Novel Approaches to Expand the Therapeutic Index of T cell Engagers

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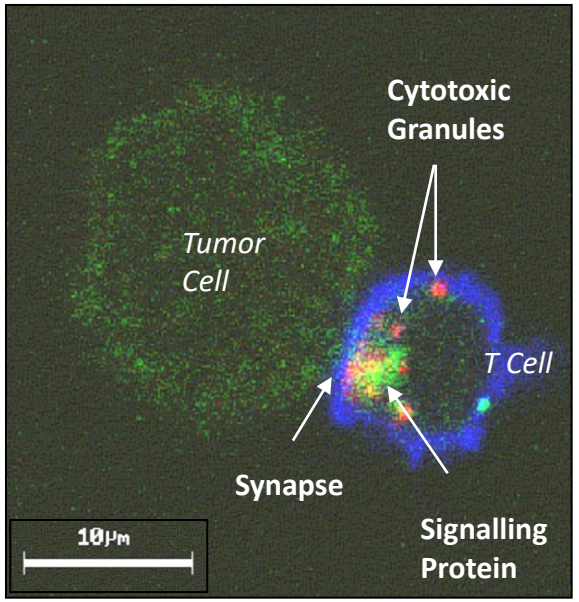
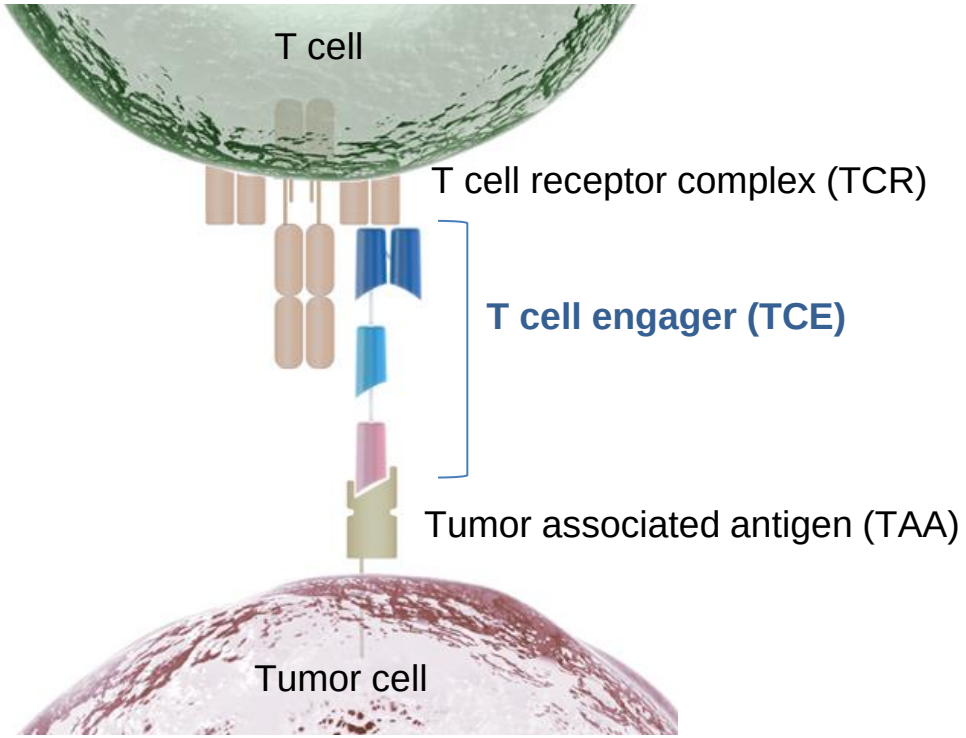
T Cell Engagers Work By Physically Connecting a T Cell to a Tumor Cell



Confocal Microscopy

Perforin
Lck
LFA-1 (CD11a)



- Transient connection will vigorously activate T cell and make it kill attached cancer cell

- Does not require a T cell clone with specific T cell receptor
- Any T cell can recognize a surface antigen
- Does not require MHC expression for recognition by T cell

The First T Cell Engager Was Approved in the US in 2014

- T cell engagers can work
  - Blincyto (CD19) approved for ALL in 2014
  - Tebentafusp (PMEL) approved for uveal melanoma in 2022
  - Promising earlier stage clinical data for several targets (e.g., CD20, BCMA, DLL3)
- T cell engagers don’t always work
  - Cytokine release syndrome (CRS) apparently part of the mechanism of action
  - Many T cell engagers are limited by toxicities and have narrow therapeutic windows
  - In solid tumors, need for higher exposures increases tox risks

