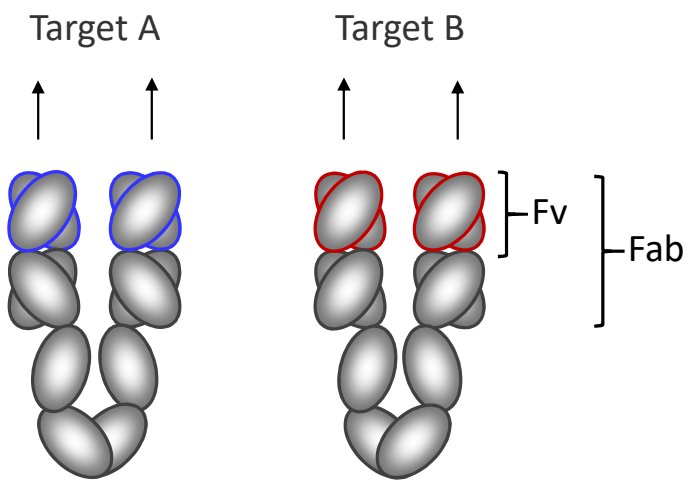
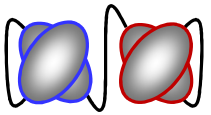
Mobilizing the Immune System with Bispecific Antibodies

Disclosures

- Officer and shareholder of Xencor, Inc.
- Abexxa, Inc. Scientific Advisory Board

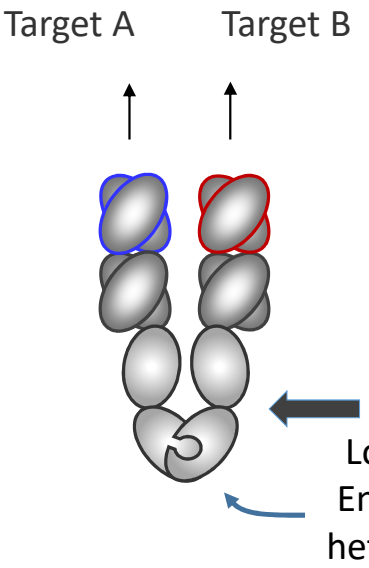
Bispecific antibodies bind two different target antigens





scFv
(single chain Fv)

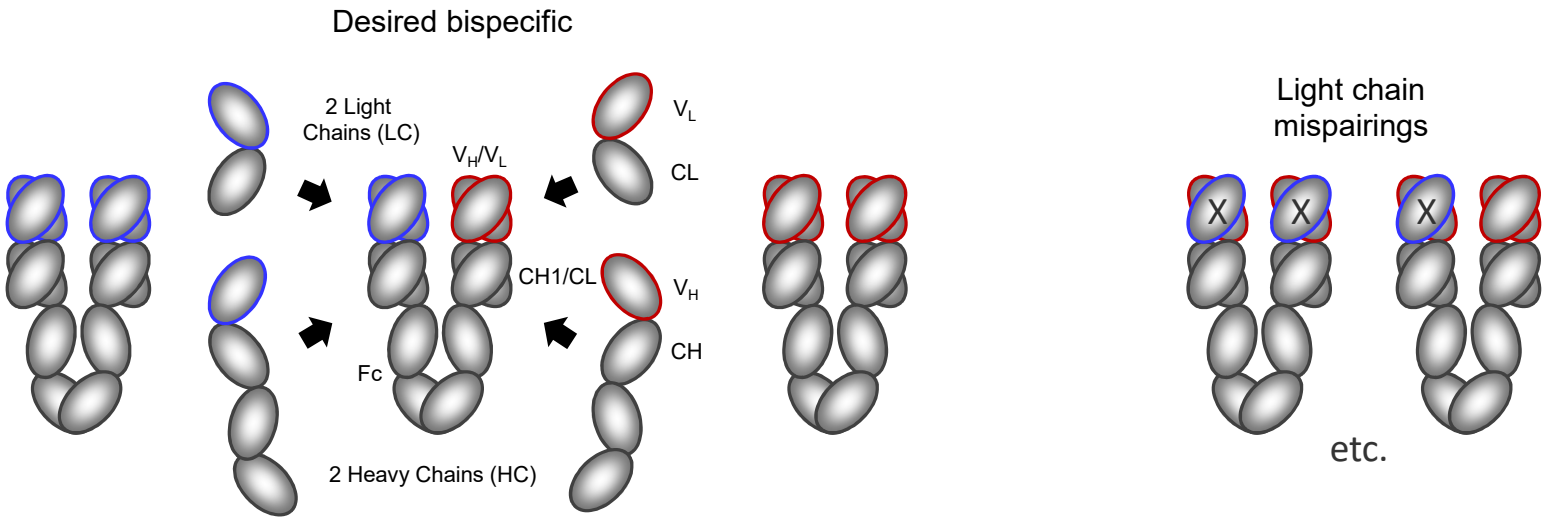
BiTE®
Bispecific T cell Engager
High potency
Short half-life
(blinatumomab)



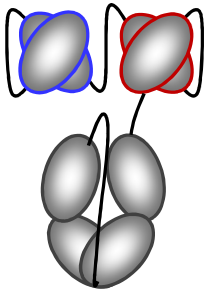
Bivalent antibodies:
- One specificity
- Two binding sites

Bispecific antibodies:
- Two specificities
- Monovalent for each

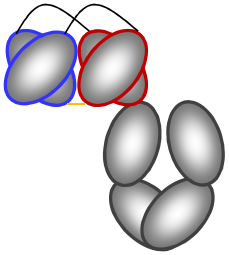
Light chains can mis-pair with the wrong heavy chains, creating a challenge for bispecific production



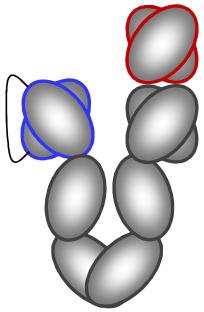
A variety of platforms have evolved to solve the light chain mispairing problem



