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

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ABSTRACT

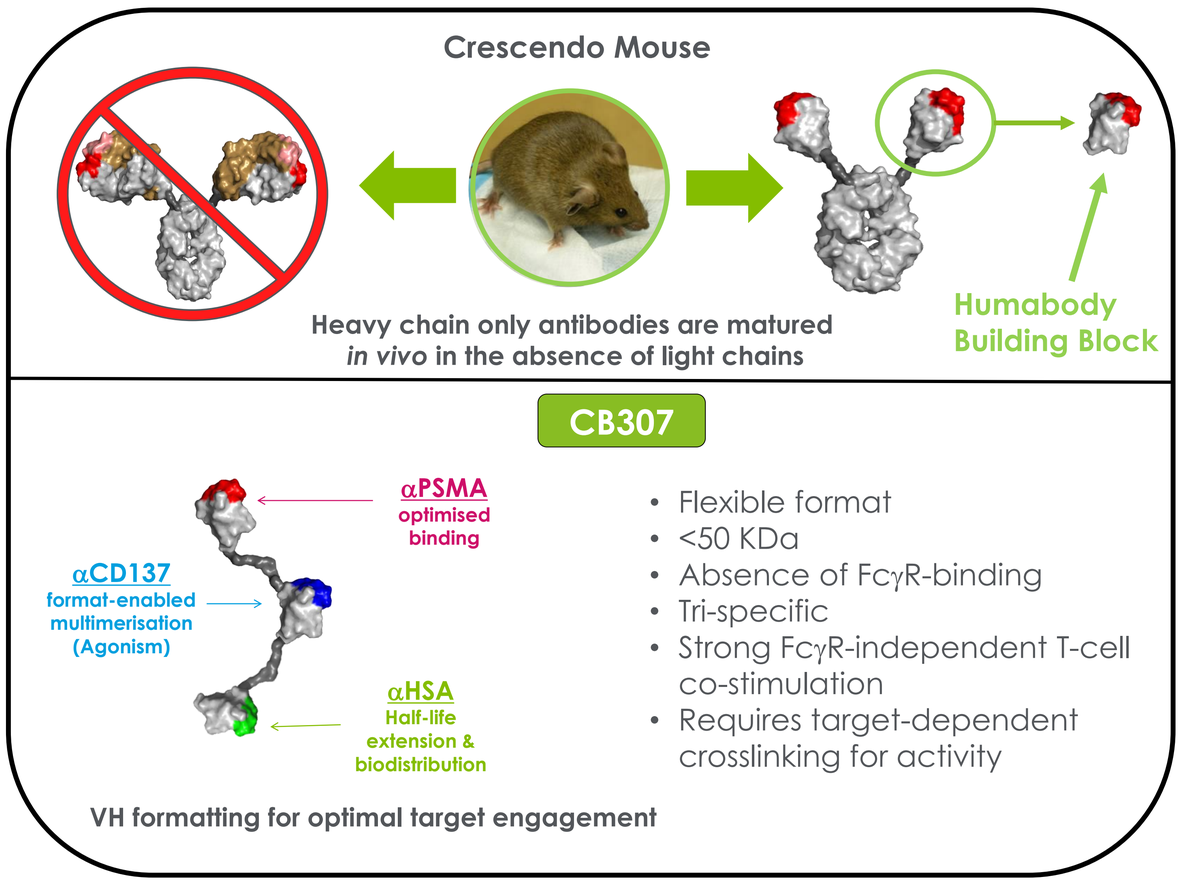
Agonistic monoclonal antibodies targeting CD137 have shown much preclinical promise but their clinical development has been slowed due to a poor therapeutic index, in particular liver toxicity.

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, enabling tumour specific T cell activation whilst minimising systemic activation. The molecular weight of CB307 is <50 kDa and it does not contain an Fc domain. Half life extension is achieved through a VH domain which binds HSA.