T Cell Engager Toxicities Are Either On- or Off-Target

- Toxicities observed in the clinic can be grouped:
  - Off target toxicities
    - In general, target-independent T cell activation
    - Often manifests as dose limiting CRS
    - Caused by T cell engager aggregates, can be Fc-receptor mediated
  - On target tissue damage
    - Elimination of normal tissue that expresses target
    - Tends to get worse with longer treatment
  - On target CRS
    - Overstimulated immune response when T cells engage and eliminate target
    - Tends to improve during the course of treatment

Several Approaches to Expand Therapeutic Index Are Being Pursued

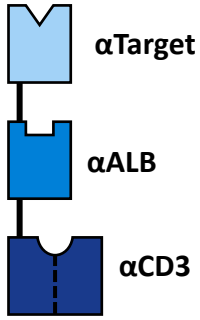
- Tumor target selection
  - Minimize expression on critical normal tissues
- Management of side-effects in the clinic
  - Step dosing and pre-medication for CRS management
  - Dosing holidays (e.g., myeloid targeting T cell engager)
- Protein engineering approaches
  - Optimize affinities of binding moieties
  - Pursue co-stimulatory molecules on T cells
  - Optimize biophysical properties of T cell engager platform
  - Conditionally active T cell engager

Harpoon Developed Three T Cell Engager Platforms To Address Specific Safety Challenges and To Maximize Therapeutic Window

TriTAC

CONSTITUTIVELY ACTIVE
Minimize off-target toxicities (CRS)

Active

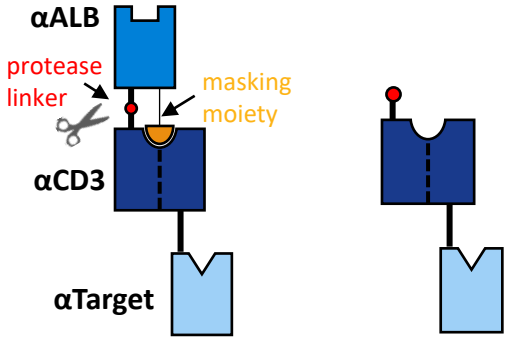


- **Three active clinical-stage programs**
- Least complex platform
- Solid tumors and heme malignancies with limited on-target tox concerns

ProTriTAC

SPATIAL CONTROL
Minimize on-target tissue tox

Prodrug Long-lived → ***Activation in tumor micro-environment*** → **Active** Short-lived

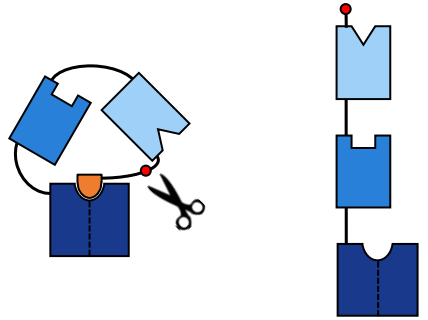


- **Lead program in IND-enabling studies**
- Minimize systemic exposure by acting locally at disease site
- Primarily solid tumors

TriTAC-XR

TEMPORAL CONTROL
Minimize on-target CRS

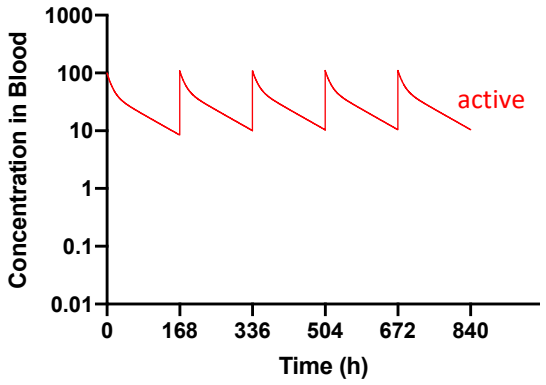
Prodrug → ***Slow activation in circulation*** → **Active**



- **Finalizing platform validation**
- Maximize systemic exposure while minimizing CRS
- Heme malignancies and solid tumors with potential expansion to non-oncology