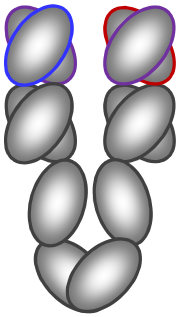
HLE-BiTE®
Amgen



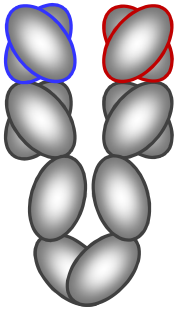
Fc-DART
Macrogenics



scFv-Fab-Fc
Xencor
Zymeworks
Glenmark

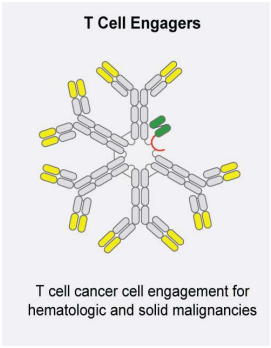


Common light chain
(Both Fabs use same light chain)
Regeneron, Merus, other

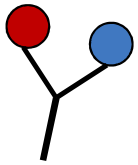


Crossmab
Roche
or
Duobody
Genmab

IgM bio

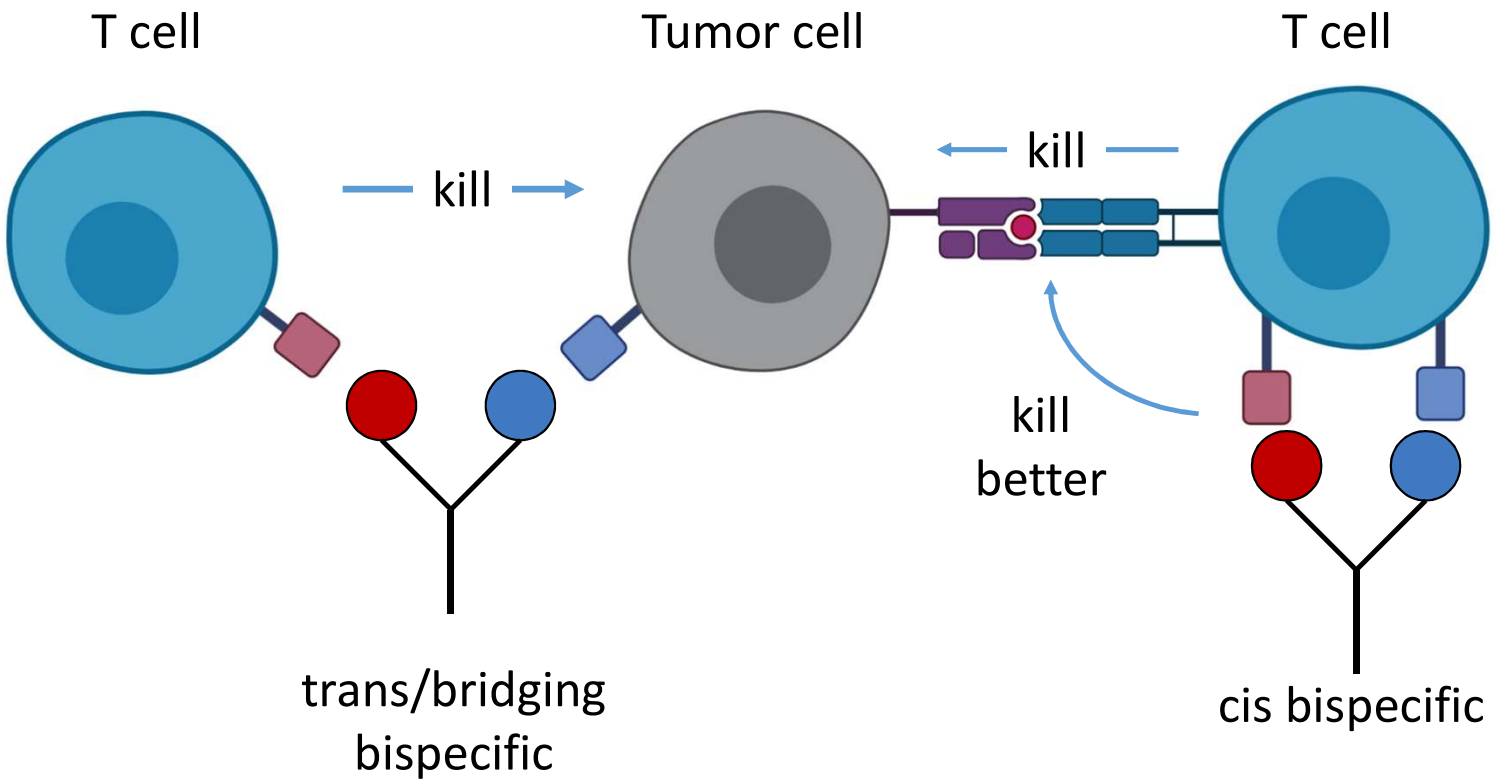


There are many others!



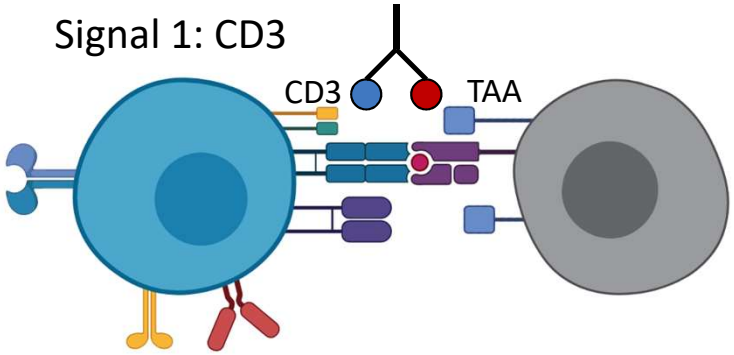
Cartoon bispecific

Bispecific antibodies can target in trans or cis

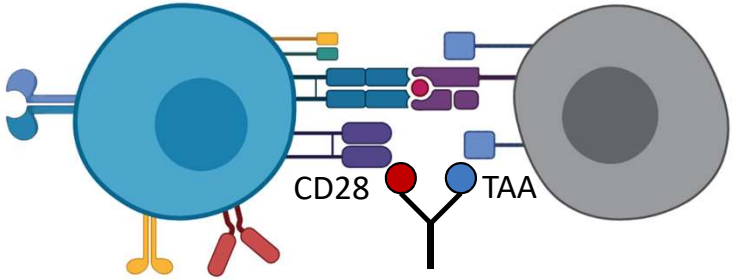


Bispecific antibodies seek to selectively promote T cell activation in multiple ways

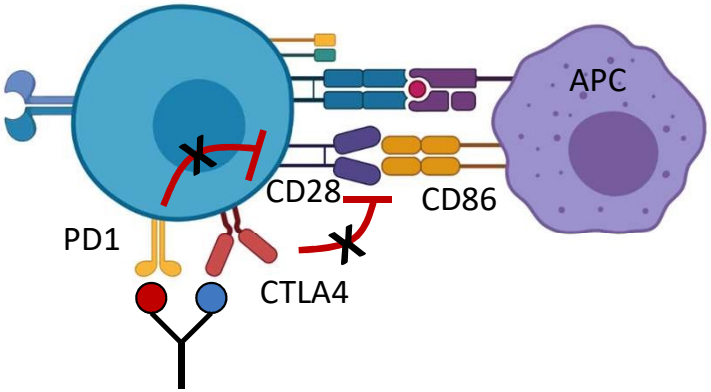
Signal 1: CD3



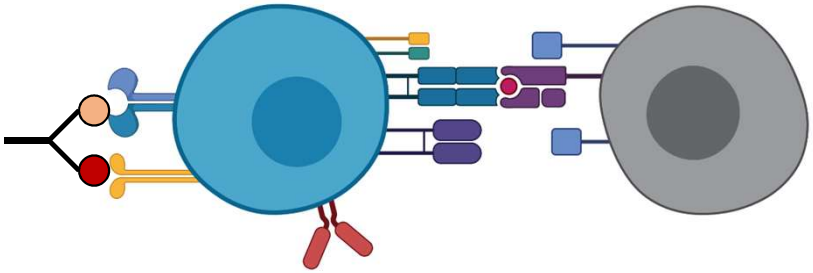
Signal 2: Direct Costimulation



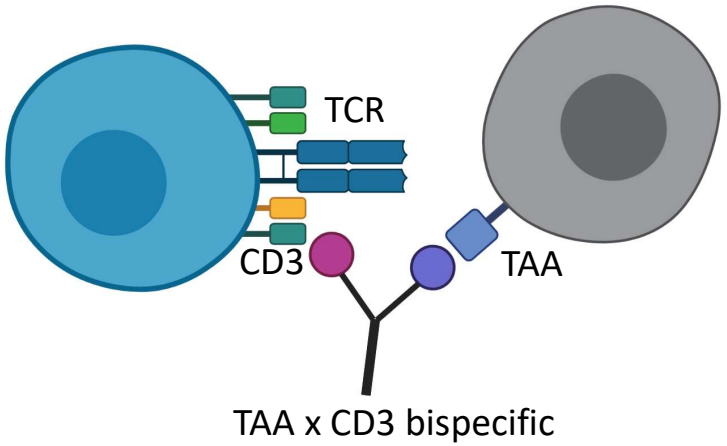
Signal 2: Indirect Costimulation
(dual checkpoint blockade)



