HPN601 Is A Protease-Activated EpCAM-Targeting T Cell Engager with an Improved Safety Profile for the Treatment of Solid Tumors

S. Jack Lin, Sony S. Rocha, Kathryn Kwant, Maria Rosalyn Dayao, Tessie M. Ng, Raphaela Rose Banzon, Wade Aaron, Evan Callihan, Maria Gamez-Guerrero, Golzar Hemmati, Kevin J. Wright, Manasi Barath, Yinghua Xiao, Timothy Yu, Patrick Chew, Thomas Evans, Jessica O'Rear, Scott Gatto, Michael Cremin, Stephen Yu, Purbasa Patnaik, Avneel Hundal, Richard Austin, Bryan Lemon, Holger Wesche

Harpoon Therapeutics, Inc.

South San Francisco, CA

November 12, 2020

HARPOON Therapeutics

Disclosure

- All authors are current or former employees and are shareholders of Harpoon Therapeutics

The Need for a Conditionally Active T Cell Engager Prodrug To Target More Broadly Expressed Tumor Antigens

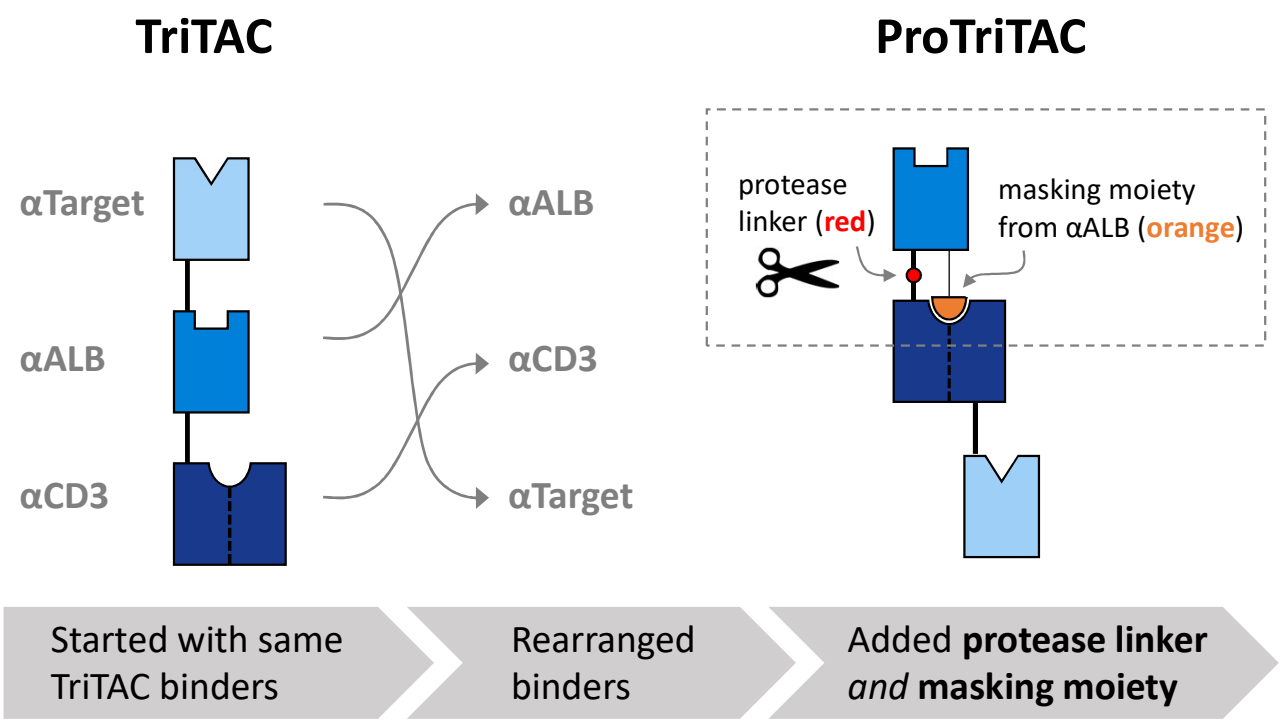
PROBLEM:

- T cell engagers are potent, but limited to tumor antigens with restricted normal tissue expression
- Many solid tumor antigens have normal tissue expression liabilities
- Several T cell engager targets have encountered dose-limiting toxicities in the clinic
  - Examples: EpCAM, gpA33, B7-H3, CEACAM5

SOLUTION:

- Design a T cell engager prodrug that is active in tumor and spares normal tissues
- Enables targeting of more solid tumor antigens

ProTriTAC Is a T Cell Engager Prodrug Platform Based on Harpoon's Clinically Validated TriTAC Components

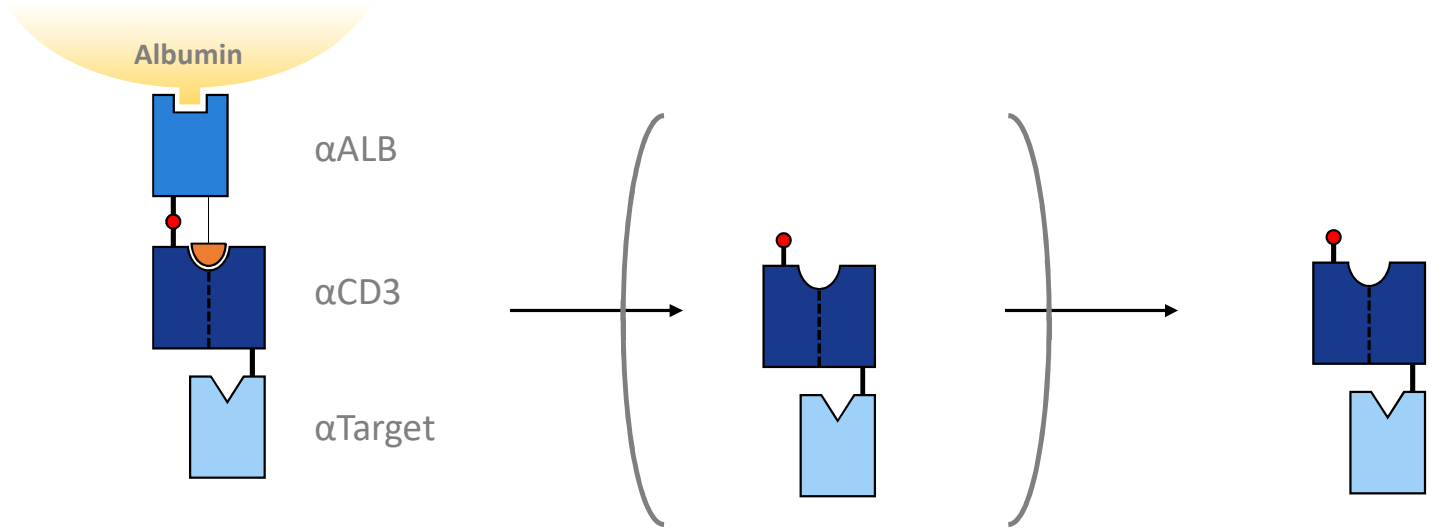


ProTriTAC Links Masking with Half-Life Extension To Improve the Therapeutic Index (TI)

Long-lived prodrug

Activation by tumor proteases & T cell-directed killing

Rapid clearance in circulation



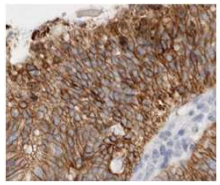
CIRCULATION

TUMOR

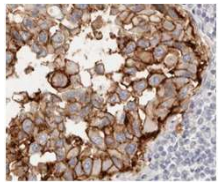
CIRCULATION

EpCAM Is a Broadly Expressed Epithelial Tumor Antigen

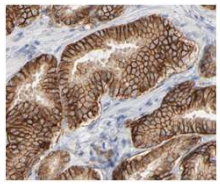
- Epithelial Cell Adhesion Molecule (EpCAM, CD326)
- Highly expressed on many solid tumors[1]
- Marker for circulating tumor cells[2]
- Therapeutic potential hindered by its normal tissue expression



CRC



NSCLC



mCRPC

1. Spizzo, J Clin Pathol 2011. 2. de Wit, Oncotarget 2018. EpCAM IHC images taken from ProteinAtlas.org

Efficacy of Past EpCAM T Cell Engagers Was Limited Because of On-Target Toxicity in Normal Tissues