Harpoon's Platforms Are Designed to Optimize Exposures for Specific Applications

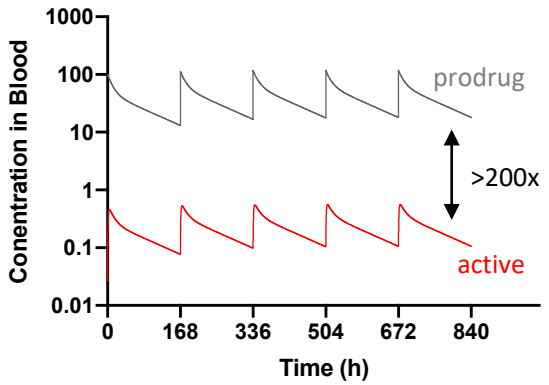
TriTAC



Constitutive Activity

- Active drug administered systemically
- Ideal for targets with minimal expression in normal tissues

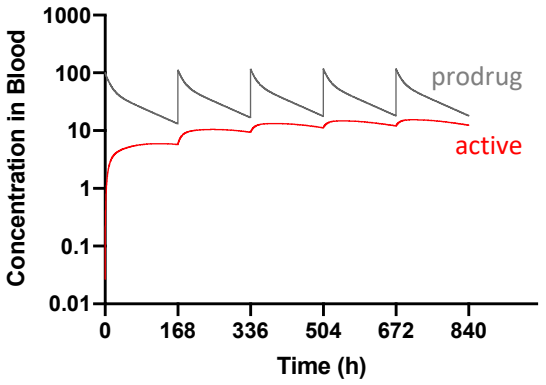
ProTriTAC



Spatial Control

- Prodrug administered systemically
- Active drug formed through local activation at tumor site
- Active drug has short half-life

