

# Discovery and Characterization of CD28 Bi and Trispecific Antibodies to Treat Solid Tumors

XmAb<sup>®</sup> Antibody Therapeutics

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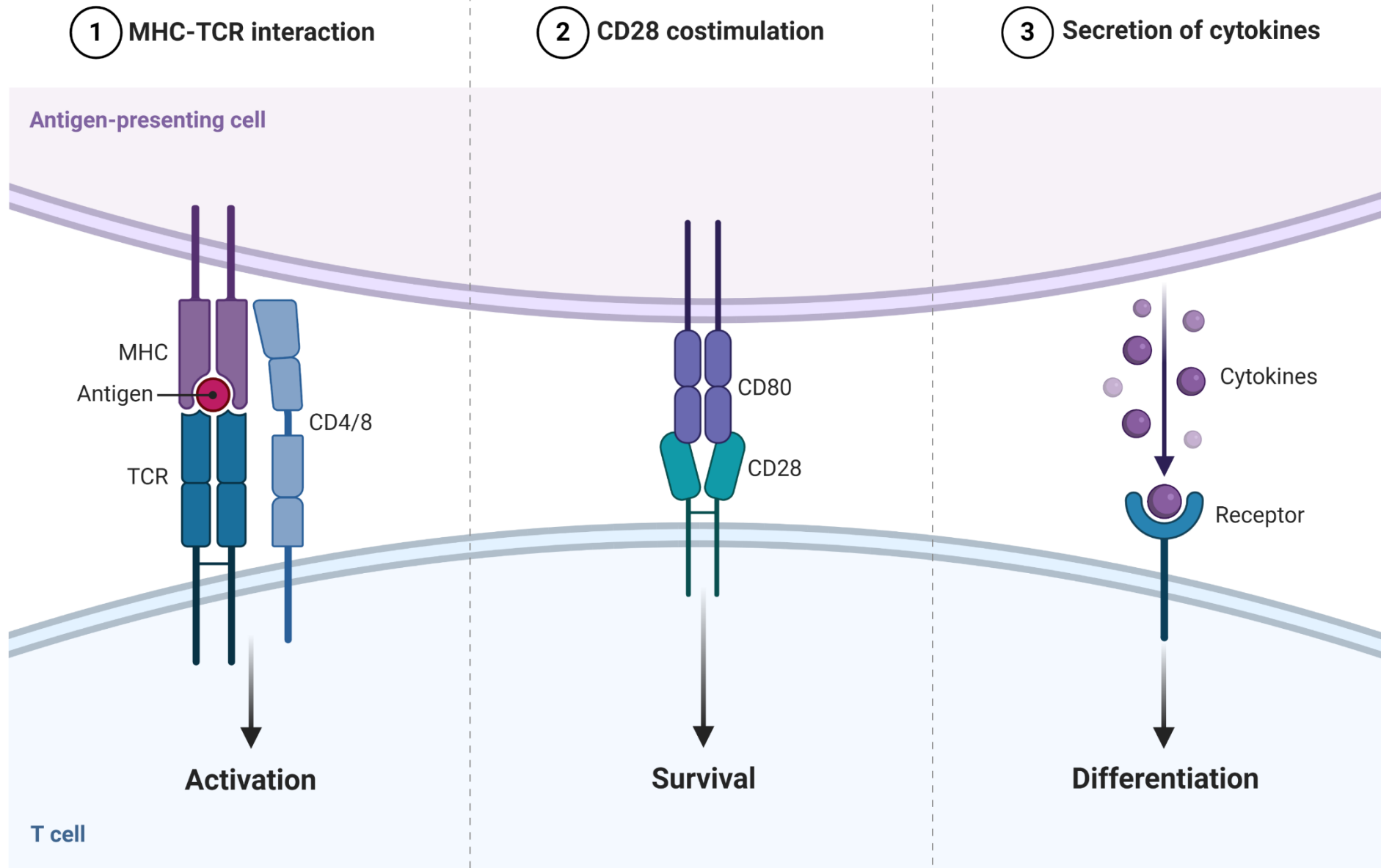
Protein Sciences & Technology



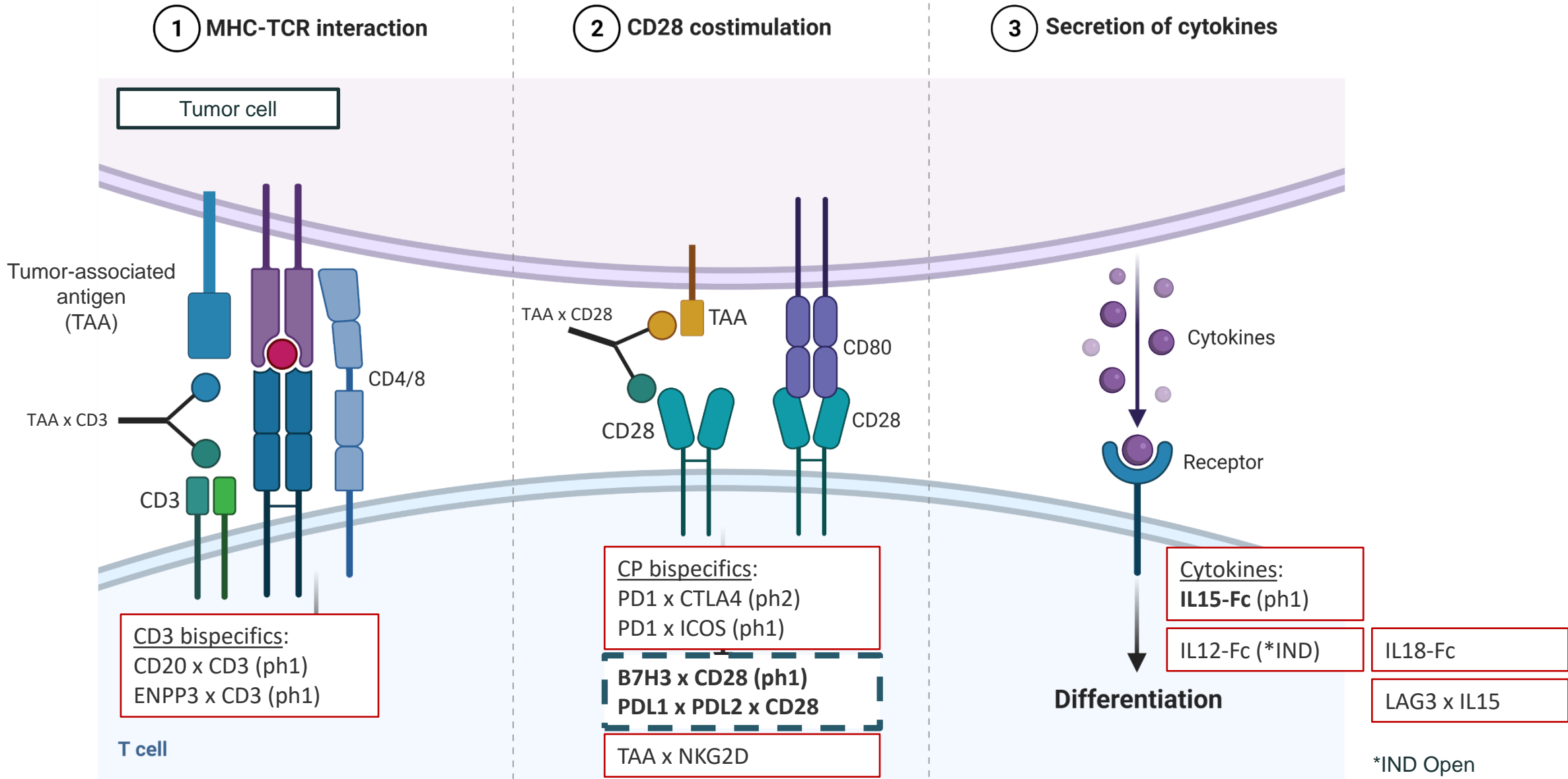
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# Multiple signals are required for optimal T cell responses

