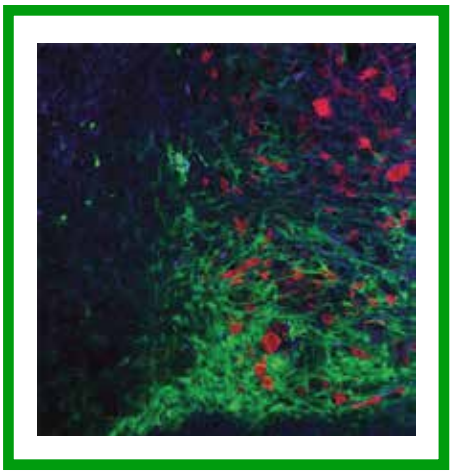
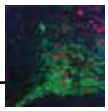
Brain Tumor 2015



Program and Abstracts
(Plenaries, Orals and Posters)

May 28 - 29, 2015

Campus Berlin-Buch
Max Delbrück Communications Center (MDC.C)
Robert-Rössle-Str. 10
D-13125 Berlin



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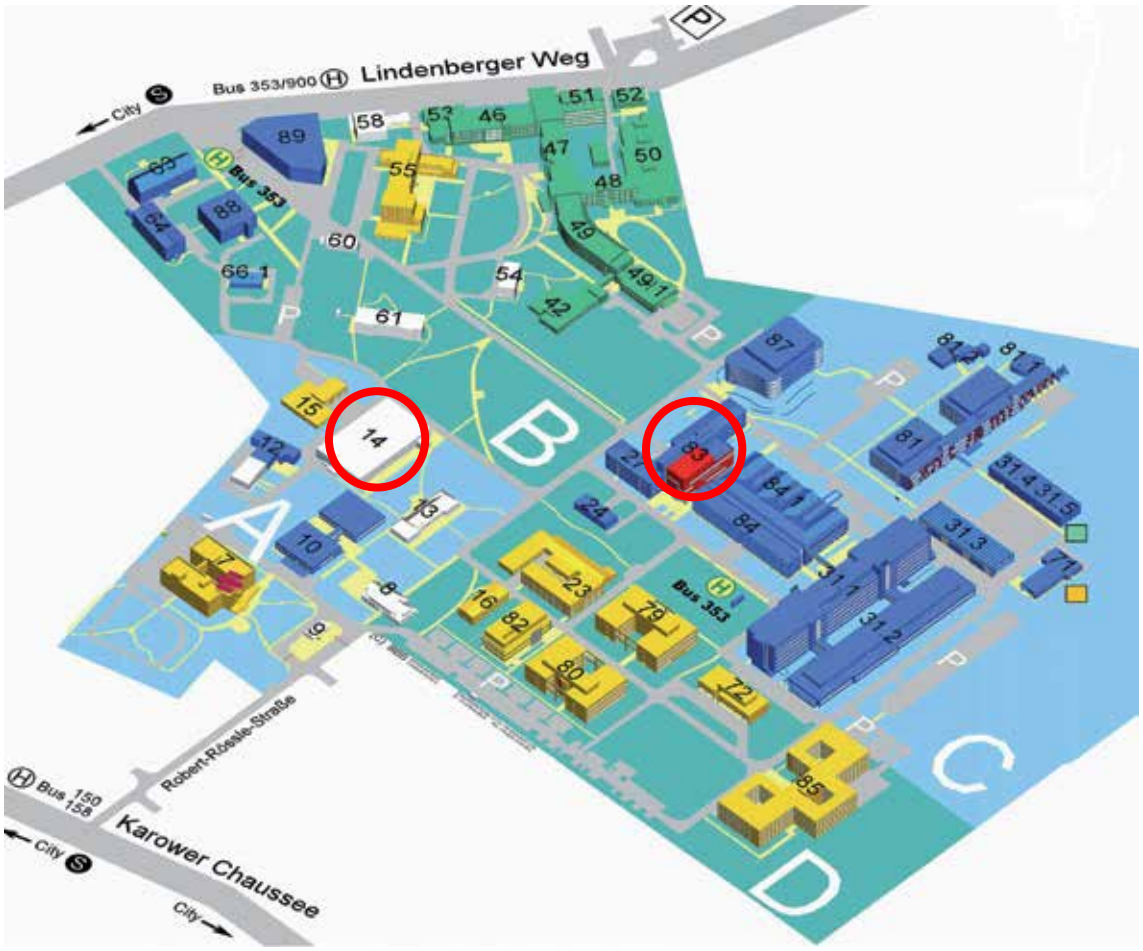

