Antibodies by Design:

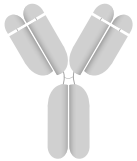
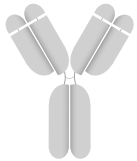
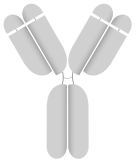
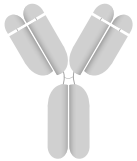
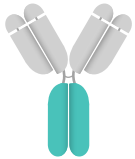
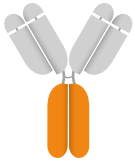
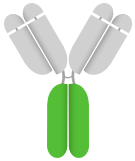
XmAb® Antibody Therapeutics

November 2017

Forward-Looking Statements

Certain statements contained in this presentation, other than statements of historical fact, may constitute forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Such statements include, but are not limited to, statements regarding Xencor's development plans and timelines; potential regulatory actions; expected use of cash resources, the timing and results of clinical trials; and the potential markets for Xencor's product and development candidates. Forward-looking statements are based on the current expectations of management and upon what management believes to be reasonable assumptions based on information currently available to it, and involve numerous risks and uncertainties, many of which are beyond Xencor's control. These risks and uncertainties could cause future results, performance or achievements to differ significantly from the results, performance or achievements expressed or implied by such forward-looking statements. Such risks include, but are not limited to, potential delays in development timelines or negative preclinical or clinical trial results, reliance on third parties for development efforts and changes in the competitive landscape including changes in the standard of care, as well as other risks described in Xencor's filings with the Securities and Exchange Commission. Xencor expressly disclaims any duty, obligation or undertaking to update or revise any forward-looking statements contained herein to reflect any change in Xencor's expectations with regard thereto of any subsequent change in events, conditions or circumstances on which any such statements are based, except in accordance with applicable securities laws. For all forward-looking statements, we claim the protection of the safe harbor for forward looking statements contained in the Private Securities Litigation Reform Act of 1995.

XmAb® Fc Domains Augment Natural Antibody Functions

Natural Fc Function	 Immune regulation Antigen clearance	 Cytotoxicity (immune cell)	 Circulating half-life	 Stable homodimer structure
Fc Receptor	FcγRIIb	FcγRIIa, FcγRIIIa	FcRn	N/A
Fc Domain Redesigns				
XmAb Enhanced Function	 **Immune Inhibitor Domain** Immune inhibition Rapid clearance	 **Cytotoxic Domain** Enhanced cytotoxicity (immune cell)	 **Xtend Domain** Prolonged half-life	 **Bispecific Domain** Stable heterodimer structure

Additional Fc domains: stability, complement activation

99.5% identical to natural antibody
Plug-and-play substitution into any antibody

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Development Pipeline Focused on Immune Inhibitor and Bispecific Fc Domains

Program (Target)	Fc Domain	Primary Indication	Discovery Lead	Preclinical	Phase 1	Phase 2	Commercial Rights
XmAb5871 (CD19)	Immune Inhibitor	IgG4-RD SLE					xencor
XmAb7195 (IgE)	Immune Inhibitor	Asthma/ allergy					xencor
XmAb14045 (CD123 x CD3)	Bispecific	AML					xencor NOVARTIS*
XmAb13676 (CD20 x CD3)	Bispecific	B-cell malignancy					xencor NOVARTIS*
XmAb18087 (SSTR2 x CD3)	Bispecific	Neuroendo-crine tumors					xencor
XmAb20717 (PD-1 x CTLA-4)	Bispecific Xtend	Oncology					xencor
XmAb22841 CTLA-4 x LAG-3	Bispecific Xtend	Oncology					xencor
XmAb23104 PD-1 x Costim	Bispecific Xtend	Oncology					xencor
IL-15/IL-15Ra	Bispecific	Oncology					xencor

* Novartis licensed ex-US commercial rights, worldwide co-development

XmAb® Fc Domains Have Created Numerous Differentiated Antibodies for Technology Partners

Program	Fc Domain	Primary Indication	Preclinical	Phase 1	Phase 2	Phase 3	Commercial Rights
Undisclosed	Xtend	Undisclosed					Alexion
XmAb5574/MOR208	Cytotoxic	NHL/CLL/ ALL					morphosys
Talacotuzumab	Cytotoxic	Leukemia					CSL Janssen
BI 836826	Cytotoxic	Oncology					Boehringer Ingelheim
BI 836858	Cytotoxic	Oncology					Boehringer Ingelheim
Undisclosed	Stability	Autoimmune					MERCK
VRC01LS	Xtend	HIV					NIH
XmAb13551	Bispecific	Myeloma					AMGEN
XmAb bispecific x5	Bispecific	Oncology Inflammation					AMGEN
XmAb bispecific x4	Bispecific	Oncology					NOVARTIS

Technology licensing expands pipeline with very little opportunity cost

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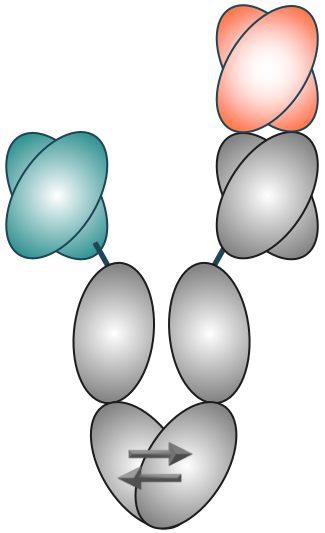
Plug-and-play scFv-Fab format is stable and well-behaved, and easily purified

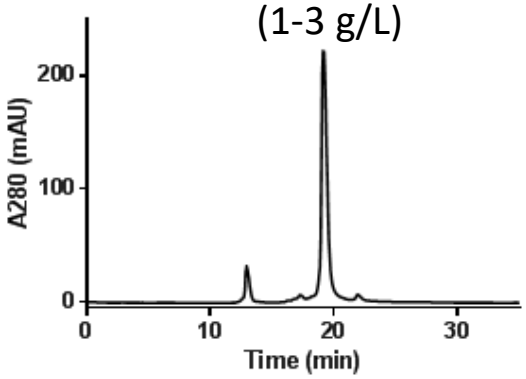
Tumor-targeting Fab domain

Anti-CD3 scFv: Stability optimized (Tm 72°C)

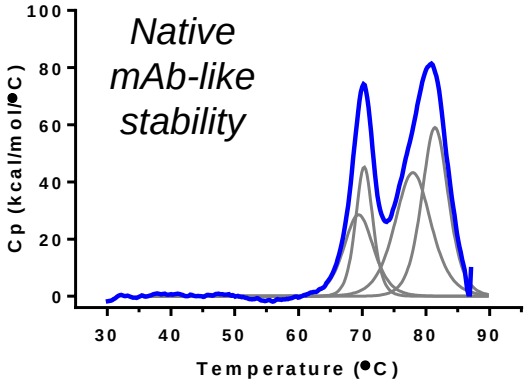
Heterodimeric Fc



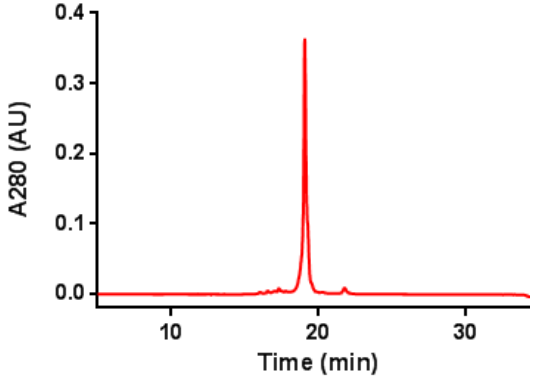
High yield stable cell lines (1-3 g/L)



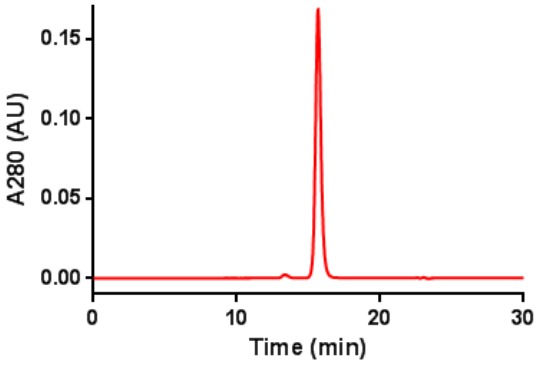
Ion Exchange Chromatography



High purity bispecific (IEX)



Favorable solution properties (SEC)

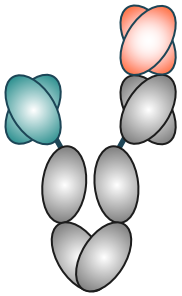


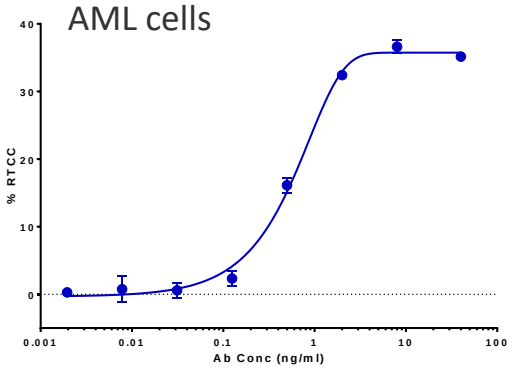
Plug-and-play CD3 bispecifics are highly active and have antibody-like half-life in vivo

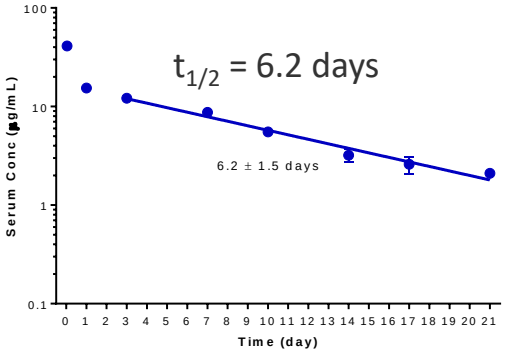
Antibody-like PK!

