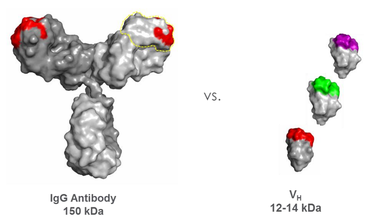
Multifunctional Humabody® Biologics for Immune-Oncology, Based on In Vivo Matured Fully Human V_H Domains

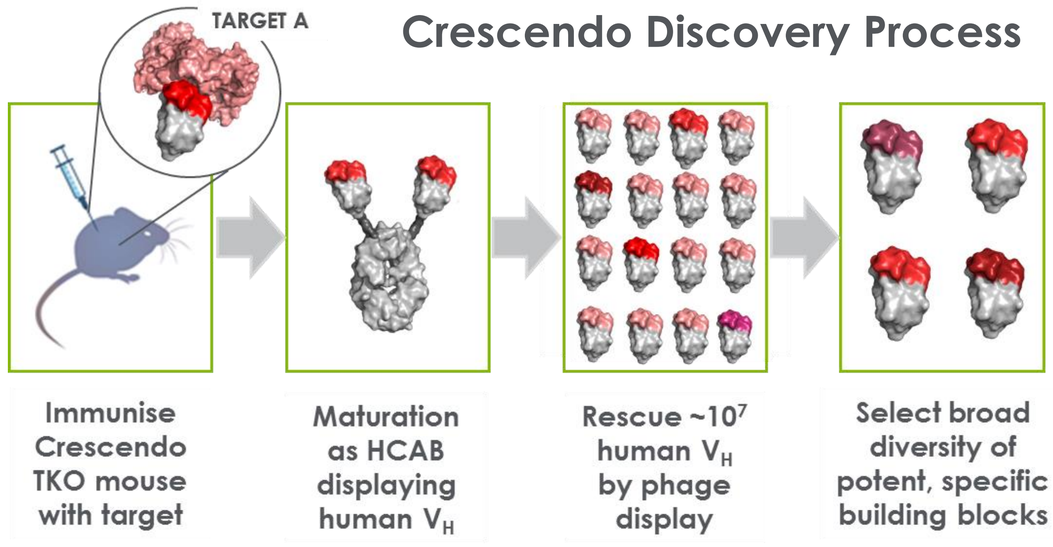
H.L. Thompson; G. Benedetti; A. Sette; L. Eghobamien; C. Edwards; B. Revi; M. Lewandowska; Y. Teng; C. Johnston; D. Sydoruk; E. De Juan; E. Hames; S. Archer; J. Majithiya; P. Hayes; S. Vance; C. Wyre; C. Wilson; J. Craigen; J. Arizanova; N. Birkett; N. Royle; S. Fiaska; W. Wang; B. Di Fiore; Y Surani; C Enever; S. Stelter; D Granger; J. Legg; P. Bland-Ward; P. Pack.

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

Introduction

- Crescendo Biologics has created a proprietary transgenic mouse devoid of any antibody light chains from which it generates highly diverse fully human V_H domain Humabody® building blocks.
- *In vivo* maturation creates Humabody® V_H with optimal potency and biophysical properties
  - High diversity
  - 1/10 of IgG size
  - 100% human
  - pM/nM affinities
  - High yields
  - Stable
- Here we provide example data showing that Humabody® V_H can easily be configured to create multifunctional formats, capable of engaging targets for optimal therapeutic efficacy.

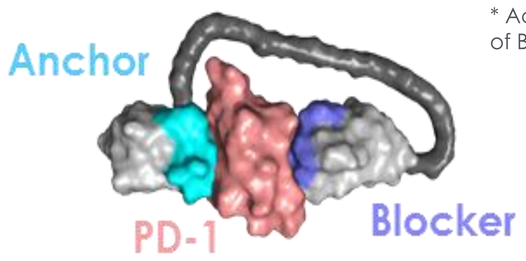




Immuno-Oncology Humabody® V_H

Biparatopic PD-1 antagonist

CB213

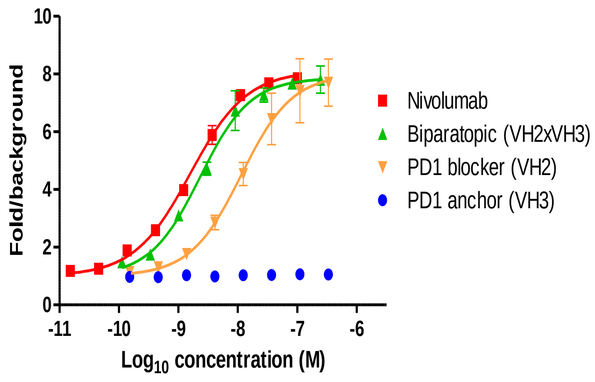


* Actual epitope/binding site of Blocker not determined

Figure 1. Model of interaction of Humabody® PD-1 anchor and Humabody® PD-1 blocker on PD1 molecule (B). Anchor and blocker bind two distinct epitopes, of which only one disrupts the PD-1/PD-L1 interaction.