Signal 3: Targeted cytokine delivery



CD3 bispecifics (aka T cell engagers/TCE) are the most common bispecifics



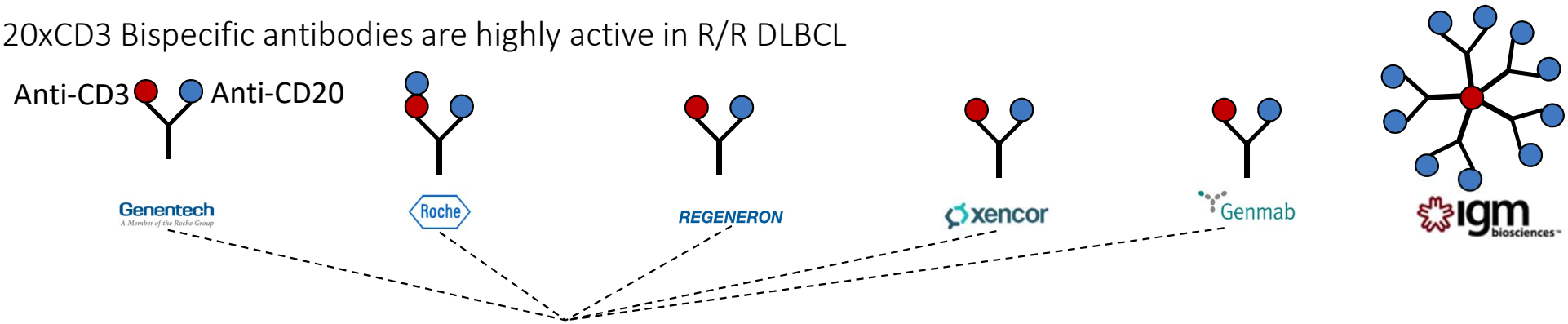
CD3 bispecifics:

- Engage CD3, a component of the TCR
- Circumvent MHC restriction
- Activate T cells
- Promote target cell killing
- Target tumor-associated antigens (TAA) on tumor cells

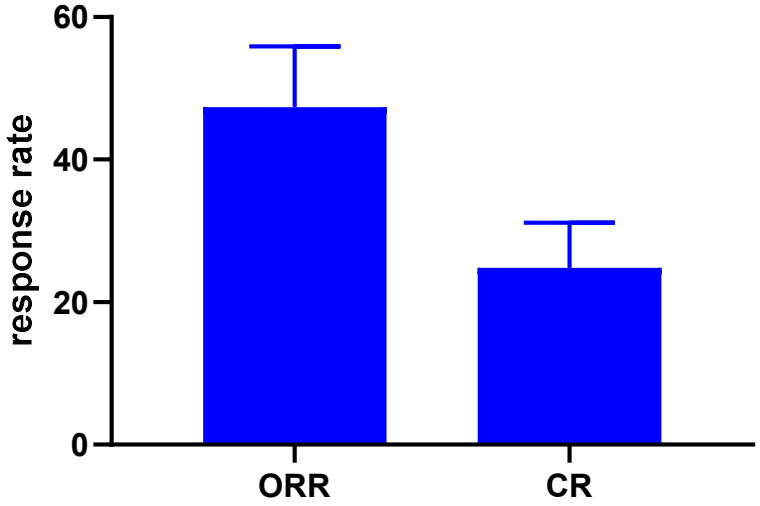
Tumor Associated Antigens (TAA) for Development stage CD3 bispecifics

Indication	Phase 1-2	Phase 3	Approved
B cell malignancies	CD20, CD19		CD19
Myeloma	BCMA, GPRC5D, CD38, FCRH5		
AML	CD123, CD33, CLEC12A, FLT3		
Prostate	PSMA, PSCA, STEAP1		
Ovarian	MSLN, MUC16		
Colon cancer	CEA, A33		
Gastric	MUC17, CLDN18.2		
Liver	GPC3		
Breast	Her2		
Neuroendocrine	SSTR2		
Neuroblastoma	GD2		
Glioblastoma	EGFRvIII		
SCLC	DLL3		
Solid tumors	B7H3, EpCAM, MUC1, 5T4, NY-eso-1, MAGE-A4, PRAME		

CD20xCD3 Bispecific antibodies are highly active in R/R DLBCL

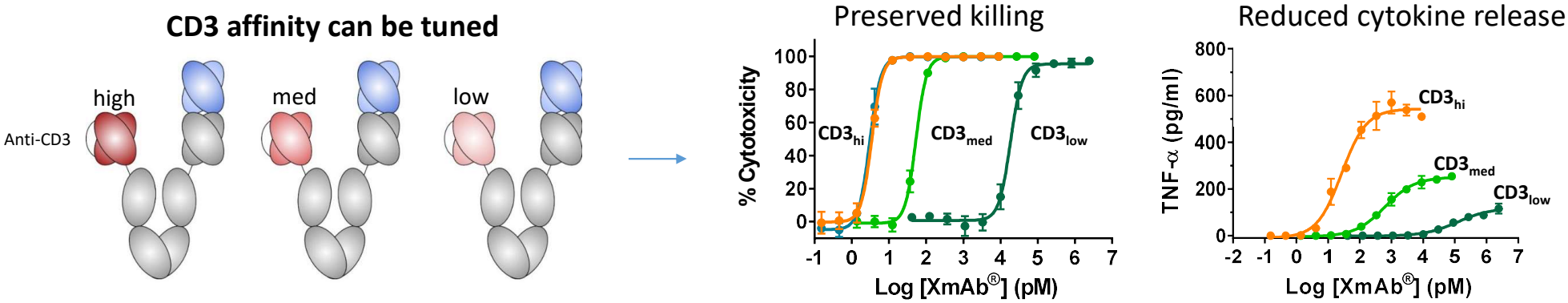


ORR/CR rates similar across multiple programs



- Data sets still maturing
- Some programs still in dose escalation
- Grade3+ CRS: 7-11%
- Common use of priming/step-up dosing to mitigate CRS