CD123 x CD3

NOVARTIS

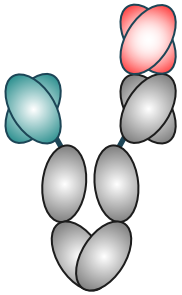


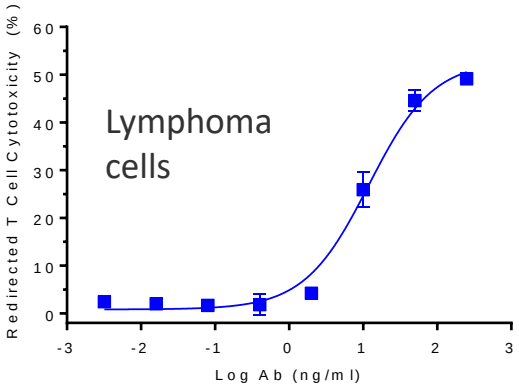


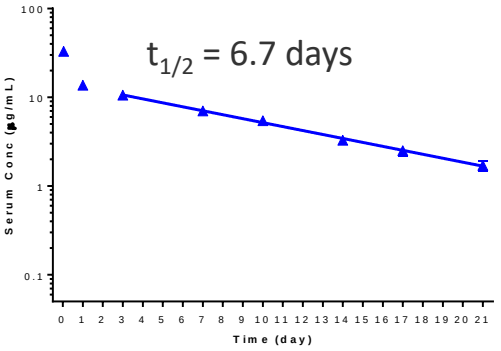


CD20 x CD3

NOVARTIS

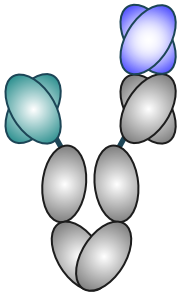


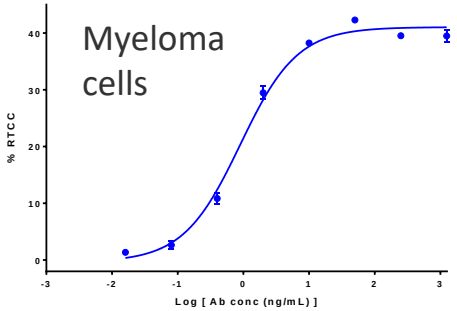


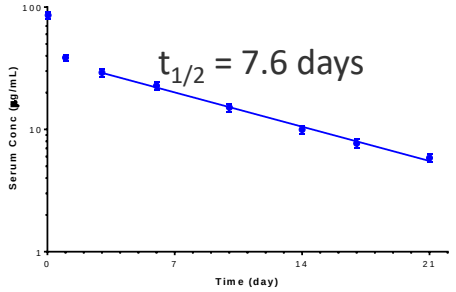


CD38 x CD3

AMGEN







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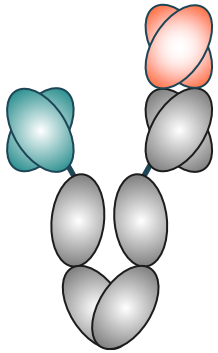
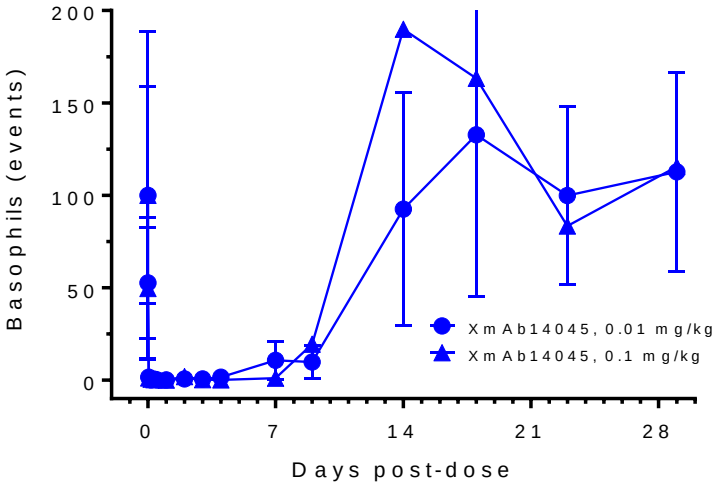
Plug-and-play CD3 bispecifics are highly active and have antibody-like half-life in vivo

