Targeted local combination therapy with checkpoint inhibitors and CAR-NK cells in glioblastoma using DARPin-linked AAV vectors

Glioblastoma cells inhibit the activity of the immune system by producing immunosuppressive molecules such as PD-1 ligand. During the previous funding period, we already have demonstrated that this mechanism, which is detrimental for glioblastoma therapy, can be overcome by infecting tumor cells with a viral system derived from human adeno-associated viruses (HER2-AAV). After infection of the tumor with HER2-AAVs, antibody fragments (so-called checkpoint inhibitors) are produced locally, releasing the blockade of the immune response. This significantly enhanced the effectiveness of natural killer cells targeted against glioblastoma cells (CAR-NK cells), due to an improvement of the endogenous immune response against glioblastoma cells triggered by CAR-NK cell therapy. This is an effect that is crucial for long-term tumor control.

Laboratory experiments hinted to an increase of natural killer T cells (NKT cells) by the combination therapy with checkpoint inhibition and CAR-NK cells. In the immune system, NKT cells are responsible for the defense against lipid antigens. We also observed an increase in NKT cells in tumor tissue derived from patients who were treated with the combination of CAR-NK cell therapy and a checkpoint inhibition as part of the ongoing CAR2BRAIN study.