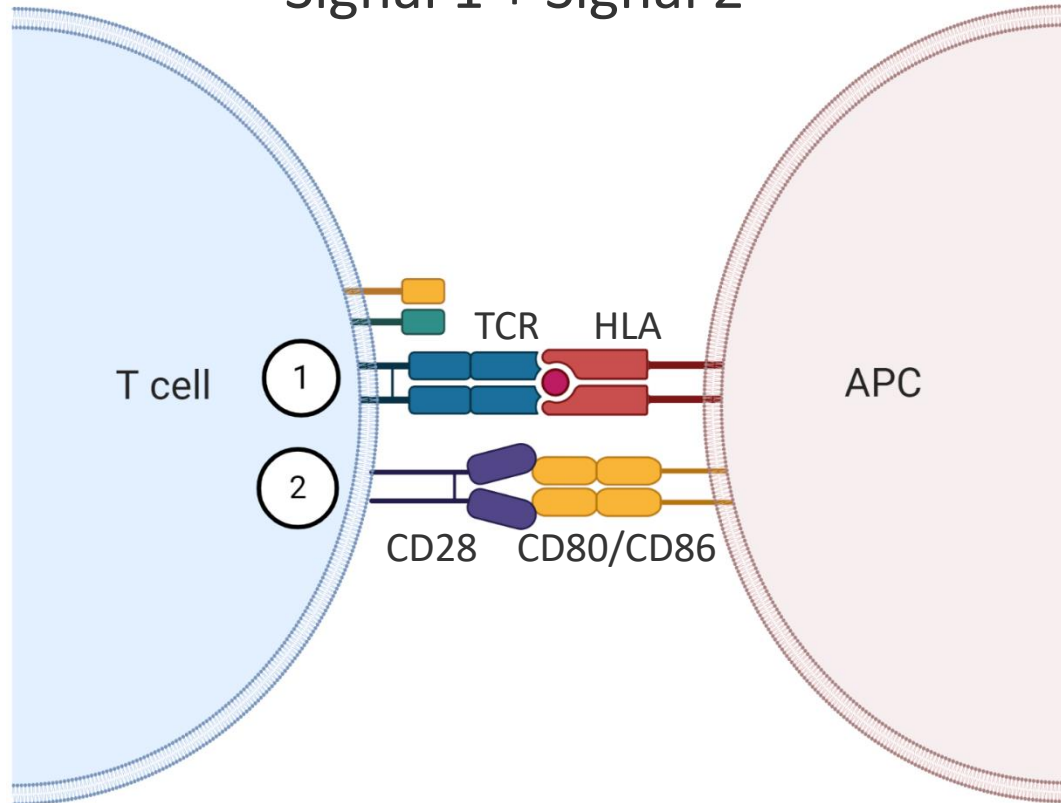


# Growing portfolio of XmAb<sup>®</sup> molecules mimicking signals 1, 2, or 3 in the tumor

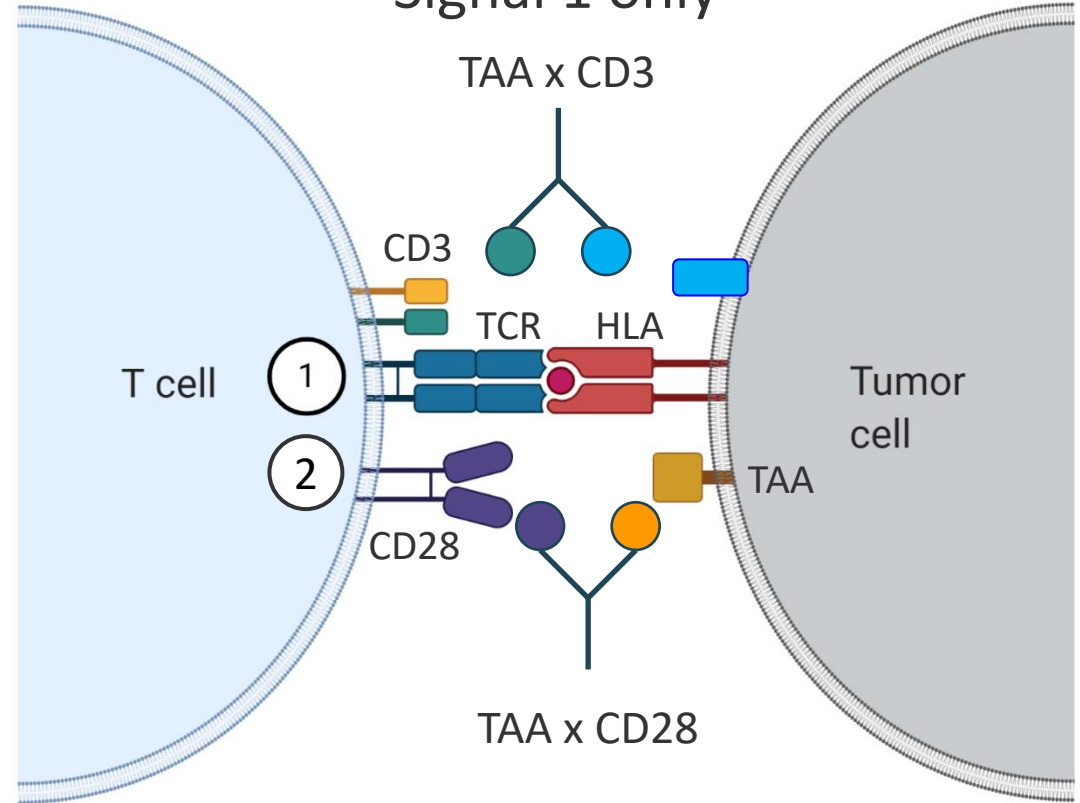


# Targeted CD28 costimulation can activate T cells at the solid tumor interface

Classic T cell/APC interaction  
Signal 1 + Signal 2



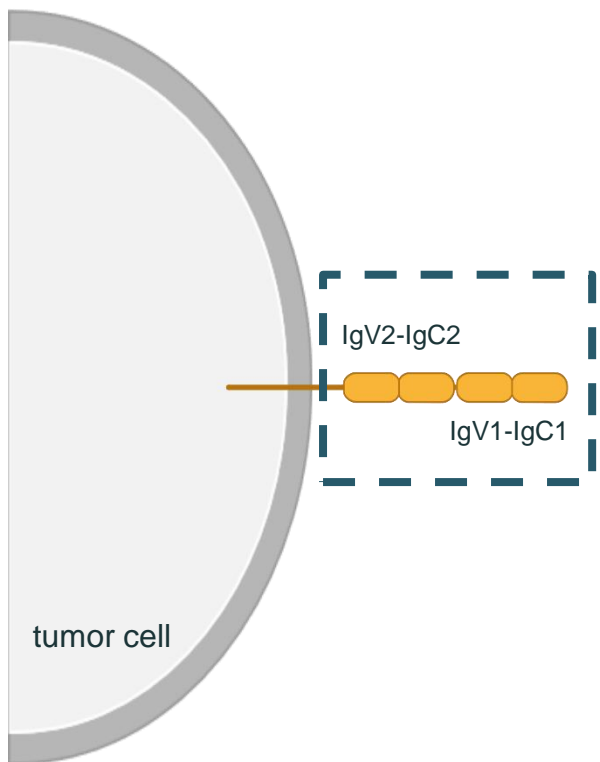
T cell/Tumor cell interaction  
Signal 1 only



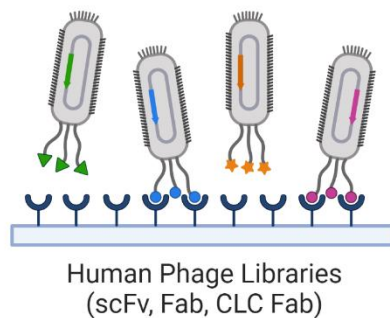
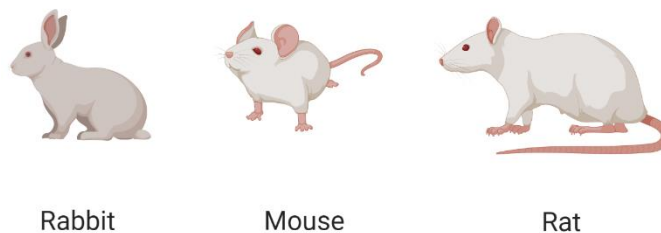
- CD28 costimulation promotes activation and proliferation
- Superagonism is avoided with epitope selection, low affinity, monovalency, Fc silencing