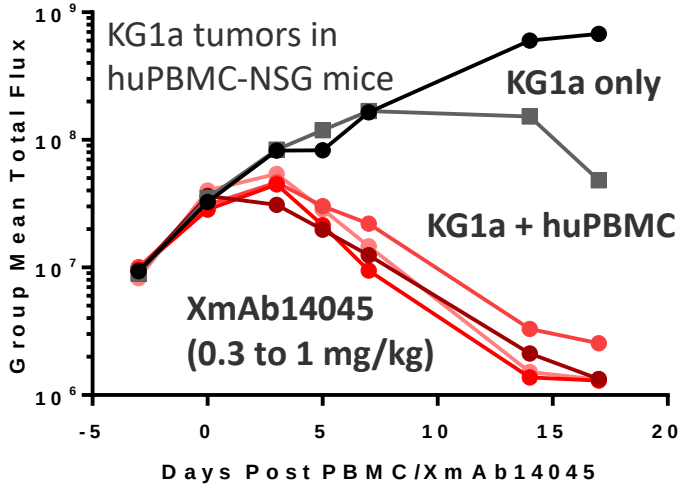
CD123 x CD3



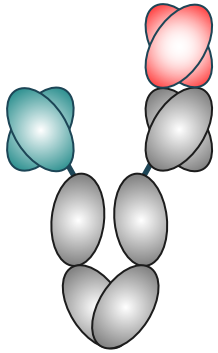
Basophil depletion in monkeys



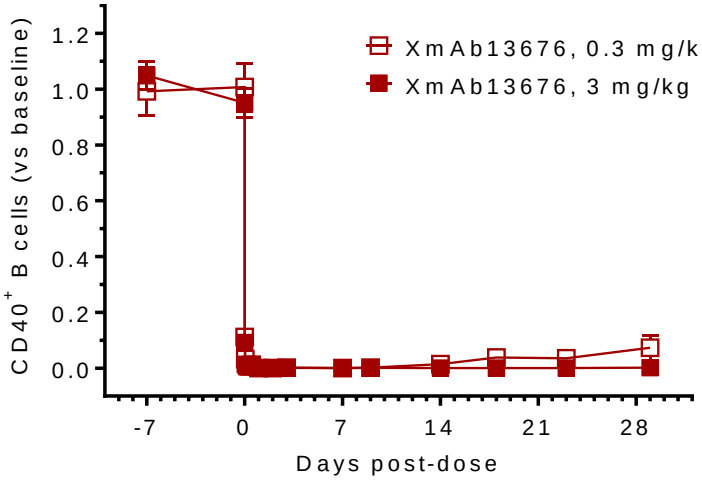
Anti-tumor activity in mice



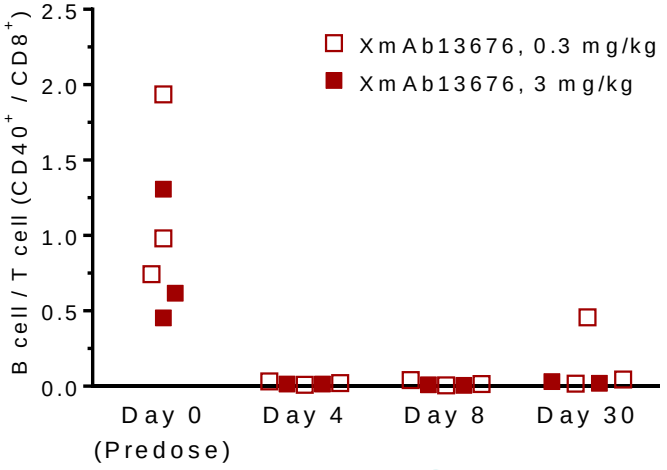
CD20 x CD3



Peripheral B cell depletion in monkeys



Lymph node depletion



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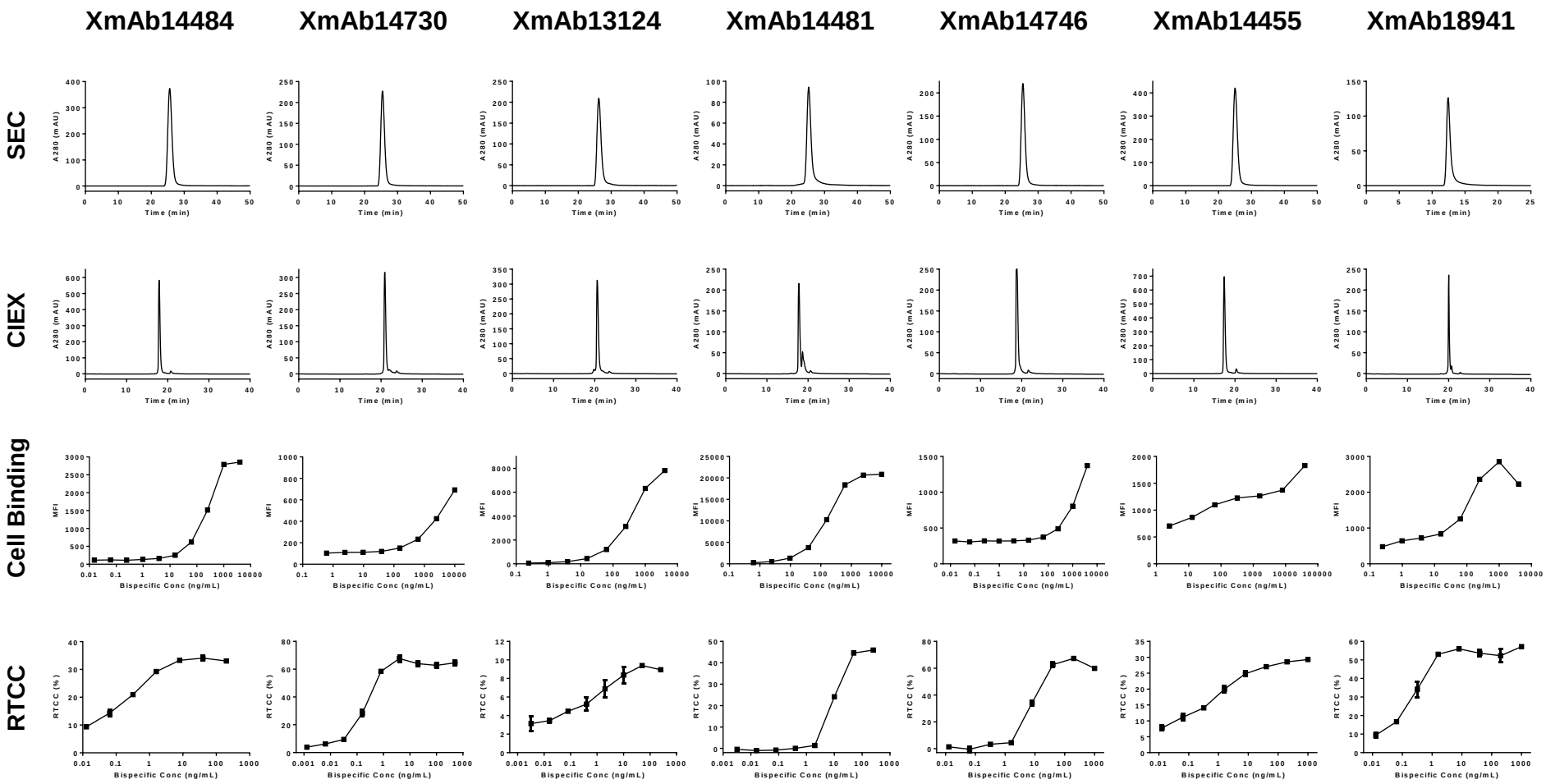
Plug-and-play platform enables rapid prototyping and lead generation



Numerous other CD3 and non-CD3 bispecifics produced

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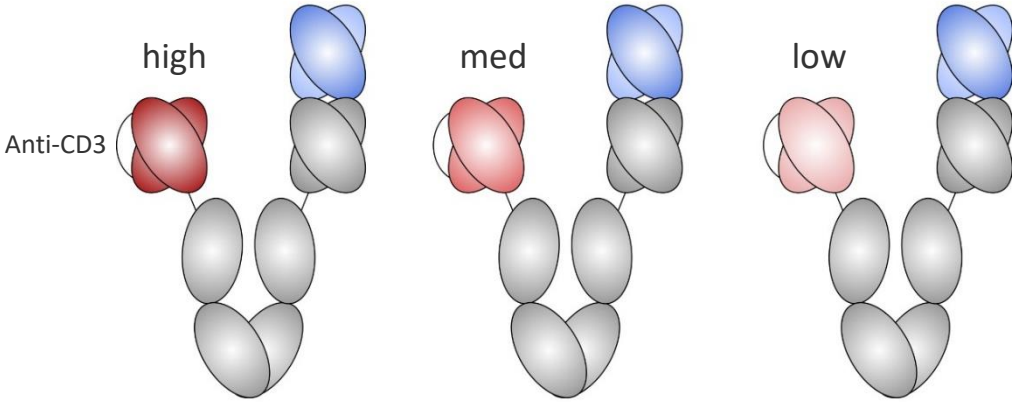
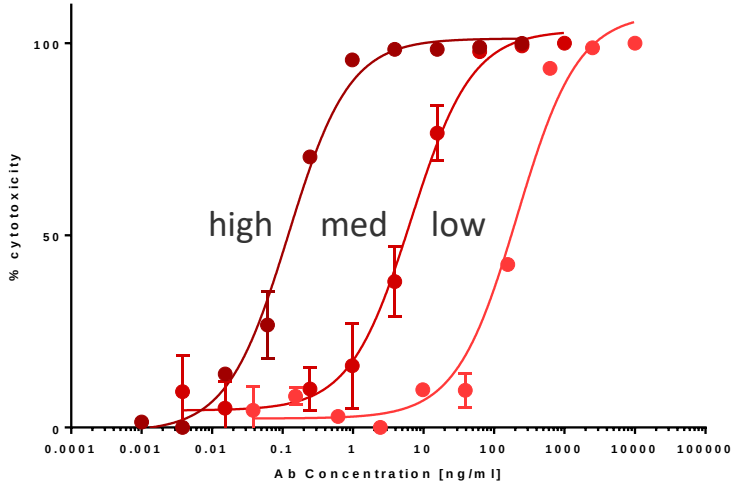
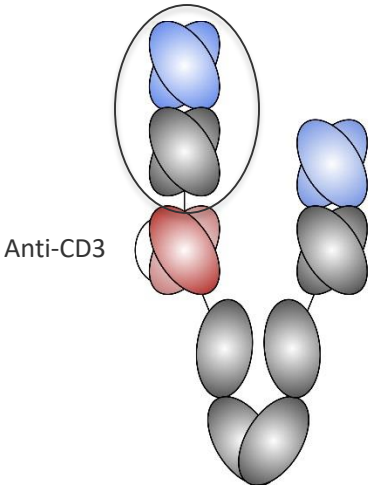
Xencor's bispecific platform is highly tunable

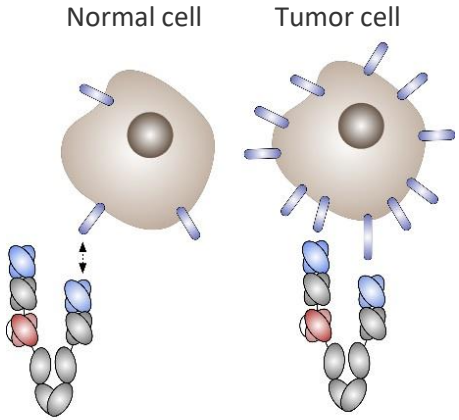
CD3 affinity can be tuned





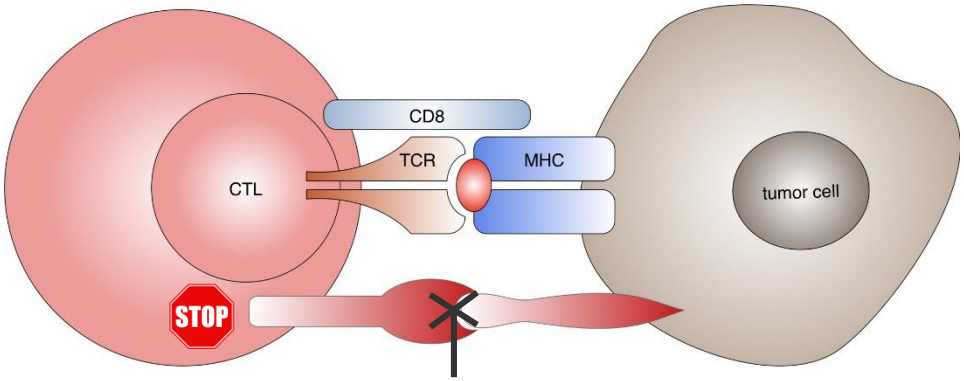
2nd Fab domain can be added for bivalent tumor targeting (2+1 format)





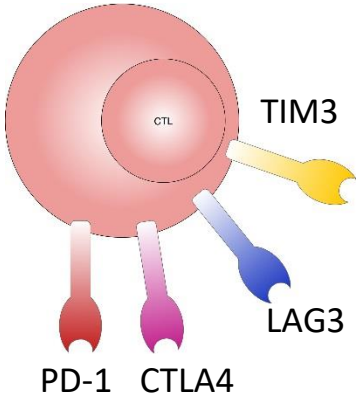
Tumor to normal selectivity is enhanced

Bispecific checkpoint inhibitors can improve on combinations



anti-PD1, anti-CTLA4

Tumor T cells typically co-express multiple checkpoints
(Matsuzaki 2010, Fourcade 2012, Gros 2014, Daud 2016)

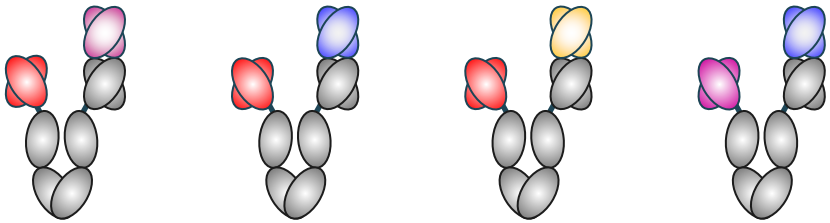


Co-Inhibition
CTLA4, LAG3, TIM3, TIGIT, BTLA, etc.,

Plug-and play
(e.g. PD1 x A/B/C)

Why Bispecifics?

