CB307: A novel T-cell costimulatory Humabody® therapeutic for PSMA-positive tumors

James W. Legg, Brian McGuinness, Sophie Archer, Phili Bland-Ward, Verena Brucklacher, Jenny Cragan, Carolyn Edwards, Emma Hames, Guy Majithiya, Pavel Pisa, Sindhra Revi, Nikki Royalle, Magdalena Boller, Yumi Tseng, Lorraine Thompson, Wenshin Wang, Chris Wilson, Chris Wyne, Chris Ressant

Crescendo Biologics Ltd., Babraham Research Campus, Cambridge, CB22 3AT, UK.

ABSTRACT

Agnostic monoclonal antibodies targeting CD137/4-1BB have shown much preclinical promise but their clinical development has been slowed due to a poor therapeutic index, in particular liver toxicity. CB307 is a novel tri-specific Humabody therapeutic targeting CD137 (4-1BB), prostate specific membrane antigen (PSMA) and human serum albumin (HSA). The design of CB307 enables agonism of CD137 selectively in the presence of PSMA positive tumour cells and in this way enables tumour selective T cell activation whilst minimising systemic activation. The molecular weight of CB307 is less than 50 kDa (around a third of the size of a standard IgG) and it does not contain an Fc domain, thereby avoiding interaction with Fc receptors. Half life extension is achieved through the inclusion of a VH domain with specificity for HSA. Here we describe the identification of CB307 using the Crescendo Mouse™, which develops fully human VH domains in a background devoid of light chains, along with characterisation of the key properties of the molecule in vitro and in vivo models. In dual target binding assays CB307 shows potent co-binding to both PSMA and CD137 targets and mediates CD137 signalling in an NFB cell reporter assay in the presence of PSMA positive cells but not PSMA negative cells. Co-incubation of primary human T-cells from healthy individuals or cancer patients together with PSMA positive tumour cells and CD3 stimulation induces T-cell activation and cytokine release. In an in vivo model using NSG mice engrafted with human PBMCs the growth of PSMA positive DU145 prostate tumour cells is inhibited by a surrogate bispecific. Together these data support progression of CB307 into pre-clinical development.

HUMABODY VHs

CB307: A novel T-cell costimulatory Humabody® therapeutic for PSMA-positive tumors

CB307 In vitro CHARACTERISATION

CB307 Co-Binds PSMA and CD137

CB307 Cross-reacts with Cynomolgus Targets

CB307 Agonists CD137 only in Presence of PSMA

CB307 Binds Potent PSMA-Dependent T Cell Activation

CB307 Binds Production of cytokines, Granzyme B and markers of proliferation and survival

CB307 Activity in QM: Proliferation, Migration Assay

CB307 In vivo CHARACTERISATION

PSMA in C127/AC10 Sarcoma Molecule Activity in a Prostate Tumour Model

SUMMARY

Crescendo has developed CB307, a novel tri-specific T-cell enabler for the selective activation of tumour-specific T-cells exclusively within the tumour microenvironment. CB307 is capable of delivering highly potent tumour cell killing whilst avoiding systemic toxicity. This highly modular format can be re-configured to create a pipeline of therapeutic candidates.