SFB 1389 UNITEGLIOBLASTOMA

FOCUS A – TUMOR INTRINSIC MECHANISMS | FOCUS B – TUMOR MICRO-ENVIRONMENT | FOCUS C – TECHNOLOGICAL INNOVATION | FOCUS D – UNITE CORES

A06 – RESISTANCE MECHANISMS OF GLIOBLASTOMA AGAINST ALKYLATING AGENTS AND RADIOTHERAPY

Violaine Goidts & Felix Sahm


SUMMARY

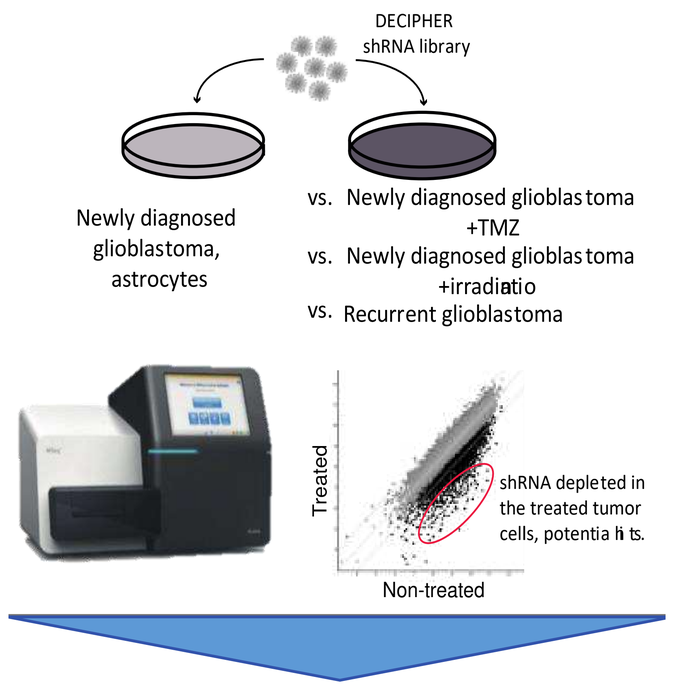
In this project, loss-of-function screens will be performed to decipher the mechanisms of *isocitrate dehydrogenase (IDH)* wildtype glioblastoma resistance to alkylating agents and radiotherapy. Presence and activation of these mechanisms will also be confirmed on human glioma tissue, also with regard to intra-tumoral heterogeneity. We aim to overcome current therapy resistance and ultimately recurrence of glioblastoma.

TASK

VISUAL ABSTRACT

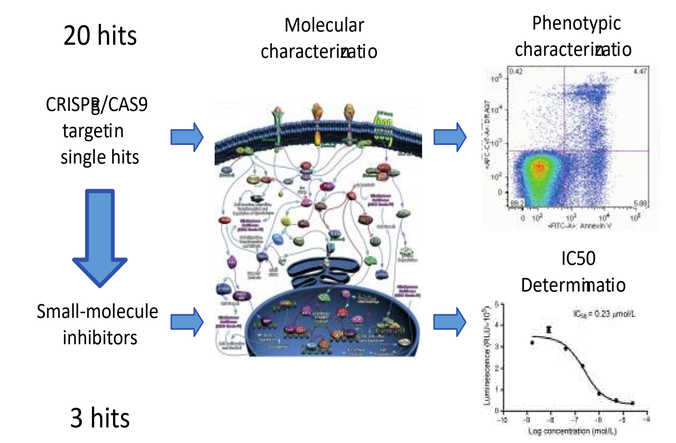
WORKFLOW

Task 1 –
Identification of drug targets to increase chemo- and radiotherapy sensitivity



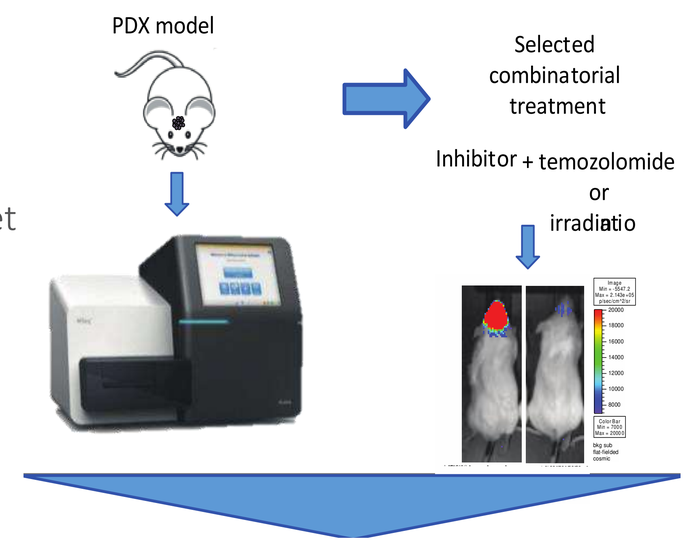
- (Epi-)genomic and translational characterization of recurrent and newly diagnosed glioblastoma samples with MGMT methylated or unmethylated promoter.
- Loss-of-function screen with or without temozolomide or high-dose irradiation.
- Selection of the best hits.

Task 2 –
In vitro validation of the identified hits



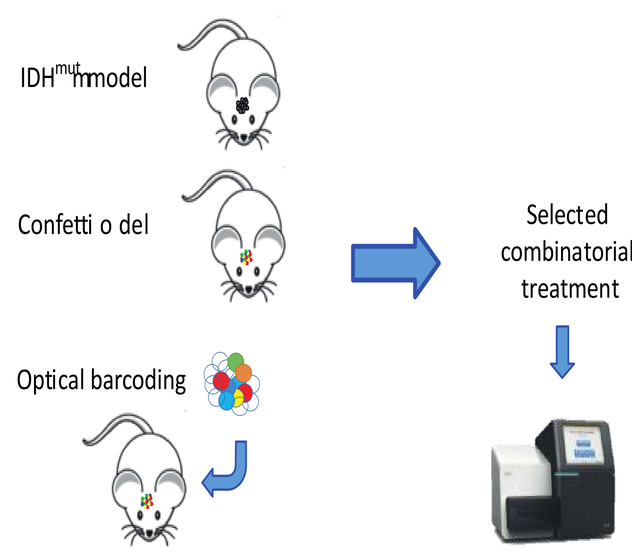
- Validation via CRISPR/Cas9 system (FACS, caspase assay,...).
- Confirmation of the phenotype using available inhibitors and selection of the most effective and selective one.
- (Epi-)genomic and transcriptional monitoring of the inhibition.

Task 3 –
In vivo preclinical studies of small-molecule inhibitors to target recurrent glioblastoma and increase current therapies sensitivity



- Establishment of orthotopic PDX models (including monitoring of the genetic changes by high-throughput sequencing).
- In vivo test of the established combinatorial treatments from tasks 1 and 2.

Task 4 –
Assessment of potential clonal selection of the combinatory treatment



Verification of a potential clonal selectivity of the treatment by single-cell sequencing using
- IDH mutant mouse model
- Confetti mouse model
- Optical barcoding

UNIVERSITÄT HEIDELBERG ZUKUNFT SEIT 1386

DFG