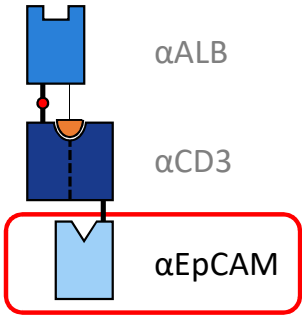
T Cell Engager	Route of Admin.	Clinical Experience
Solitomab	Systemic (intravenous)	MTD = 24 µg/day Clinical activity noted at dose levels 2-4x above MTD[1]
Catumaxomab	Local (intraperitoneal)	Approved for malignant ascites in Europe[2] Not tolerated as systemic therapy[3]

- Systemic administration not tolerated, but highest (non-tolerated) doses for solitomab had clinical activity
- Local administration had more success, but cannot target all metastatic tumors

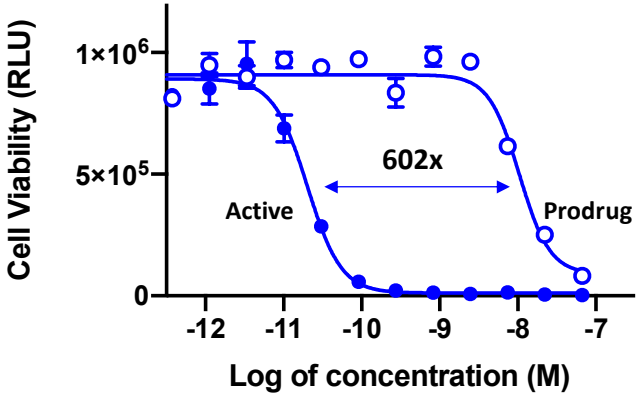
Goal of EpCAM ProTriTAC = systemic administration + local activity in all tumors

1. Kebenko, OncoImmunol 2018. 2. https://www.ema.europa.eu/en/medicines/human/EPAR/removab. 3. Mau-Sorensen, Cancer Chemother Pharmacol 2015.

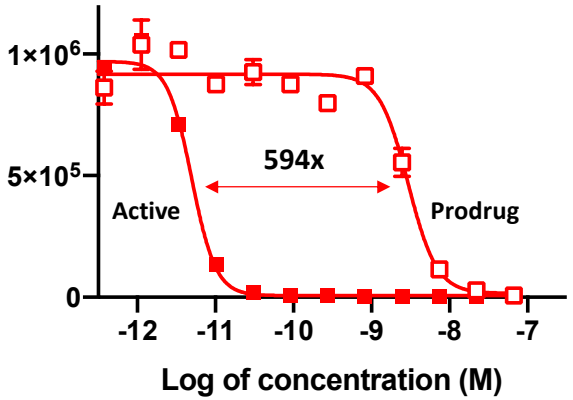
Two EpCAM-Specific Binders Were Chosen for Further Efficacy and Toxicity Assessments In Vivo



Mouse Cross-Reactive Binder
(Binds Human/Cyno/Mouse EpCAM)

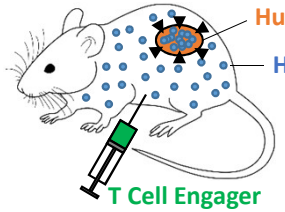


Clinical Candidate Binder
(Binds Human/Cyno EpCAM)



- Comparable masking observed in functional T cell killing (TDCC) assays
- ProTriTAC with the mouse cross-reactive binder used for TI assessment

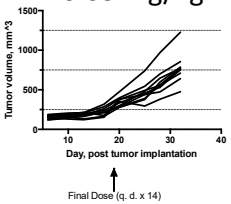
EpCAM ProTriTAC Is 3x Less Potent than the Tool TriTAC in Shrinking LoVo Colon Tumors in Mice