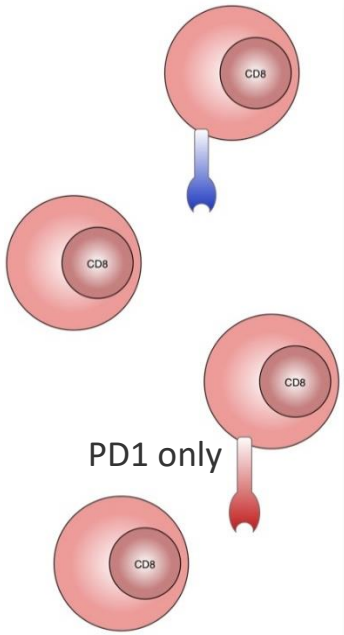
- Reduced costs
- Improved selectivity & safety



Xencor Checkpoint Bispecifics are Designed to Promote Tumor-Selective T cell Targeting

Periphery

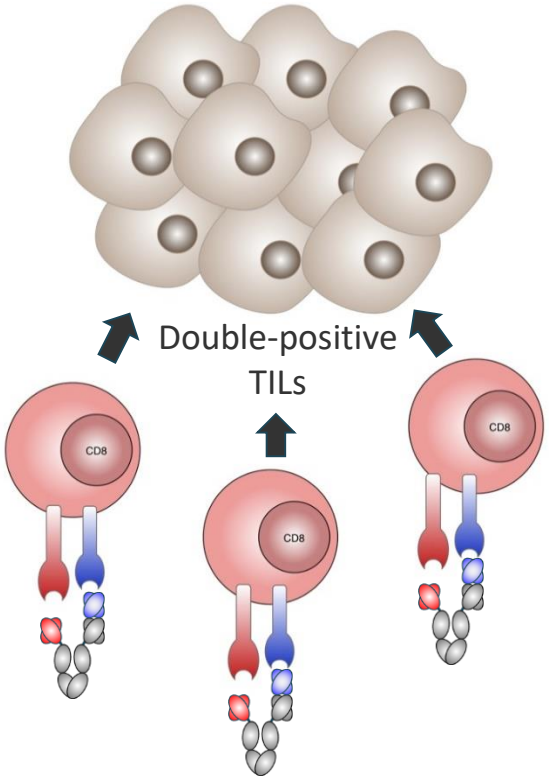
Weak interactions



PD1 only

Tumor Environment

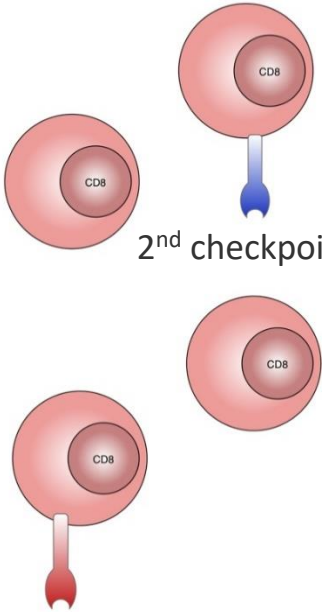
- Strong interactions
- TIL activation



Double-positive TILs

- TILs coexpress multiple checkpoints
- Bivalent binding increases avidity

No activation



2nd checkpoint only

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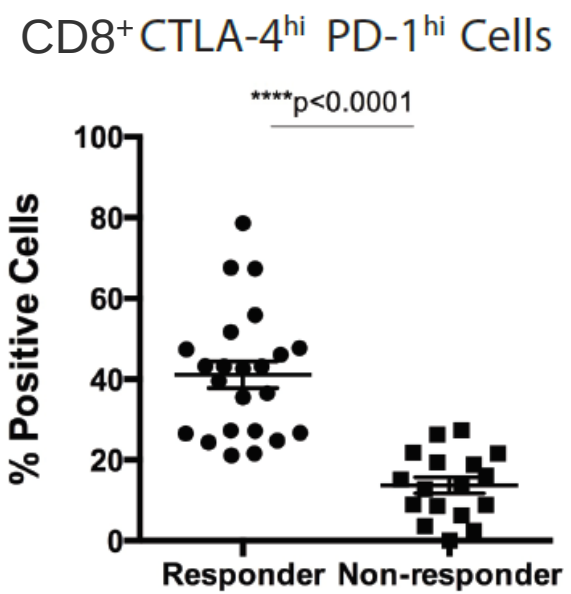
Tumor immune profiling predicts response to anti–PD-1 therapy in human melanoma (J Clin Invest 2016)

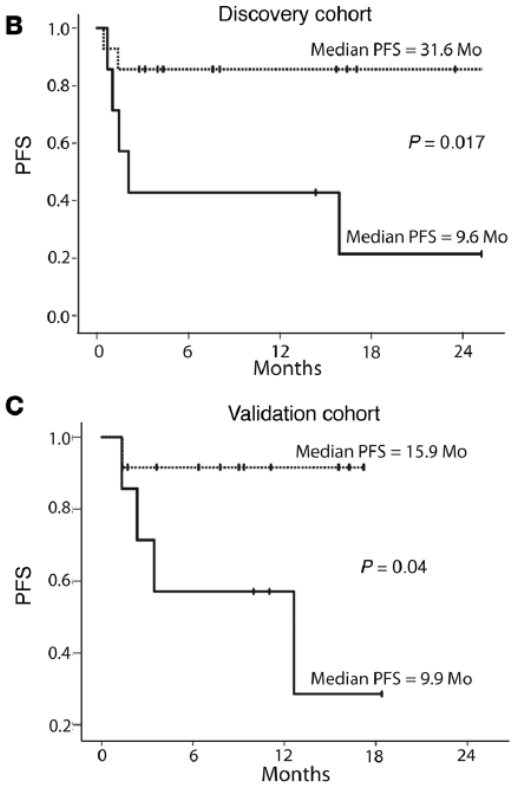
Adil I. Daud,[1] Kimberly Loo,[1] Mariela L. Pauli,[2] Robert Sanchez-Rodriguez,[2] Priscila Munoz Sandoval,[2] Keyon Taravati,[2] Katy Tsai,[1] Adi Nosrati,[1] Lorenzo Nardo,[3] Michael D. Alvarado,[1] Alain P. Algazi,[1] Miguel H. Pampaloni,[4] Iryna V. Lobach,[1] Jimmy Hwang,[1] Robert H. Pierce,[5] Iris K. Gratz,[6] Matthew F. Krummel,[4] and Michael D. Rosenblum[2]

[1]Helen Diller Comprehensive Cancer Center, [2]Department of Dermatology, [3]Department of Radiology, and [4]Department of Pathology, UCSF, San Francisco, California, USA. [5]Oncosec Inc., San Diego, California, USA. [6]Department of Molecular Biology, University of Salzburg, Salzburg, Austria.

Combined expression of CTLA-4 and PD-1 on tumor-infiltrating CD8+ T cells strongly correlates with clinical response to anti-PD-1 therapy.



Relative abundance of CTLA-4^{hi}PD-1^{hi} CTLs predicts response to anti–PD-1 therapy.



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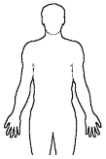
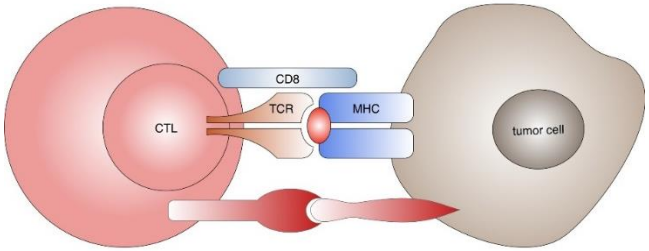
Xenogeneic graft-vs-host disease is a model for checkpoint blockade

Human tumors

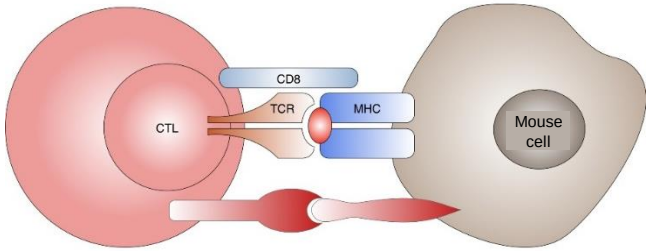


Human PBMC →  NSG mice

Human T cell Tumor cell

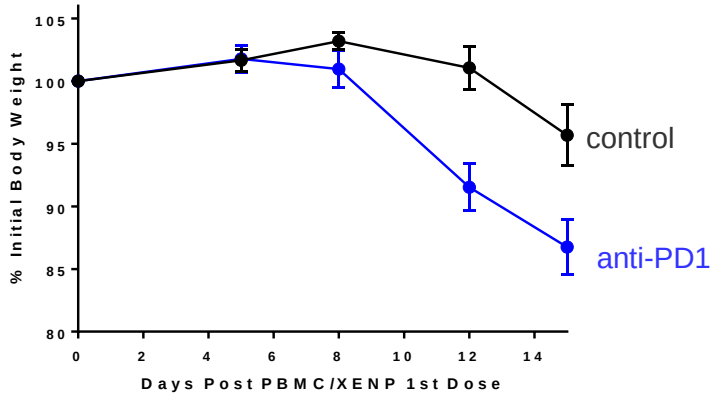


Human T cell Mouse cell

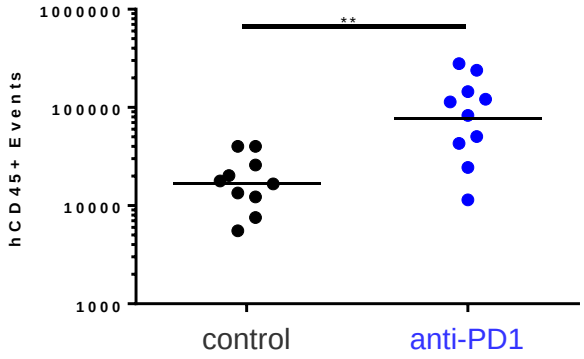


PD1 blockade enhances GVHD

Mice get sicker (GVHD)