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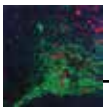

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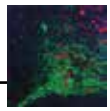

Acknowledgement

We gratefully acknowledge the financial support of the following sponsors:

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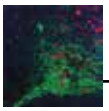
SFB TRR 43 The Brain as a Target of Inflammatory Processes



Scientific Program

Thursday, May 28, 2015

14.00 – 14.05 Welcome Address: Helmut Kettenmann

14:05 – 15:25 Session I
Chair: Helmut Kettenmann

14:05 – 14:45 **Plenary Lecture I**
Kenneth D. Aldape *(University of Texas MD Anderson Cancer Center, Houston, USA)*
Molecular classification of brain tumors

14:45 – 15:05 **Oral Presentation I**
Carsten Hagemann *(Department of Neurosurgery, University of Würzburg, Germany)*
MACC1 regulates migration and invasion of glioblastoma cells

15:05 – 15:25 **Oral Presentation II**
Roland Friedel (Icahn School of Medicine at Mount Sinai, New York, USA)
Plexin-B2 promotes invasive growth of malignant glioma

15:25 – 16:00 Poster Session and Coffee Break

16:00 – 17:20 Session II
Chair: Peter Vajkoczy

16:00 – 16:40 **Plenary Lecture II**
David H. Gutmann *(Washington University School of Medicine, St. Louis, USA)*
Defining the basis of clinical heterogeneity in pediatric brain tumors

16:40 – 17:00 **Oral Presentation III**
Fredrik Swartling *(Immunology, Genetics and Pathology, Uppsala University, Sweden)*
Metastatic tumor recurrence from rare SOX9-positive cells in medulloblastoma

17:00 – 17:20 **Oral Presentation IV**
Luca Tiberi (IRIBHM, ULB, Brussels, Belgium)
A BCL6/BCOR/SIRT1 complex triggers neurogenesis and suppresses medulloblastoma by repressing SHH signaling

17:20 – 17:40 Coffee Break and Poster Session

17:40 – 19:00 Session III
Chair: Frank Heppner

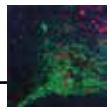
17:40 – 18:20 **Plenary Lecture III**
Claudia Petritsch *(University of California, San Francisco, USA)*
Targeting cell division mode regulation in glioma stem cells

18:20 – 18:40 **Oral Presentation V**
Florian Siebzehnrubl *(European Cancer Stem Cell Research Institute, Cardiff University, Cardiff, UK)*
Disparate radiation response of slow proliferating glioblastoma initiating cells

18:40 – 19:00 **Oral Presentation VI**
Lisa Sevenich *(Memorial Sloan Kettering Cancer Center, New York, USA)*
Analysis of tumor- and stroma-supplied proteolytic networks reveals a brain-metastasis-promoting role for cathepsin S

19:15 – 20:00 Bus Transfer to Berlin Museum of Medical History / Charité

20.00 Reception in the Berlin Museum of Medical History / Charité



Friday, May 29, 2015

9:00 – 10:00 Session IV
Chair: Michael Synowitz

9:00 – 9:40 **Plenary Lecture IV**
Harald W. Sontheimer *(Neurobiology Research Center, University of Alabama at Birmingham, USA)*
A neurocentric look at tumor invasion

9:40 – 10:00 **Oral Presentation VII**
Etty Benveniste *(Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, USA)*
Exploiting therapeutic macrophages against glioblastoma growth

10:00 – 10:30 Poster Session and Coffee Break

10:30 – 11:30 Session V
Chair: Susanne Wolf

10:30 – 11:10 **Plenary Lecture V**
Nader Sanai *(Barrow Brain Tumor Research Center, Phoenix, USA)*
Human glioma infiltration of an adult neural stem cell nich