Here we describe the generation of CB307 by formatting fully human VH domains matured *in vivo* by the Crescendo Mouse™. We show characterisation *in vitro* and in an *in vivo* model. CB307 shows potent co-binding to both PSMA and CD137 targets and is cross reactive to the cynomolgus orthologues. In a reporter assay, CB307 mediates CD137 signalling in the presence of PSMA positive cells but not PSMA negative cells. Co-incubation of primary human T-cells 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 VH



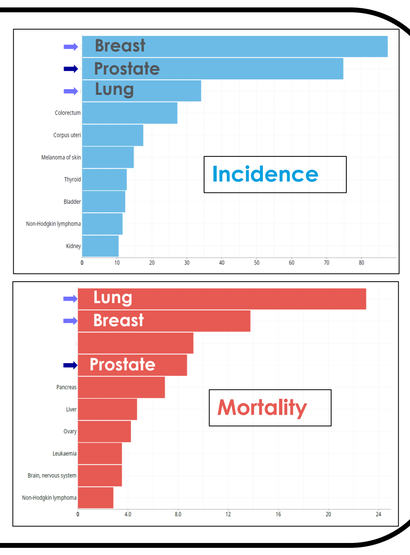
BACKGROUND

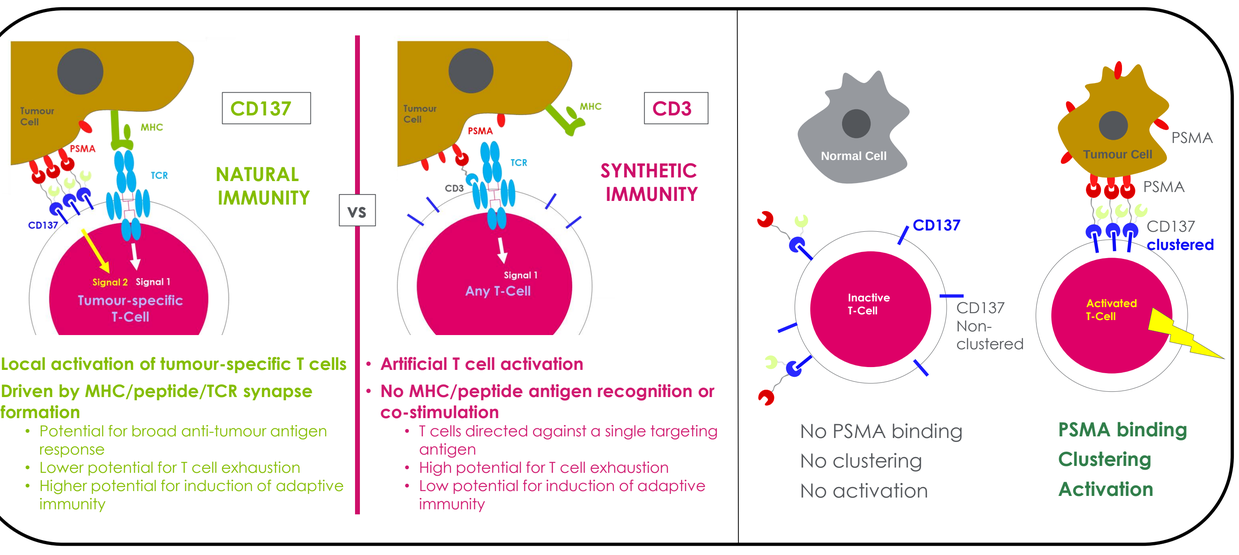
CD137

- CD137 is a T cell receptor with tightly regulated expression
- Delivers highly potent co-stimulatory signal to cytotoxic CD4+ and CD8+ T cells
- Native ligand binding results in trimerization, activation & signaling
- CD137 mAbs can cross-link via FcR interaction
- CD137 mAbs have a narrow therapeutic index in the clinic due to liver toxicity