# B7-H3 Discovery

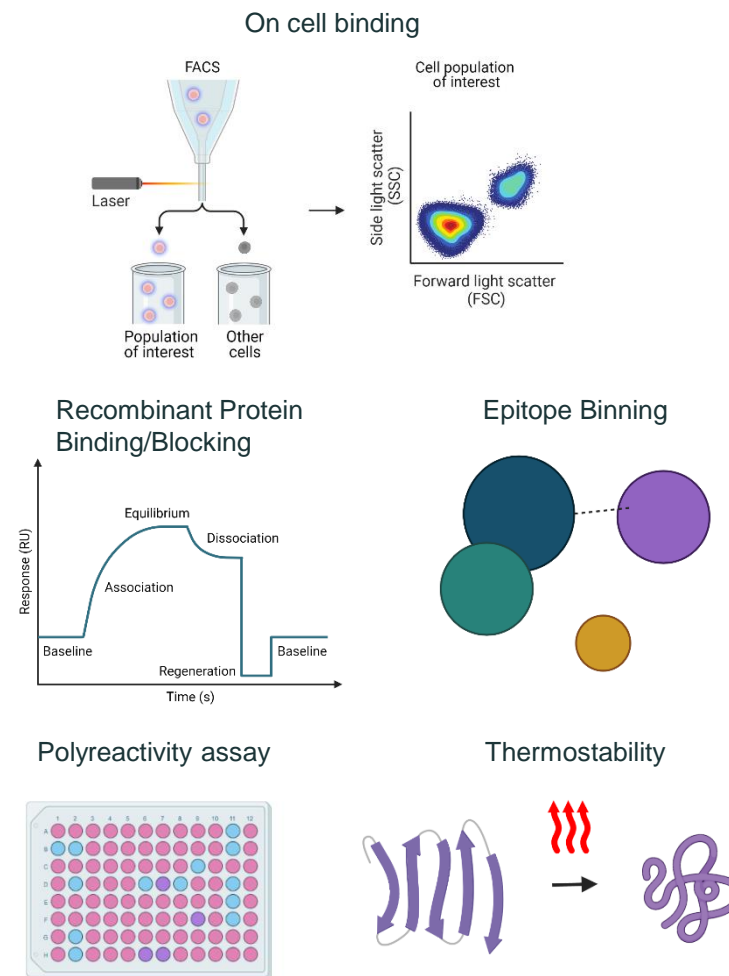
## Antigen Design & Production



## Immunization & Biopanning

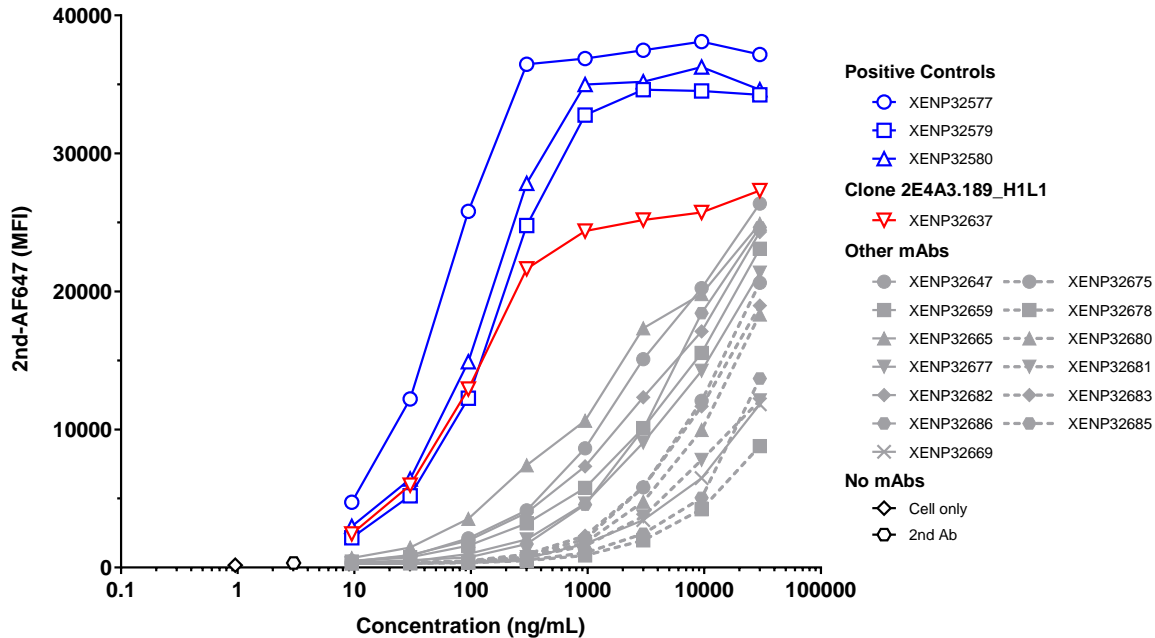


## Screening & Characterization

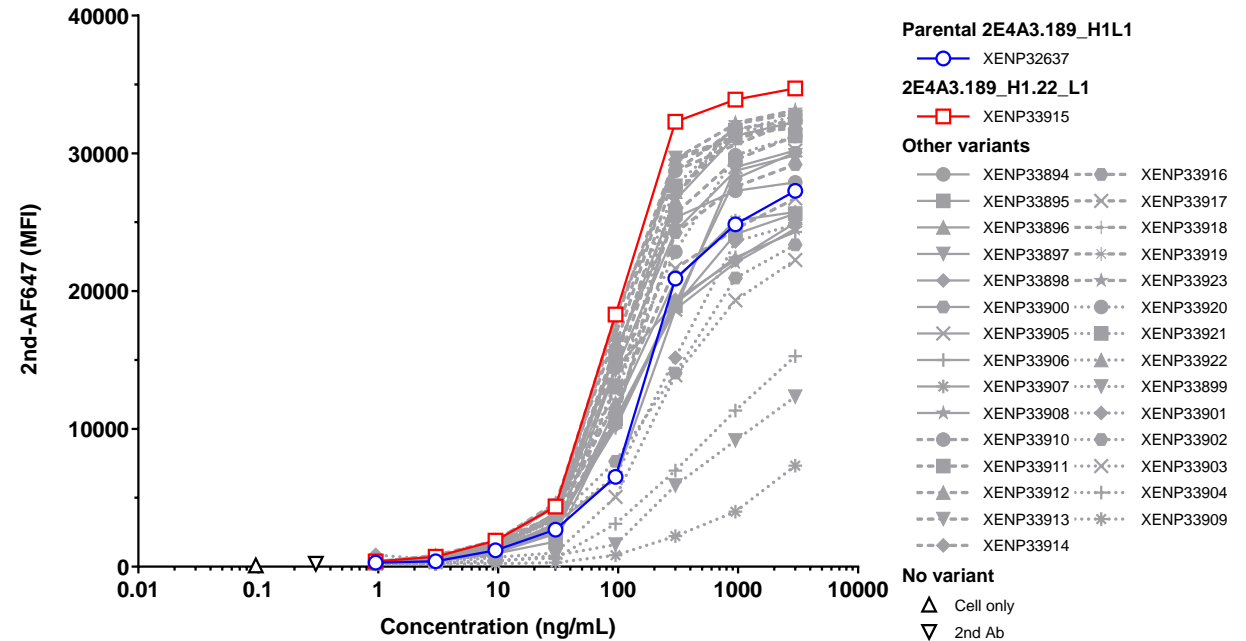


# B7H3 clones bind to B7H3+ cells with a range of affinities

## Library Screening



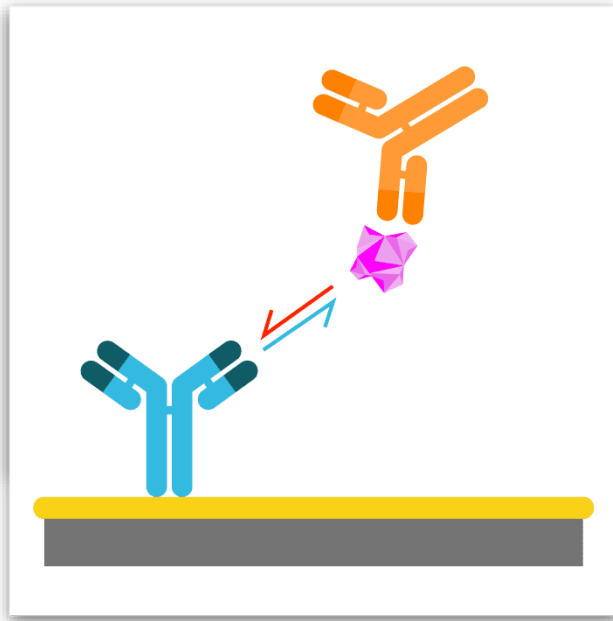
## Affinity Maturation



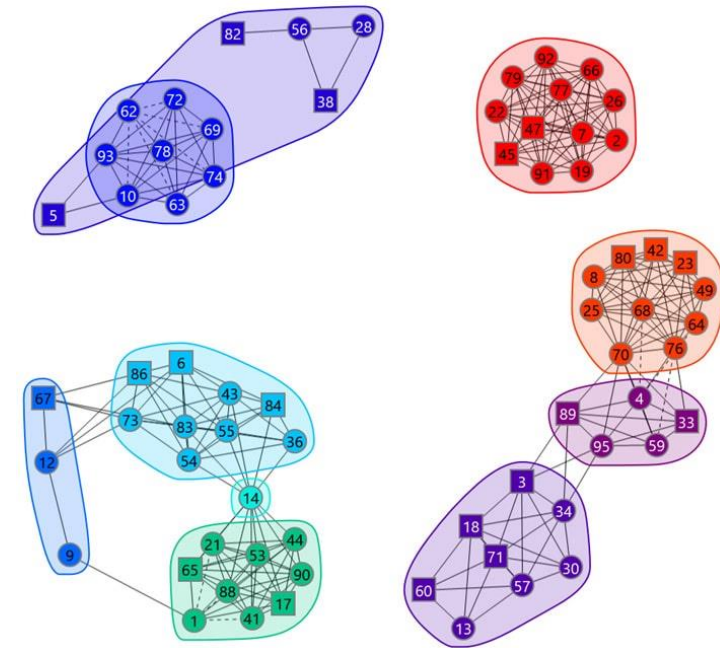