11:10 – 11:30 **Oral Presentation VIII**
Bozena Kaminska *(Laboratory of Molecular Neurobiology, Neurobiology Center, Nnecki Institute, Warsaw, Poland)*
Glioblastoma misuse macrophage activating signals to shape the proinvasive, immunosuppressive microenvironment

11:30 – 13:30 Lunch (Cafeteria) and Poster Session

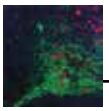
13:30 – 14:50 Session VI
Chair: Jürgen Kiwit

13:30 – 14:10 **Plenary VI**
Stefan Pfister *(German Cancer Research Center Heidelberg, Germany)*
Genomics entering the clinical stage - new diagnostic and therapeutic options in neurooncology

14.10 – 14:50 **Plenary Lecture VII**
Erwin G. Van Meir *(Winship Cancer Institute of Emory University, Atlanta, USA)*
BAI1 is a brain-specific tumor suppressor and regulates spatial learning and memory

14:50 – 15:00 Awarding of Poster Prizes

15:00 Departure



List of Plenary Lectures

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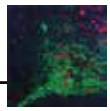


Abstracts of Plenary Lectures

DEFINING THE BASIS OF CLINICAL HETEROGENEITY IN PEDIATRIC BRAIN TUMORS

David H. Gutmann
Washington University School of Medicine, St. Louis, USA

Solid cancers represent complex ecological systems composed of neoplastic and non-neoplastic cell types. The interdependence of these cellular components is nicely illustrated by the benign nervous system tumors arising in the neurofibromatosis type 1 (NF1) cancer predisposition syndrome. In this regard, 15-20% of children with NF1 develop low-grade neoplasms affecting the optic nerve, frequently leading to visual decline. These optic gliomas can be modeled in genetically-engineered mouse (GEM) strains, revealing new cellular and acellular elements in the tumor ecosystem amenable to therapeutic targeting. Dr. Gutmann will use Nf1 GEM models of optic glioma to illustrate their unique cellular and molecular topology as well as the presence of a new neoplastic cellular species (cancer stem cells) germane to the management of children with low-grade glial neoplasms.

TARGETING CELL DIVISION MODE REGULATION IN GLIOMA STEM CELLS

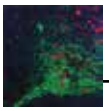
Robin Lerner, Ian Meyers, Banafsheh Kadkodhaei, Stefan Grossauer, Charles David James*, Claudia Petritsch
*Department of Neurosurgery, Brain Tumor Research Center, University of California San Francisco, *Feinberg School of Medicine, Northwestern University, Chicago, Illinois*

Despite aggressive standard and novel targeted therapies, malignant gliomas recurinvariably and develop therapy resistance. It is our broad goal to contribute to the development of novel treatment approaches for malignant glioma. Within this aim, we address if asymmetric cell divisionsof stem and progenitor cells are a point of disruption to which novel therapies can be targeted. Our previous studies have shown that oligodendrocyte progenitor cells (OPCs) undergo asymmetric cell division whereby they generate self-renewing and differentiating cells in a single division by unequally segregating cell fate determinants. We found that premalignant OPC, the origin of glioma in genetically engineered mouse models, exhibit disrupted asymmetric divisions, together with other hallmarks of cancer, including hyper-proliferation(Sugiarto et al., 2011, Cancer Cell 20:328-40). Yet, it is not clear whether disruption of asymmetricdivision of OPCs is a contributing factor or a consequence of neoplastic transformation. Lethal giant larvae 1 (Lgl1), a gene that was initially identified as a tumor suppressor in Drosophila, has been implicated in the asymmetric localization of cell fate determinants in neural progenitor cells (Klezovitch et al., 2004, Genes Dev 18:559-571). We investigated the effects of Lgl1 depletion on distinct hallmarks of glioma. We find that in murine OPC carrying conditional null alleles of Lgl1, depletion of Lgl1 resulted in reduced rates of asymmetric cell division and other defects previously associated with glioma precursors. Our data suggest that loss of asymmetric divisions contribute to neoplastic transformation. Underlying mechanisms for the phenotypes of Lgl1 knockout and their relevance for malignant glioma will be discussed. Stem-like glioma cells, frequently referred to as cancer stem cells (CSC) are culprits for recurrence due to their intrinsic resistance to standard therapy and their ability to regrow the parental tumor in xenografts. We recently began to investigate CSC responses to novel targeted therapies, in specifically, small molecule inhibitors of BRAFV600E, a mutant kinase frequently found in pediatric malignant astrocytoma. Similar to normal neural stem cells CSCs self-renew through symmetric and asymmetric cell divisions (Lathia, JD. et al, Cell Death Dis, 2011, 2 e200).Our investigations showed that CSCs have higher asymmetric cell divisions than progenitor-like glioma cells. We find that the mitotic checkpoint kinase and polarity regulator Plk1 is more active in CSCs and links asymmetric division and mitotic entry. Ongoing work is investigating if Plk1 controls a polarity checkpoint, the integrity of which is especially important in the therapy–evasive compartment in GBM and that provides a rationale for combination therapy.

