Synthetic double stranded RNA for Glioblastoma treatment

Glioblastoma multiforme (GBM), a brain cancer and one of the deadliest human diseases, cannot be cured by any therapy available today. For a new and effective therapy, high selectivity, fast cell killing and induction of a strong bystander effect are important features. We have developed a method for selective and rapid killing of GBM cells over-expressing the epidermal growth factor receptor (EGFR), without affecting cells that express normal levels of the receptor is necessary for a successful therapy. Double-stranded RNA (dsRNA) activates antiviral cellular mechanisms, including the strong antiproliferative dsRNA dependent protein kinase, PKR. The dsRNA-induced mechanisms efficiently kill the infected cells and induce expression of immune system activators, such as antiproliferative interferons.

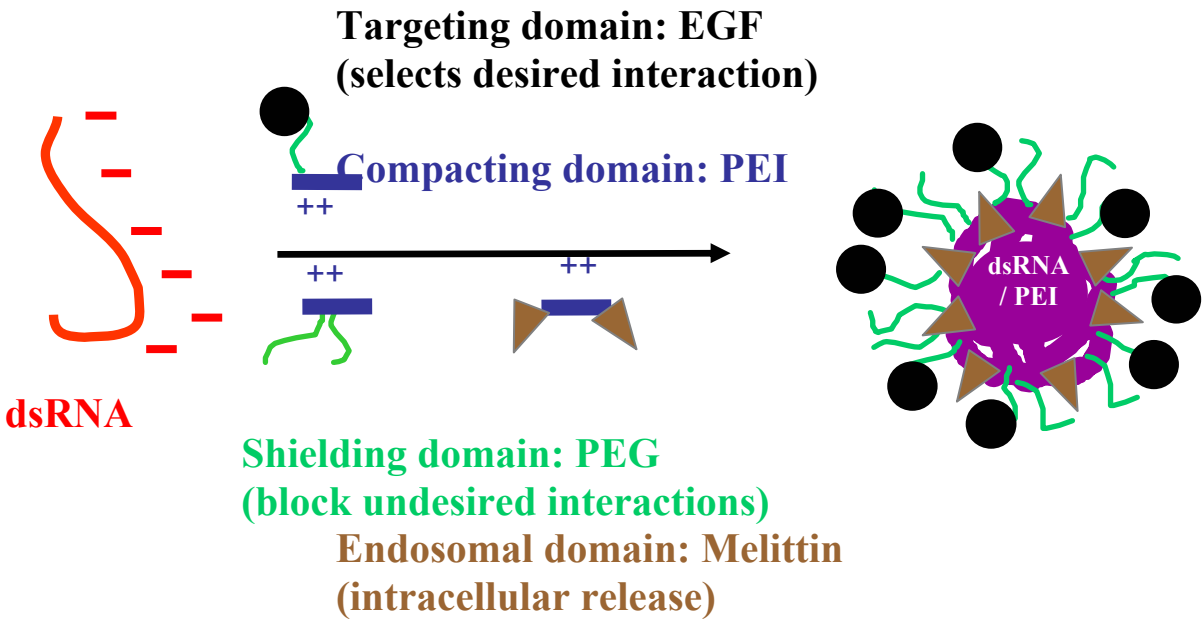

Fig.1: Synthetic, double stranded RNA (pIC) is condensed by the polycation polyethylenimine (PEI) into virus sized dimensions forming a so called polyplex. Selective targeting of EGFR overexpressing cell is possible with the help of epidermal growth factor (EGF) covalently coupled to PEI. To circumvent non-specific binding of the polylex to non- target cells, the hydrophilic polymer polyethyleneglycol (PEG) is also covalently attached to PEI. After internalization into target cells, release of the polyplex from the endosome can be hampered. For this reason the membrane active peptide melittin is also incorporated into the polyplex forming. Additionally, we have also generated a conjugate for generation of pIC polyplexes containing all four components (PEI, PEG, EGF and melittin) in one molecule.

In vitro data revealed that EGF targeted and endosomolytically active pIC polyplexes induced rapid cell killing in EGF receptor overexpressing glioblastoma cells, whereas tumor cells not

overexpressing the EGF receptor were not affected. No effect was found with non-targeted polyplexes. Incorporation of melittin peptide led to highly efficient endosomal release of the polyplexes into the cytoplasm. The rapid cell killing was shown to be due to apoptosis induced by cytotoxic cytokines (interferon alpha and others). Nude mice carrying orthotopically implanted human glioblastoma tumors were treated with the synthetic RNA virus by implanting Alzet osmotic micropumps into the tumors. Whereas control animals died within 30 days after tumor implantation, all treated animals survived for >1year and were completely cured. Similar results were also achieved with other EGF receptor overexpressing tumors.

Further reading:

Shir A, Ogris M, Wagner E, Levitzki A. EGF Receptor-Targeted Synthetic Double-Stranded RNA Eliminates Glioblastoma, Breast Cancer, and Adenocarcinoma Tumors in Mice.
PLoS Med. 2005 Dec 6;3(1):e6