Mice have more T cells



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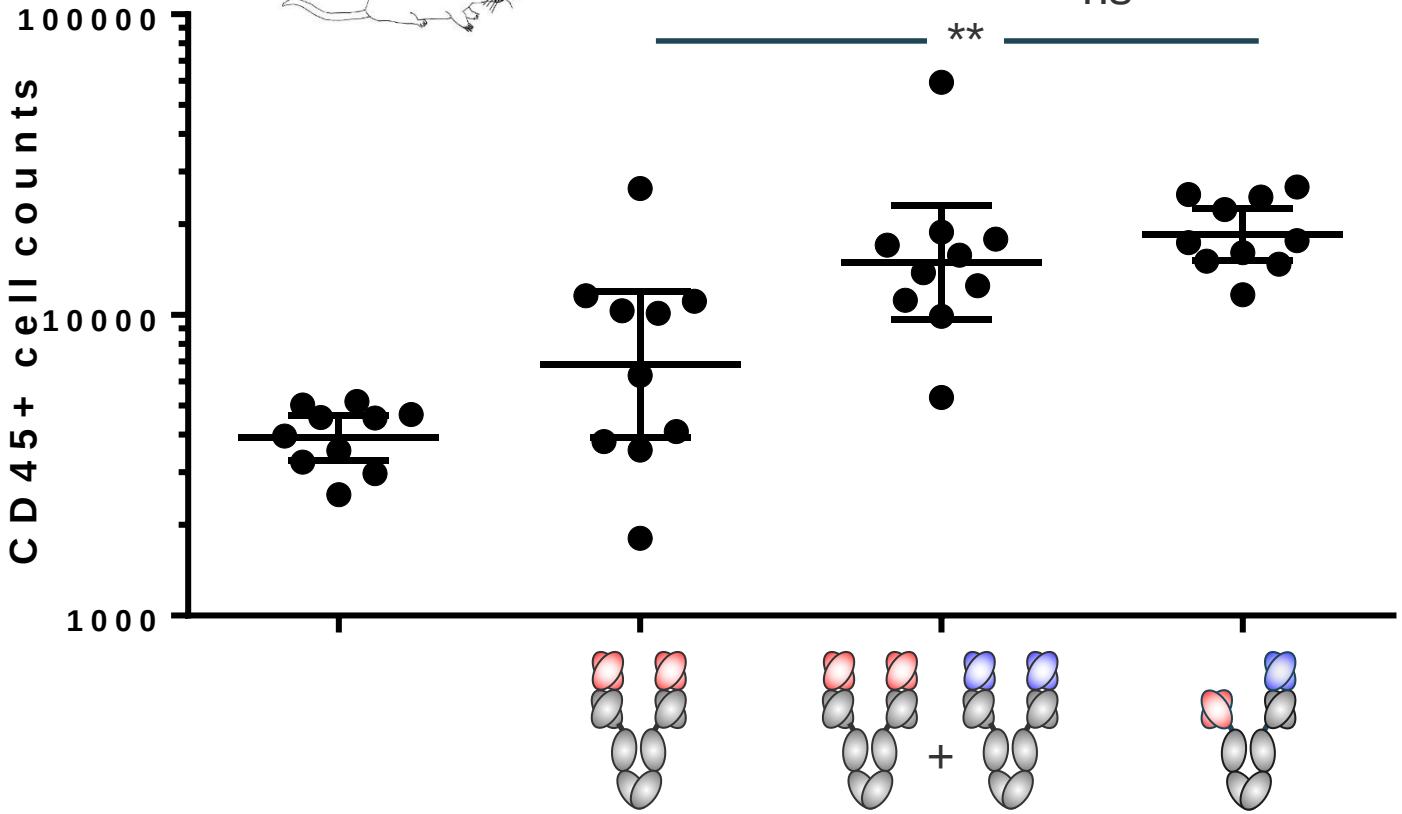
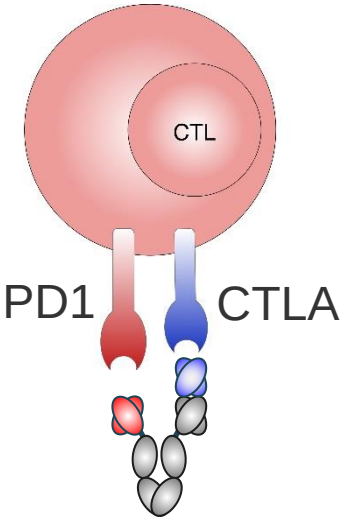
PD1 x CTLA4 bispecific antibody is highly active in a mouse model for checkpoint blockade

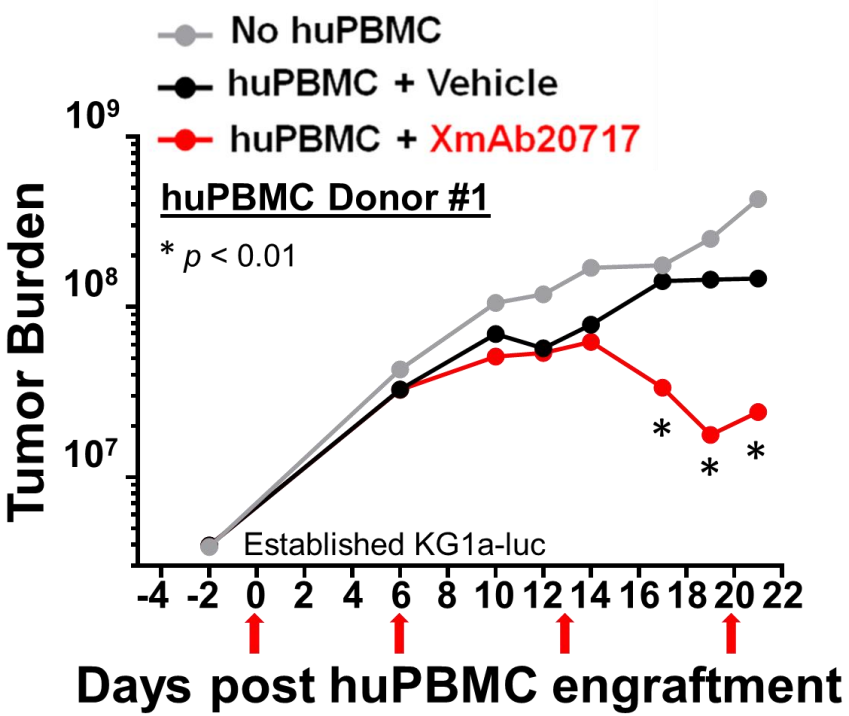
Human PBMC → NSG mice → count human T cells

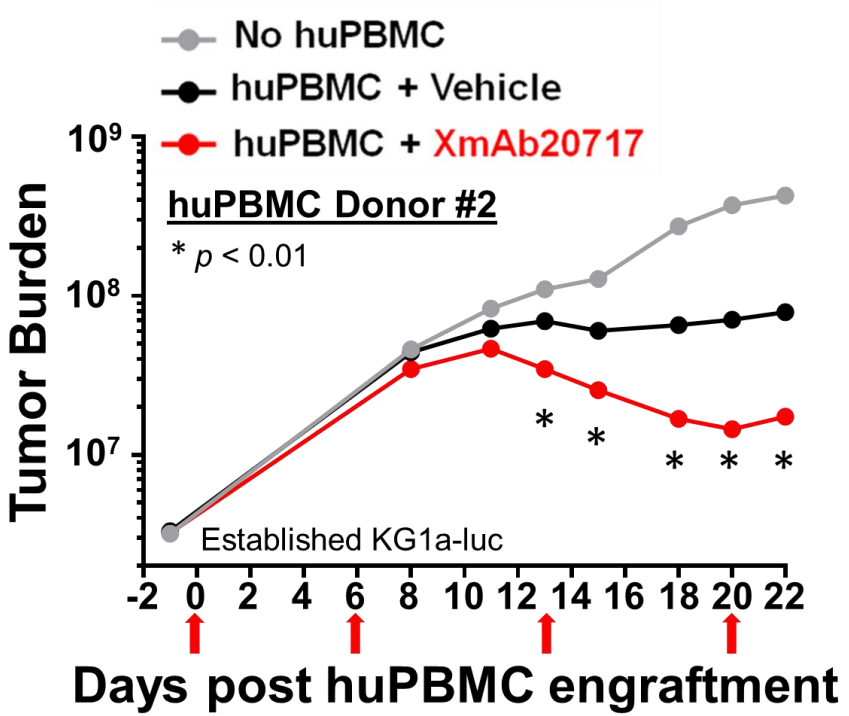




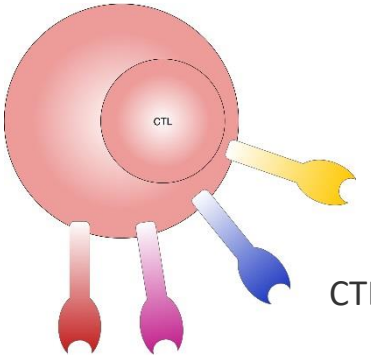
PD1 x CTLA4 bispecific antibody enhances allogeneic anti-tumor response

