XmAb30819, an XmAb® 2+1 ENPP3 x CD3 bispecific antibody for RCC, demonstrates safety and efficacy in in vivo preclinical studies

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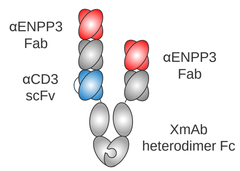
Introduction

- Ectonucleotide pyrophosphatase/phosphodiesterase 3 (ENPP3 or CD203c), a nucleotide hydrolase known to convert ATP to AMP, is differentially expressed in renal cell cancer (RCC) as measured by bulk RNAseq and IHC.
- A type II integral membrane protein, ENPP3's expression profile makes it a potential target for a CD3 bispecific approach against clear cell and papillary RCC as well as segments of other tumor indications such as hepatocellular carcinoma (HCC).
- Unlike targets for hematopoietic cancers, solid cancer targets like ENPP3 are not tumor restricted and therefore can exhibit basal levels of expression on normal cells.
- Normal tissue expression of ENPP3 has been described on tubules of the kidney cortex, and subsets of cells in gastrointestinal, adrenal, and endometrial tissues.
- To create a selective T-cell engaging antibody against ENPP3, we extended our XmAb heterodimeric Fc platform to create the 2+1 Fab$_2$-scFv-Fc format, which is bivalent for ENPP3 and monovalent for CD3.

A XmAb 2+1 Fab$_2$-scFv-Fc format enables selective tumor targeting

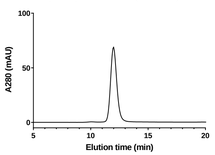
① **XmAb heterodimeric Fc platform allows for well-behaved, high-yielding, and easily manufactured 2+1 bispecific antibodies**

- Modified Fc domain eliminates FcγR affinity, but preserves FcRn affinity for antibody-like half-life
- Fc substitutions promote heterodimer formation and facilitate purification by standard methods such as Protein A + ion-exchange chromatography
- An αENPP3 Fv was humanized, affinity-tuned, and inserted into our CD3 bispecific platform.

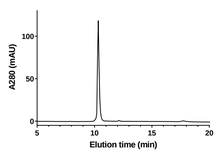


XmAb30819, 2+1 ENPP3 x CD3

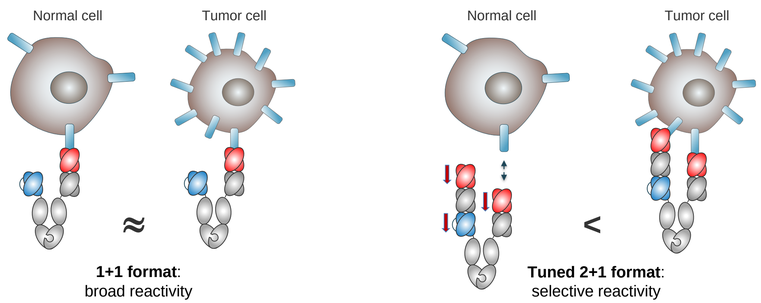
Favorable solution properties (SEC)



High purity bispecific (IEX)



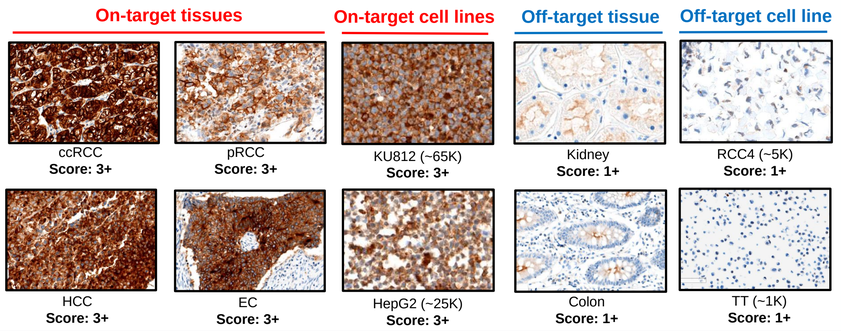
② **Affinity tuned 2+1 bispecific antibodies allow for selective engagement of high-expressing tumor target cells over low-expressing normal cells**



B Cell line proxies for "on-target" and "off-target" tissue identified by IHC

- ENPP3 prevalence was surveyed by IHC scoring of tumor and normal tissue FFPE cores
- Antigens/cell on various endogenous ENPP3+ cell lines ranged from ~65K to ~1K, and were correlated against tumor and normal tissues by IHC