TriTAC-XR

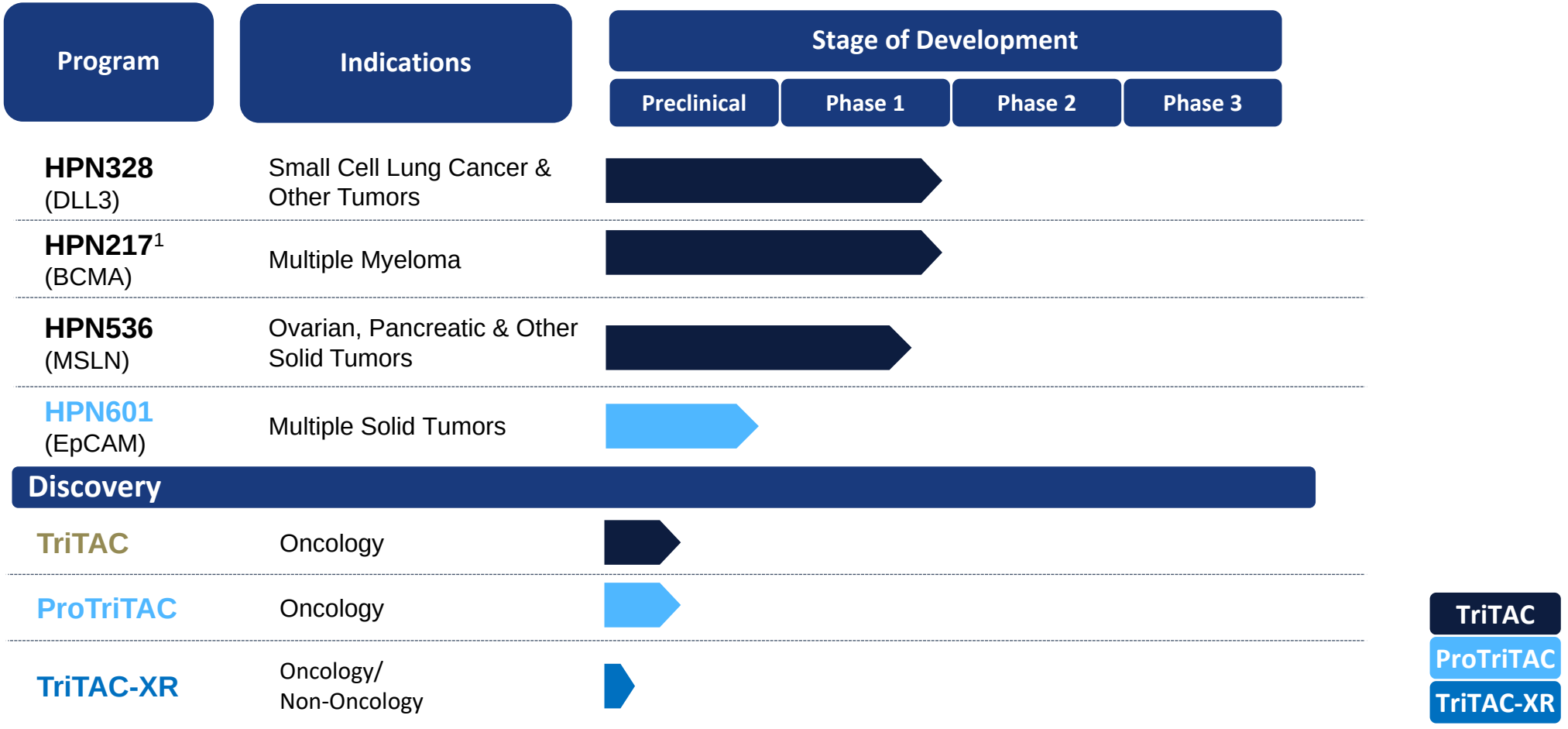


Temporal Control

- Prodrug administered systemically
- Active drug formed systemically, but in a slow, controlled fashion
- Active drug has long half-life

Harpoon Is Developing a Broad Portfolio of T Cell Engagers

Three Clinical Stage TriTAC Programs, Three Distinct TCE Platforms



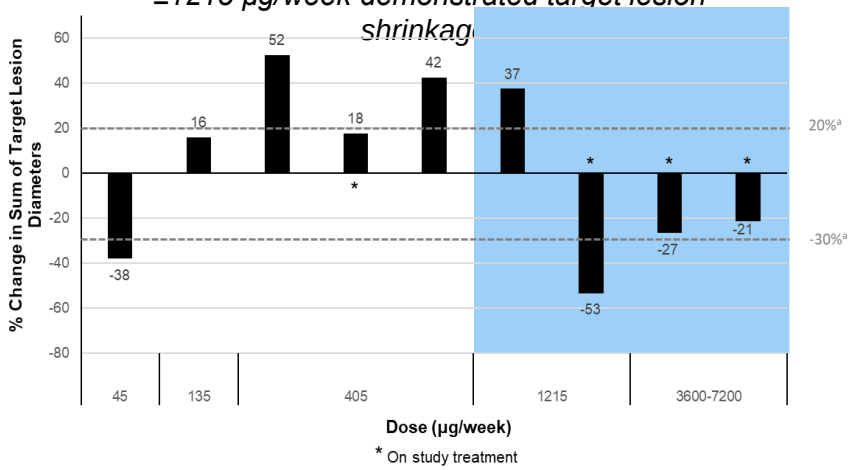
(1) AbbVie retains option to worldwide exclusive rights

TriTAC Clinical Summary: Validation of the TriTAC Platform in Both Solid Tumors and Hematologic Malignancies

- Compelling initial clinical activity for HPN328 (DLL3 targeting) and HPN217 (BCMA targeting) programs observed in escalation phase
- Confirmation of half-life extension using albumin-binding approach
- Clinical validation of TriTAC components obtained

HPN328: Clinical Activity at Doses ≥1215 µg/week

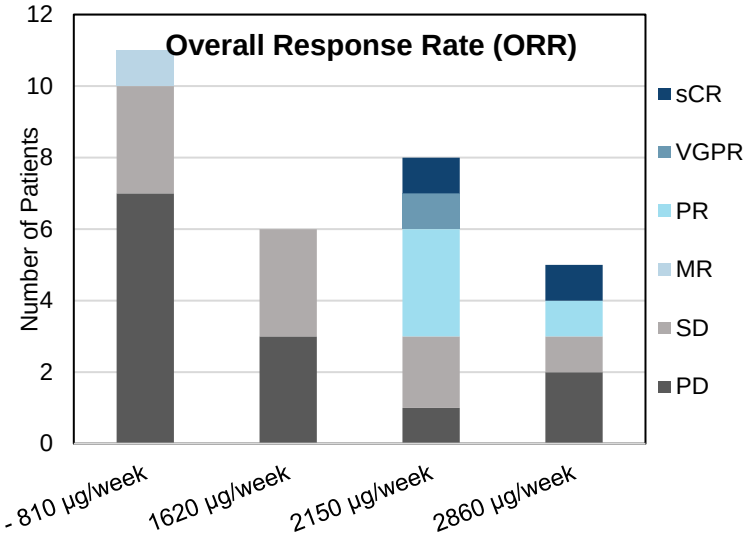
(3 of 4 small cell lung cancer patients in cohorts ≥1215 µg/week demonstrated target lesion shrinkag