Evolution of CD3 bispecifics includes reducing potency to improve safety

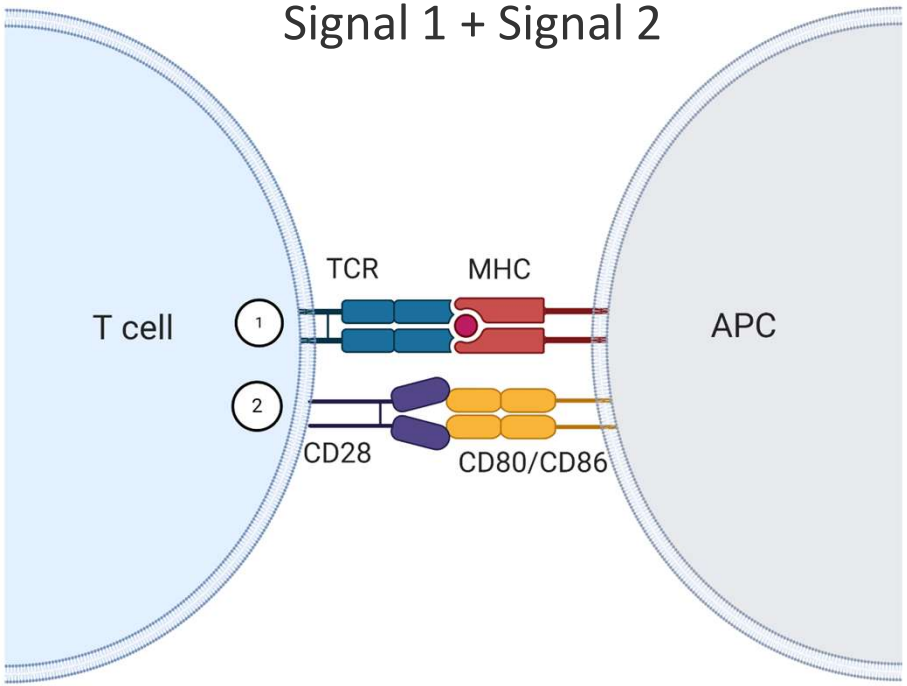


Zuch de Zafra et al., Clin Canc Res 2017

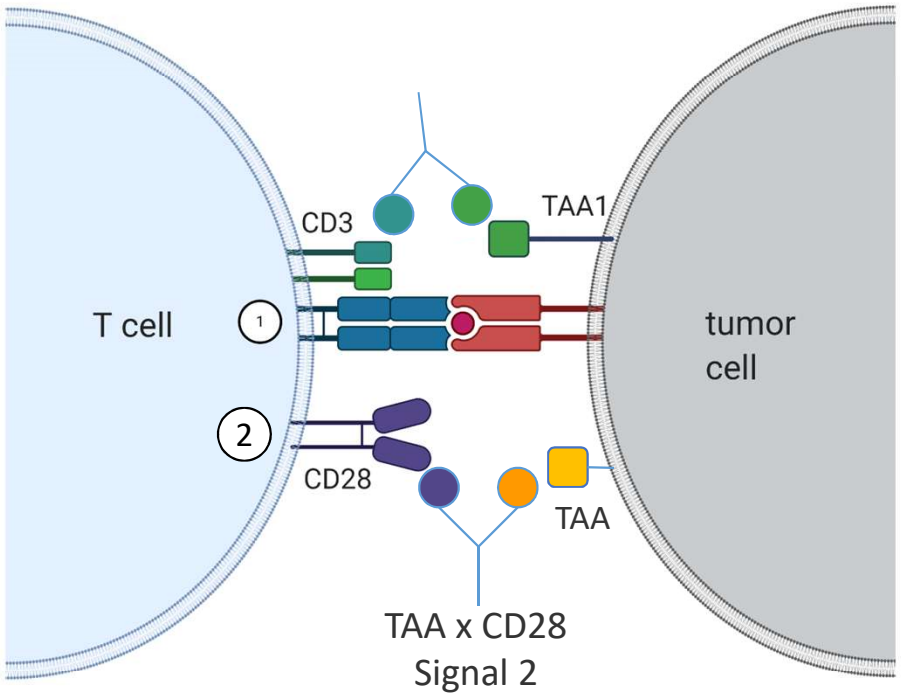
Potency reduction may reduce CRS incidence and severity in patients

