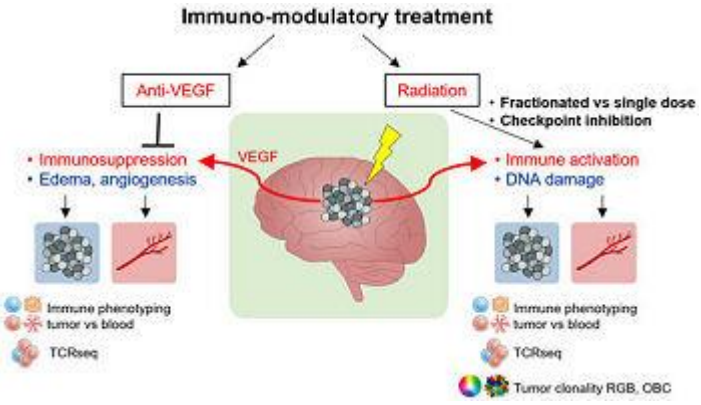
Immunomodulatory effects of anti-angiogenic treatment and radiotherapy in glioblastoma models

The current era of glioblastoma treatment is being redefined by immunotherapeutic approaches. Immune checkpoint inhibitors, viral therapies and vaccination strategies are the most prominent modalities and progressively enter the clinical practice. However, the effects of immunotherapy have not yet reached their full potential and the biology of cancer immune escape, which hinders the execution of efficient immune-mediated cancer elimination, is not yet fully understood. An important problem in immunotherapy of glioblastomas is that the vast majority of patients require corticosteroids to treat tumor-associated brain edema and that steroids have potent immunosuppressive effects. Avastin is an antibody directed against vascular endothelial growth factor (VEGF) that has anti-angiogenic as well as anti-edematous effects and can be combined with immunotherapy. Interestingly, VEGF further has immunosuppressive effects, so that its antagonization in glioblastoma patients may bring dual benefit. A major goal of our project is therefore to investigate whether the blockade of VEGF creates a more immunostimulatory tumor microenvironment and can help to harness the efficacy of the immune system to eradicate the tumor cells. In addition, the standard treatment regimen of glioblastomas usually involves radiotherapy. Radiation causes an immunogenic type of cell death, which can potentially be exploited to support immunotherapy. Hence, another goal is to characterize the effects of radiotherapy on immune cells in the tumor and periphery as well as to determine how clonal heterogeneity is affected by radiation and immunotherapy. The proposed project will provide novel insight into the immunomodulatory impact of anti-angiogenic therapy and radiotherapy, which is highly important to consider when glioblastoma patients are treated with multiple of these modalities. *Abbreviations: VEGF, vascular endothelial growth factor, FACS, fluorescence activated cell sorting; TCRseq, T cell receptor sequencing; RGB, red-green-blue lentiviral marking; OBC, optical barcoding.*


Immuno-modulatory treatment
Anti-VEGF
Radiation
+ Fractionated vs single dose
+ Checkpoint inhibition
• Immunosuppression
• Edema, angiogenesis
VEGF
• Immune activation
• DNA damage
Immune phenotyping
tumor vs blood
TCRseq
Immune phenotyping
tumor vs blood
TCRseq
Tumor clonality RGB, OBC