# B7H3 Epitope Binning on the Carterra LSA

- B7H3 was our 1<sup>st</sup> binning assay on the LSA!
- Pre-mix style
- EDC/NHS amine coupling chemistry on CMD200M
- Epitope Binning and species cross reactivity on the same chip

Pre-Complex Style Binning

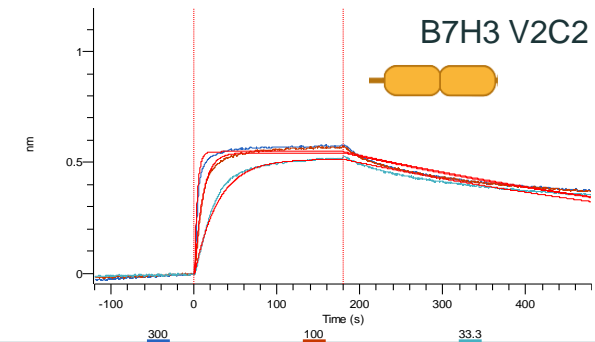
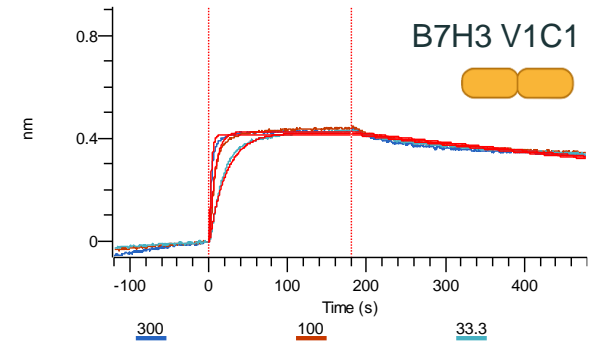
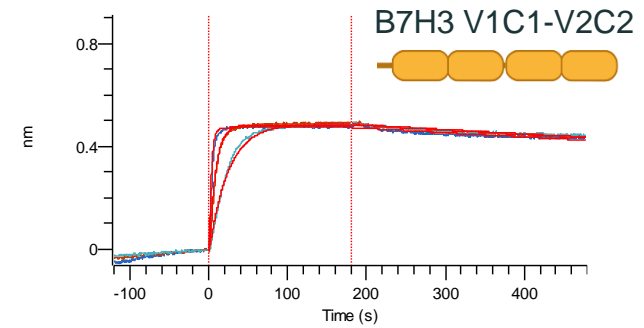
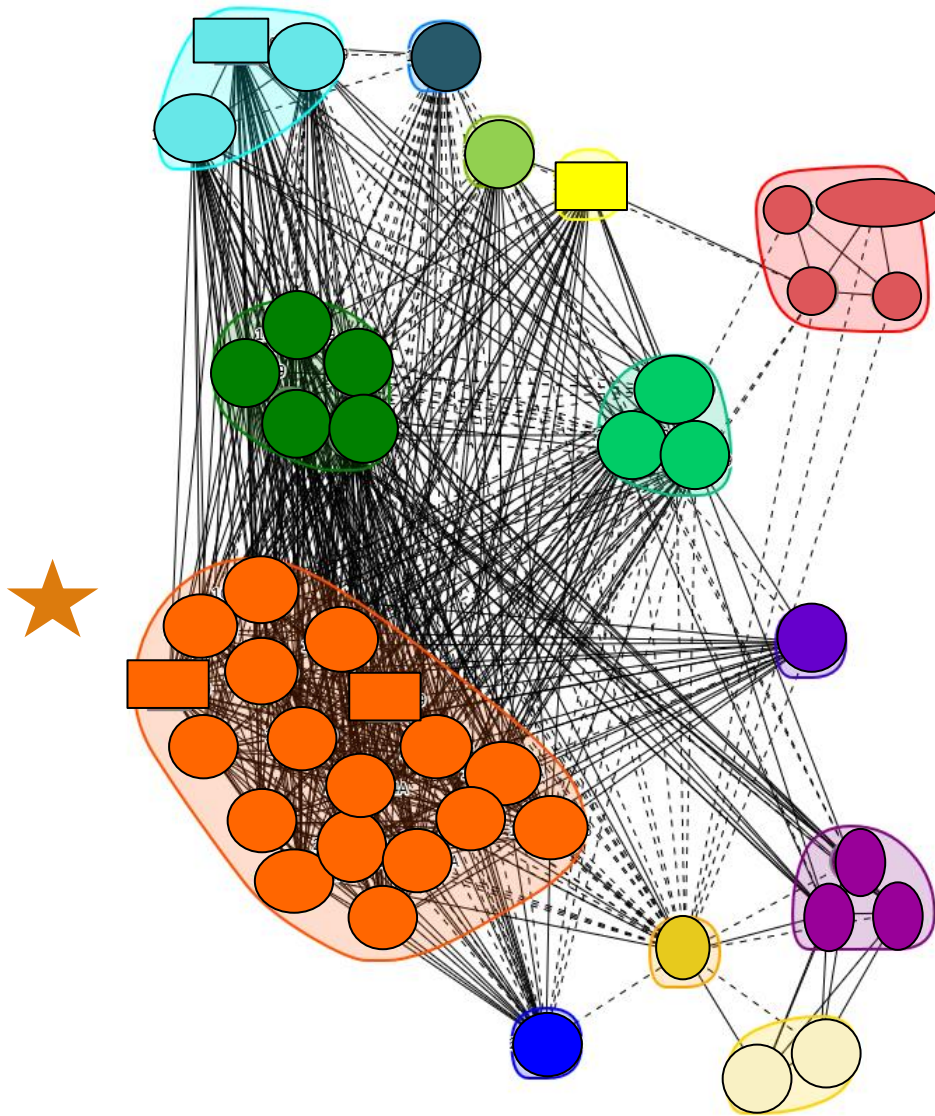


