induction of apoptosis of pancreatic cancer cells by N.Ren et al in Academic Journal of Second Military Medical University 2008, vol. 28(5), 676-478.

US2005/244370 and corresponding WO2004/035794 disclose the construct of TRAIL95-281 as an effector domain linked by a peptide linker with extracellular part of another member of TNF family ligands CD40 as a cell surface binding domain. It is stated that activation of the construct is via binding of its CD40 part.

Moreover, the problem connected with TRAIL therapy has proved to be its low stability and rapid elimination from the body after administration.

Although many clinical cancer therapies are currently available, they are often insufficiently effective and have many well-known disadvantages, of which one of the most distressing and restricting the treatment are the lack of selectivity towards cancer cells, severe side effects and resistance - primary or acquired during treatment. Currently, a limited number of anticancer agents that are both effective and selective to cancer cells is known. Therefore, there remains an urgent and unmet need for new anticancer agents that would allow both to broaden the range of available agents and to find agents that are more effective (cytotoxic) and selective. There is also a need for new selective agents with increased stability and improved pharmacokinetics.

The present invention proposes a solution of this problem by providing new fusion proteins that contain a domain derived from TRAIL and a short effector peptide domain not including TRAIL fragments having intrinsic (intracellular) or extrinsic (extracellular) proapoptotic activity, that potentiates or complements the action of TRAIL. Moreover, it turned out that in many cases the fusion proteins of the invention show more potent activity than soluble TRAIL and its variants, including a fragment of the sequence, and in many cases also overcome the resistance to TRAIL. Moreover, the addition of an effector peptide results in prolonged half-life and increased retention of protein in the tumour and finally increases its efficiency.

Summary of Disclosure

In one embodiment, there is provided a fusion protein comprising: domain (a) which is the functional fragment of soluble hTRAIL protein sequence, wherein said functional fragment is capable of inducing apoptotic signal and begins with an amino acid at a position not lower than hTRAIL95, or a sequence having at least 70% homology thereto; and domain (b) which is the sequence of a pro-apoptotic effector peptide, which effects its pro-apoptotic action via intrinsic apoptosis pathway, wherein the sequence of domain (b) is attached at the C-terminus and/or the N-terminus of domain (a).

In one embodiment, there is provided a polynucleotide sequence, coding the fusion protein as defined herein.

In one embodiment, there is provided a pharmaceutical composition, comprising as an active ingredient the fusion protein as defined herein in combination with a pharmaceutically acceptable carrier.

In one embodiment, there is provided a use of the fusion protein as defined herein or the pharmaceutical composition as defined herein for the preparation of a medicament for the treatment of cancer diseases in a mammal, including human.

Description of Figures.

The invention will now be described in detail with reference to the Figures of the drawing.