Established tumor model

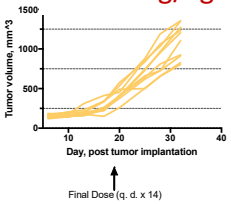
Control

0.03 mg/kg

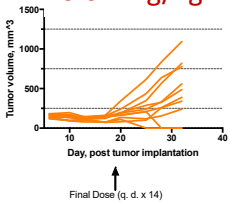


TriTAC

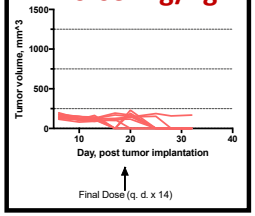
0.003 mg/kg



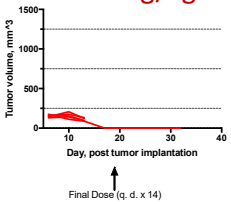
0.01 mg/kg



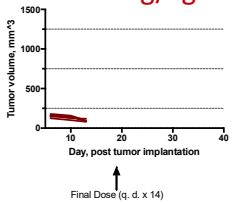
0.03 mg/kg

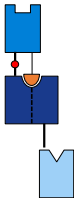


0.1 mg/kg



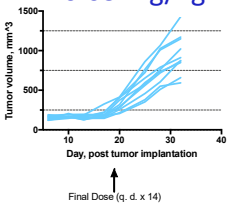
0.3 mg/kg



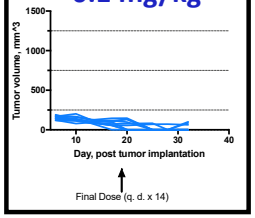


ProTriTAC

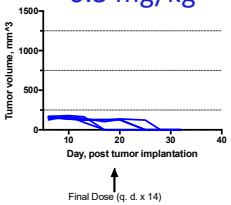
0.03 mg/kg



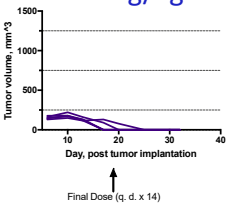
0.1 mg/kg



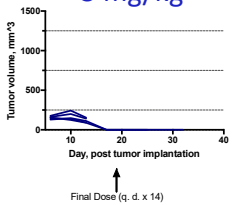
0.3 mg/kg



1 mg/kg

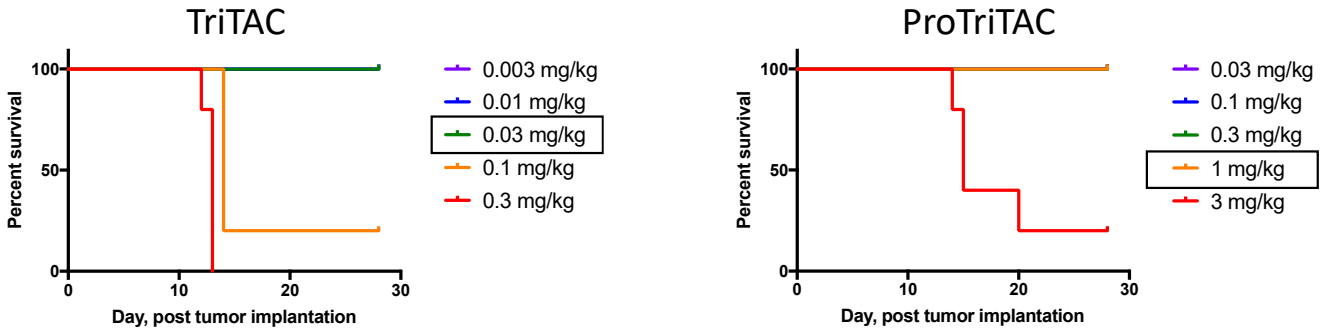


3 mg/kg

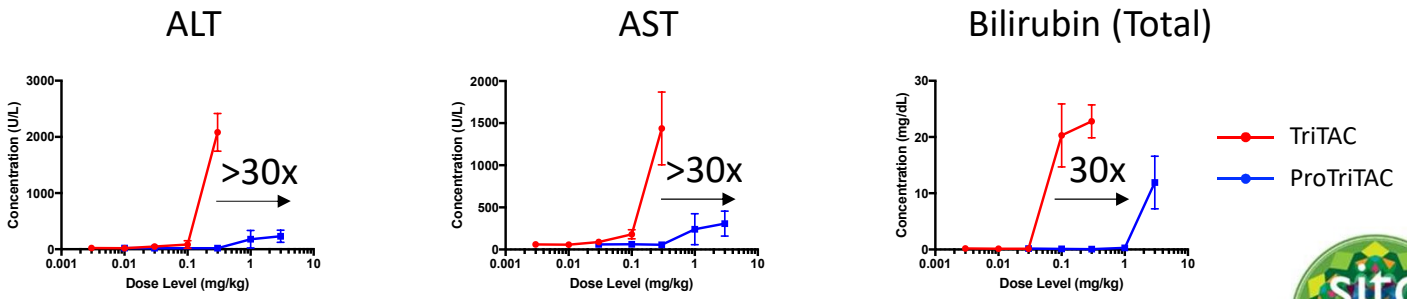


EpCAM ProTriTAC Is 30x Safer than the Tool TriTAC in the Same Tumor-Bearing Mice

Survival:



Clinical Chemistry:



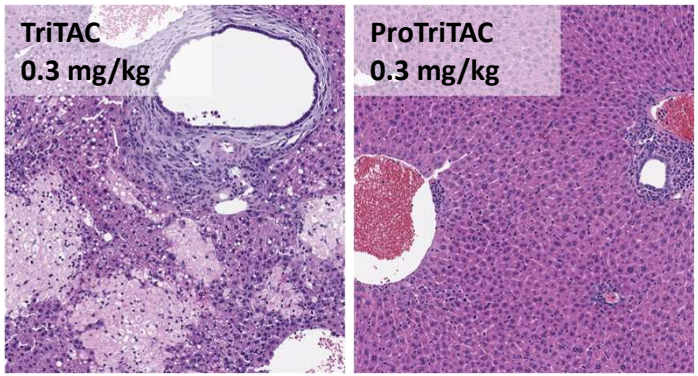
The 30x Improved Safety of EpCAM ProTriTAC Is Further Supported by Mouse Histopathology in the Same Tumor-Bearing Mice

Mouse Liver Histopathology Findings

	Ctrl	TriTAC					ProTriTAC				
