TRAIL Fusion Protein: Novel Gene Therapy for Oncology

A novel genetic construct encoding a CD40L-TRAIL fusion protein which kills cancer cells selectively and with high potency.

Reference: TRAIL Fusion Protein

IP Status
Patented

Seeking
Development partner

About University of Liverpool
By facilitating access to our expertise, facilities and networks, the University of Liverpool offers the means to transform ideas into creative solutions, improved performance, new technologies, strategies, applications, products or skills.
Background

TNF-related apoptosis-inducing ligand (TRAIL), is a protein functioning as a ligand that induces the process of cell death (apoptosis). TRAIL is a cytokine that is produced and secreted by most normal tissue cells. It causes apoptosis primarily in tumour cells, by binding to certain death receptors (DR4- TRAIL-RI and DR5- TRAIL-RII). The process of apoptosis is caspase-8-dependent. Caspase-8 activates downstream effector caspases including procaspase-3, -6, and -7, leading to activation of specific kinases.

TRAIL and its receptors have been used as the targets of several anti-cancer therapeutics since the mid-1990s, such as Mapatumumab. However, these have not shown significant survival benefit. In clinical trials only a small proportion of cancer patients have responded to various drugs that target TRAIL death receptors. Many cancer cell lines develop resistance to TRAIL and this limits the efficacy of TRAIL-based therapies.

The present invention addresses this issue.

Tech Overview

University of Liverpool researchers are developing a novel gene therapy, which kills cancer cells selectively and with high potency. The invention consists of a novel genetic construct encoding a CD40LTRAIL fusion protein.

The TRAIL death receptor pathway is a well validated target for cancer therapeutics, with multiple agonistic antibodies entering clinical trials in the last 10 years. However many of these mAbs failed in the clinic due to poor efficacy. This novel fusion protein overcomes these issues by generating a more potent apoptotic signal.

The improvements employ the use of membrane-anchoring moieties to amplify the effectiveness of this modality of TRAIL-based therapeutic inventions. Significantly improved cancer cell-killing activity has been observed compared to the natural derivatives or soluble equivalents.

Features:

- CD40LTRAIL fusion protein induces cell death in DR4- and DR5- positive carcinomas (Figure 1).
- CD40LTRAIL fusion protein induces more potent growth inhibitory effects compared to wild type TRAIL or treatment with soluble TRAIL ligand in a range of cancer cell lines (pancreatic, cervical and bladder).
- CD40LTRAIL fusion protein induces caspase 3/7 activation suggesting specific activation of the death receptor pathway.

Benefits

- TRAIL is a member of TNF superfamily that upon binding to its receptors induces cell death with high specificity for carcinoma cells
- Novel construct tethers the death receptor ligand TRAIL to the cell membrane
- Membrane anchorage increases the cytotoxicity of TRAIL in a range of TRAIL receptor-positive carcinomas

Applications

Significant market opportunity:

- Widespread TRAIL expression in cancer tissue suggests this therapy has the potential to treat various forms of cancer.
- Potential to combine with other chemotherapies and targeted therapies in difficult-to-treat cancers.

Opportunity

Stage of Development - early stage project:

- Preliminary in vitro results suggest great potential for this approach in overcoming efficacy issues with TRAIL mAbs
- Ongoing studies to trial different delivery vehicles for gene construct

Seeking partners to advance project through preclinical and clinical development. The technology is most applicable to those companies developing viral delivery vector based oncology products.

Patents

Appendix 1

Figure 1

B

% Control Viability

<table>
<thead>
<tr>
<th></th>
<th>CNT</th>
<th>AdM</th>
<th>AdwL</th>
<th>AdnL</th>
<th>sTRAIL (100ng/ml)</th>
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</thead>
<tbody>
<tr>
<td>EJ</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Suit-2</td>
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<tr>
<td>Panc1</td>
<td></td>
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C

Control Relative Caspase 3/7 Activity

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<tr>
<th></th>
<th>CNT</th>
<th>AdM</th>
<th>AdwL</th>
<th>AdnL</th>
<th>sL</th>
</tr>
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<td>zVAD</td>
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AdM = mock; AdwL = recombinant adenoviral WT TRAIL; AdnL = recombinant adenoviral CD40L-TRAIL fusion; CNT = negative control; SL = soluble TRAIL ligand