SFB 1389 UNITEGLIOBLASTOMA

FOCUS A – TUMOR INTRINSIC MECHANISMS

FOCUS B – TUMOR MICRO-ENVIRONMENT

FOCUS C – TECHNOLOGICAL INNOVATION

FOCUS D – UNITE CORES

C01 – COMPREHENSIVE PRECLINICAL PHARMACOLOGY TESTING OF DRUGS USED FOR GLIOBLASTOMA TREATMENT IN CHILDREN AND ADULTS

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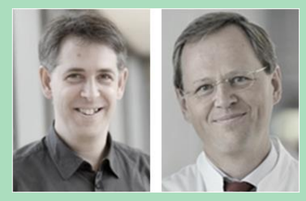


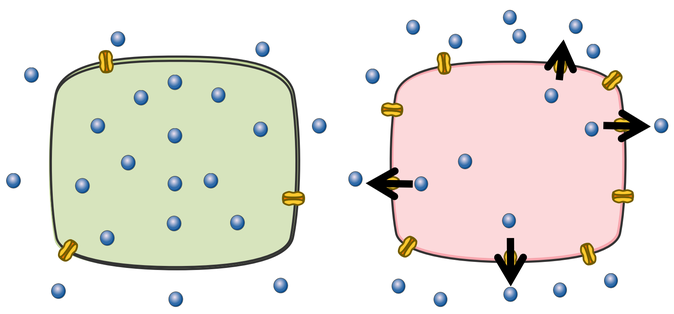
SUMMARY

This project aims to comprehensively assess the tumor exposure of drugs & biologicals commonly used for the treatment of adult and pediatric glioblastoma in order to preclinically prioritize and de-prioritize drugs & biologicals (and combinations thereof) based on their pharmacological properties and thus suitability for the treatment of patients with brain tumors. We will utilize a large spectrum of methodologies and the UNITE Core Collection of orthotopic preclinical models of different molecular subgroups of glioblastoma (genetic mouse models with an intact immune system and patient-derived xenograft models transplanted into immunodeficient mice). This information will be integrated with molecular information including immune microenvironment, the transportome, imaging information, and response evaluation in the same models.

TASK

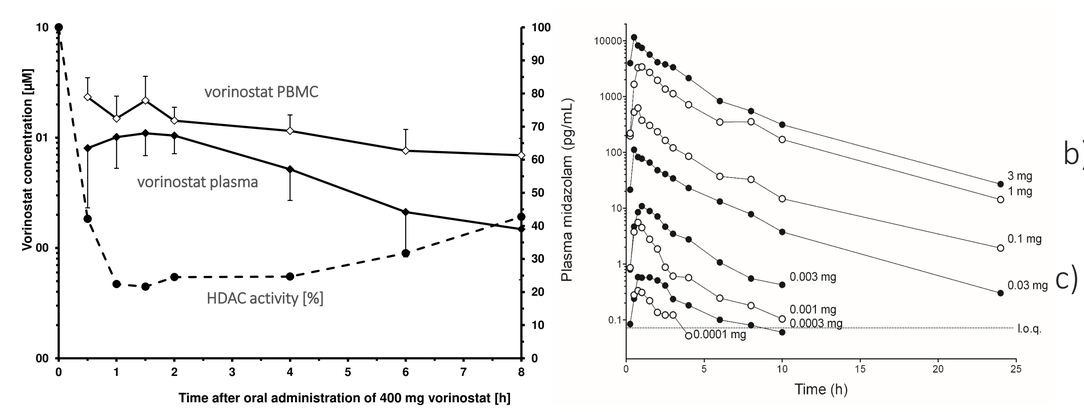
Task 1 –

Selection of antineoplastic drug candidates on the basis of their *in silico* and *in vitro* characteristics



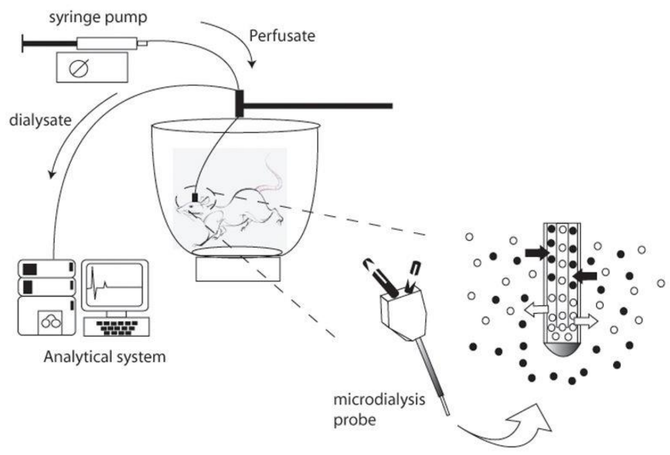
Task 2 –

Ultrasensitive quantification of candidate drugs against glioblastoma using validated UPLC-MS/MS and QTOF methods



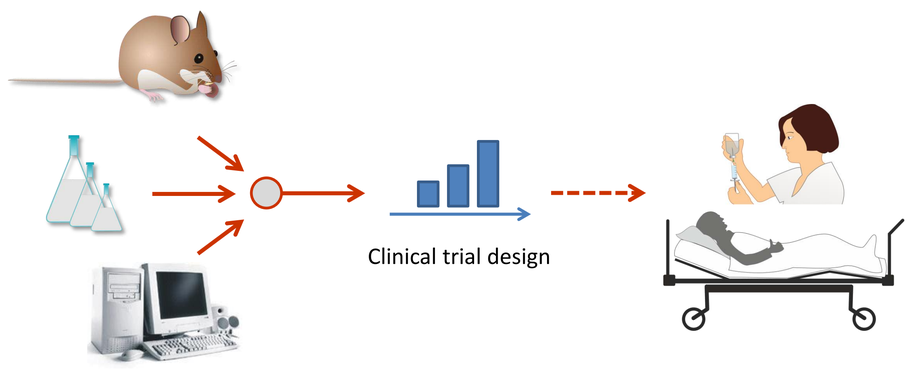
Task 3 –

In vivo assessment of disposition and effect of promising antineoplastic drug candidates in mice



Task 4 –

Integrative analysis of the results of tasks 1-3 and development of at least one clinical trial design



WORKFLOW

a) in silico pre-selection of promising drug candidates against brain tumours
b) in vitro permeability screening with growth inhibition assays
c) validation of screening results with specific uptake/efflux assays

a) FDA/EMA-compliant development of validated assays for quantification of drugs in relevant biological matrices
b) quantification of drug exposure at the site of action
c) pharmacokinetic analysis of drug candidates

a) in vivo assessment of drug disposition using brain and intratumour microdialysis, plasma, CSF, and tissue samples (blood-brain permeability)
b) definition of concentration-effect relationship (tumour response, efficacy, potency, and tolerability)

a) identification of target indication
b) allometric scaling
c) development of study design and dosing schedule
d) preparation of scientific advice by competent authority