SFB 1389 UNITEGLIOBLASTOMA

FOCUS A – TUMOR INTRINSIC MECHANISMS

FOCUS B – TUMOR MICRO-ENVIRONMENT

FOCUS C – TECHNOLOGICAL INNOVATION

FOCUS D – UNITE CORES

B03 – TARGETING IMMUNOSUPPRESSIVE PROGRAMS IN ISOCITRATE DEHYDROGENASE MUTANT GLIOMAS

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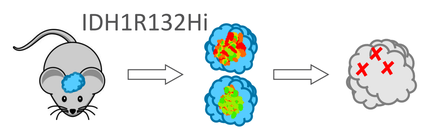
SUMMARY

This project aims at evaluating and targeting immunosuppressive glioma cell-intrinsic and -extrinsic metabolic programs and microenvironmental immunomodulation to develop combinatorial targeted (immuno-) therapies for *isocitrate dehydrogenase* (*IDH*) mutant gliomas. The strategic aim is to utilize immunosuppressive IDH-associated metabolic vulnerabilities in pathophysiologically relevant preclinical glioma models for rationalizing combinatorial clinical trials.

TASK

Task 1 –

Preclinical investigation of R-2-HG-associated transcriptomic, metabolic and proteomic immune cell signatures and their intratumoral heterogeneity

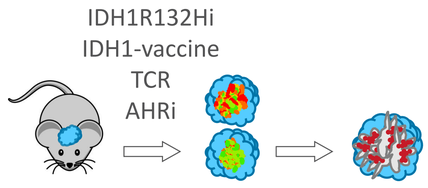


GL261
-S/MAR-IDH1WT
-S/MAR-IDH1R132H
TLX-CreERT2$^{Cre/+}$ PTEN$^{fl/fl}$ P53$^{fl/fl}$
-S/MAR-IDH1WT
-S/MAR-IDH1R132H

Immunohistochemistry
proximity ligation assay
RNAscope®
MALDI-TOF
RNA-seq
scRNA-seq
FACS

Task 2 –

Evaluate efficacy and dynamics of the inflammatory glioma microenvironment upon preclinical combinatorial therapeutic interventions for IDH1-mutant gliomas



GL261
-S/MAR-IDH1WT
-S/MAR-IDH1R132H
TLX-CreERT2$^{Cre/+}$ PTEN$^{fl/fl}$ P53$^{fl/fl}$
-S/MAR-IDH1WT
-S/MAR-IDH1R132H
IDH1R132H-A2DR1 glioma

radiomics
iron oxide nanoparticles
MALDI-TOF
RNA-seq
scRNA-seq
FACS

Task 3 –

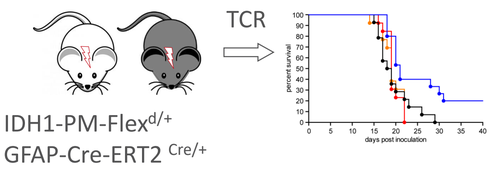
Identify routes and evaluate potential druggable targets of R-2-HG transport in IDH1 mutant gliomas

patient-derived gliomas
R-2-HG transport
pharmacological inhibition
CRISPR-Cas9

R-2-HG measurements
MALDI-TOF
RNA-seq
FACS

Task 4 –

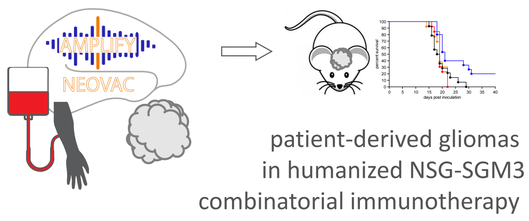
Evaluate mechanisms of natural immune surveillance of single in vivo-induced IDH1 mutated cells



IDH1-PM-Flex$^{d/+}$
GFAP-Cre-ERT2 $^{Cre/+}$
IDH1-PM-Flex$^{d/+}$
TLX-Cre-ERT2 $^{Cre/+}$
RAG2/WT

Task 5 –

Generation of PBMC-humanized, patient-derived IDH1R132H-mutant brain tumour xenograft models from patients enrolled in the AMPLIFY-NEOVAC trial to study response and resistance mechanisms after combinatorial immunotherapy



patient-derived gliomas
in humanized NSG-SGM3
combinatorial immunotherapy

VISUAL ABSTRACT

WORKFLOW

a) spatial resolution immunological tissue analyses combined with local R-2-HG levels
b) Evaluation of R-2-HG-associated AHR-dependent immunosuppressive intratumoral programs
c) Paired single immune and tumour cell analyses in infiltrative preclinical glioma
d) reversibility of immunosuppressive programs by IDH1R132Hi

a) antigen processing and presentation capacity of myeloids
b) evaluation of IDH1R132Hi and T cell therapy in preclinical mutant IDH1 A2DR1 gliomas
c) evaluation of AHRi and mutant IDH1-specific immunotherapy in preclinical gliomas

a) verification of SLC13A3 as R-2-HG transporter in human gliomas
b) CRISPR-Cas9 screen in patient-derived IDH1-mutant glioma tumour spheres
c) pharmacological inhibitors of R-2-HG export in patient-derived IDH1 mutant glioma tumour spheres
d) Effect of identified inhibitors on the microenvironment

a) evaluate existence of a natural immune surveillance of single IDH1-mutant astrocytes
b) evaluate existence of a natural immune surveillance of single IDH1-mutant neural stem cells
c) immunosurveillance by MHCII-restricted mutant IDH1-specific T cell receptors

a) establish NSG-SGM3 humanization protocols
b) establish AMPLIFY-NEOVAC PDX
c) evaluate combinatorial immunotherapy including IDH1-vaccine, mutant IDH1-specific T cell transfer, and checkpoint inhibition in combination with a mutant IDH1 inhibitor, respectively

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