Introduction

• Crescendo Biologics has created a proprietary transgenic mouse devoid of any antibody light chains from which it generates highly diverse fully human V\textsubscript{H} domain Humabody\textsuperscript{®} building blocks.
• In vivo maturation creates Humabody\textsuperscript{®} V\textsubscript{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\textsuperscript{®} V\textsubscript{H} can easily be configured to create multifunctional formats, capable of engaging targets for optimal therapeutic efficacy.

Immunoo-Oncology Humabody\textsuperscript{®} V\textsubscript{H}

Biparatopic PD-1

Anchor

PD-1

Blocker

Figure 1. Model of interaction of Humabody\textsuperscript{®} PD-1 anchor and Humabody\textsuperscript{®} 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\textsuperscript{®} increases signalling in PD-1/PD-L1 reporter assay by blocking the inhibitory action of PD-L1. PD-1/PD-L1 interaction suppresses NFAT-mediated luciferase activity. B. In vivo study shows PD-1 biparatopic Humabody\textsuperscript{®} 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

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-PD-1 and anti-LAG benchmark antibodies alone or in combination.

T-cell Empowering tumour Targeting Humabody\textsuperscript{®}

Bispecific PSMAxC137

Figure 5. Unique tumour targeting T-cell activating format. Model with tumour cell where PSMA causes clustering of C137 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 no effect on tumour growth. However the CD137xPSMA bispecific dosed Days 35-45 had a rapid and significant effect on tumour growth.

Conclusions: Novel T cell targeted Humabody V\textsubscript{H}

Using Humabody\textsuperscript{®} V\textsubscript{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.