Harnessing the immune system to turn cold tumors hot

Heat Biologics’ innovative T cell activation platform provides transformative potential to improve clinical responses of checkpoint inhibitors.

In recent years, checkpoint inhibitors have demonstrated great promise for the treatment of diverse tumor types by releasing the brakes on the immune system. However, for patients with ‘cold’ tumors that express low levels of tumor-infiltrating lymphocytes, checkpoint inhibitors are typically ineffective, resulting in lower response and survival rates.

To address this unmet medical need, Heat Biologics is developing drug candidates that turn immunologically ‘cold’ tumors ‘hot’ with a fresh infiltrate of CD8+ killer T cells, enhancing the effectiveness of checkpoint inhibitors and other cancer therapies. Using its proprietary T-cell Activation Platform (TCAP), the company has developed cell-based therapies designed to expose a broad swath of tumor antigens to the immune system and prime T cell recognition of these antigens. Heat’s unique TCAP approach offers many advantages over autologous personalized therapies. These allogeneic, off-the-shelf, low-cost therapies are produced to scale and require no patient-specific manufacturing.

To date, Heat has developed two innovative TCAP therapies: Immune Pan-antigen Cytotoxic Therapy (ImPACT) and Combination Pan-antigen Cytotoxic Therapy (ComPACT). Both therapies are based on an engineered form of the heat shock protein gp96—a molecular warning system that serves as a natural sentinel, alerting the immune system to the presence of foreign antigens. gp96 is a powerful immune stimulator that directs antigen cross-presentation and enhances T cell costimulation on activated dendritic cells.

“We formed Heat with the singular goal of developing innovative and powerful tools to harness the body’s natural immune system to treat cancer,” said Heat’s founder and CEO Jeffrey Wolf. “Heat strives to offer a less toxic, more effective approach to treating cancer patients.”

Activating the immune sentinel

Using the ImPACT and ComPACT technologies, off-the-shelf cancer cell lines are reprogrammed to continually secrete their own cancer-associated antigens bound to an engineered gp96 chaperone, which has a deleted membrane leash. This engineered form of gp96 bound to tumor antigen is efficiently secreted, making it proficient in presenting tumor antigens to dendritic cells, activating a powerful T cell-driven immune response. In addition, gp96 stimulates Toll-like receptor 2 (TLR2) and TLR4 on dendritic cells, further enhancing antigen presentation and the costimulatory activation of CD8+ T cells. Because the ImPACT and ComPACT technologies use irradiated cancer cells, these cells do not replicate and propagate after injection.

Heat’s lead biologic product candidate in the ImPACT series is HS-110; the drug is currently the focus of an exploratory phase 2, multicenter clinical trial in combination with Bristol-Myers Squibb’s checkpoint inhibitor, nivolumab, in patients with non-small-cell lung cancer that have progressed after first-line therapy. Preliminary data suggest that HS-110 plays an integral role in tumor reduction and may enhance the efficacy of checkpoint inhibitors in lung cancer patients (Fig. 1). In particular, durable responses are observed in patients with low levels of tumor-infiltrating lymphocytes. These patients would not normally respond to checkpoint blockade—an area of significant unmet need.

The company is also developing HS-130 as the first ComPACT immunotherapy. Similar to ImPACT, ComPACT enhances the secretion of tumor-associated antigens bound to gp96. In addition, ComPACT delivers a costimulatory fusion protein, OX40L—Ig, to enhance T cell activation. ComPACT is the first potential dual-acting immunotherapy designed to deliver T cell activation and costimulation in a single product, simplifying combination immunotherapy while offering the potential for superior immune activation with reduced treatment costs.

Preclinical Investigational New Drug (IND)-enabling studies have shown that ComPACT outperforms an OX40 agonist monoclonal antibody (mAb), eliciting superior primary and memory T cell responses as well as improved survival in response to tumor challenge. The therapy stimulates T cell memory function and has the potential to provide a durable antitumor response. ComPACT is a potential paradigm shift that can simplify combination cancer immunotherapy. Furthermore, ComPACT has implications for local T cell costimulation, mimicking a natural immune synapse, versus costimulation with systemically delivered conventional mAbs.

Other development programs

IND-enabling studies are also being conducted with PTX-35 by Heat. PTX-35 is a potential best-in-class T cell costimulator (part of the Pelican Therapeutics acquisition). PTX-35 is an agonist mAb against tumor necrosis factor receptor superfamily member 25, a costimulatory receptor expressed predominantly on antigen-experienced CD8+ and CD4+ T cells. PTX-35 is unique compared with competing T cell costimulators, in that it is antigen-specific and its effects are most pronounced for the expansion of memory CD8+ T cells, the cells crucial for eliminating tumors. When combined with ImPACT and ComPACT, the murine pre-cursor of PTX-35 has been shown to enhance antigen-specific T cell activation to eliminate tumor cells in mice.

Heat’s pipeline is well positioned to enhance responses to checkpoint inhibitors through combination immunotherapies that drive CD8+ T cell-driven tumor reduction and clearance. The potential to treat ‘cold’ tumors could make a meaningful dent in addressing the need for patients that show suboptimal responses to checkpoint inhibitor therapies.

Fig. 1 | TIL infiltration is associated with clinical response in patients treated with HS-110. Tumor-infiltrating lymphocytes (TILs) evaluated at baseline and ten weeks post-treatment by immunohistochemistry.