TECHNOLOGY

Anthrax toxin protective antigen proteins engineered to target membrane-anchored serine proteases overexpressed on tumor cells

OVERVIEW

Bacillus anthracis is the bacterium that produces the anthrax toxin, which consists of the three distinct proteins protective antigen (PrAg), lethal factor (LF), and edema factor (EF). In order for the toxin to be activated, the PrAg moiety of the toxin must bind to cell-surface proteins and become proteolytically cleaved by the proprotein convertase furin. To target cancer cells, the PrAg's native activation sequence of the anthrax toxin can be re-engineered to be cleaved by cell-surface membrane proteases that are over-active on tumors. This technology is a prodrug system where the mutant zymogen-like PrAg (ZMT) binds to the ubiquitous cell surface receptors, ANTXR1/TEM8 and ANTXR2/CMG2, present on ovarian tumor cells. Once bound, the ZMT is cleaved by over-active serine proteases on the tumor surface or in the tumor pericellular microenvironment, to deliver a potent cytotoxin (such as FP59, a chimeric lethal factor-Pseudomonas exotoxin fusion protein or LF) to the cytoplasm of the tumor cell.

This technology is an anthrax toxin engineered to target ovarian tumors. Once bound to the tumor surface, activation would occur via the tumor-bound serine proteases and cytotoxin delivery, inducing the death of ovarian tumor cells. The cytotoxic activity of the engineered ZMTs has been demonstrated in vitro in pancreatic, prostate, lung and ovarian tumors. In vivo studies in xenograft tumor-bearing mice, showed substantially growth inhibited of subcutaneous tumors, reduction in intraperitoneal ovarian tumor burden, and extension of mouse survival with no adverse side effects on normal tissues. These data suggest that targeting ovarian tumor cells with ZMTs may provide a an effective first- or second-line approach for treating women with recurrent ovarian cancers.

APPLICATIONS

Ovarian cancer is the 5th most common cancer in women with approximately 22,440 diagnosed and 14,080 patients deaths in 2016. If ovarian cancer is detected early, the chances of survival are significantly greater. However, the majority of ovarian cancers are found after metastasis (60%) which holds a 5-year survival rate of only 28.9%. No screening method currently exists to detect early-stage ovarian cancer which often remains asymptomatic. Targeted peptide toxin therapies are a promising approach that manipulates a tumor's own proteases as an anti-tumor therapy. The membrane-anchored serine proteases are a unique group of trypsin-like serine proteases that are tethered to the cell surface via transmembrane domains or glycosylphosphatidylinositol (GPI)-anchors. Overexpressed proteases in tumors, with pro-tumorigenic properties, are attractive targets for protease-activated, anti-tumor therapies.

ADVANTAGES

Targeted therapy

STAGE OF DEVELOPMENT

Tested in xenograft tumor-bearing mouse models

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LICENSING POTENTIAL

Available for licensing
Available for sponsored research

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PATENT STATUS

PCT Application

LICENSE STATUS

Available for licensing; Available for sponsored research

CATEGORIES

- Therapeutics
- Biologics

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ATTACHMENTS

- Download TA-2016-015 Market Summary 1-26-18.pdf

EXTERNAL RESOURCES

- Targeting the membrane-anchored serine protease testisin with a novel engineered anthrax toxin prodrug to kill tumor cells

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