SFB 1389 UNITEGLIOBLASTOMA

FOCUS A – TUMOR INTRINSIC MECHANISMS

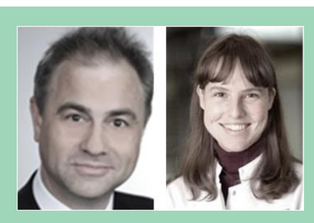
FOCUS B – TUMOR MICRO-ENVIRONMENT

FOCUS C – TECHNOLOGICAL INNOVATION

FOCUS D – UNITE CORES

C04 - IDENTIFICATION AND SPATIAL MAPPING OF PREDICTIVE BIOMARKER SIGNATURES BY MALDI MASS SPECTROMETRY IMAGING (MSI)

Carsten Hopf & Christiane A. Opitz



SUMMARY

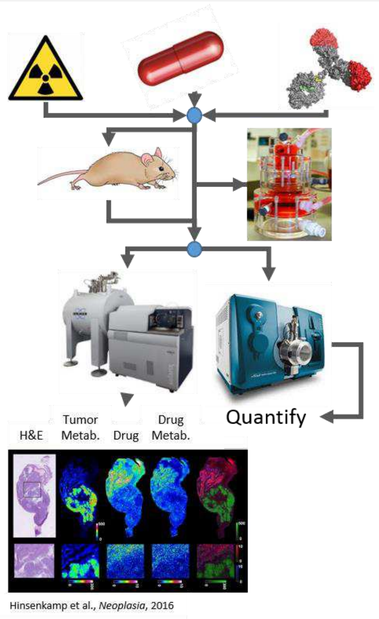
The spatial distribution of amino acid (and other) metabolite profiles in glioblastoma, which are potent promoters of tumor progression and mediators of resistance induced by glioblastoma therapies, will be investigated by statistical mass spectrometry imaging in orthotopic glioma models and clinical samples. This project aims at adopting mass spectrometry imaging (MSI) technology for identification and spatial visualization of metabolite profiles associated with response and resistance in glioblastoma.

TASK

Task 1 –

Targeted MS Imaging of amino acid metabolites: Changes by standard glioblastoma therapies or immunotherapies?

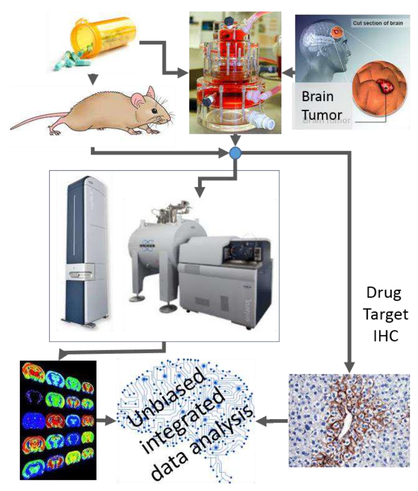
VISUAL ABSTRACT



Hinsenkamp et al., *Neoplasia*, 2016

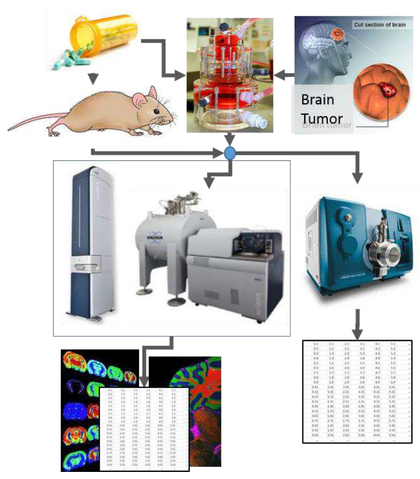
Task 2 –

Unbiased spatially-resolved search for metabolite pharmaco-dynamic biomarkers for small molecule inhibitors targeting amino acid degrading enzymes: Does lack of target engagement contribute to drug resistance?



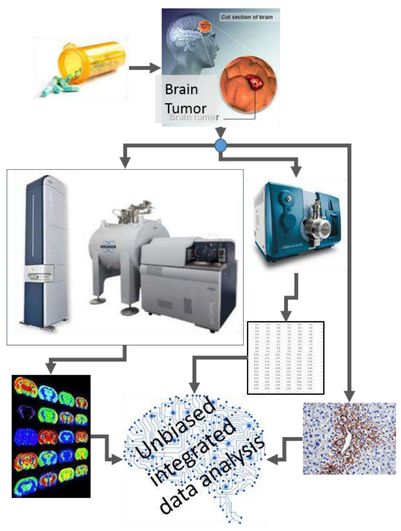
Task 3 –

Quantitative spatially resolved PK-PD relationships by simultaneous MS Imaging of small molecule inhibitors and suitable metabolites as PD markers



Task 4 –

Translational research on metabolite patterns relating to resistance in patients:
Identification of novel metabolic signatures associated with resistance or response using untargeted MSI in tumor specimens from UNITE-accessible clinical cohorts



WORKFLOW

a) Treatment of glioma mice and human glioblastoma in bioreactor with radiation, small molecule drugs or immunotherapies.

b) Targeted MALDI-MS Imaging for distribution of drugs and known amino acid metabolites; LC-MS/MS for their quantification.

c) Multivariate statistical analysis of integrated MSI- and LC-MS/MS- datasets.

d) Translate to primary human glioblastoma resectates.

a) Treatment of glioma mice and human glioblastoma in bioreactor with small molecule drugs targeting amino acid metabolism.

b) Untargeted “as many metabolites as possible” MALDI-MSI (and IHC to visualize drug targets)

c) Employ machine learning to extract putative metabolite patterns that indicate drug response or resistance

a) Treatment of glioma mice and human glioblastoma in bioreactor with innovative small molecule drugs targeting amino acid metabolism.

b) Untargeted as well as targeted quantitative MALDI-MSI (and LC-MS/MS for reference quantification)

c) Visualize drug and response distribution by quantitative MSI

a) Untargeted MALDI-MSI (supported by LC-MS/MS) and IHC of glioma patient samples (e.g. N2M2, INFORM, AMPLIFY-NEOVAC cohorts)

b) Machine learning to extract metabolite patterns that may indicate drug response or resistance in patient tissue

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DFG