iv KG1a^{luc2} (AML) → NSG  → established leukemia → treatment





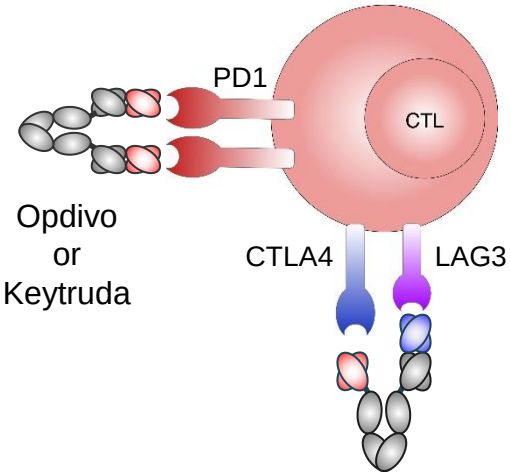
Many hypotheses to explore …



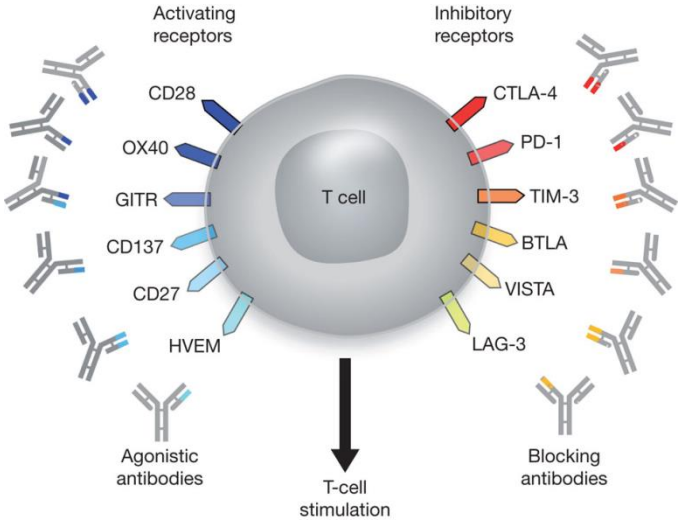
PD-1

CTLA4, LAG3, TIM3, BTLA, etc.

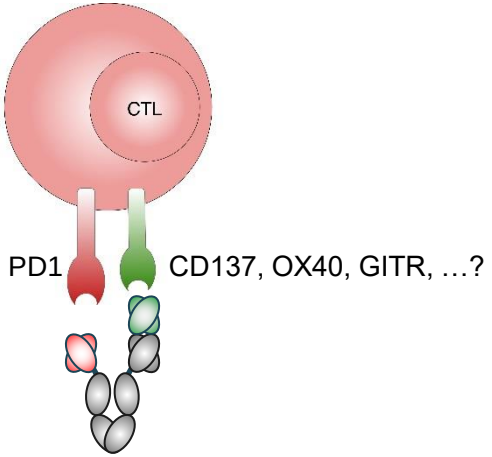
Triple checkpoint blockade?



Other combinations?

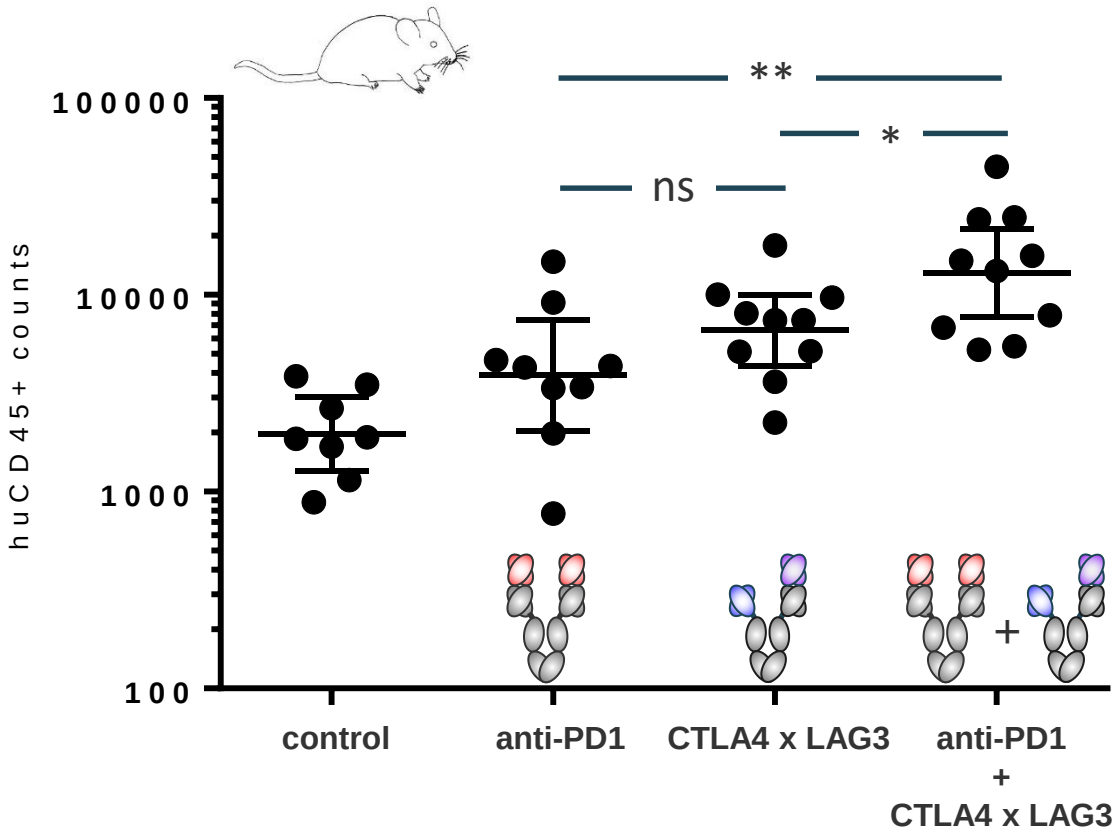


Checkpoint x costim?

