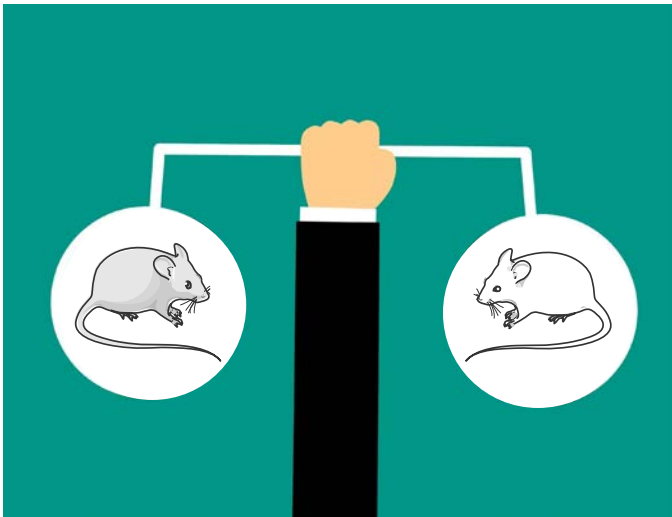
Treg cells.[3-4] This major difference has been linked to a single non-conserved amino acid in CD28 intracellular domain (ICD).[4] As a result, a humanized mouse model with a human ICD could recapitulate human-like signaling, but the activation of mouse cells would no longer be physiological, hence compromising the accuracy of efficacy studies. Alternatively, a CD28 humanized mouse model with a mouse ICD would maintain a physiological signaling in mouse cells, but would then not be relevant for safety and toxicity studies.

genOway has developed a CD28 humanized mouse model with a human extracellular domain (ECD), which confers the versatility to test any biologics targeting the hCD28 ECD, and a mouse transmembrane and ICD to preserve a functional signaling. This optimized model was shown to have a functional CD28 axis, did not show any major defect in the immune system, and proved relevant for efficacy assessment studies. In addition, CD28 bispecific antibodies (BsAb) treatment of splenocytes from the double-humanized hCD28/hCD3ε model, in the presence of suboptimal concentrations of CD3 BsAb, resulted in the enhanced proliferation of T cells (A), and induced secretion of IFN-ɣ (B).

A
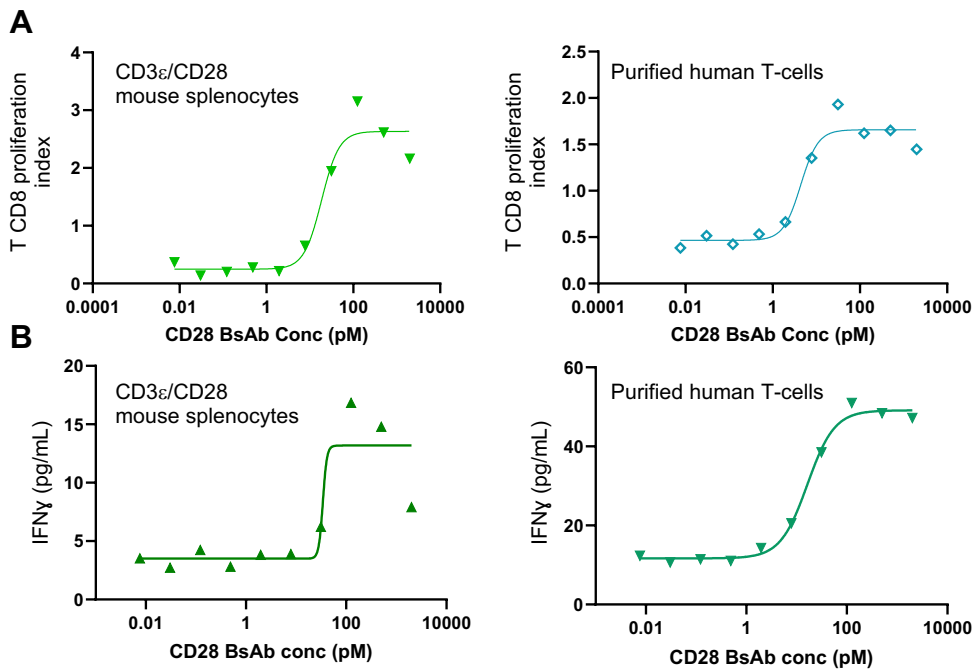
CD28 stimulation induces cytokine production in hCD3ε/hCD28 mice.

Isolated splenocytes from hCD3ε/hCD28 mice and purified human T cells were incubated for 24h with various concentrations of CD28 bispecific antibodies (BsAb), in the presence of a suboptimal concentration of CD3 BsAb. A. Treatment triggered T cell proliferation in isolated splenocytes (left) and purified human T cells (right). B. Treatment induced IFN-□ secretion in both isolated splenocytes (left) and purified human T cells (right).

B

Despite its ability to produce cytokines upon CD28 stimulation, the hCD28 mouse model is not recommended for safety and toxicity studies, due to its genetic design, as it might not trigger a cytokine release syndrome (CRS) with the same intensity than that in humans. Of note, genOway's reconstituted mouse model BRGSF-HIS has proved most relevant to recapitulate CRS in a preclinical model.

The CD28 example perfectly illustrates the central importance of a relevant preclinical research model. Indeed, the choice of the most appropriate model entirely depends on the application. This is why genOway has developed and offers a set of catalog models fit for a variety of applications, including optimized models for T-cell-targeting bispecific antibodies and combination therapies.

References:

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