Pelican Therapeutics
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PELICAN Therapeutics
A Division of Heat Biologics

Activating antitumor activity

Pelican Therapeutics' PTX-35, a novel agonist antibody, amplifies CD8⁺ antitumor T cell responses via a novel costimulatory target.

Current immuno-oncology (IO) treatments represent a breakthrough in the treatment of advanced solid tumors, with immune checkpoint inhibitors demonstrating broad antitumor activity in a diverse range of cancers. Unfortunately, for the majority of patients (60–80%), releasing a brake on the immune system is not enough to generate a response—something more is needed. Costimulatory molecules, the signals of which act in tandem with those from the T cell receptor (TCR) to activate cellular immunity, can help fuel antitumor activity. The promise of costimulatory agonist antibodies is widely recognized and is a focus of intensive drug development efforts.

Pelican Therapeutics, a division of Heat Biologics, has a lead product candidate in this area, PTX-35, a novel costimulatory agonist antibody directed against tumor necrosis factor receptor superfamily 25 (TNFRSF25). Preclinical data support a selective and potent effect of PTX-35 on activated CD8⁺ T cells, the cells responsible for eliminating tumor cells in patients. Although multiple companies have development programs that target costimulatory molecules, Pelican has a unique intellectual property portfolio and is the only company poised to file an investigational new drug (IND) for a candidate anti-TNFRSF25 agonist in 2018.

The TNFRSF25 gene shares homology and chromosomal localization with genes for other costimulatory molecules, but is most closely related to TNFR1. Because TNFRSF25 appears to be divergent from other costimulatory receptors and is evolutionarily older, Gordon Freeman, professor of medicine at the Dana-Farber Cancer Institute, Harvard Medical School has suggested it may have a unique function.

The complementary role of TNFRSF25

Current understanding supports a specific role for TNFRSF25 in expanding and enhancing the function of activated antigen-specific CD8⁺ T cells. TNFRSF25 is most highly expressed on activated T cells and has a narrower expression profile than other costimulatory molecules. In primary T cells, TNFRSF25 agonists enhance survival, proliferation, and effector functions, including cytokine release and targeted cell killing. These effects require prior TCR engagement. This restriction to antigen-stimulated T cells and a more pronounced expansion of memory CD8⁺ T cells differentiates TNFRSF25 from other T cell costimulators, which activate CD8⁺ T cells independent of antigens (4-1BB; also known as TNFRSF9), may be more effective at activating CD4⁺ T cells (OX40; also known as TNFRSF4), or, conversely, are broadly expressed on T cells, B cells and antigen presenting cells (CD27; also known as TNFRSF7). According to Pelican CEO Rahul R. Jasuja, "Because of its specificity for tumor-antigen-driven 'memory' CD8⁺ T cells, PTX-35 has the potential to become a best-in-class T cell costimulator."

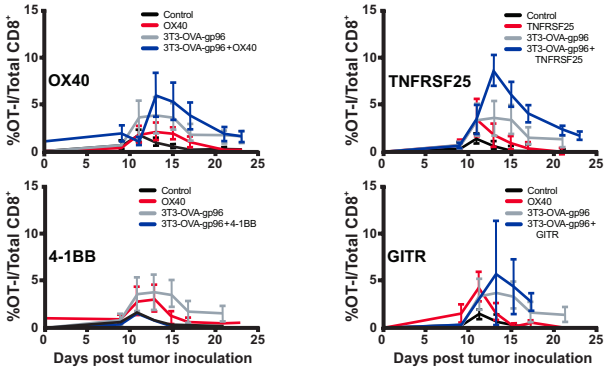

Fig. 1 | Data comparing antitumor activity. Tumor necrosis factor receptor superfamily 25 (TNFRSF25) has the most pronounced effect on antigen-specific CD8⁺ T cell expansion and correlates with survival.

Pelican's preclinical results with anti-TNFRSF25 agonists confirm a specific and potent effect on CD8⁺ T cells and demonstrate the ability to enhance survival in rodent tumor models. In a study with ovalbumin-specific TCR transgenic mice, vaccination with antigen plus the murine precursor to PTX-35 increased antigen-specific CD8⁺ T cell expansion upon boost. This expansion was greater than that seen with an anti-OX40 agonist antibody. When the two antibodies were given together, they stimulated greater expansion of CD8⁺ T cells than either alone, implying they stimulate nonredundant pathways.

In murine models of colon cancer and melanoma, the addition of anti-TNFRSF25 agonist antibody enhanced antitumor responses (**Fig. 1**). Notably, in a B16-F10 melanoma model, in which the tumor was allowed to grow for 9 days prior to treatment, CD8⁺ antigen-specific T cells underwent significant expansion in mice injected with an anti-TNFRS25 antibody and antigen. Further, survival was significantly extended in mice that received anti-TNFRSF25 antibody compared with controls (Mantel–Cox $P = 0.0002$). In contrast, when agonist antibodies to other costimulatory molecules were tested in the model, they failed to prolong survival (GITR; also known as TNFSF18) or had a less significant effect on both CD8⁺ T cell proliferation and survival (OX40 and 4-1BB).

Promising data trigger funding

Based on the promise of TNFRSF25 agonists as an IO target, Pelican was awarded a $15.2m Cancer Prevention Research Institute of Texas grant by the state of Texas to support a first-in-human, phase 1a/b/c study in up to 70 patients. Pelican is currently preparing an IND for PTX-35 and envisions a broad clinical development program that will include combination therapy with costimulatory agonists, checkpoint inhibitors, or other immune modifiers. Given the requirement for TCR antigen recognition to support TNFRSF25 responses, there is a particularly strong rationale for the codelivery of tumor antigen and PTX-35 to maximize CD8⁺ T cell responses. To enable this type of approach, Heat Biologics, Pelican's parent company, has developed ImPACT, an antigen-presentation platform comprised of off-the-shelf cell lines engineered to deliver multiple common tumor antigens and enhance IO responses.

HS-110, the first candidate ImPACT product to enter the clinic, in combination with an anti-programmed cell death protein 1 antibody has shown promising interim results in a phase 2 study in non-small-cell lung cancer (NSCLC) and bladder cancers. Responders in the NSCLC trial included patients with 'cold' tumors with low levels of tumor-infiltrating lymphocytes, which do not respond to checkpoint inhibitor monotherapy. Preclinical results with combined PTX-35 and an ImPACT cell line demonstrated enhanced CD8⁺ T cell expansion over either stimulus alone. Pelican believes that tumor-antigen-driven therapy, for example, the combined use of HS-110 and PTX-35 to stimulate de novo and memory CD8⁺ T cell expansion, respectively, is a unique and promising path to address unmet need in checkpoint-inhibitor-refractory cancer.

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