Community Plots



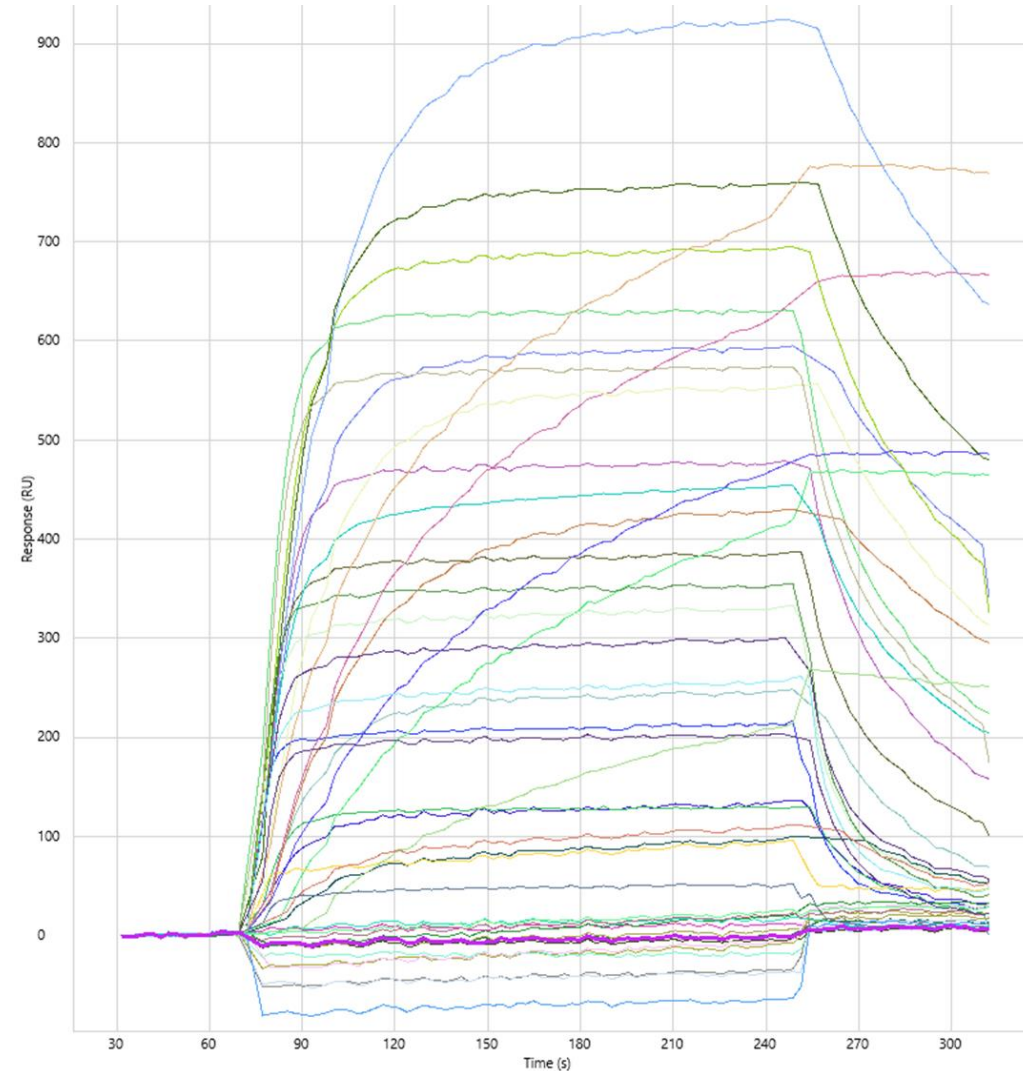


# Clones in Orange Bin Bind to B7H3 V1C1 and V2C2 Domains

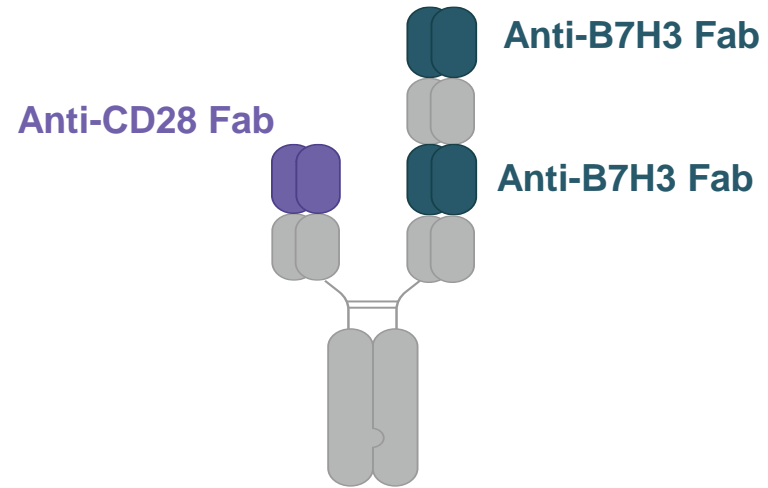


# Species cross reactivity – same chip

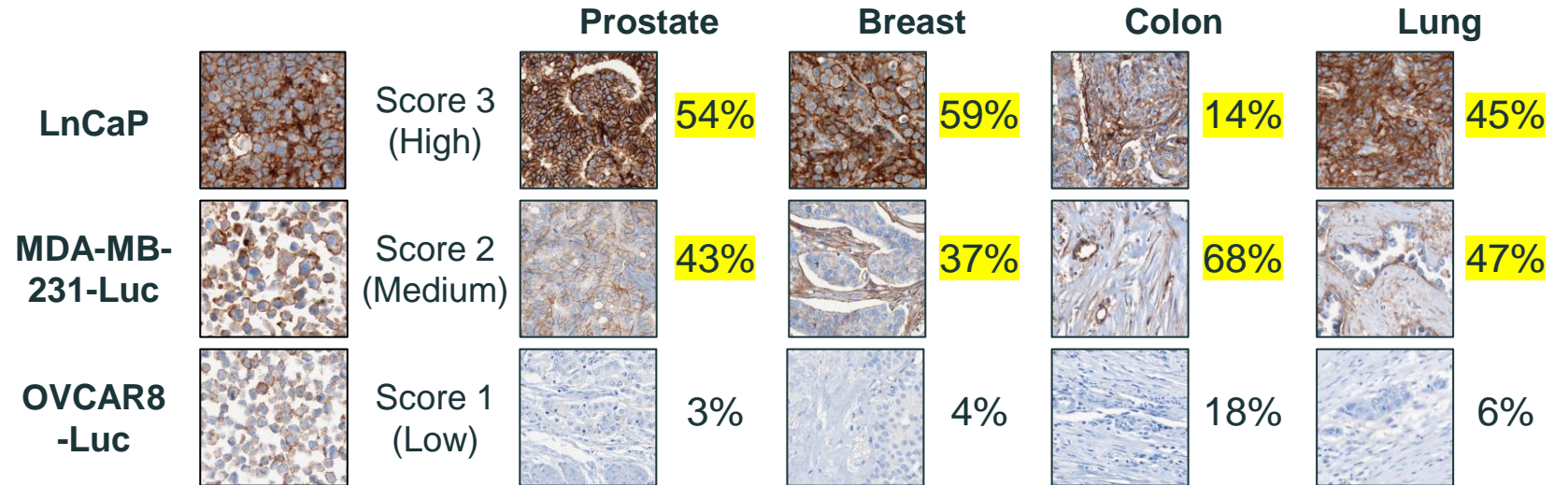
Mouse B7H3 (V1C1)



# Building XmAb808: B7H3 x CD28, 2+1 CLC



## Active on cells with tumor relevant B7H3 density



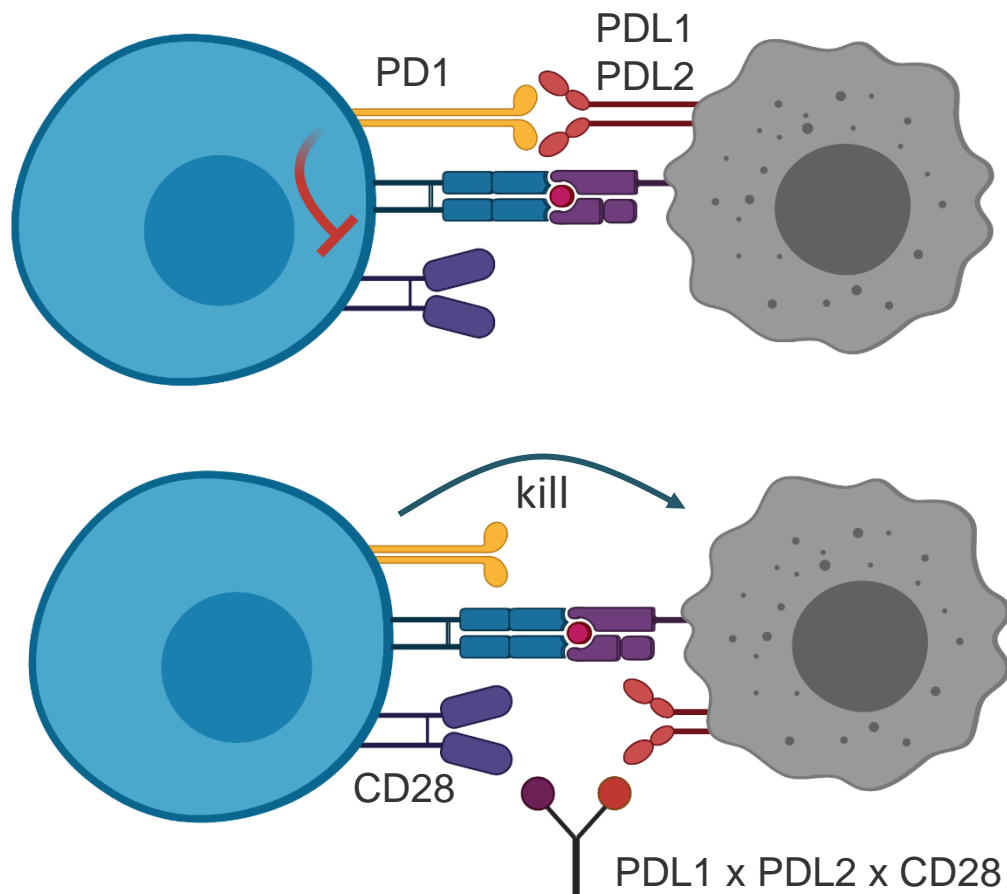
### B7H3 x B7H3 x CD28

- 2+1 format (monovalent CD28)
- Common Light Chain
- Avid Binding to B7H3
- Fc $\gamma$ R interactions silenced
- Xtend (LS) half-life extension
- Combines with Anti PD1

