APO-T

www.apo-t.com

Tapping into MAGE potential to develop next-generation cancer therapies

Biotech company APO-T is developing bispecific T cell engagers (BiTEs) that facilitate the attraction of immune effector cells exclusively to cancer sites by targeting cancer cell antigens known as melanoma-associated antigen A (MAGE-A) proteins.

The key challenge of cancer therapies is to effectively kill cancer cells while sparing healthy ones. Despite the success of immunotherapies in some cancer indications, new, truly cancer-specific approaches are needed to treat a broader range of cancers and to overcome the resistance to therapy that evolves over time.

APO-T, a biotech company based in Oss, the Netherlands, is developing bispecific T cell engagers (BiTEs) to facilitate T cell-driven removal of exclusively cancer cells. APO-T's BiTEs attract T cells to cancer sites by targeting truly tumor-specific, validated cancer antigens: members of the melanoma antigen gene A (MAGE-A) family. MAGE-A proteins, which were discovered more than 30 years ago, have emerged as an attractive group of targets for immunotherapy in recent years owing to their unique expression profile. Besides their expression in testis and placenta, they are prevalent in a wide range of cancer types, including lung, ovarian, breast and colon cancers.

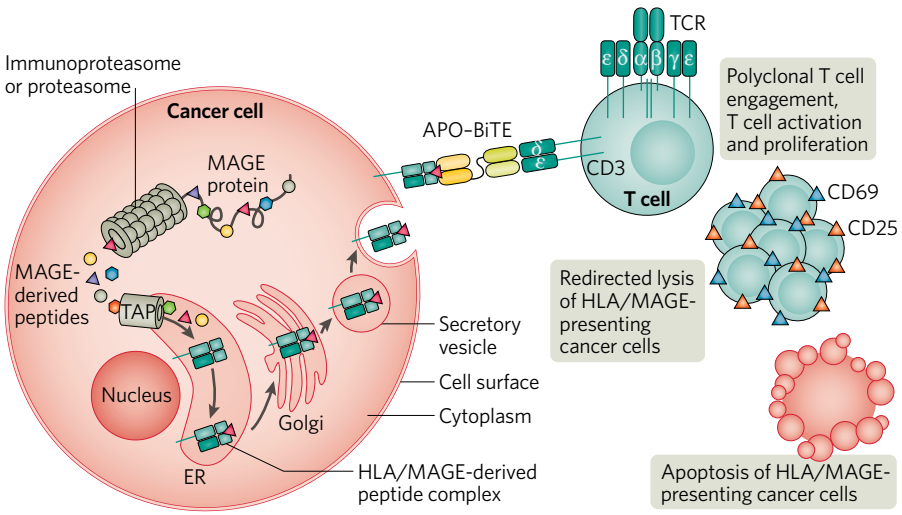

Fig. 1 | APO-T's BiTEs facilitate removal of cancer cells by immune cells. The bispecific T cell engagers of APO-T (APO-BiTE) attract T cells exclusively to cancer cells that present on their surface the MAGE-A-derived peptides in complex with human leukocyte antigens (HLAs). ER, endoplasmic reticulum; MAGE, melanoma-associated antigen; TAP, transporter associated with antigen processing; TCR, T cell receptor.

Ensuring broad patient coverage

Unlike most other cancer markers, MAGE-A proteins are expressed intracellularly, not on the cell surface. APO-T's BiTEs target MAGE-A proteins once they have been degraded into short peptides by the proteasome and are presented on the cell surface as a complex with human leukocyte antigen (HLA), which is encoded by major histocompatibility complex class I (MHC-I) genes (Fig. 1).

Crucially, the only other tissues of the body that express MAGE-A proteins—the testes and placenta—do not express MHC-I genes and lack the HLAs needed to present MAGE-A-derived peptides. As a consequence, APO-T's BiTEs facilitate the attraction of immune effector cells exclusively to cancer sites because they combine specificity to HLA/MAGE and CD3 (which is a marker present on T cells) in a single molecule.

MAGE-A protein expression is linked to pro-tumorigenic processes, such as p53 dysregulation and cellular proliferation, and is clinically associated with a poor prognosis. MAGE-A proteins are encoded by 12 highly homologous genes that are often co-expressed. Importantly, owing to this high homology the proteasomal degradation of different, individual MAGE-A protein family members may lead to the generation of MAGE-A peptides having exactly the same amino acid sequence. Such peptides are referred to as multi-MAGE peptides. APO-T's BiTEs are specifically designed to recognize complexes of such multi-MAGE peptides and pre-defined HLA molecules. Because of this unique feature APO-T's BiTEs have the potential to counter the resistance that so often develops with other anticancer therapies, when, as a result of selective pressure, the target is no longer expressed.

APO-T's BiTEs recognize multi-MAGE peptides in the context of HLA proteins. The prevalence of HLA proteins differs between different populations. Taking this into account, APO-T BiTEs are specifically designed to ensure broad coverage of patients by combining the multi-MAGE approach with a focus on highly prevalent HLA types. APO-T is developing a range of multi-MAGE BiTEs that could be given sequentially in response to changes in the expression profile of the tumor in order to maintain therapeutic effect.

APO-T's problem-solving BiTEs

Although MAGE proteins have been targeted with a range of immunotherapeutic modalities, including vaccines, adoptive T cell therapies and T cell receptor (TCR)-based fusion proteins, to date there are no approved MAGE-targeting therapies. APO-T's antibody-based approach solves the drawbacks of other MAGE-targeting modalities. Unlike vaccines, APO-T BiTEs take immediate effect, mobilizing pre-existing $CD4^+$ and $CD8^+$ T cell populations. In contrast to TCR-based therapies, they do not require in vitro affinity maturation, which carries a risk of inducing off-target toxicity, as they have high affinity and specificity from the start of development. Further, their manufacturing and purification processes are well established, comparatively inexpensive and allow for the creation of a range of off-the-shelf therapies.

APO-T is currently completing in vivo studies to confirm pre-clinical efficacy in relevant animal models, results of which are expected before the end of 2020. These studies will set the stage for toxicity studies, and an anticipated investigational new drug (IND) application filing and launch of phase 1/2 studies in 2023. APO-T seeks discussions with potential investors, and potential partner companies that have proprietary technology for the creation of new bispecific formats that could be applied to targeting tumors via HLA/MAGE.

CONTACT
Marta Kijanka
APO-T
Oss, the Netherlands
Tel: +31 85 1300529
Email: marta.kijanka@apo-t.com