Signal 2 can be triggered with TAA x CD28 bispecifics

Classic T cell/APC interaction
Signal 1 + Signal 2

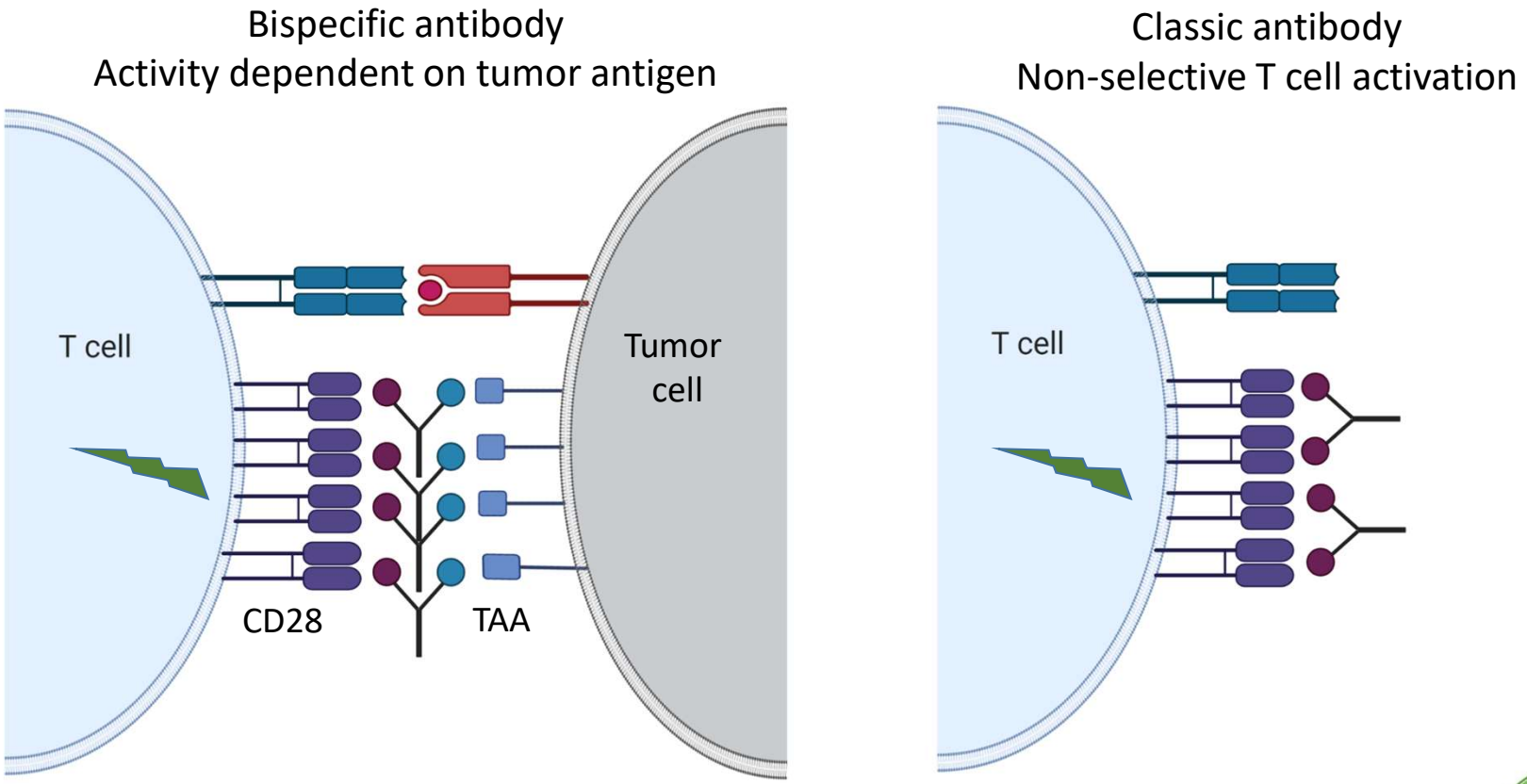


T cell/tumor interaction

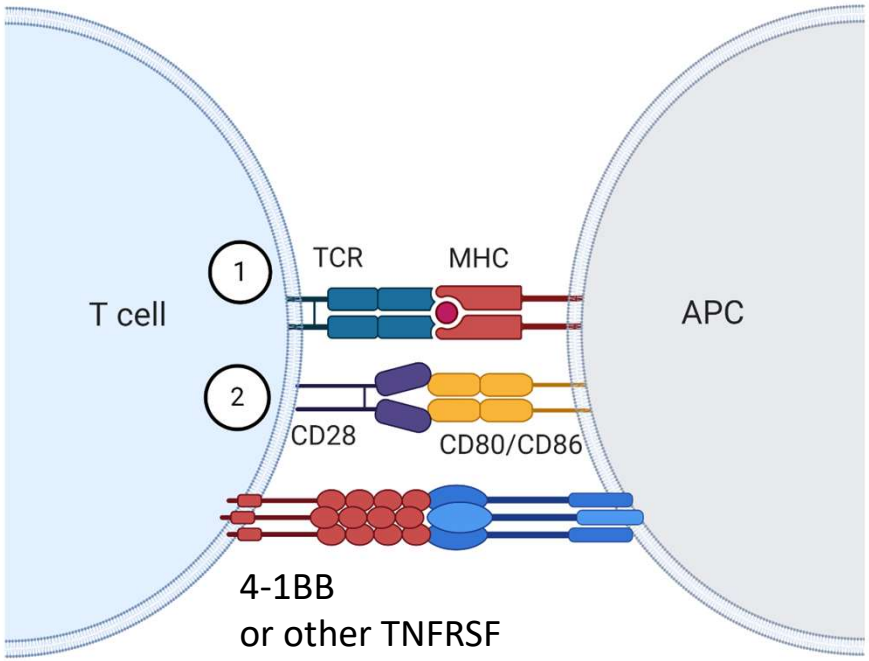


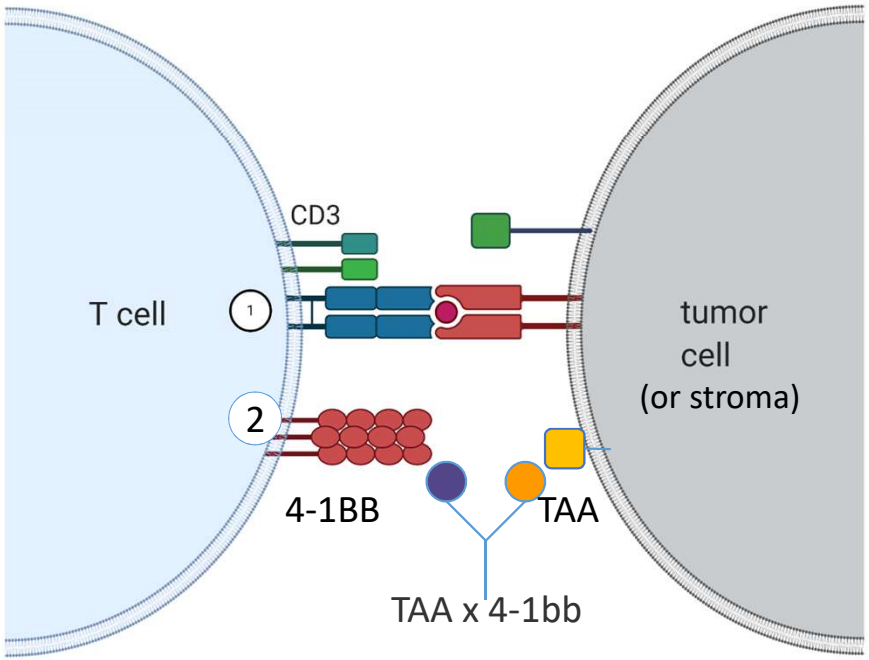
- CD28 costimulation promotes activation and proliferation
- Superagonism is avoided with low affinity, monovalent binding

Bispecifics targeting tumor-associated antigens (TAA) conditionally cluster agonist receptors



Targeted costimulation includes TAA x TNFSFR

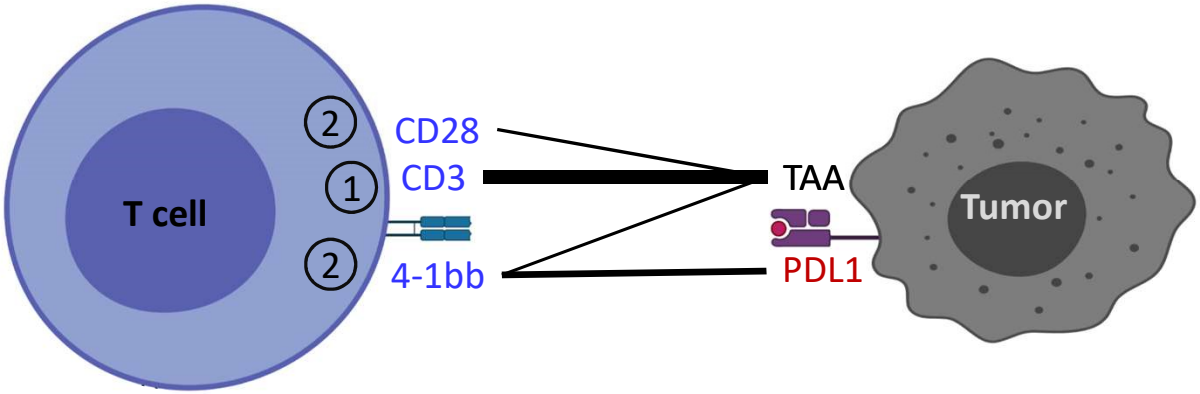




TNFSFRs:
- 4-1bb
- CD27
- OX40
- GITR

TAAs
- PD-L1
- FAP
- Her2

Bispecific connectivity map, Signal 1 + Signal 2

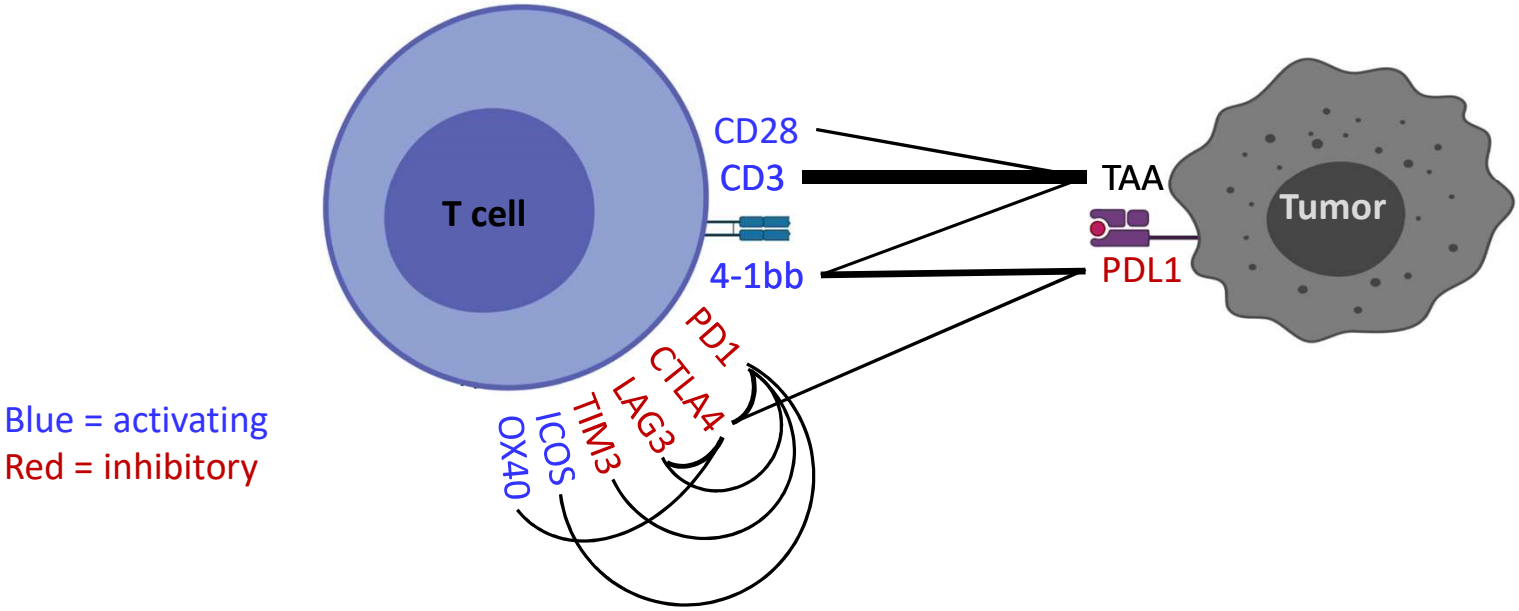


Blue = activating
Red = inhibitory

Tumor-targeted T cell costimulation

- TAA x CD28 (e.g. PSMA x CD28)
- TAA x 4-1bb (e.g. Her2 x 4-1bb, PDL1 x 4-1bb)