HPN328 data as of December 2, 2021

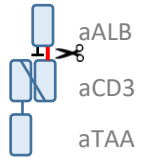
HPN217 – Clinical Activity at Doses ≥2150 µg/week

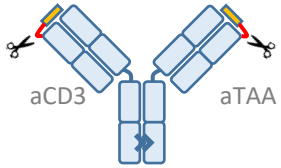
(7 of 8 relapsed refractory multiple myeloma patients in the 2150 µg/week cohort demonstrated clinical benefit)

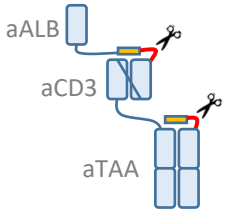


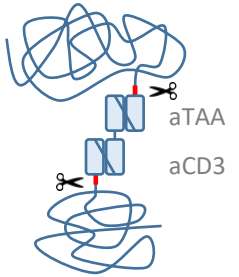
HPN217 data as of November 10, 2021

ProTriTAC Is Designed to Be Differentiated from Other Masked T Cell Engager Platforms Poised To Enter the Clinic in 2022









HARPOON Therapeutics

CytomX Therapeutics

JANUX

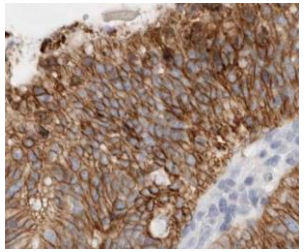
AMUNIX

Acquired by Sanofi (Dec 2021)

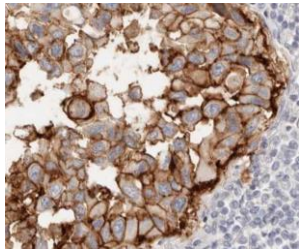
	Harpoon	CytomX	Janux	Amunix (Sanofi)
One protease cleavage site for efficient prodrug conversion in tumor	Yes	No	No	No
Plug-and-play “universal” masking	Yes	No	No	Yes
No active drug accumulation systemically	Yes	No	Yes	Yes
TI expansion assessed in the same animal	Yes	No	No	No
Clinical experience of T cell engager	Yes	No	No	No

Harpoon's First ProTriTAC HPN601 Is Designed To Target EpCAM, Potentially Addressing Large Unmet Medical Need

Tumor	EpCAM Expression[1] (% moderate/high expression by IHC)	HPN601 Population[2] (estimated annual incidence in USA)
Prostate	89	171,000
NSCLC	74	147,000
Breast	46	128,000
Colon	94	99,000
Endometrial	88	58,000
Thyroid	87	46,000
SCLC	75	22,000
Gastric	74	21,000
Ovarian	73	16,000
Esophageal	65	12,000
Neuroendocrine	88	11,000
Gallbladder	66	8,000
Total		**729,000**