**PDL1 x PDL2 x CD28 Tri-specific**



# A PDL1 x PDL2 x CD28 trispecific antibody blocks both PDL1 and PDL2 to bolster its own mechanism



PDL1 and PDL2 engage PD1 to inhibit T cell signaling

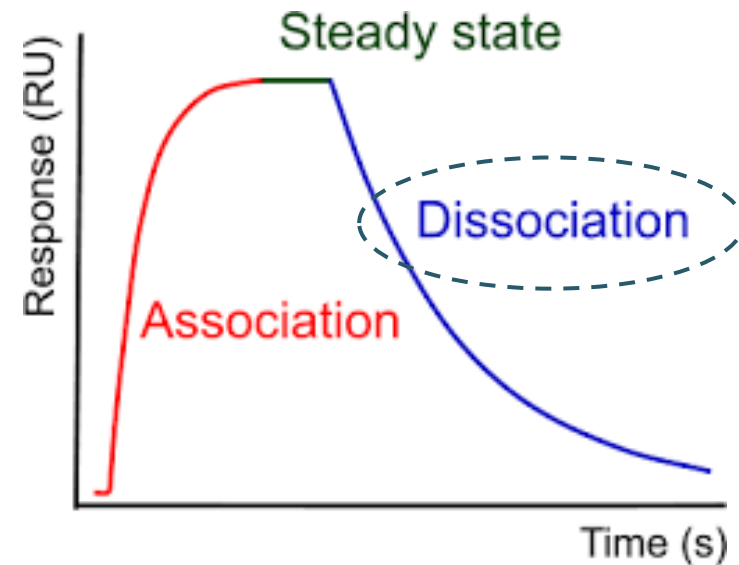
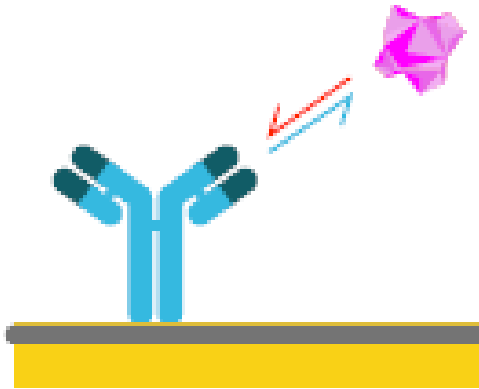
PDL1 x PDL2 x CD28 trispecific creates new CD28 signal  
AND  
Prevents suppression of that signal by PD1

Potentially superior to PD(L)1 blockade

Combinable with CD3 engagers

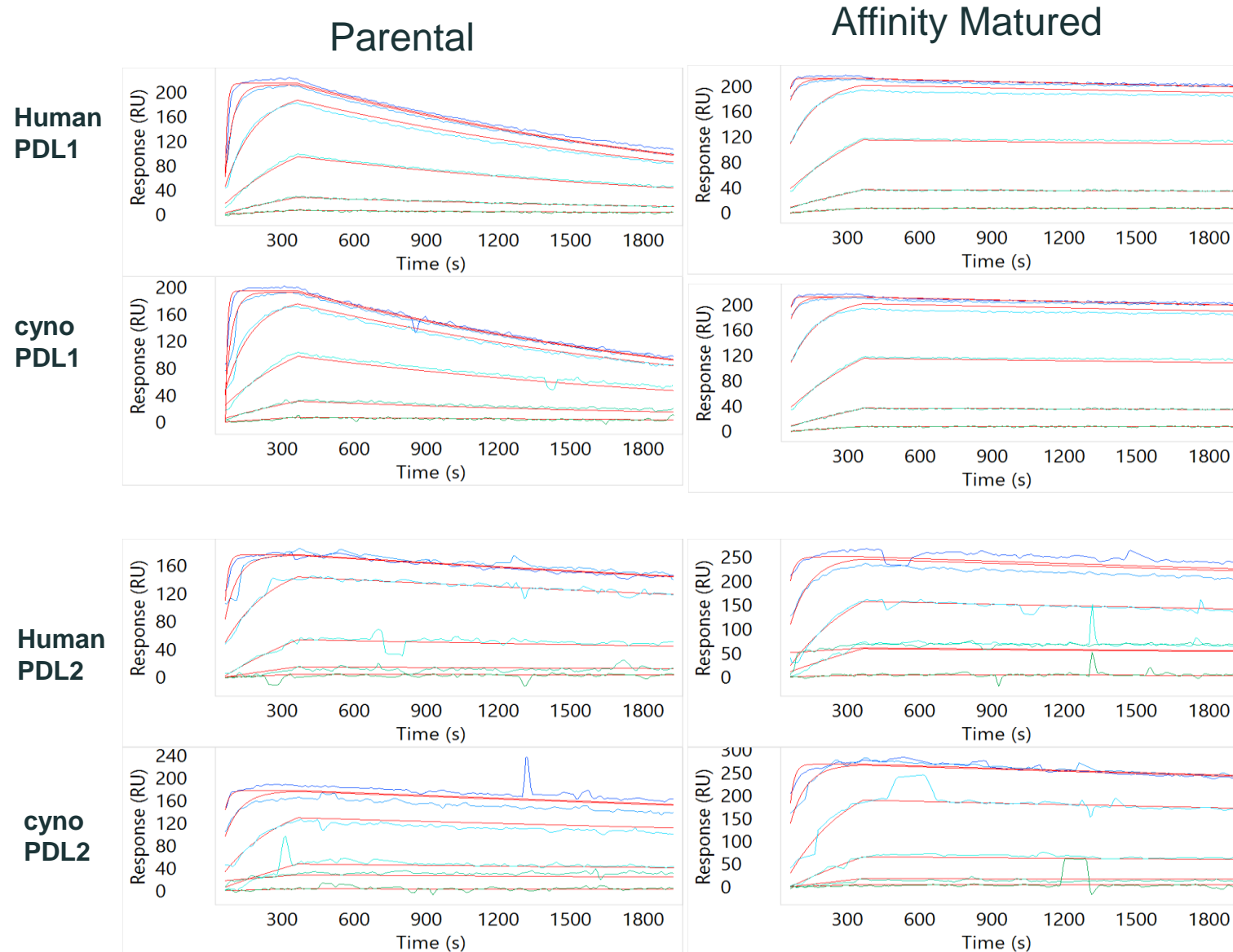
# Low Density Requires High Affinity = Affinity Maturation

- Favorite PD-1 Blocking Clones Chosen from original libraries
- Affinity Maturation Libraries produced at bivalent IgGs
- Lawn of Anti-huFc capture mAb
- Print library of mAbs at different densities (high, mid, low)
- Flow Human and cynomolgus monkey PDL1 or PDL2 as analyte
- Monitor dissociation phase for 30 min.
- Data collection in replicate aids in selection





