A NOVEL FULLY HUMAN CD28 ANTIBODY THAT CROSS-REACTS WITH CTLA-4 AND MOUSE CD28 FOR POTENTIAL APPLICATIONS IN CANCER IMMUNOTHERAPY

Background T cell activation is initiated through engaging T cell receptor (TCR)/CD3 complex upon recognizing antigenic peptides presented by major histocompatibility complex (pMHC). However, TCR/CD3 complex alone is not sufficient for full T cell activation. It has been found that an additional signal induces T cell exhaustion and thus impaired activation of T cells. CD28 is a crucial co-stimulatory receptor that enhances T cell proliferation, survival and production of key cytokines such as IL-2, IFN-γ, and TNF-α. Despite the potential key role of CD28 in cancer immunotherapy, there have been safety concerns following the TeGenero disaster in 2006. Here we describe the generation of a fully human anti-CD28 antibody named “VE19ZH”. VE19ZH features a unique combination of desirable properties in comparison to other currently available mAbs such as TGN1412.

Methods We isolated a new fully human antibody (VE19ZH) against human CD28 by phage display technology. Binding was validated by flow cytometry on primary human T cells. The co-stimulatory effect in combination with anti-CD3(OPT3) was assessed in vitro by proliferation of human PBMCs and cytokine release. To rule out the undesirable super-agonistic effect observed by TGN1412, VE19ZH was tested for its capability to activate human PBMCs in the absence of TCR/CD3 signaling. Cross-reactivity against CTLA-4 and mouse CD28 were evaluated by ELISA and flow cytometry. Finally, the binding epitope of VE19ZH was revealed using PepSpot™ technology.

Results VE19ZH is a fully human antibody that binds selectively to both human and murine CD28. VE19ZH IgG4 exhibited a strong and significant co-stimulatory effect on human PBMCs when combined with anti-human CD3 (OKT3). Unlike TGN1412, VE19ZH did not activate T cells without TCR/CD3 signaling. In addition, VE19ZH was shown to bind to CTLA-4. VE19ZH binds to an epitope similar to the natural ligand (CD80/CD86) as revealed by PepSpot™ technology. In vitro killing activity was validated using BiTE formats and showed synergism with low concentrations of CD3 bispecifics.

Conclusions VE19ZH is a promising module for cancer immunotherapy with unique properties: (i) Fully human mAb for minimal immunogenicity (ii) Potent co-stimulator for full T cell activation (iii) Conventional agonist of CD28 and not super-agonistic like TGN1412 (iv) cross reacts with mouse CD28 for better assessment in immunocompetent mouse models (v) Binds to human CTLA-4 for potential checkpoint inhibition. The potential of VE19ZH to boost T cell response via CD28 activation and CTLA-4 blockade is currently being investigated in vitro and in vivo.

REFERENCES