Functional activity of PD-1 biparatopic

A. PD-1/PD-L1 Reporter Assay



B. In vivo activity

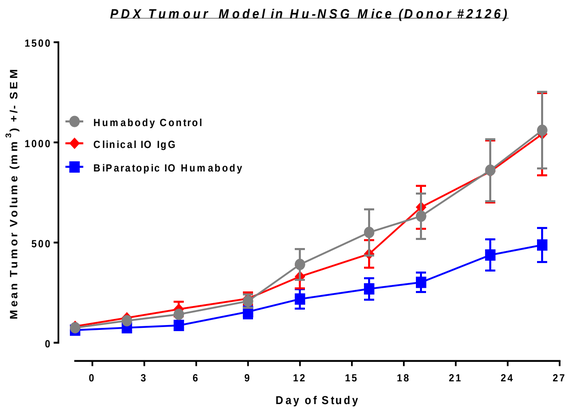


Figure 2. A. PD-1 biparatopic Humabody® increases signalling in PD-1/PD-L1 reporter assay by blocking the inhibitory action of PD-L1. PD-1/PD-L1 interaction supresses NFAT-mediated luciferase activity. **B.** *In vivo* study shows PD-1 biparatopic Humabody® activity in humanised mouse model insensitive to clinical IgG. PD-1 mAbs are highly effective in only some patients, our PD-1 biparatopic has the potential to target patients who do not respond to mAb PD-1 antagonists in clinic.

Bispecific PD-1xLAG-3 antagonist

CB201

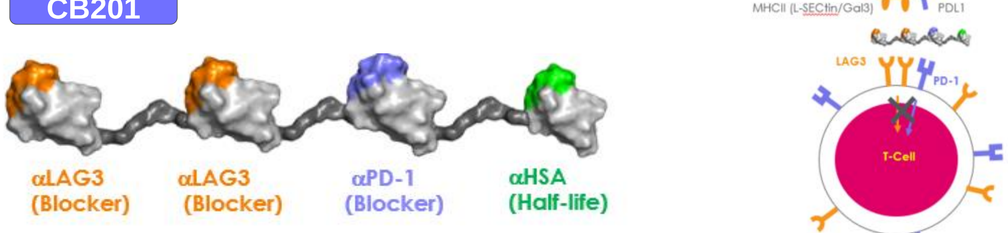


Figure 3. A novel bispecific PD-1 x LAG-3 antagonist designed to deliver highly potent simultaneous dual checkpoint blockade in patients non-responsive to PD-1 blockade alone.

Functional activity of PD-1 X LAG-3 Antagonist

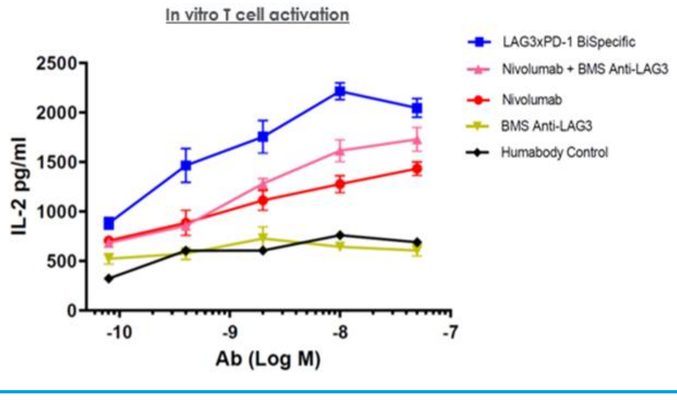
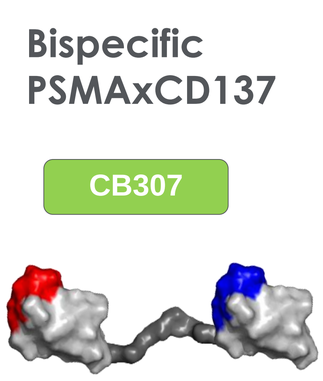


Figure 4. PD-1xLAG-3 antagonist shows enhanced IL-2 release in SEB stimulated PBMC assay when compared to anti-PD1 and anti-LAG benchmark antibodies alone or in combination.