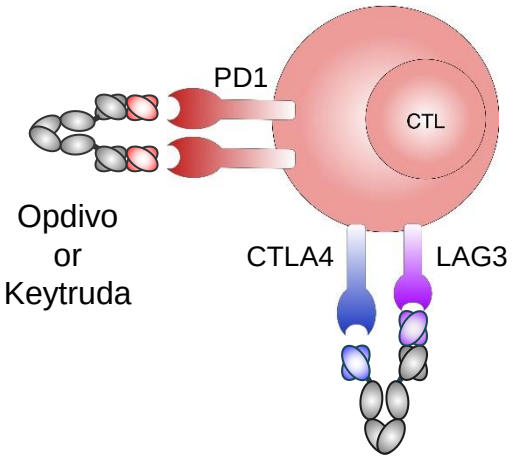


CTLA4 x LAG3 bispecific is active and combines with anti-PD1 for triple blockade

Human PBMC → NSG mice → count human T cells

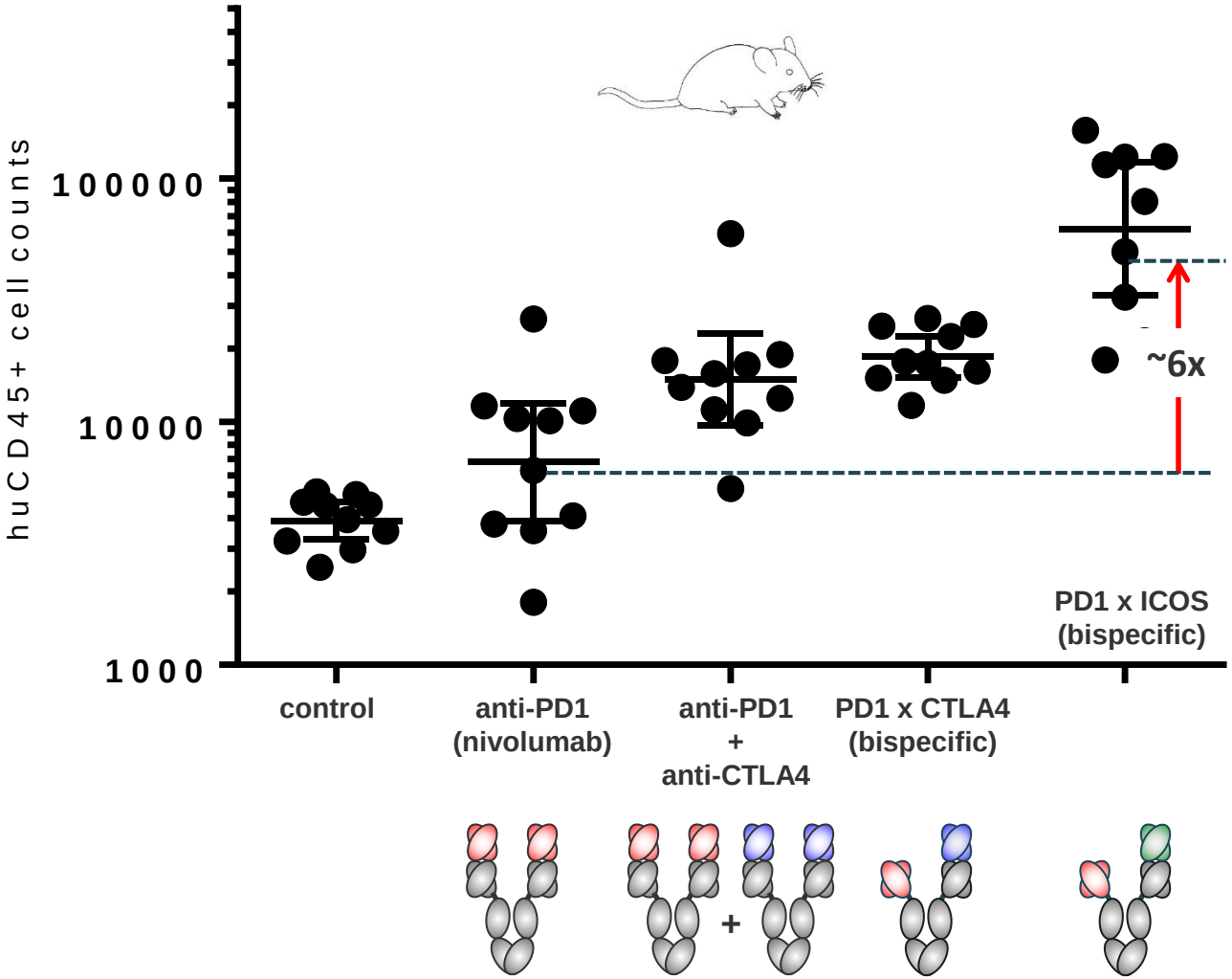


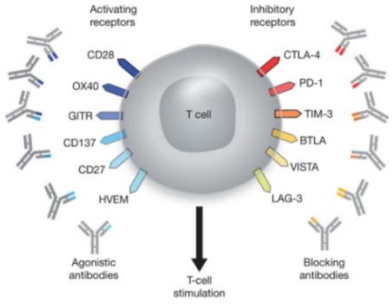
Triple checkpoint blockade



PD1 x ICOS bispecific is highly active in vivo

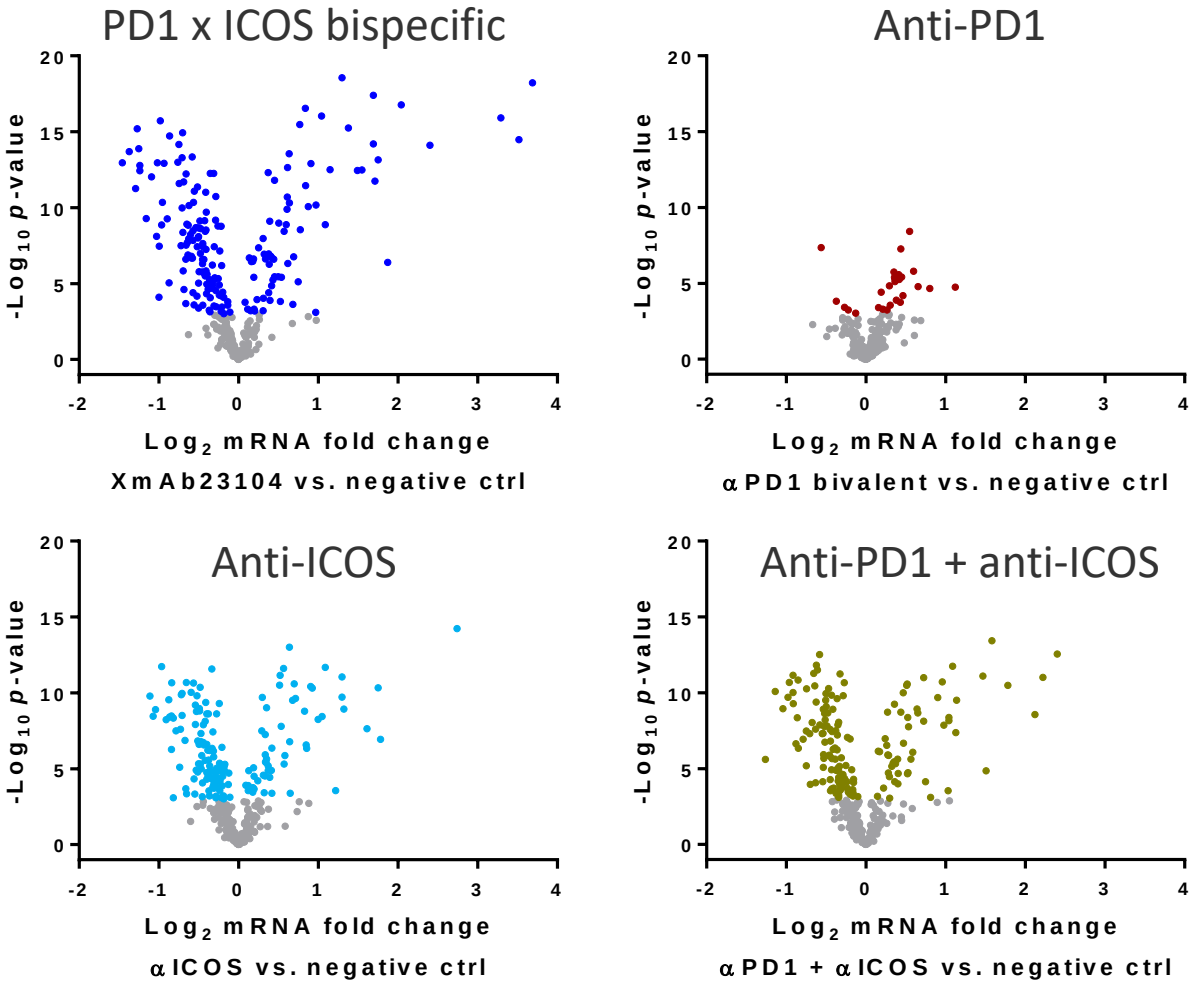
Human PBMC → NSG mice → count human T cells





PD1 x ICOS bispecific antibody exhibits synergistic activity

Nanostring RNA expression analysis of SEB-stimulated human PBMCs

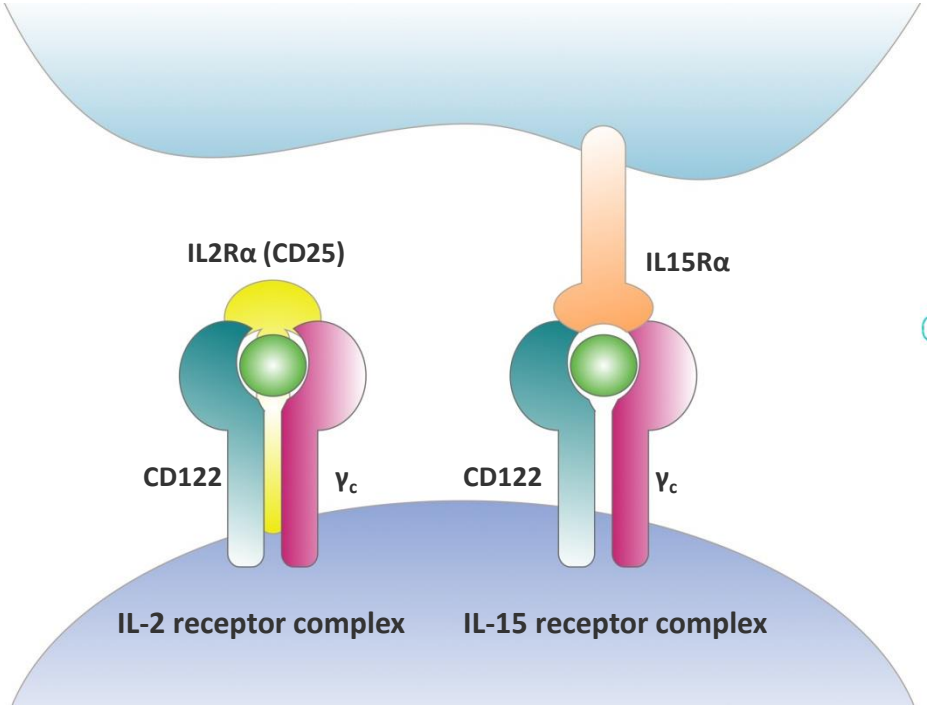


IL15 enhancement with using heterodimeric Fc domain

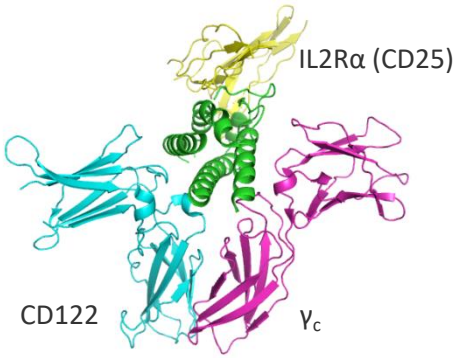
IL2 (Proleukin):

