SFB 1389 UNITEGLIOBLASTOMA

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

A02 – DEVELOPMENT OF A SPECIFIC COMBINATION THERAPY FOR HISTONE H3-MUTANT PEDIATRIC GLIOBLASTOMA

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SUMMARY

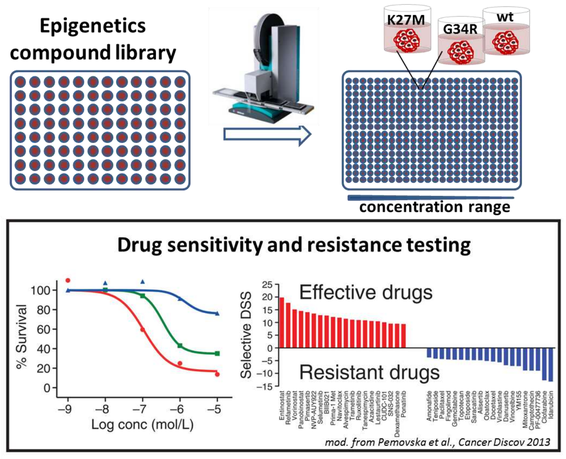
In this project we will use a combination of high-throughput drug and shRNA screening in vitro and in orthotopic animal models to identify molecular mechanisms underlying response and resistance to epigenetic therapies. Our goal is the preclinical development of a histone H3 mutation- specific combination therapy for H3.3-mutant glioblastoma.

TASK

VISUAL ABSTRACT

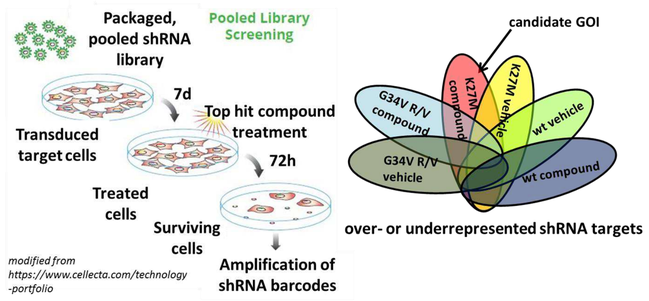
WORKFLOW

Task 1 –
Epigenetic targeted drug profiling of patient-derived tumor samples



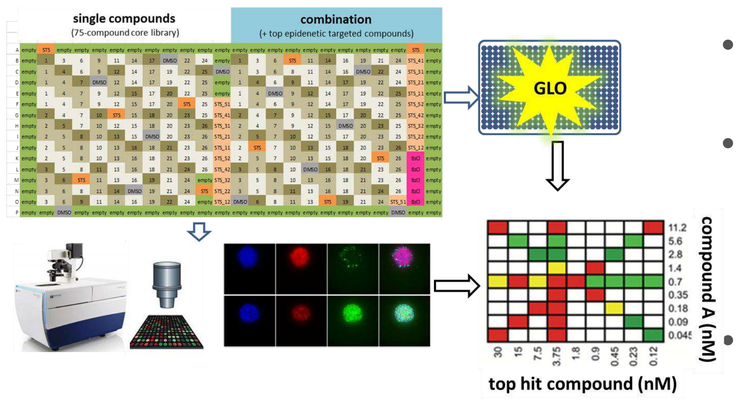
- epigenetic compound screening of all H3 K27M, G34V/R and wt models;
- identification of top hit compounds
- analysis of molecular determinants of response

Task 2 –
Molecular mechanisms underlying K27M-specific response to epigenetic targeted therapy



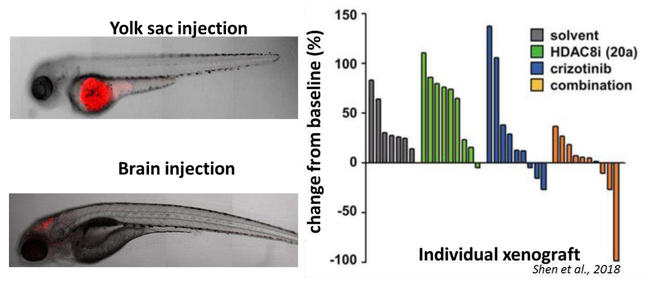
- RNA interference screen
- identification of over- and underrepresented shRNA targets
- CRISPR/Cas mediated knock-out of genes of interest in cell culture validation

Task 3 –
High-content compound combination screen



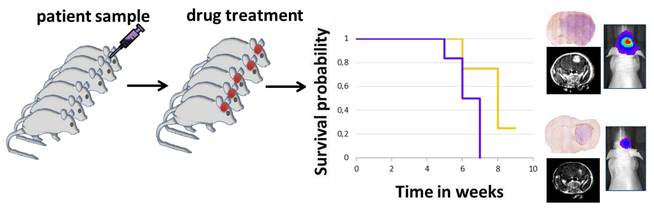
- cell culture combination screen
- generation of dose response profiles and identification of top hit combinations
- cell culture validation

Task 4 –
In vivo validation of drug combinations and RNAi target genes in the zebrafish xenotransplant model



- tumor cell inoculation
- medium-throughput hit validation (drug/drug and drug/target gene combinations)
- determination of drug-induced changes in tumor volume

Task 5 –
Validation of top hits/ combinations in preclinical murine PDX models



- orthotopic tumor cell injection with bioluminescence/MRI imaging
- drug treatment & Kaplan-Meier-analysis
- histologic and molecular characterization

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