Colorectal

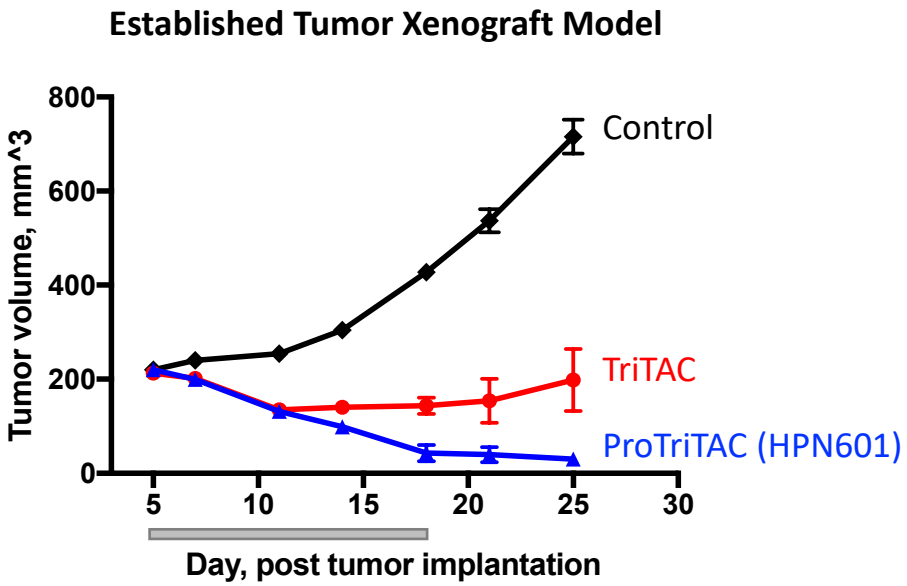


NSCLC

[1]Based on Spizzo et al., J Clin Pathol, 2011. [2]Estimated annual incidence in US, rounded to the nearest 1,000, based on the American Cancer Society's (ACS) publication, *Cancer Facts & Figures 2020,* multiplied by the percentage of moderate and high EpCAM expression. The neuroendocrine tumor annual incidence taken from ASCO Cancer.net. Exemplary IHC figures adapted from proteinatlas.

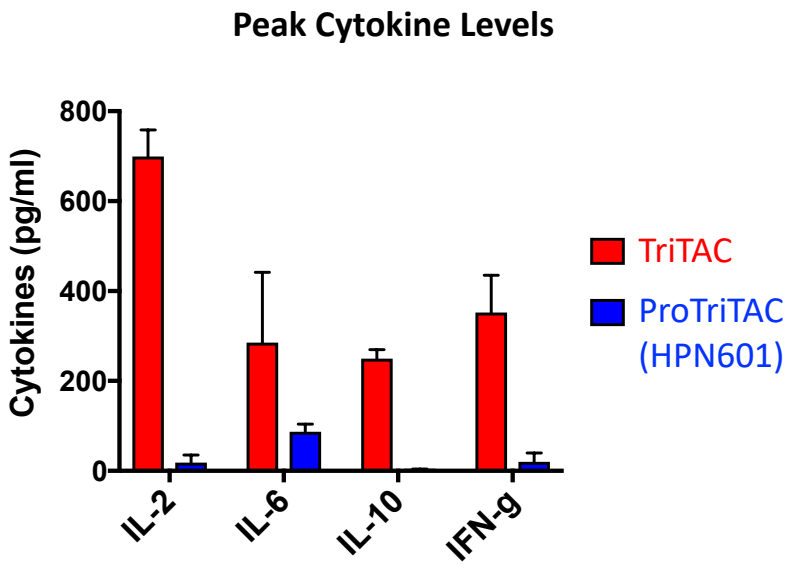
Evidence of TI Expansion for EpCAM-Targeting HPN601: Harpoon's First ProTriTAC Clinical Candidate

Better Efficacy in Rodents



Both TriTAC and ProTriTAC dosed at 100 µg/kg

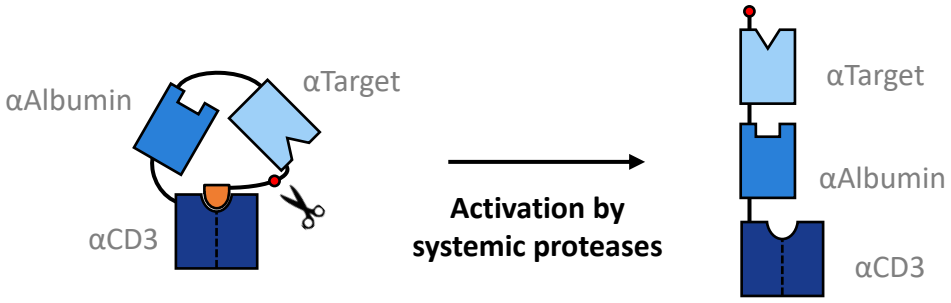
Better Safety in Non-Human Primates

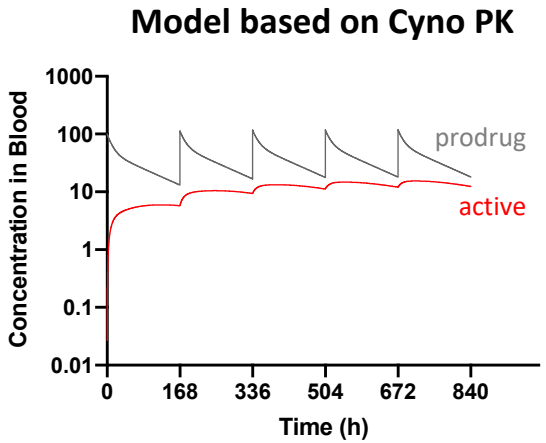


Both TriTAC and ProTriTAC dosed at 30 µg/kg

TI expansion also supported with combined mouse efficacy/toxicity models (Lin et al., SITC 2020 presentation).

