Methods: Rats were intra-cranially injected with GBM F98 cells. Seven days later, TTFields (100kHz) or heat were applied to the rat's head. After 72h, rats were i.p. injected with PTX and TTFields administration continued for another 24h. 48h after end of TTFields the Ki67 tumor cell status was determined by immunofluorescence. 96h after TTFields application the tumor volume was analyzed with MRI. 4-8 rats were assessed per group.
Results: The tumor volume increase in rats combined treated with TTFields and PTX was significantly reduced compared to the controls or the single TTFields and PTX applications. These data point to an opening of the BBB by TTFields, allowing PTX to target tumor cells. In addition, a significantly reduced Ki67/DAPI ratio in rats combined treated with TTFields and PTX compared to TTFields alone was seen, accompanied by a strongly reduced proliferation rate of tumor cells in the combination.
Conclusions: TTFields (100kHz) in rats led to alterations in BBB permeability and enabled the BBB-impermeable drug PTX to reach the rat's brain to target GBM brain tumors *in vivo*. Hence, TTFields are a possible clinical approach to enable drug delivery through the BBB for treatment of CNS disorders, which should be further investigated.

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DEXAMETHASONE TREATMENT LIMITS EFFICACY OF RADIATION, BUT DOES NOT INTERFERE WITH GLIOMA CELL DEATH INDUCED BY TUMOR TREATING FIELDS

B. Linder [1], A. Schiesl [1], M. Voss [2], F. Rödel [3], S. Hehlgans [3], Ö. Güllülü [3], V. Seifert [4], D. Kögel [1], C. Senft [4], D. Dubinski [5]. [1] *Uniklinik Frankfurt, Experimental Neurosurgery, Frankfurt, Germany;* [2] *Uniklinik Frankfurt, Dr. Senckenberg Institute of Neurooncology, Frankfurt, Germany;* [3] *Uniklinik Frankfurt, Department of Radiotherapy and Oncology, Frankfurt, Germany;* [4] *Uniklinik Frankfurt, Neurosurgery, Frankfurt, Germany;* [5] *Uniklinik Frankfurt, Klinik für Neurochirurgie, Germany*

Background: Dexamethasone (Dex) is the most common corticosteroid to treat edema in glioblastoma (GBM) patients. Recent studies identified the addition of Dex to radiation therapy (RT) to be associated with poor survival. Independently, Tumor Treating Fields (TTFields) provides a novel anti-cancer modality for patients with primary and recurrent GBM. Whether Dex influences the efficacy of TTFields, however, remains elusive.
Methods: Human GBM cell lines MZ54 and U251 were treated with RT or TTFields in combination with Dex and the effects on cell counts and cell death were determined via flow cytometry. We further performed a retrospective analysis of GBM patients with TTFields treatment +/- concomitant Dex and analysed its impact on progression-free (PFS) and overall survival (OS).
Results: The addition of Dex significantly reduced the efficacy of RT in U251 and MZ54 cells. TTFields (200 kHz/250 kHz) induced massive cell death in both cell lines. Concomitant treatment of TTFields and Dex did not reduce the overall efficacy of TTFields. Further, in our retrospective clinical analysis, we found that the addition of Dex to TTFields therapy did not influence PFS nor OS.
Conclusion: Our translational investigation indicates that the efficacy of TTFields therapy in patients with GBM and primary GBM cell lines is not affected by the addition of Dex.

BRAIN AND SPINE 1 (2021) 100307 100538
INTRA-OPERATIVE MICRODIALYSIS FOR TUMOR BIOMARKER DISCOVERY–A CANDIDATE PLATFORM FOR ACCELERATED PHARMACODYNAMIC FEEDBACK

