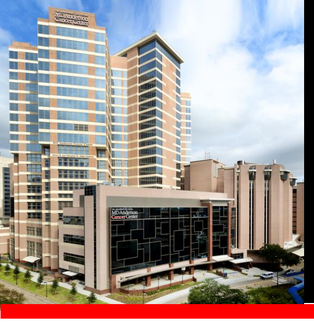

Modified bispecific antibodies blocking both PD-L1 and PD-L2 engagement of PD-1 show higher ADCC potential and *in vivo* anti-tumor response

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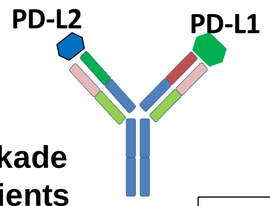
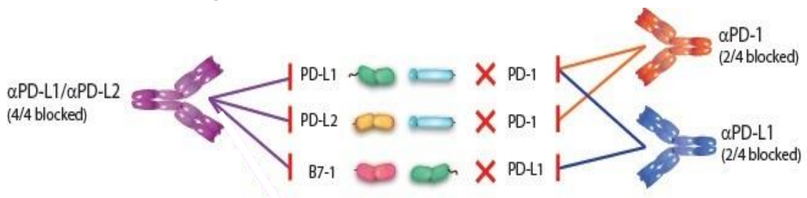


Background

- High efficacy of Immune Checkpoint Blockade
- Restricted to some cancers and some patients
- PD-L1 and PD-L2 are widely expressed by tumor cells and the immunosuppressive stroma
- Blocking only PD-1 or PD-L1 does not address the whole pathway
- Bispecific antibodies offer dual ligand blockade
- Fc region modification can enhance antibody functionality

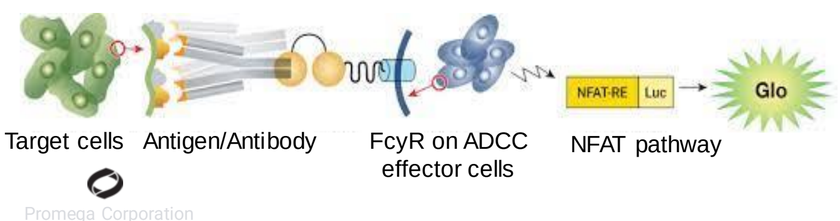


Objectives

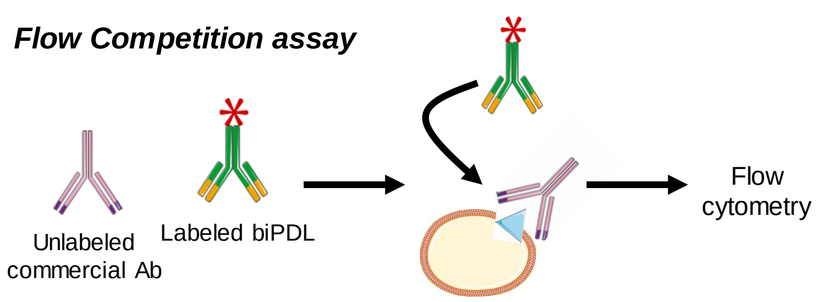
- Compare the efficacy of Fc-modified human anti-PD-L1/2 bispecific antibodies (BsAbs) and clinical anti-PD-L1 antibodies to induce antibody dependent cell-mediated cytotoxicity (ADCC).
- Investigate whether the human anti-PD-L1/2 BsAbs have the same binding region on PD-L1 or PD-L2 as clinical or commercial antibodies.
- Examine the *in vivo* efficacy of anti-PD-L1/2 BsAbs within a cancer cell model.

Methodology

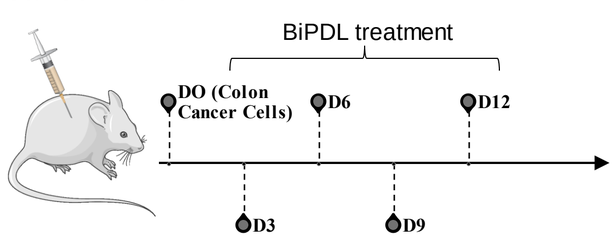
ADCC assay



Flow Competition assay



Colon cancer model



Results

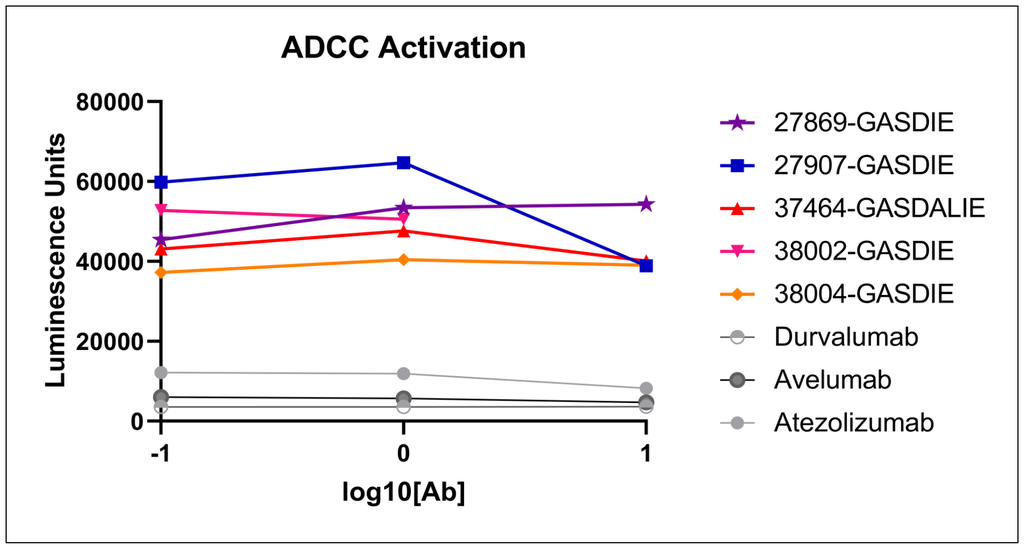


Figure 1: Modified bsAbs induce higher ADCC activation than clinical anti-PD-L1 antibodies.