Dose level (mg/kg)	**0.3**	**0.003**	**0.01**	**0.03**	**0.1**	**0.3**	**0.03**	**0.1**	**0.3**	**1**	**3**
Coagulation necrosis	-	-	-	-	100%	100%	-	-	-	-	100%
Portal fibrosis	10%*	10%*	10%*	10%*	100%	100%	20%*	20%*	-	-	100%
Bile ductule dilation	-	-	-	-	100%	100%	-	-	-	-	100%

Note: percentages represent proportion of animals with the finding, asterisks denote findings were all of minimal severity

Mouse Liver Sections (H&E stain)



ProTriTAC enables better discrimination of tumor vs. normal tissue to reduce on-target tissue damage

10x Therapeutic Index Expansion Achieved for ProTriTAC in a Tumor Xenograft Model in Mice

	Minimum Efficacious Dose	Maximum Tolerated Dose	Therapeutic Index (TI)
TriTAC	0.03 mg/kg	0.03 mg/kg	1
ProTriTAC	0.1 mg/kg	1 mg/kg	10
		ProTriTAC Advantage	**10x**

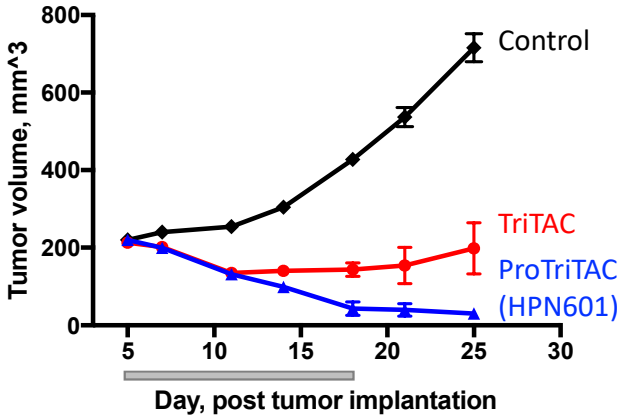
- **TI expansion demonstrated in vivo :** efficacy + tox in the same animal
- **Preclinical model validated:** similar on-target tox in mouse and in human[1]

1. Kebenko, OncoImmunol 2018

EpCAM ProTriTAC with the Clinical Candidate Binder (HPN601) Confirms TI Improvement by Comparing Across Species

