ProTriTAC: A Protease-Activatable T Cell Engager Platform that Links Half-Life Extension to Functional Masking


INTRODUCTION

• T cell engagers transiently tether T cells to tumor cells and mediate T cell-directed tumor killing
• T cell engagers, such as blinatumomab (BlinCyto®), have demonstrated clinical activity in several hematologic malignancies
• Harpoon has developed a proprietary half-life extended T cell engager format (TriTAC™), with lead asset HPN424 targeting PSMA/CD3 in Ph1 clinical testing
• Adoption of T cell engagers in solid tumors is limited by the scarcity of tumor antigens with sufficient differential expression between tumor and normal tissue
• T cell engagers that are preferentially active in the tumor microenvironment may enable the safe targeting of more solid tumor antigens
• ProTriTAC™ represents a new and improved approach to engineer conditionally active T cell engagers

PLATFORM

Engineering of Inhibitory Non-CDR Loops in the Anti-Albumin sdAb Domain that Confers Half-Life Extension

• Combines both steric masking (via binding to bulky serum albumin) and specific masking (via non-CDR loops binding to the CDRs of anti-CD3 scFv domain)
• Modifying non-CDR loops does not affect albumin binding
• Single proteolytic event required for activation = more efficient conversion in tumor

Anticipated Mode of Action of ProTriTAC

Long-lived, target-binding prodrug
Local activation and T cell-mediated tumor killing
Rapid clearance in circulation

αAlbumin
αCD3
αTarget

Circulation
Tumor
Circulation

• Tumor-associated proteolytic activation reveals active T cell engager with minimal off-tumor activity after activation

ProTriTACs Are Activatable by Tumor-Associated Proteases

• Proprietary library of substrate linkers with different cleavability engineered

IN VITRO POC

Biological Activity In Vitro Is Dependent on Protease Activation

250x CD3 Binding Differential in ELISA

>1000x Human Primary T Cell Binding Differential in Flow Cytometry

550x Functional Differential in T Cell Killing Assay

• Plug-and-play: made ProTriTACs with >20 binders to 5 different targets

IN VIVO EFFICACY

Potent, Protease-Dependent, Anti-Tumor Activity in HCT116 Colorectal Tumor Xenograft Model in NCG Mice

EGFR control TriTAC
EGFR non-cleavable ProTriTAC (0.03 mg/kg)
EGFR ProTriTAC (0.03 mg/kg)

• Activated ProTriTAC not detected in circulation
• Consistent with intratumoral activation of ProTriTAC

MANUFACTURABILITY

ProTriTACs Are Stable and Can Be Expressed at Scale

• Substrate linker is sufficiently stable in circulation: 50% conversion every 194 hr
• Active drug does not accumulate in circulation: below 0.5% of prodrug at all times

SUMMARY

• ProTriTAC is a T cell engager prodrug designed to be preferentially active in the tumor and enables targeting of a wider selection of solid tumor antigens
• Combines the best attributes of several prodrug approaches:
  • Steric (albumin) + specific (non-CDR loop) masking
  • Half-life differential of prodrug vs. active drug = additional safety
  • Plug-and-play with different tumor target binders
• Platform proof-of-concept:
  • Potent, protease-dependent, anti-tumor activity in mice
  • Evidence of functional masking in vitro and in vivo
  • Initial CMC assessments suggest feasible large-scale production
• ProTriTAC pipeline established: first clinical candidate to be nominated in 2019