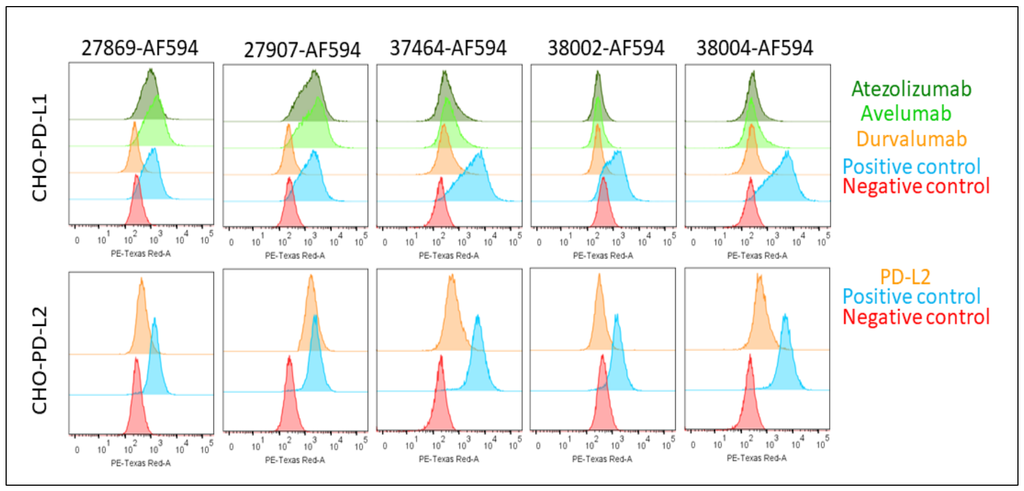


Figure 2: Modified bsAbs mostly share the same binding region on PD-L1 as clinical anti-PD-L1 antibodies.

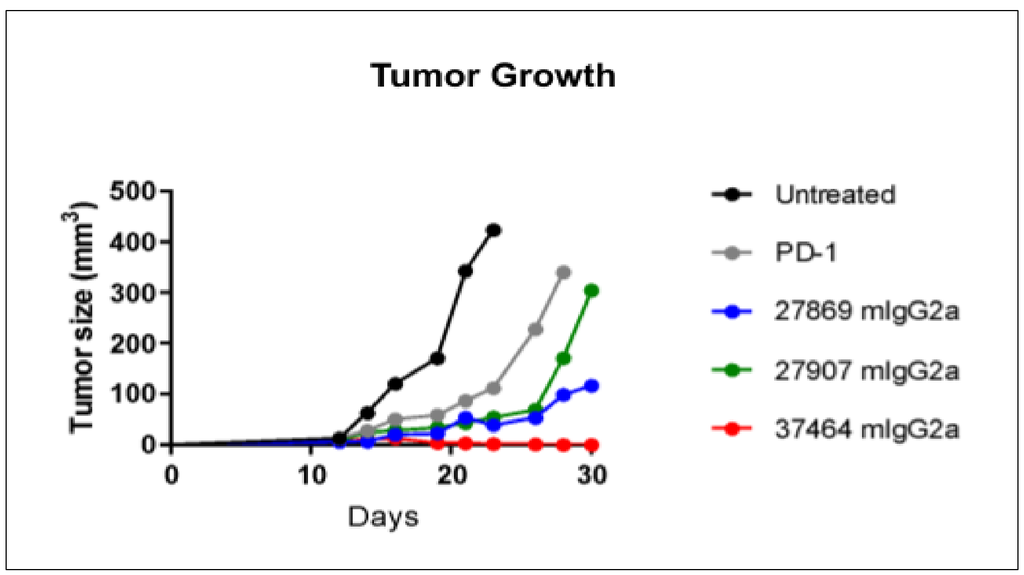


Figure 3: Modified bsAbs demonstrate higher *in vivo* efficacy than an anti-PD-1 antibody

Conclusions

BsAbs:

- targeting PD-L1 and PD-L2 and bearing the Fc modification promote superior ADCC activity against target cells that express either ligand by effector cells expressing Fc receptors.
- mostly share the same epitope as clinical anti-PD-L1 monospecific antibodies.
- possess higher in vivo efficacy than a reference anti-PD-1 therapeutic antibody.

Future Directions

- Assess the survival benefit of targeting PD-L1/2 for ADCC and its combination with other immunotherapies *in vivo*.
- Investigate the interactions between the structure of human PD-L1/2 extracellular regions and the anti-PD-L1/2 BsAbs using nuclear measured resonance (NMR).
- Determine and compare the binding affinity of these interactions measured by surface plasmon resonance.

Acknowledgements

- All Curran members

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