HERA-LIGANDS ARE NOVEL POTENT CO-STIMULATORY TNF RECEPTOR AGONISTS FOR IMMUNO-ONCOLOGY THERAPIES

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Apogenix' TNFSF Receptor Agonists

The diverse functions of the immune system are orchestrated by a complex and delicately balanced interplay of stimulatory and inhibitory signals. Many key regulators of immune cell function belong to the tumour necrosis factor superfamily (TNFSF) and their cognate receptors, the TNF receptor superfamily. The TNFSF consists of 19 structurally related ligands, each binding to one or more of the 29 members of the TNF receptor superfamily. TNFSF receptors are of great importance in the anti-tumour immune process. They are expressed by a wide variety of immune cells including T cells and antigen-presenting cell populations, such as dendritic cells and macrophages, as well as by tumour cells themselves. This diverse expression pattern highlights the critical role that TNFSF receptors play in many parts of the body and in the various phases of the anti-tumour immune response.

TNFSF-mediated signaling induces a wide range of biological effects, including programmed cell death (i.e., apoptosis), proliferation, differentiation, and tumour growth. Therefore, TNFSF signaling is an attractive target for therapeutic intervention. TNFSF ligands naturally exist as homo-trimers with three receptor binding sites. The interaction of trimeric TNFSF ligands with their specific cell surface receptors leads to clustering of these receptors, followed by intracellular signal transduction. The trivalent structure of the TNFSF proteins and the resulting receptor clustering are prerequisites for the transmission of a signal delivered into the cell.

Apogenix is developing a novel class of TNFSF receptor agonists (HERA-ligands, see Figure) for the treatment of various types of cancer. Their unique hexavalent molecular structure perfectly mimics the endogenous ligands and overcomes the known limitations of antibodies and other biologics targeting TNFSF receptors. Antibodies can only bind two TNFSF receptors in a spatially undefined manner and require secondary cross-linking via Fcy receptors. In contrast, Apogenix' HERA-ligands lead to well-defined TNFSF receptor clustering without the need for further cross-linking. This results in a sufficient level of the appropriate signal being transmitted into the target cell, whereas agonistic antibodies transmit these signals at insufficient levels. Preclinical work at Apogenix has demonstrated the producibility and biological activity of these novel TNFSF receptor agonists as well as their superiority over agonistic antibodies.

HERA-CD40L Induces T-Cell-Mediated Anti-Tumour Immune Response through Activation of Antigen-Presenting Cells

Exemplarily, efficacy data for one HERA-ligand family member are presented here. CD40 - the receptor for HERA-CD40L - is expressed on the surface of antigen presenting cells (APCs) as well as some tumour cell types. Binding of CD40 to its natural ligand leads to increased APC activation and an enhanced immune response. CD40 agonist therapy plays an important role in APC maturation and their migration from the tumour to the lymph nodes, resulting in elevated antigen presentation and T cell activation.

HERA-CD40L provides efficient receptor agonism on CD40-expressing cells and, importantly, does not require FcyR-mediated cross-linking. Strong activation of NFκB signaling was observed upon treatment of B cells with HERA-CD40L. Monocyte treatment with HERA-CD40L promoted differentiation towards the M1 spectrum and repolarization of M2 spectrum macrophages towards the M1 spectrum phenotype. Treatment of in vitro co-cultures of T and B cells with HERA-CD40L triggered robust anti-tumour activation of T cells, which depended upon direct interaction with B cells. In contrast, bivalent anti-CD40 antibodies and trivalent soluble CD40L displayed weak activity which critically depended on cross-linking.

In vivo, a murine surrogate of HERA-CD40L stimulated clonal expansion of OT-I specific murine CD8+ T cells without affecting non-specific immune cells. In the syngeneic CT26wt mouse model mHERA-CD40L treatment converts cold into hot tumours by increasing infiltration of CD8+ and CD4+ T cells. In addition, mHERA-CD40L showed single-agent anti-tumour activity in the CD40-negative syngeneic MC38-CEA mouse model, suggesting an involvement of the immune system in controlling tumour growth.

In summary, HERA-CD40L is a potent agonist that is able to establish single-agent anti-tumour immune responses. In comparison to bivalent benchmark antibodies, HERA-CD40L showed superior biological activity which qualifies this molecule as an ideal candidate for combinatorial cancer treatments.

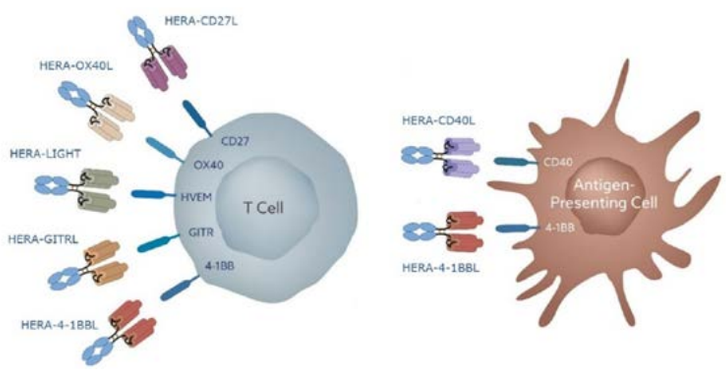

Fig: Apogenix' HERA-ligands in preclinical development