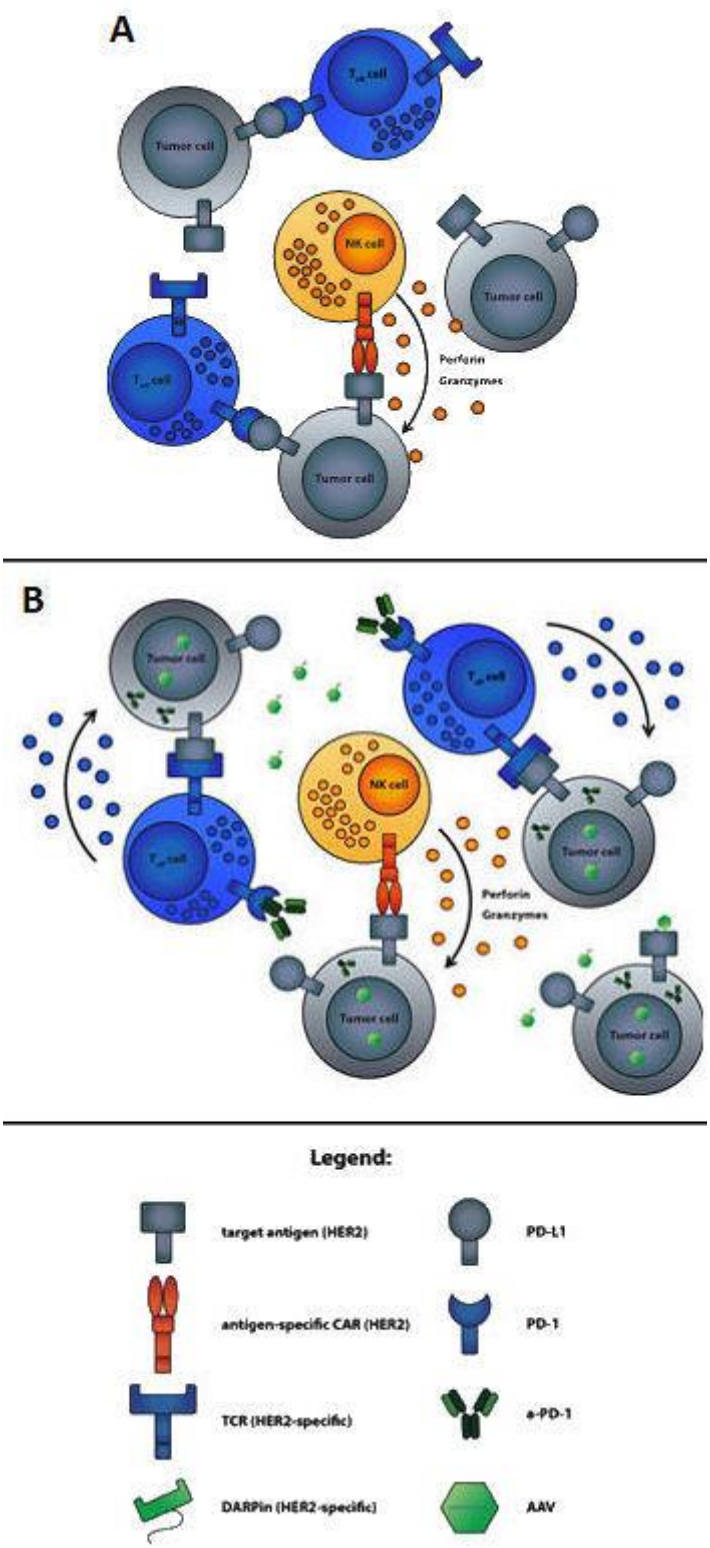
Targeted local combination therapy with checkpoint inhibitors and CAR-NK cells in glioblastoma using DARPin-linked AAV vectors

The intratumoral blockade of the immune system is characteristic for glioblastoma and can be counteracted with immune checkpoint inhibitors (ICI). However, side effects and complications often occur after intravenous administration of ICI. The combination of multiple ICI results in an amplification of potential side effects, which means that such combination therapies are only feasible to a very limited extent. Local intratumoral production of ICI in glioblastoma can be achieved by the administration of "adeno-associated viruses" (AAVs). The AAVs used in this project are replication-incompetent viral vectors which harbor the coding sequence for ICI and are specifically targeted against the HER2 protein by a “designed ankyrin repeat protein” (DARPin), so that only HER2-positive cells can be transduced. HER2 is often present on the surface of glioblastoma cells, but not on the surface of other brain cells. The local production of ICI results in a high intratumoral concentration, counteracting the immunosuppressive microenvironment. Only a small proportion of the ICI produced in the tumor reaches the blood, potentially minimizing the risk for side effects. The combination of local ICI therapy with local cellular immunotherapy with CAR-NK cells is particularly promising. CAR-NK cells are natural killer cells, which by means of a “chimeric antigen receptor” (CAR) are directed against the HER2 protein. CAR-NK cells can thus specifically identify and destroy glioblastoma cells, thereby triggering an anti-tumor immune response. The local ICI production results in a reduction of the immunosuppressive microenvironment, and an increase of the immune response. The aim of this project is to characterize the possibly synergistic effects of the local ICI therapy in addition to the local cellular immunotherapy with CAR-NK cells. As a perspective, we aim to investigate whether local combination therapies with multiple HER2-AAVs can be harnessed to resolve the blockade of the immune system in the tumor.



Scheme depicting the intended synergistic effect between CAR-NK cells and HER2-AAVs. CAR-NK cells induce an immune reaction directed against the tumor cells, which however is inhibited by the immunosuppressive microenvironment (A). HER2-AAVs transduce HER2+ tumor cells and thereby induce the local production of an immune checkpoint inhibitor (B). The combination of local CAR-NK cell therapy and local immune checkpoint blockade might modify the

immunosuppressive microenvironment and induce an immune response even in advanced tumors.