Bispecific antibody connectivity map, adding T cell x T cell (cis) bispecifics



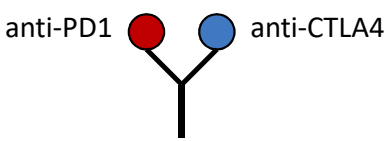
Dual checkpoint blockade

- PD1 x CTLA4
- PD1 x LAG3
- PD1 x TIM3
- CTLA4 x LAG3
- PDL1 x CTLA4

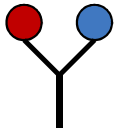
Checkpoint blockade + costimulation

- CTLA4 x OX40
- PD1 x ICOS

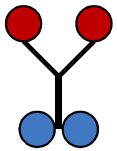
Unlocking Signal 2 with Dual checkpoint blockade: PD1 x CTLA4



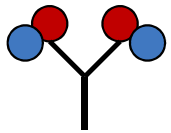
MEDI5752
Medimmune



XmAb20717
Xencor



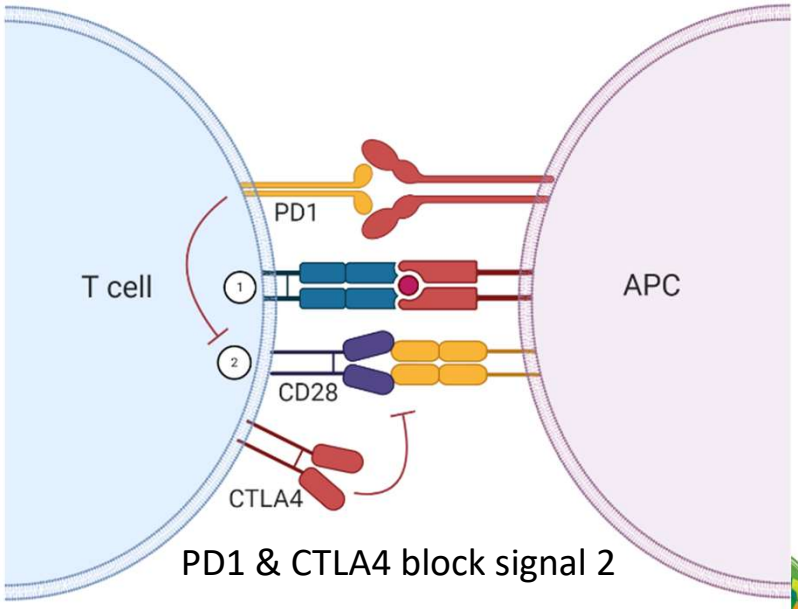
AK104
Akeso



MGD019
Macrogenics

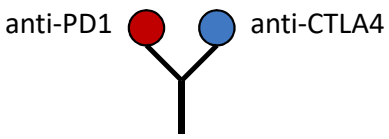
General Goals:

- Block both PD1 and CTLA4
- Improve therapeutic index compared to anti-PD1 + anti-CTLA4 (e.g. nivo + ipi)
- More selective for PD1+CTLA4+ cells
- Inactive Fc domains!
- Clinically active

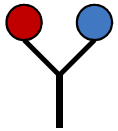


PD1 & CTLA4 block signal 2

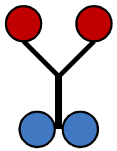
Dual checkpoint blockade: PD1 x CTLA4



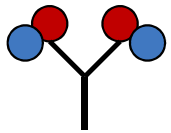
MEDI5752
Medimmune



XmAb20717
Xencor



AK104
Akeso



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Macrogenics

General Goals:

- Block both PD1 and CTLA4
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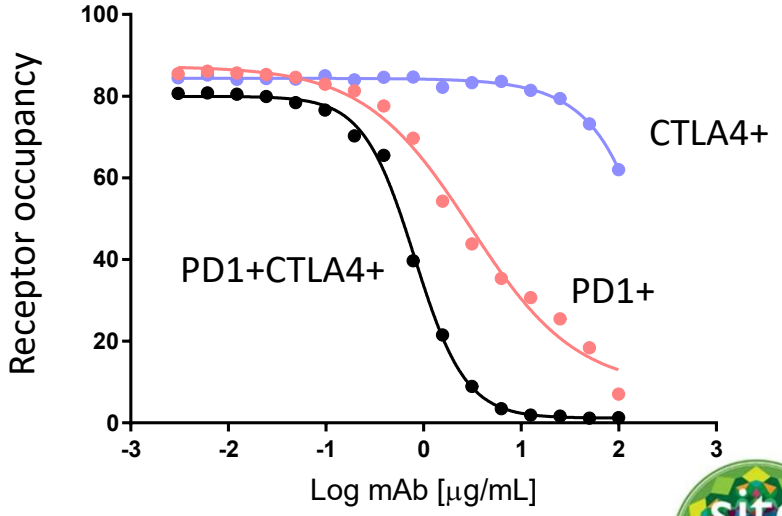
- More selective for PD1+CTLA4+ cells
- Inactive Fc domains!
- Clinically active

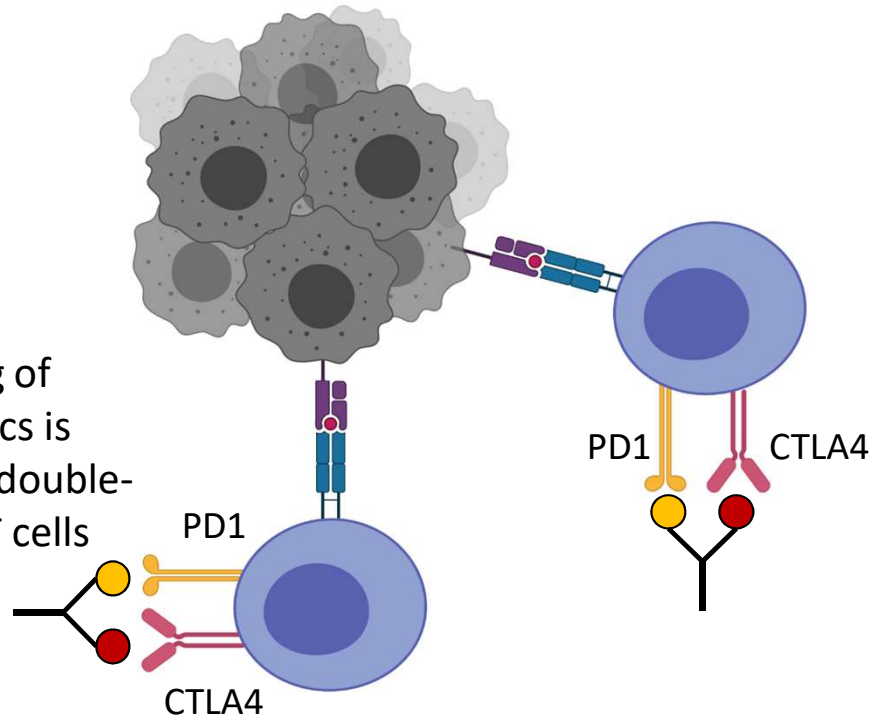
XmAb20717 binds preferentially to PD1+CTLA4+ cells