T. Burns [1], K. Rajani [1]. [1] *Mayo Clinic, Rochester, United States*

Background: Progress for gliomas is slowed in part by the paucity of mechanistic feedback during teatment with experimental therapies. Access to CSF or extracellular tumor pharmacodynamic biomarkers could provide an avenue to accelerate progress. We have initiated a program of intra-operative microdialysis to accelerate biomarker discovery and to identify candidate outcome measures for translational therapies.
Methods: Intraoperative microdialysis was performed with M-dialysis 100kDA catheters and 107 variable rate pumps under an IDE. Four IDH-mutant and two IDH-WT lesions were studied intraoperatively with 3 divergently placed catheters. Microperfusate (artifical CSF + 3% dextran) was perfused at 2uL/min and collected in 20 min increments. Paired CSF was also obtained when accessible. A parallel cohort of nude mice bearing human IDH-mutant (GBM164), IDH-WT (GBM12), or sham intracranial xenografts (n=9-18) underwent intratumoral microdialysis. A pilot murine study of intracranial drug delivery was performed via concurrent microdialysis during convection-enhanced delivery (CED) of saline or the IDH-inhibitor AG120.
Results: Microdialysate from IDH-mutant intracranial xenografts revealed >100 differentially abundant metabolites compared to sham or IDH-WT tumors, including D2-HG (21x) and MTA (18x), 2-O'methylcytidine (5x) and DMA (4x), $p<1x10^{-7}$). 15-1000nM D2-HG was recovered from intra-operative human IDH-mutant tumors with highest levels in non-enhancing tumor regions; 1-2nM from normal brain adjacent to IDH-mutant gliomas and <1nM in all IDH-WT samples. CSF D2-HG were also elevated in IDH-mutant gliomas, but microdialysate D2-HG exceeded CSF D2HG by >10x. Serial aliquots of microdialysate during saline CED yielded steady D2-HG levels whereas CED with AG120 yielded undetectable D2-HG within 6 hours.
Conclusion: The extracellular metabolic landscape of glioma is diverse, dynamic and reflects tumor biology and response to therapy. Collectively, these studies suggest that intra-tumoral drug testing should be feasible with realistic expectation of gaining metabolic feedback–potentially even within a single day. Leveraging this paradigm may provide opportunities to accelerate therapeutic translation for gliomas.

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^{18}F-FET PET IMAGING FOLLOWING IMMUNOTHERAPY WITH DC VACCINATION IN GLIOBLASTOMA PATIENTS

M. Rapp [1], A. Stamtsis-Datsi [2], J. Felsberg [3], N. Galldiks [4], K.-J. Langen [5], R. Dorf [2], M. Sabel [1]. [1] *Heinrich Heine University Duesseldorf, Neurosurgery, Duesseldorf, Germany;* [2] *Heinrich Heine University Duesseldorf, Institute for Transplantation Diagnostics and Cell Therapeutics, Duesseldorf, Germany;* [3] *Heinrich Heine University Duesseldorf, Neuropathology, Duesseldorf, Germany;* [4] *University of Cologne, Neurology, Cologne, Germany;* [5] *Institute of Neuroscience and Medicine (INM-3, -4), Jülich, Germany*

Objective: In the ongoing phase-II GlioVax trial, patients with newly diagnosed glioblastoma are treated with DC vaccination as add-on to standard chemoradiation after surgery. Due to the multimodal therapy, the specificity of contrast-enhanced MRI to differentiate between tumor recurrence and treatment-related changes is low. We examined the diagnostic value of O-(2-[^{18}F]-Fluoroethyl)-L-Tyrosine (^{18}F-FET) PET for this important differentiation.
Methods: Patients with progressive MRI findings underwent additional ^{18}F-FET PET imaging. Treatment-related changes on ^{18}F-FET PET were considered if the mean tumor-to-brain ratio was $\leq$ 2.0. Subsequently, MRI and ^{18}F-FET PET findings were correlated with the clinicoradiological follow-up or neuropathological findings.
Results: Seventeen patients (n=10 vaccinated patients; n=7 control group) received 23 additional ^{18}F-FET PET scans (n=14 scans in vaccinated patients). In vaccinated patients, the median time between radiotherapy completion and progressive MRI was 6 months (range, 1-18 months). In the control group, the median time to MRI progression was 2 months (range, 1-7 months).
In 8 ^{18}F-FET PET scans (4 vaccinated patients,4 patients with standard therapy) PET and MRI were congruent indicating tumor progression. Further treatment: Vaccinated patients: 2 were referred to best supportive care, in two patients a re-resection was performed (NP diagnosis: 1: therapy induced changes; 1: recurrent tumor). Control group: one patient was referred to best supportive care, in 3 patients a re-resection was performed and tumor recurrence was confirmed.
In contrast to MRI, findings of 15 ^{18}F-FET PET scans (performed in 10 vaccinated patients, and in 5 patients with standard therapy) were consistent with treatment-related changes and the patients remained stable for at least 3 months.
Conclusions: Following multimodal therapy including DC vaccination, treatment-related changes occurred more often and later than in patients undergoing standard therapy. Additional ^{18}F-FET PET imaging is helpful to distinguish tumor progression from treatment-induced changes related to the applied multimodal therapy including DC vaccination.

BRAIN AND SPINE 1 (2021) 100307 100540
SYNTHESIS OF NOVEL THIORIDAZINE DERIVATES: IN-VITRO CYTOTOXICITY AND ANTICANCER EFFECT ON GLIOBLASTOMA

S. Schwab [1,2], K. Sarnow [1], E. Alme [3], H.-R. Bjørsvik [3], R. Bjerkvig [1,4]. [1] *University of Bergen, Department of Biomedicine, Bergen, Norway;* [2] *University of Cologne, Department of Neurosurgery, Cologne, Germany;* [3] *University of Bergen, Department of Chemistry, Bergen, Norway;* [4] *Luxembourg Institute of Health, Department of Oncology, Strassen, Luxembourg*