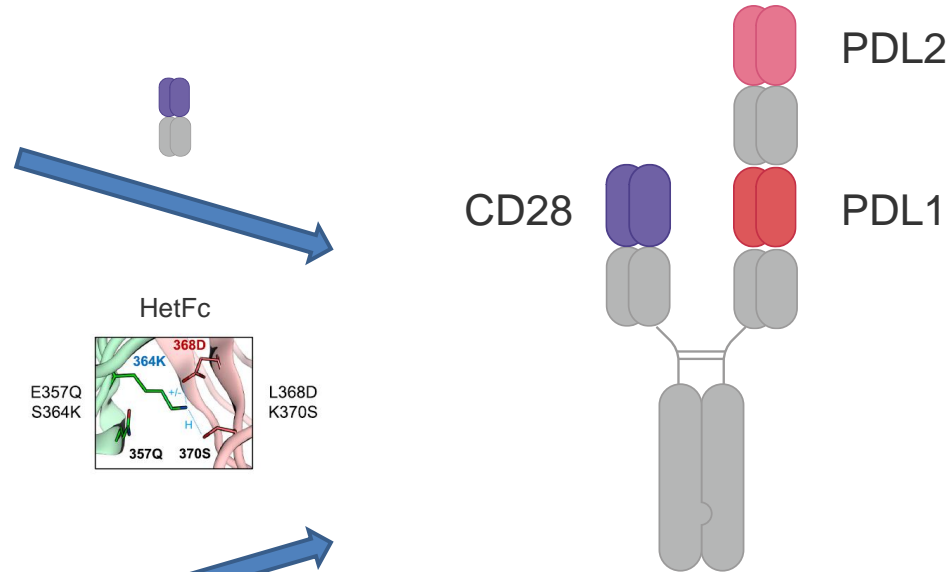
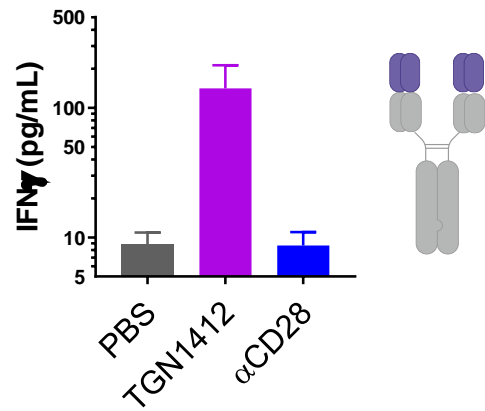
# Affinity Maturation with Carterra LSA



# PDL1 x PDL2 x CD28 was constructed using a non-superagonist $\alpha$ CD28 and antagonist $\alpha$ PDL1/ $\alpha$ PDL2

## Non-superagonist $\alpha$ CD28

Air-Dried Stebbings Assay

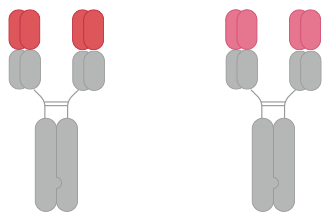


## PDL1 x PDL2 x CD28

- 1+1+1 format (monovalent CD28)
- Common Light Chain
- High affinity  $\alpha$ PDL1,  $\alpha$ PDL2
- Blocks PDL1-PD1, PDL2-PD1
- Fc̳R interactions silenced
- Xtend (LS) half-life extension

## Antagonist $\alpha$ PDL1, $\alpha$ PDL2

Common Light Chain with  $\alpha$ CD28



### Two goals:

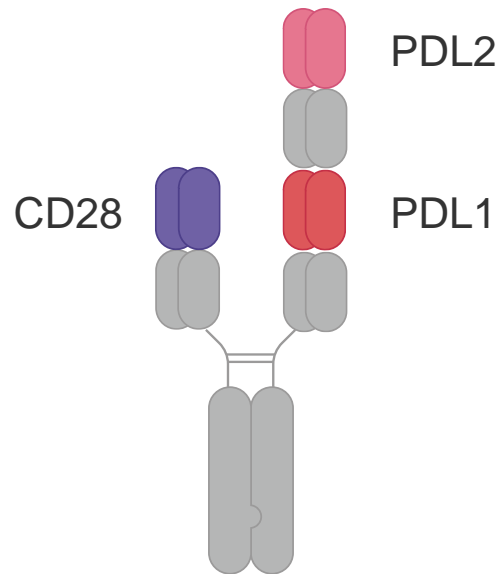
- 1) Block PDL1 and PDL2 from mediating PD1 inhibition
- 2) CD28 costimulation in the presence of PDL1 or PDL2

### Two contexts:

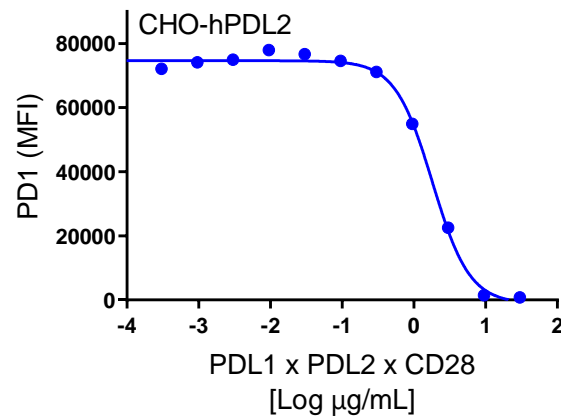
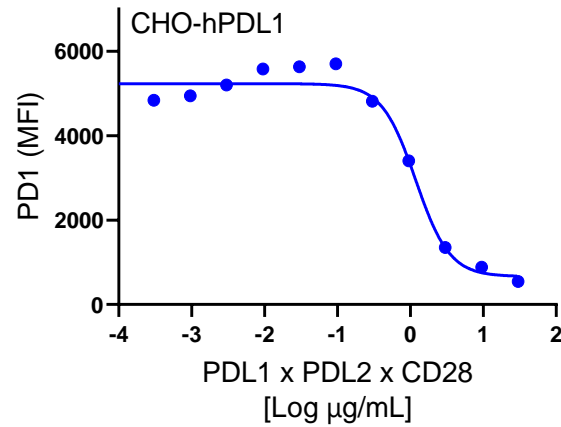
- 1) Combination with CD3 engagers
- 2) As a single agent (neoepitopes)



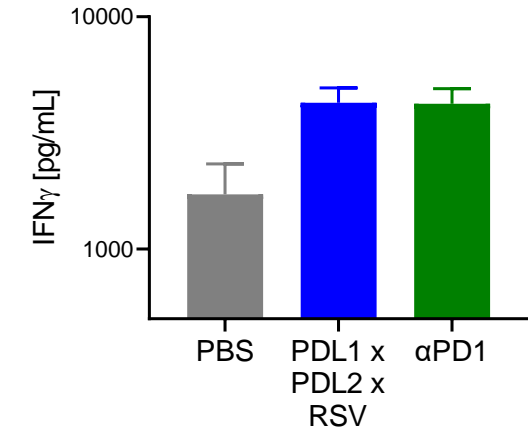
# PDL1 and PDL2 blockade alone is functionally equivalent to PD1 blockade



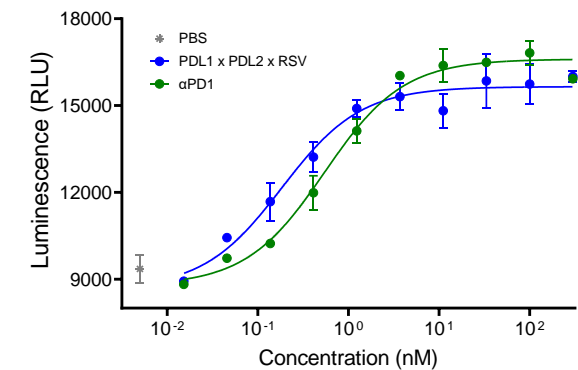
**Trispecific blocks PD1 binding to PDL1 and PDL2**  
Blockade of soluble PD1 cell binding



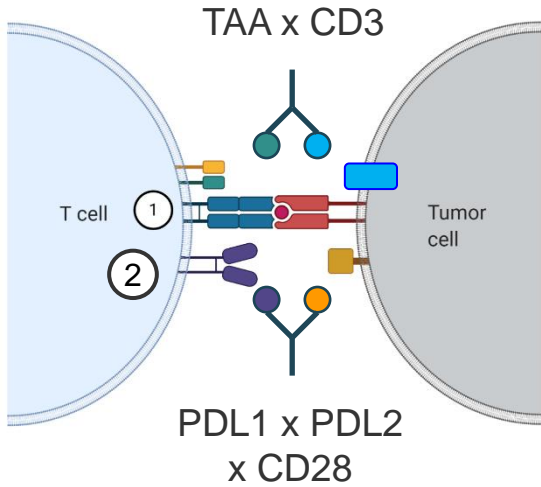
**PDL1 and PDL2 blockade alone is functionally equivalent to PD1 blockade**  
MLR assay (IFN $\gamma$  release, 5 d)



