Immunological changes and adaptation of the tumor microenvironment during glioblastoma progression

Glioblastoma are characterized by their extraordinary aggressiveness caused by the marked infiltration of tumor cells into the surrounding brain tissue. After surgical removal of the primary tumor, recurrent tumors can occur from these spreaded tumor cells. Moreover, especially in the relapse situation, the tumor suppresses the immune system (Fig. 1). Nevertheless, immunotherapies are considered to be particularly promising methods of treatment, in which, for example, the patient's own immune cells recognize tumor structures and destroy the tumor cells subsequently. Due to the systemic effect of the immune cells, disseminated tumor cells could also be targeted. However, in both the primary as well as in the recurrent tumor very little is known about the factors which influence the migration of immune cells into the tumor and an effective immune response in the presence of an immunosuppressive tumor microenvironment. Another important issue is that the target structures, against which immune responses can be initiated and thus might be suitable for immunotherapies, are yet unknown. Last but not least, there is no information on how the immunogenic repertoire changes during glioblastoma progression.

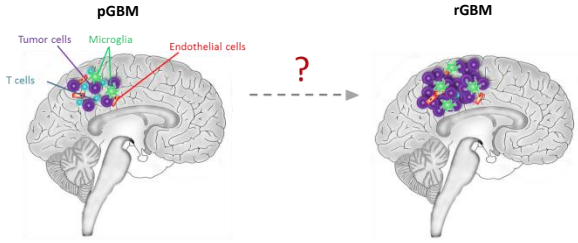

Fig. 1 During glioblastoma progression (pGBM: primary glioblastoma, rGBM: recurrent glioblastoma) the immunogenic structures as well as the molecular and cellular composition of the tumor microenvironment can change, most likely leading to a decreased immune cell infiltration and antitumoral immune response.

To address these issues, the first aim is to characterize corresponding pairs of primary and recurrent tumors regarding immune infiltration (T cells, tumor cells, microglia), and their gene and protein expression (Fig. 2). Furthermore, in the second part the immunosuppressive milieu of the tumor microenvironment during glioblastoma progression will be studied by cytokine- and chemokine analyses. To investigate the influence of the most promising genes and factors on T cell infiltration, we use T cell subpopulations, tumor endothelial cells, microglia and tumor cells, which we isolate from the primary and the corresponding recurrent tumors. In the third part of the project, we will investigate to what extent the immunogenic repertoire change during glioblastoma progression. Therefore we use a method, which combines the proteomics-based protein fractionation with a T cell activation assay.

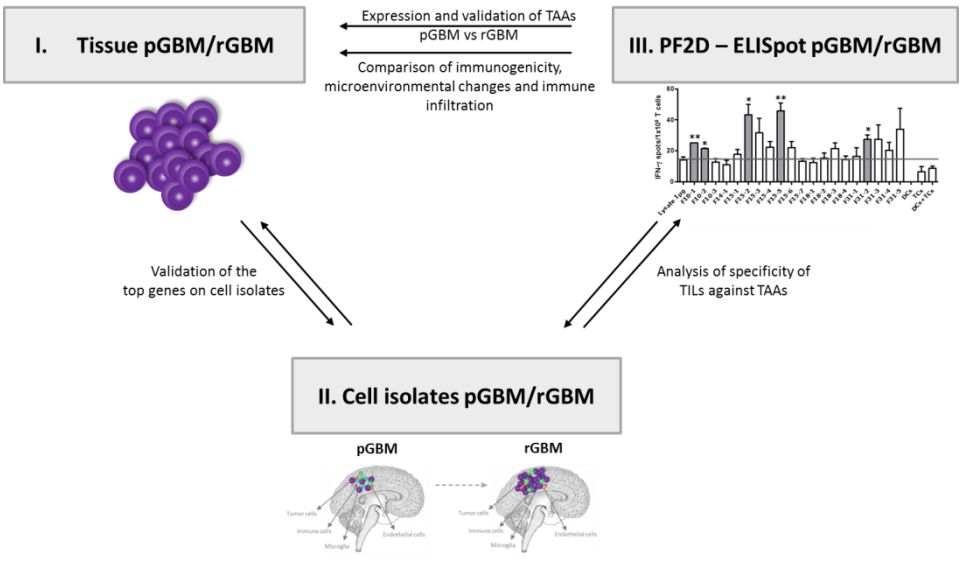

Fig.2 Study design.

- **influence of tumor-stroma-interaction on the immune response**
- **immunogenic antigens suitable for the treatment of recurrent tumors**
- **identification of patients suitable for immunotherapy**
- **identification of immunosuppressive target molecules and their inhibition**