Better Efficacy in Mouse

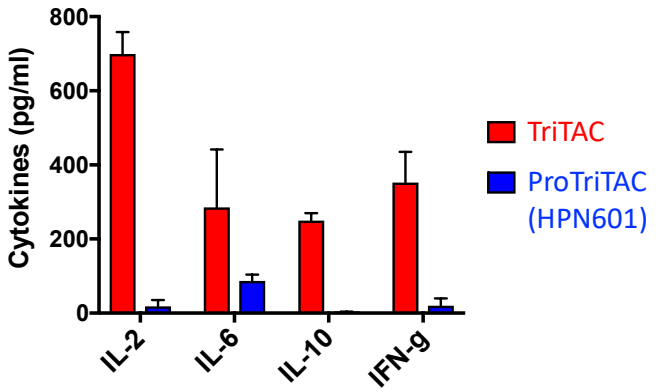
Established HT29 Tumor Xenograft Model



Both TriTAC and ProTriTAC dosed at 100 µg/kg

Better Safety in Cyno

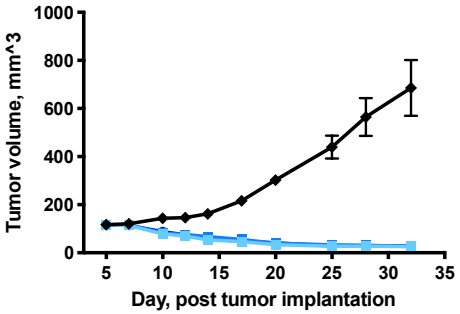
Peak Cytokine Levels



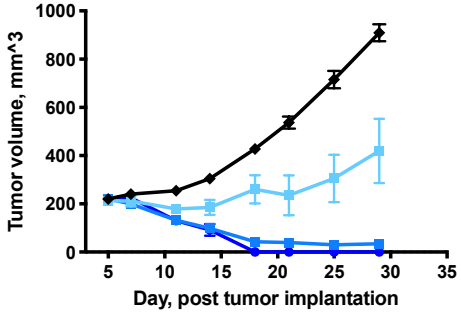
Both TriTAC and ProTriTAC dosed at 30 µg/kg

HPN601 Is Active in Multiple Established Tumor Xenograft Models

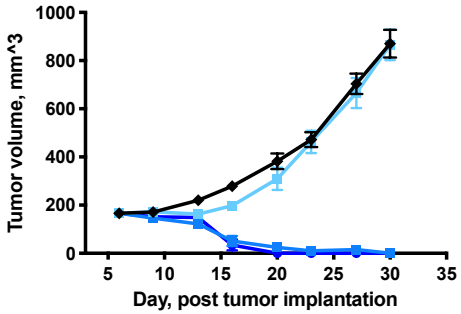
HPAF-II
(Pancreatic)



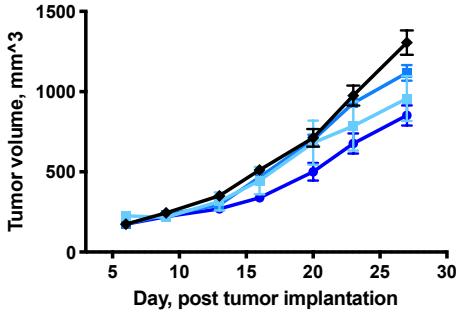
HT-29
(Colon)



22Rv1
(Prostate)



H292
(Lung)



Control 30 µg/kg 100 µg/kg 300 µg/kg dosed qdx14

Demonstrates anti-tumor activity and prodrug processing in multiple tumor types

Summary

- ProTriTAC is a new approach to engineer conditionally active T cell engager prodrugs
- HPN601 is an EpCAM-targeting ProTriTAC
- 10x improved TI compared to a constitutively active T cell engager
- Efficacious in multiple EpCAM-expressing xenograft tumor models in vivo
- IND-enabling studies initiated

Acknowledgements

Translational Medicine

- Che-Leung Law
- Laurie Tatalick
- Vaishnavi Ganti

CMC

- Susan Dana Jones
- Alpana Naresh
- Mark Wesson

We thank all other Harpoon staff members who enabled this effort.