**HPN536, a T cell-engaging, Mesothelin/CD3-specific TriTAC for the treatment of solid tumors**


**RATIONAL**

- Mesothelin (MSLN), a GPI-linked membrane bound tumor antigen.
- Normal tissue expression of MSLN is restricted to single cell, mesothelial layers lining the pleural, pericardial, and peritoneal cavities.
- MSLN is overexpressed in ovarian, pancreatic, lung and triple-negative breast cancers and mesotheliomas.
- Overexpression of MSLN is associated with poor prognosis in pancreatic, lung and triple-negative breast cancer.
- MSLN has been used as cancer target antigen for numerous modalities, including immunotherapeutics, vaccines, antibody drug conjugates and CAR-T cells: early signs of clinical efficacy have validated MSLN as target, but therapies with improved efficacy are needed to treat MSLN-expressing cancers.
- HPN536 is engineered to direct T cells to kill MSLN-expressing cancer cells.

**BACKGROUND**

HPN536 is a MSLN-targeting TriTAC

- Anti-MSLN single domain antibody targets cells expressing MSLN
- Anti-albumin single domain antibody extends half-life
- Anti-CD3e anti-CD3ε scFv engages T cells
- Molecular weight of ~90 kDa

**HPN536 binds human and cyno MSLN, albumin, and CD3e**

In vitro affinity measurements

- Human κ, (nM) 1.4 15 8
- Cynomolgus (nM) 5 9 8

**HPN536 IN VITRO PHARMACOLOGY**

**HPN536 binds OVAR3 cells expressing MSLN, albumin, and CD3e**

- EC50: 5 nM
- % killing: 80%

**HPN536 activates T cells in presence of MSLN expressing cells**

Activation of CD69 expression on T cells

- MSLN expressing cells: 80%
- Non-MSLN cells: 10%

**HPN536 directs T cells to kill MSLN expressing cells**

Killing of OVAR3 cells using T cells from 3 different donors

**HPN536 induces cell killing in presence of human serum albumin**

Killing of MSLN expressing ovarian cancer cell lines

**HPN536 directs T cell killing in presence of human serum albumin**

- EC50: 5 nM
- % killing: 60%

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**HPN536 SUMMARY**

- Binds human and cynomolgus MSLN, CD3ε, and human serum albumin
- Redirects T cells to kill MSLN expressing cells in vitro
- Inhibits tumor growth in mouse models
- Is well tolerated in cynomolgus monkeys after a single dose with data suggestive of target engagement in vivo
- Anticipated to be an efficacious, safe, and convenient therapeutic for patients with MSLN expressing malignancies
- Projected to enter the clinic within the next 12 months

**IN VIVO PHARMACOLOGY**

NCI-H292 tumor growth inhibition in mice implanted with human PBMCs and treated with HPN536

- EC50: 5 nM
- % killing: 60%

**PHARMACOKINETICS**

- Reduction in plasma cytokine levels
- MSLN expressing tissues have hyperplasia and inflammation
- 1 week after dosing with HPN536

**SAFETY**

- A single 10 mg/kg dose of HPN536 is well tolerated in cynomolgus monkeys

- Findings were similar at 0.1, 1 and 10 mg/kg
- Findings were trending towards reversible 3 weeks after dosing
- Reduced severity / incidence (small sample size)
- Most findings were associated with the known mechanism of action

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