TriTAC-XR Is a Temporally Controlled T Cell Engager Prodrug Designed for Extended Release and Reduced On-Target CRS Toxicities



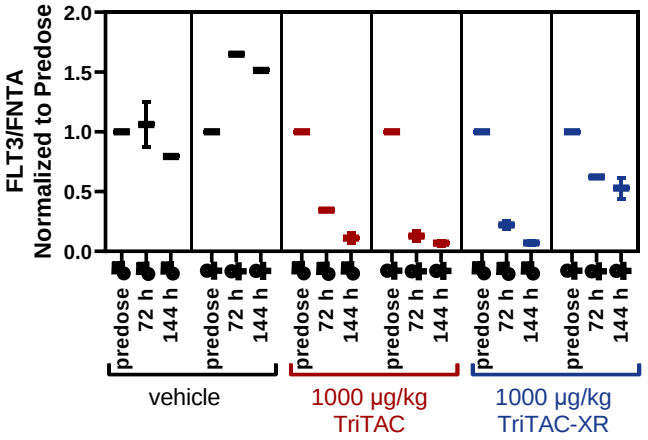


- **Hypothesis:**
  - Cmax leads to tox, Cmin is required for efficacy

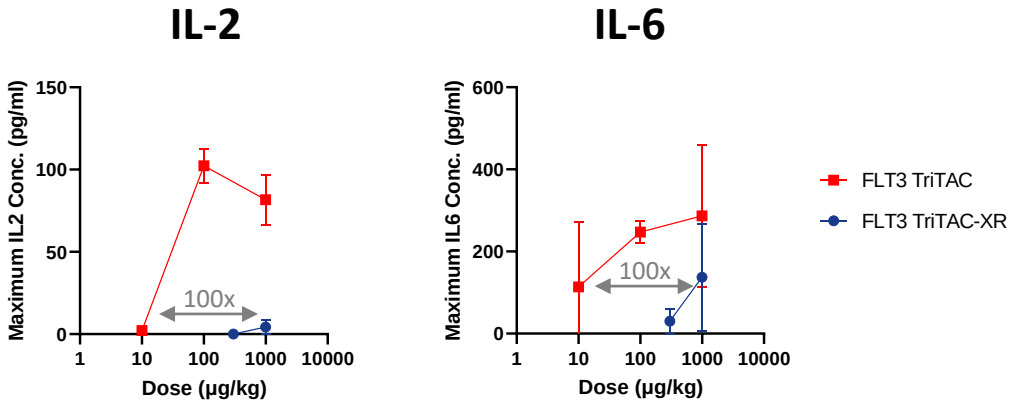
- **Two features of TriTAC-XR expected to improve safety profile:**
  - Gradual accumulation of active drug = built-in step dosing
  - Minimal Cmax/Cmin ratio = maximize exposure without CRS

Preliminary TriTAC-XR Therapeutic Index Expansion Demonstrated by Assessing Efficacy and Toxicity in the Same Animal (NHP)

Efficacy: comparable depletion of FLT3-expressing cells in bone marrow



Safety: 100x protection in peak cytokine release following IV infusion



- Magnitude of therapeutic index expansion being verified across different targets in NHPs
- Anticipate application in heme malignancies, solid tumors, and non-oncology indications

Harpoon Is Committed To Developing Next-Generation T Cell Engagers and Expanding Their Therapeutic Applications

- Three T cell engager platforms for different applications

	Solid tumor	Heme	Utility
TriTAC	✓	✓	Most robust platform minimizing off-target toxicities
ProTriTAC	✓		Spatial control of activity to address on-target tissue damage
TriTAC-XR	✓	✓	Temporal control of activity to address on-target CRS

<u>Upcoming platform milestones by the end of 2022:</u>

- ProTriTAC
  - IND for lead ProTriTAC HPN601 (targeting EpCAM)
- TriTAC-XR
  - Nomination of IND candidate