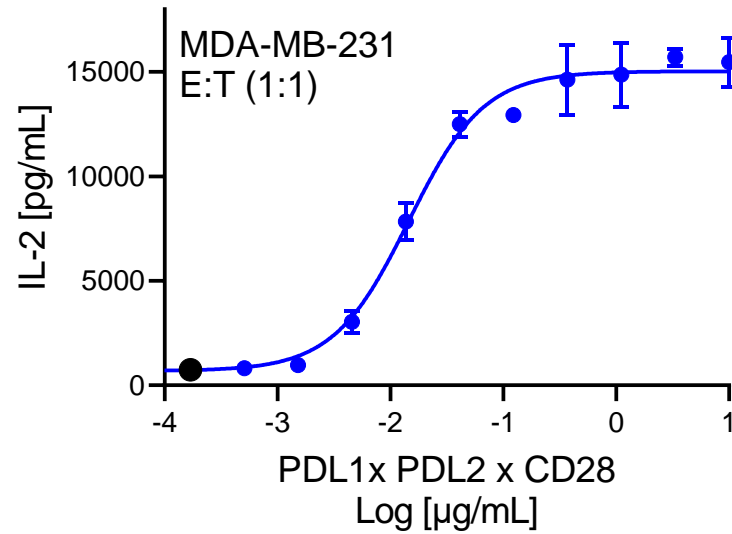
Jurkat PD1 reporter assay



# PDL1 x PDL2 x CD28 provides costimulation, enhancing the activity of a CD3 T cell engager

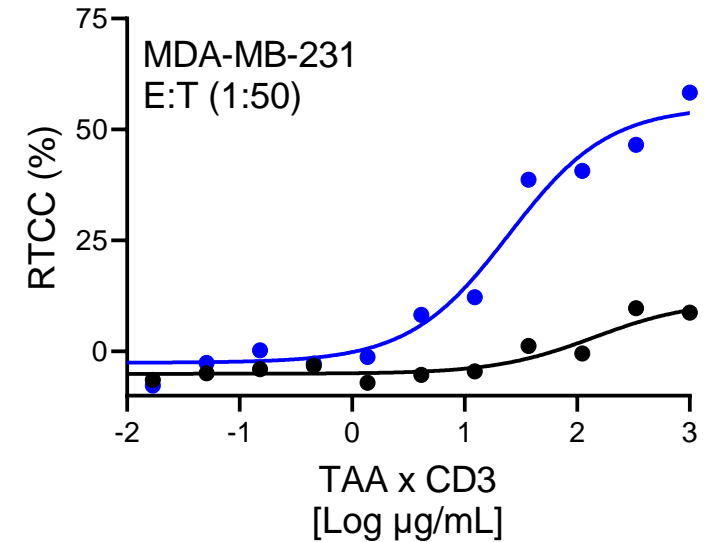


Enhancement of IL-2 release on PDL1+ target cells



● 1 µg/ml TAA x CD3 + PDL1 x PDL2 x CD28    ● 1 µg/ml TAA x CD3

Enhancement of T cell-directed cytotoxicity at low effector to target ratios

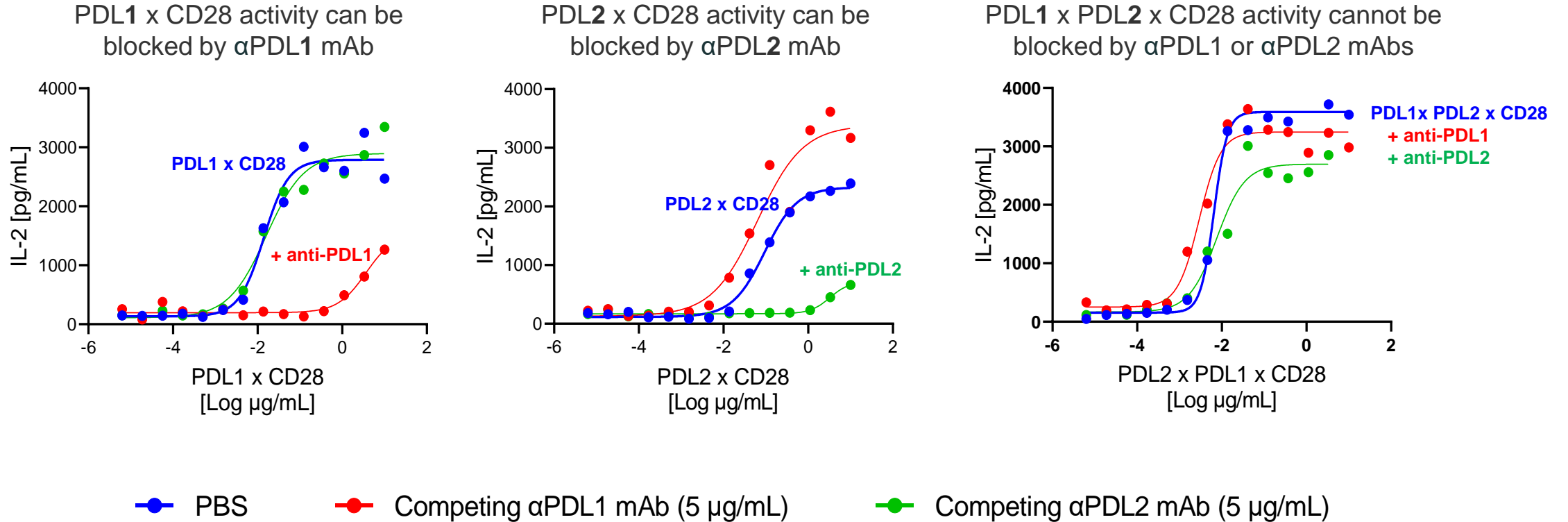


● TAA x CD3 + 1 µg/ml PDL1 x PDL2 x CD28    ● TAA x CD3

## Signal 1 = TAA x CD3

T cells were co-cultured with MDA-MB-231 cancer cells (high PDL1 surface antigens)

# PDL1 x PDL2 x CD28 requires either PDL1 or PDL2 expression for activity



Signal 1 = TAA x CD3

T cells were co-cultured with LCLC103H cancer cells (100,000 PDL1 surface antigens, 40,000 PDL2 surface antigens)

# Acknowledgements

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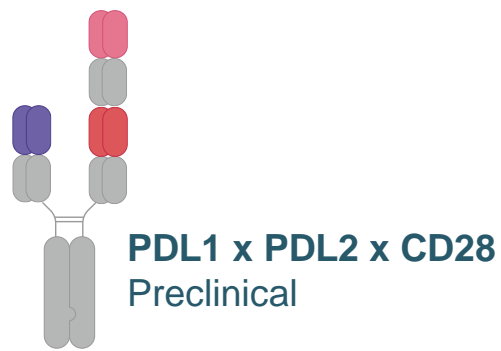
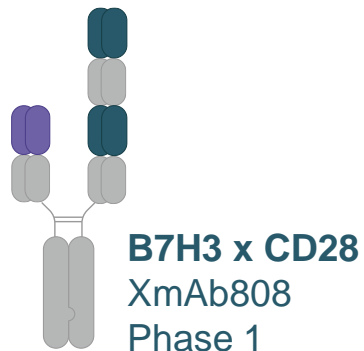
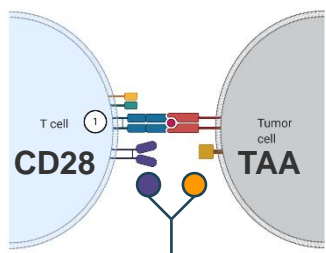
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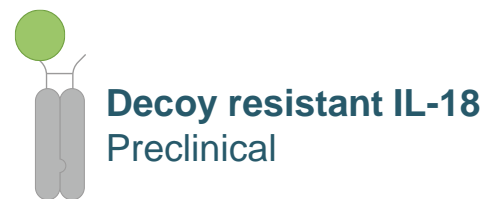
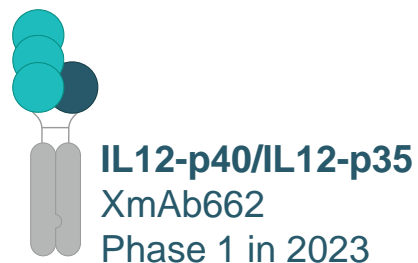
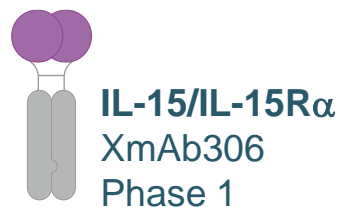
# Growing portfolio of XmAb® CD28 bispecifics and potency-reduced cytokines

**XmAb CD28 Bispecifics** – Coated tumor cells become artificial APCs



- Combinable with TAA x CD3
- Combinable with anti-PD1
- Discovery partnerships with Janssen for CD28 bispecific antibodies in prostate and B cell malignancies

**XmAb Cytokines** – Engineered to expand select immune cell populations and designed to be tolerable, active and easy to use



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