- 1st effective immuno-therapy (approved for metastatic melanoma and mRCC)
- Problem 1: Tregs really like IL2 too!
- Problem 2: Capillary leak syndrome (may be mediated by IL-2Rα)

IL15: superior solution, better balance of Teff vs Treg

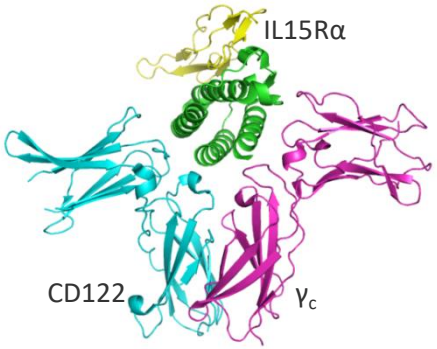


IL2 receptor complex



Wang et al., Sxuebce 2005

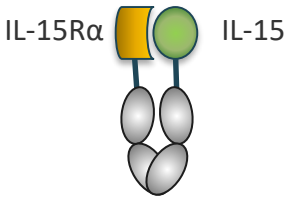
IL15 receptor complex



Ring et al., Nat Immunol 2012

xencor

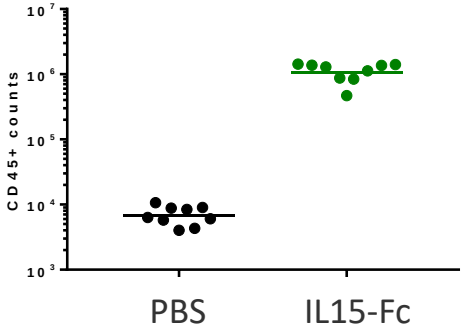
IL15/Rα-Fc is highly active in vivo



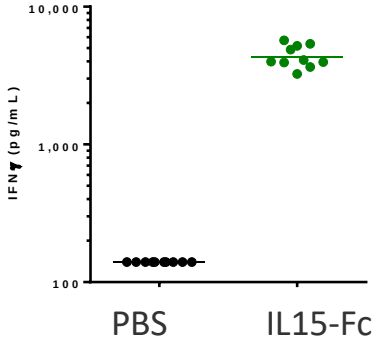
- Fc-stabilized IL15/Rα complex
- High propensity Fc heterodimer

huPBMC-NSG mice

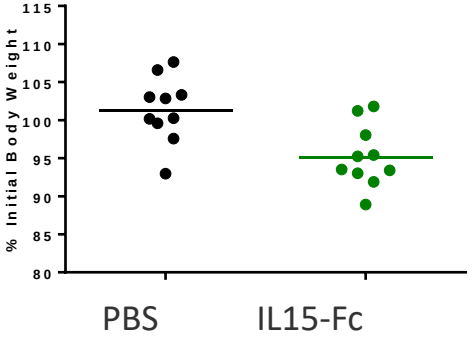
Enhanced Leukocyte Expansion (CD8, CD4, NK)



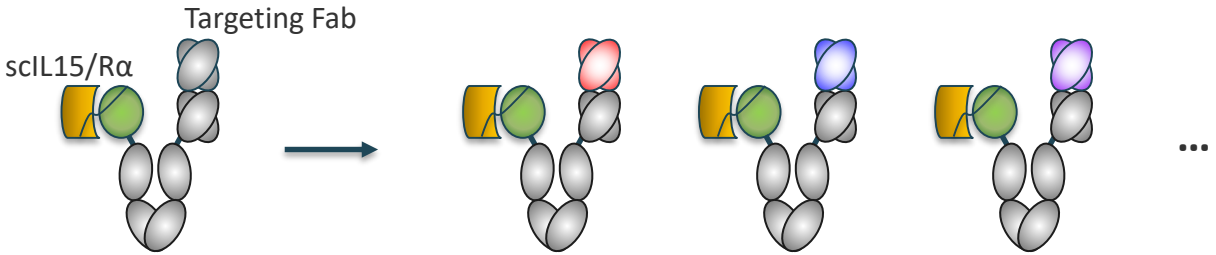
Increased IFNγ



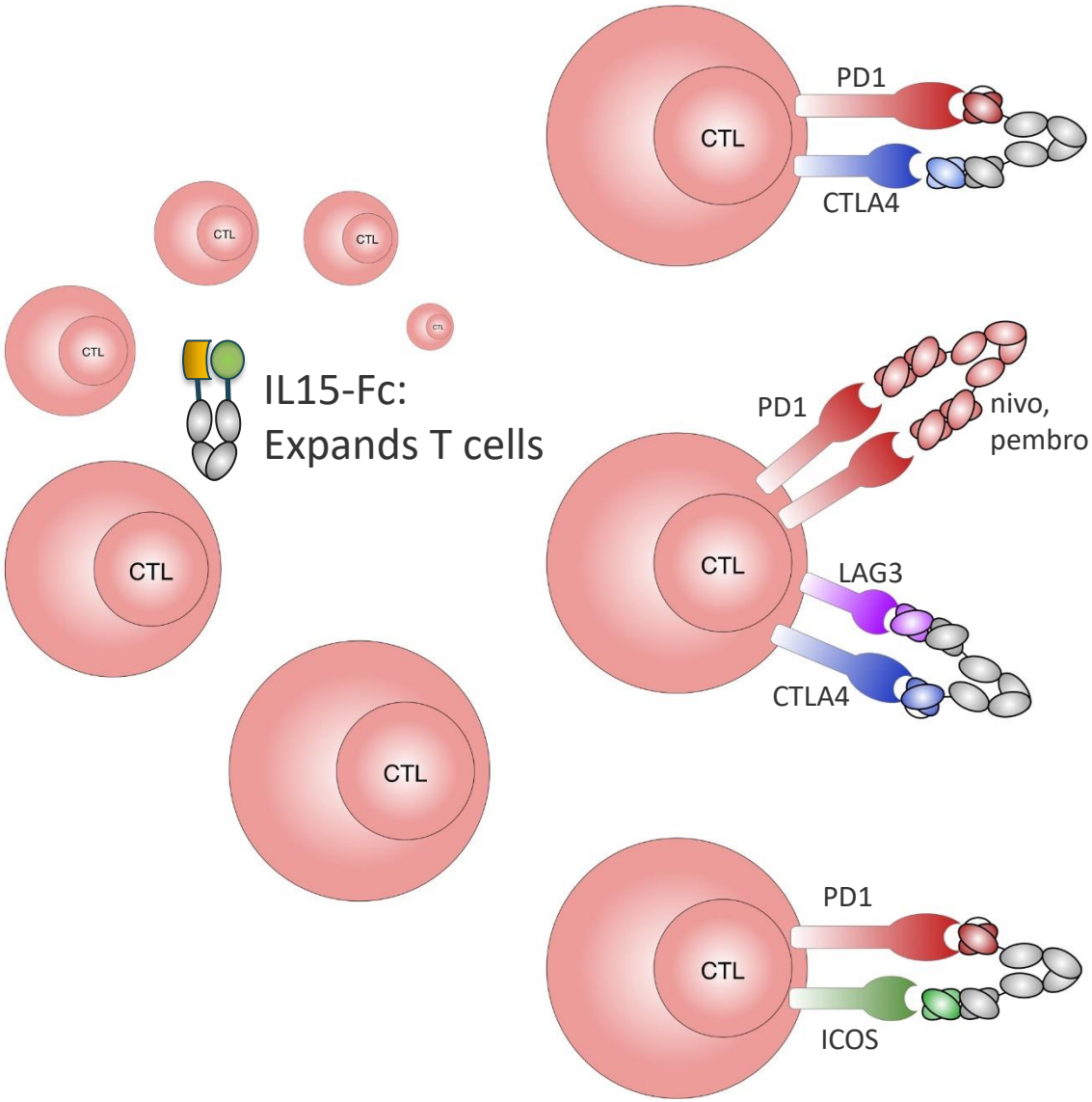
Enhanced xenogeneic response (GVHD)



Alternative scIL15/Rα format enables targeting



Distinct and novel mechanisms-of-action define Xencor's growing immuno-oncology pipeline



XmAb20717

- PD1 x CTLA4 bispecific
- Two most validated checkpoint receptors
- IND early 2018

XmAb22841

- CTLA4 x LAG3 bispecific
- Combinable with anti-PD1
- Triple checkpoint blockade
- IND 2018

XmAb23104

- PD1 x ICOS bispecific
- Novel checkpoint x costim pairing
- IND 2018

Xencor's growing immuno-oncology bispecific pipeline

Program (Target)	Fc Domain	Primary Indication	Discovery Lead	Preclinical	Phase 1	Phase 2	Commercial Rights
XmAb14045 (CD123 x CD3)	Bispecific	AML					xencor / NOVARTIS*
XmAb13676 (CD20 x CD3)	Bispecific	B-cell malignancy					xencor / NOVARTIS*
XmAb18087 (SSTR2 x CD3)	Bispecific	Neuroendo-crine tumors			IND open		xencor
XmAb20717 (PD-1 x CTLA-4)	Bispecific Xtend	Oncology			IND 2018		xencor
XmAb22841 CTLA-4 x LAG-3	Bispecific	Oncology			IND 2018		xencor
XmAb23104 PD-1 x costim	Bispecific	Oncology			IND 2018		xencor
IL15-Fc	Bispecific	Oncology			(IND 2019)		xencor
TBD	Bispecific (2+1 format)	Oncology			(IND 2019)		xencor

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