PSMA

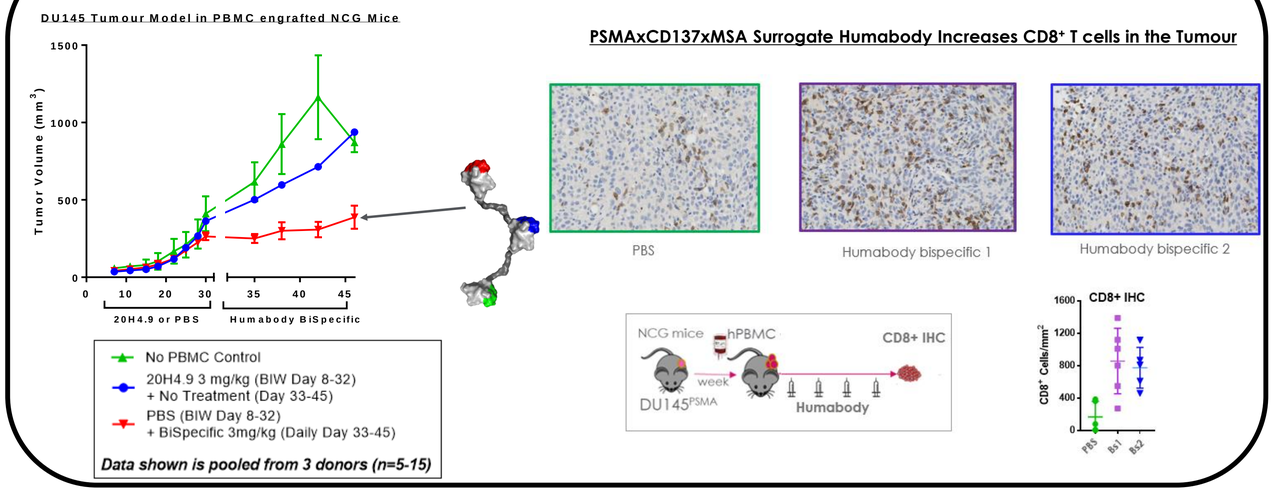
- Prostate Specific Membrane Antigen (PSMA)
- PSMA is highly expressed on prostate cancer epithelial cells
- Expression correlates with disease progression and poor prognosis
- Expressed on broader range of tumours, both on tumour cells and in the neo-vasculature





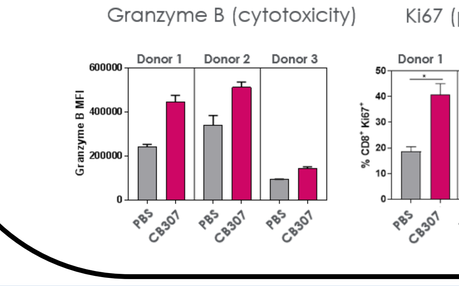
CB307 *in vivo* characterisation

PSMAxCD137xMSA Surrogate Molecule Activity in a Prostate Tumour Model

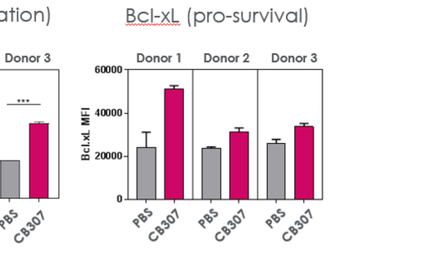


CB307 *in vitro* characterisation

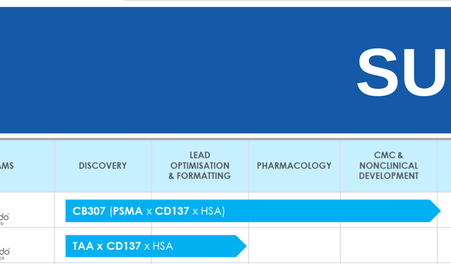
Co-binds PSMA & CD137



Cross-reacts with cynomolgus targets

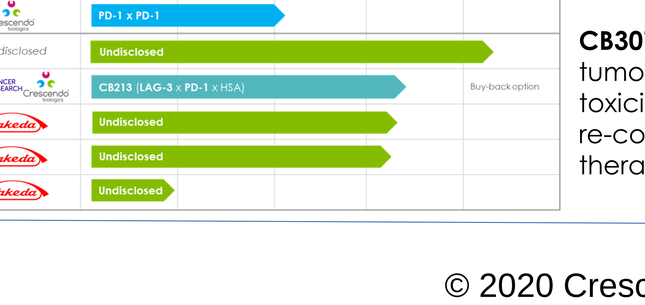


Agonises CD137 only in presence of PSMA



Elicits potent PSMA dependent T cell activation

CB307 elicits production of cytokines, Granzyme B and markers of proliferation and survival



EC_{50} (M)	Donor 1	Donor 2	Donor 3
IFNγ	1.522E-09	2.259E-09	1.796E-09
TNFα	1.368E-09	2.268E-09	2.404E-09

Granzyme B (cytotoxicity) Ki67 (proliferation) Bcl-xL (pro-survival)

SUMMARY

Crescendo has developed **CB307**, a novel trispecific T-cell enhancer 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.

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