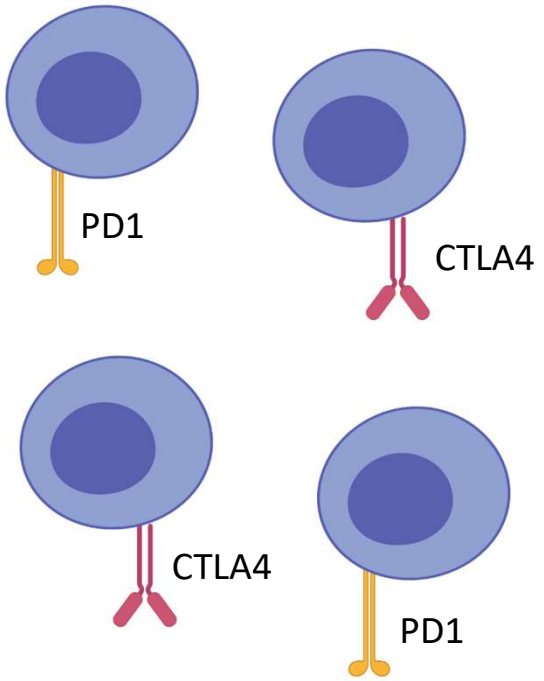
PD1 x CTLA4 bispecifics are designed to preferentially activate PD1+CTLA4+ T cells

Tumor-reactive TILs express multiple checkpoints
PD1 x CTLA4 bispecifics can selectively activate these cells

Binding of Bispecifics is stronger to double-positive T cells



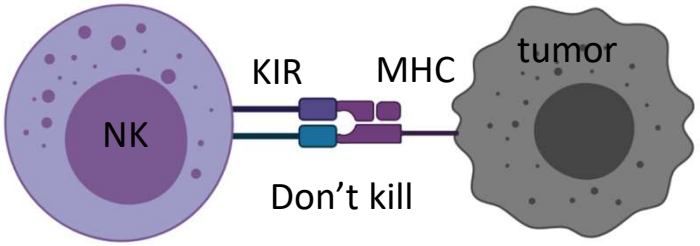
Peripheral T cells



What about other effector cells?

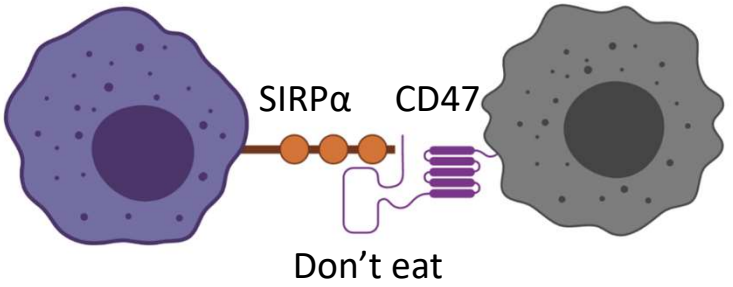
NK cells

- Highly effective killers
- Inhibited by class I MHC through KIR recognition
  - Loss of class I MHC promotes NK killing
  - Activating receptors can overcome KIR inhibition
- Uncertain prevalence in solid tumors



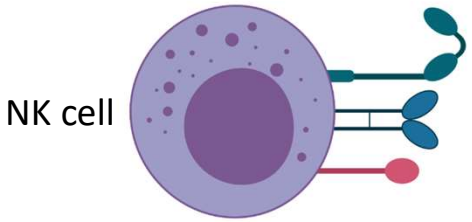
Macrophage

- Phagocytosis
- Antigen presentation
- Tumor-associated macrophage can be inhibitory
- Broadly inhibited by CD47 "don't eat me" signal



Enhancing NK recruitment

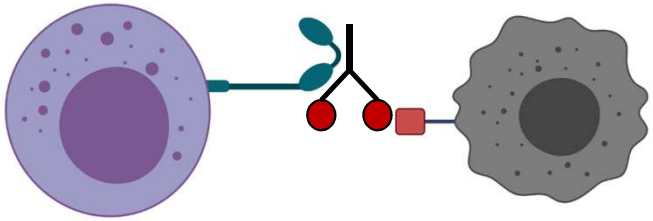
<u>NK activating receptors:</u>



CD16/FcγRIIIa

NKG2D

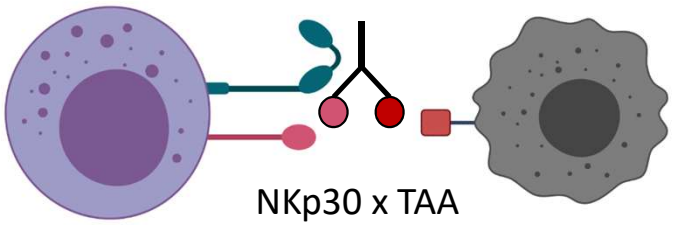
NKp30, NKp44, etc.



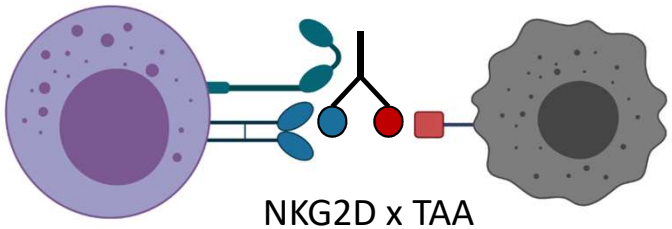
<u>Classic mAbs engage CD16</u>

- rituximab, etc: IgG1
- tafasitimab: CD16-enhanced

<u>Novel bispecifics build off CD16 signal with additional NK activating receptors</u>



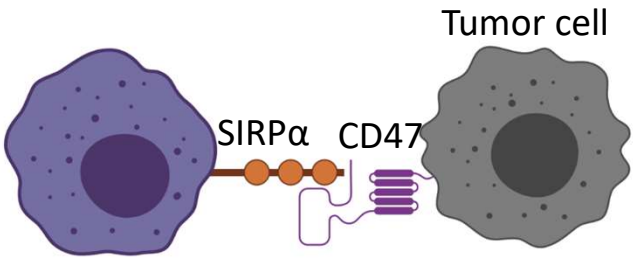
NKp30 x TAA
(w/ CD16)



NKG2D x TAA
(w/ CD16)