T-cell Empowering tumour Targeting Humabody®

Bispecific PSMAxCD137

CB307



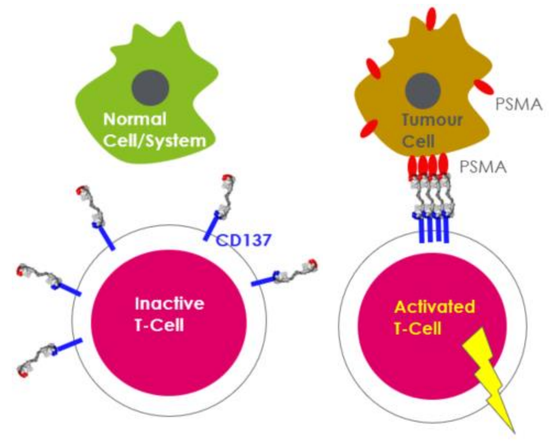
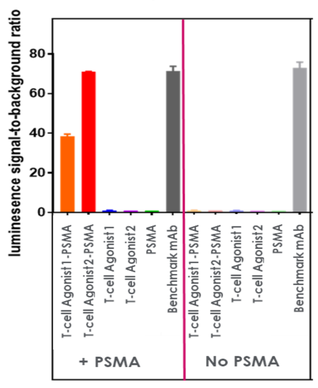


Figure 5. Unique tumour targeting T-cell activating format. Model with tumour cell where PSMA causes clustering of CD137 and results in T-cell activation .

Functional activity of CD137XPSMA Bispecific

A: T-Cell Reporter Assay



B: Primary T-Cell Activation Assay

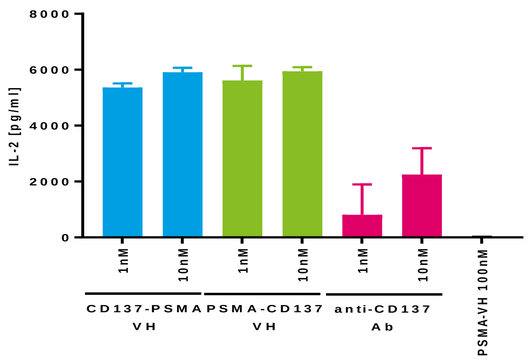


Figure 6. A: CD137xPSMA bispecific increases signalling of CD137 Jurkat reporter luciferase activity only in the presence of PSMA expressing cells. **B.** In primary T cell assay cultured with PSMA expressing cells CD137xPSMA bispecific shows enhanced IL-2 release compared to an anti-CD137 antibody.

In Vivo CD137xPSMA activity in a Mouse Prostate Tumour model

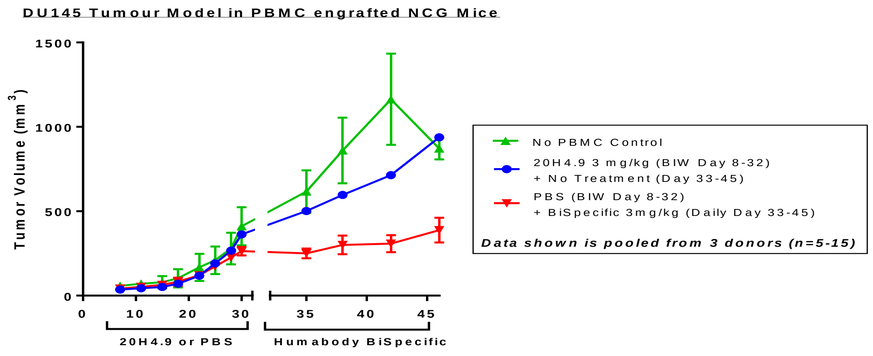


Figure 7. Anti-CD137 mAb or PBS dosed Days 8-32 had not effect on tumour growth. However the CD137xPSMA bispecific dosed Days 33-45 had a rapid and significant effect on tumour growth.

Conclusions: Novel T cell targeted Humabody V_H

Using Humabody® V_H to key targets in the immune-oncology space, Crescendo has exemplified the potential for optimally configured molecules to deliver enhanced efficacy both in vitro and in vivo:

- Targeting highly differentiated IO molecules to simultaneously engage multiple different epitopes and target antigens delivering a novel mode of action.
- Providing a unique Tumour targeting format with the first of a potential franchise of molecules enabling local activation of target-specific anti-tumour T cells.