Virulence attenuated bacteria for treatment of malignant solid tumors

The field of the invention

The present invention relates to recombinant virulence attenuated Gram-negative bacterial strains for use in a method of treating a malignant solid tumor in a subject.

Background of the invention

A major problem in treatment of malignant solid tumors is the delivery of therapeutic molecules to cancer cells in sufficient amounts, while reducing damage on non-related cells and tissue. The most common treatment approaches, surgery, chemo- and radiation-therapy, too often fail to cure patients, and side effects, like nausea and diarrhoea are massive. Thus, several other therapeutic strategies have been exploited, including angiogenesis inhibitors and immunotherapies.

To reduce damage to non-cancerogenic tissue, approaches allowing targeted drug delivery are of great interest. For example, antibodies recognizing surface structures of tumor cells and, in an optimal case, selectively bind to tumor cells are used. To improve the mechanism of such antibodies they can be conjugated to therapeutic agents or to lipid vesicles packed with drugs. One of the challenges with such vesicles is the proper release of the active reagent. Even more complex is the delivery of therapeutic proteins or peptides, especially when intracellular mechanisms are targeted. Many alternative ways have been tried to solve the problem of delivering therapeutic proteins into eukaryotic cells, among which are “cell penetrating peptides” (CPP) or similar technologies as well as various nanoparticle-based methodologies. All these technologies have the drawback of low efficacy and that the cargo taken up by the cell via endocytosis is likely to end up being degraded in lysosomes. Furthermore, the conflict between need for stability of cargo-carrier in the human body and the requirement for destabilization and liberation within the target cell constitutes an intrinsic problem of such technologies.

Various bacteria have been shown to replicate within malignant solid tumors when administered from a distal site, including *Escherichia coli*, *Vibrio cholerae*, *Salmonella enterica*, *Listeria monocytogenes*, *Pseudomonas aeruginosa* and *Bifidobacteria*. Currently, only bacillus Calmette-Guérin (BCG, derived from *Mycobacterium bovis*) is used in clinical practice. BCG is administrated to treat superficial bladder cancer, while the underlying molecular mechanism remains largely unknown.