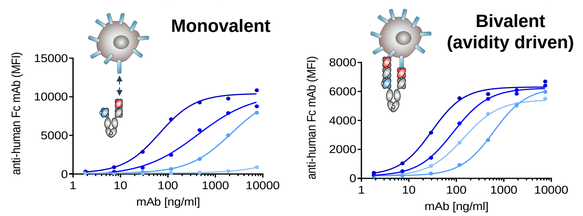
		3+	2+	1+	Absent
	(n)	% (n)	% (n)	% (n)	% (n)
Clear cell RCC (ccRCC)	17	71% (12)	12% (2)	12% (2)	6% (1)
Papillary RCC (pRCC)	10	40% (4)	10% (1)	0% (0)	50% (5)
Hepatocellular carcinoma (HCC)	9	11% (1)	33% (3)	11% (1)	44% (4)
Endometrial cancer (EC)	10	30% (3)	0% (0)	20% (2)	50% (5)
Normal Tissue	86	7% (6)	14% (12)	20% (17)	59% (51)



C Bivalent 2+1 format retains binding despite reduced monovalent affinity

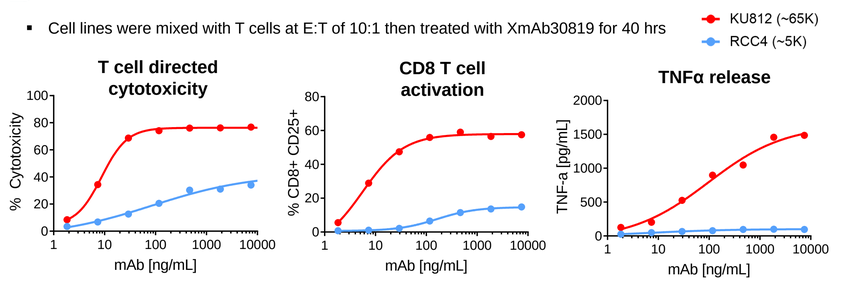
Decreasing ENPP3 affinity

- Cell binding performed on KU812 (~65K)
- XmAb30819 was selected based on its activity in mice coupled with tolerability in NHPs



D XmAb30819 selectively kills high expressing cell lines in vitro

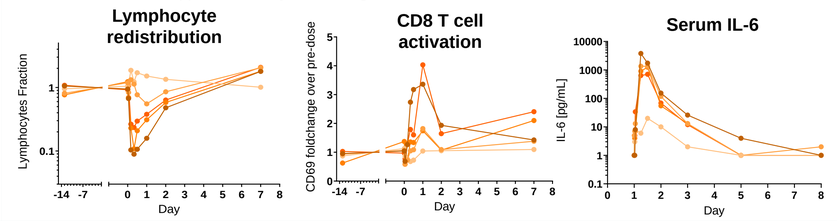
- Cell lines were mixed with T cells at E:T of 10:1 then treated with XmAb30819 for 40 hrs



E XmAb30819 is well-tolerated and shows dose dependent pharmacodynamics in NHPs

- **Phase 1:** Cyno monkeys tolerated single doses of XmAb30819 at various dose levels
- **Phase 2:** Expanded cohort to n=4 at the highest dose administered; one monkey experienced dose-limiting toxicity
- Serum half-life supports antibody-like dosing schedule

XmAb30819, Increasing dose



F XmAb30819 reverses tumor growth of two "on-target" cell lines in mice

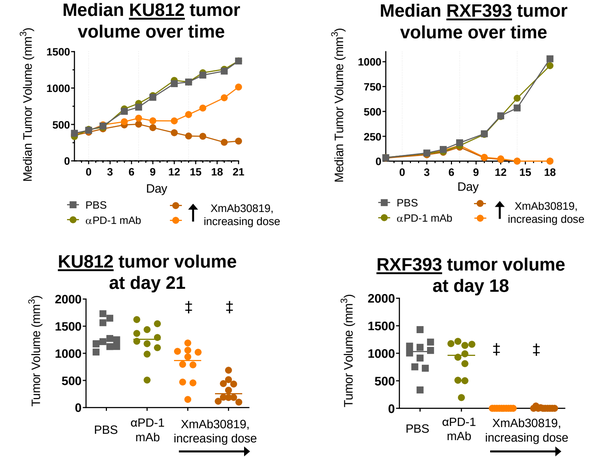
Engraft KU812 or RXF393 cancer cells intradermally

1 or 2 weeks

Engraft huPBMCs + weekly antibody treatment

Monitor tumor volume by caliper measurement

‡ p < 0.05 vs. PBS or αPD-1 mAb



Summary

The XmAb 2+1 ENPP3 x CD3 bispecific antibody XmAb30819:

- Is humanized, well-behaved, and efficiently purified and manufactured.
- Selectively recruits T cells to kill high-expressing ENPP3+ cancer cells in vitro.
- Stimulates expected pharmacodynamics in cynos and features antibody-like half-life.
- Induces potent anti-tumor activity in two tumor models with hPBMC-engrafted NSG mice at doses that are well-tolerated in cyno monkeys.

These results support clinical testing of XmAb30819 as a potential therapeutic option for patients with RCC and subsets of other ENPP3+ indications.

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