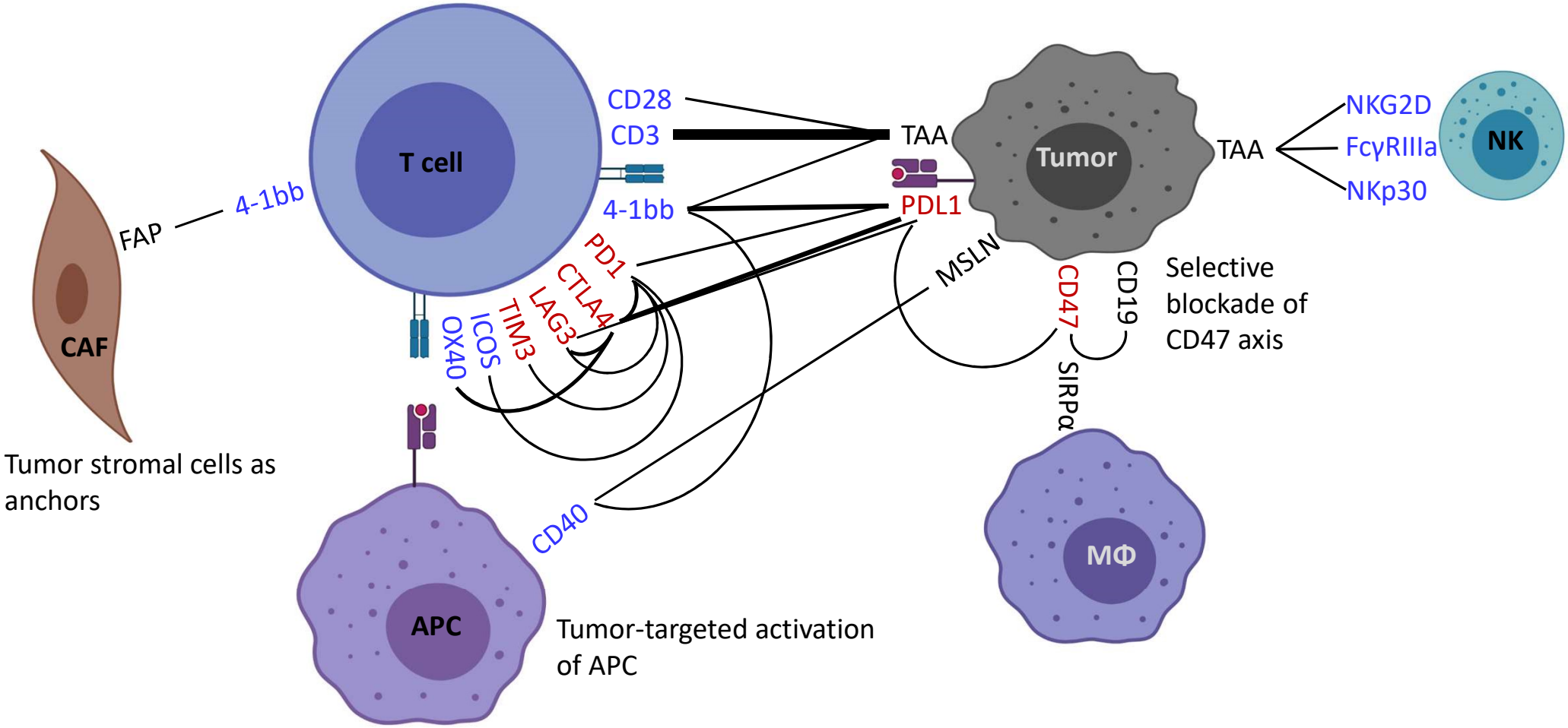
Bispecifics can selectively block the Macrophage “don’t eat me” Signal

SIRPα/CD47 engagement
Protects normal/self cells (and tumors!)
“Don’t eat me”



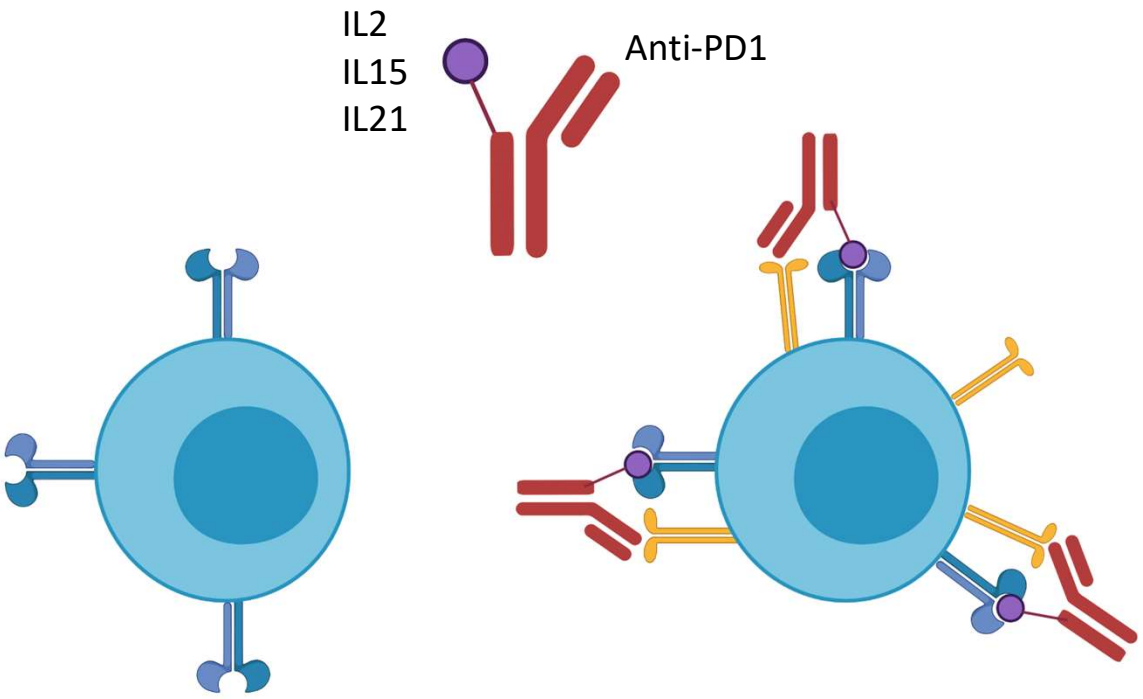
Don’t eat

Bispecific antibody connectivity map (development stage)



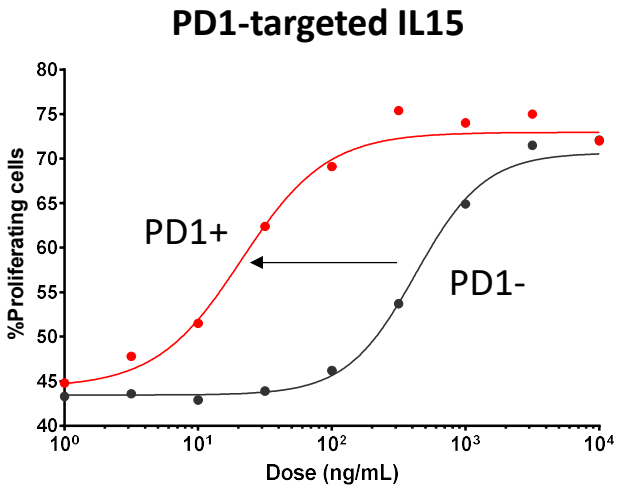
Created with BioRender.com

Bispecific antibody scaffolds can be used to target cytokines to defined lymphocyte populations



Naïve T cell (PD1-)

PD1+ T cell (tumor-reactive)



PD1 binding drives selective activation of PD1+ T cells

Take home messages

- Bispecific antibodies are a rapidly growing & evolving class of therapeutics
- Multiple classes of T cell engagers
  - TAA x CD3
  - TAA x CD28
  - TAA x 4-1bb
- Bispecifics can be used to recruit other immune effectors (NK, macrophage)
- Multiple checkpoint blockade
  - PD1 x CTLA4
  - PD1 x LAG3
  - CTLA4 x LAG3
  - etc.
- Bispecific antibody platforms can be used to target cytokines