GENOMICS ENTERING THE CLINICAL STAGE - NEW DIAGNOSTIC AND THERAPEUTIC OPTIONS IN NEUROONCOLOGY

Stefan M. Pfister
German Cancer Research Center (DKFZ) and University Hospital Heidelberg, Germany, s.pfister@dkfz.de

Background:Despite substantial progress in treating primary brain tumors, accurate classification of some entities at the time of diagnosis and relapses from high-risk entities remainmajor clinical challenges. To this end, we have developed two programs on a national level addressing these topics, namely Molecular Neuropathology 2.0 (MNP2.0) for the accurate classification of CNS tumors and the INFORMregistry study (INdividualized therapy FOr Relapsed Malignancies in Childhood), which is attempting to rapidly generate molecular profiles and identify therapeutic targets in a clinical diagnostic environment for relapse patients. Methods:In MNP2.0, DNA methylation fingerprints, which are thought to closely reflect the cell of origin, are used to accurately classify brain tumors into biologically and clinically meaningful subgroups. Amongst a total of 10.000 analyzed CNS tumor specimens, we have established a reference set of 2200 samples with very good histopathological and clinical annotation covering 70 different entities and subgroups. This reference is now being used for an individual sample as a comparison to identify the class with the best fit. A web interface to make this reference dataset available to the community is currently being built. The INFORM pilot phase assessed the feasibility of integrating rapid molecular profiling in the clinical management of pediatric cancer patients with progressive or relapsed high-risk malignancies. Whole-exome andlow-coverage whole-genome sequencing was performed on tumor and normal DNA, complemented with matchedtumor RNAsequencing (Illumina HiSeq2500, 'rapid' mode). This allowed reliable detection of copy-number changes, point mutations, InDels, fusion genes and deregulated gene expression. Identified alterations were prioritized according to tumor biological relevance and potential as an actionable drug target, with resultsdiscussed ina weekly moleculartumor board composed of clinicians, scientists and pharmacists. Results:First evidence from ~1000 diagnostic cases within the MNP2.0 study suggests that in about 10% of cases the histopathological diagnosis will be changed in a way that affects clinical management of the patient. In about an additional 20% of cases, the diagnosis is refined by revealing a meaningful subgroup that cannot be established by conventional neuropathology alone (e.g., molecular subgroup of medulloblastoma or ependymoma). Ongoing round robin experiments with other centers indicate that the methodology is very robust and it is very well feasible to establish this diagnostic pipeline at other centers. In 2015, a population-based study is starting, which will enable all pediatric brain tumor patients across Germany to benefit from this new diagnostic aid.From Oct 2014 to Jan 2015, 57 patients (average age 13 years) were enrolled from >20 centers throughout Germany in the INFORM pilot phase.Tumor tissue was sufficient for DNA analysis of 52 cases and RNA-seqof 47. The average turnaround time from tissue arrival to molecular results was 25 days. Actionable targets with at least 'borderline' evidence (according to a prioritization score harmonized with the other major pediatric precision oncology programs across Europe) were identified in 28 patients (49%). Based on the findings, targeted therapeuticswere incorporated in the treatment regime of several patients, with anecdotal reports of marked responses. Conclusion: Nationwide diagnostic and individualized treatment approachesforneurooncology patients based on rapid methylation profiling and next-generation sequencing is feasible. Through MNP2.0 we have already analyzed more than 1.000 CNS tumor samples prospectively and find changes or refinement of the diagnosis in about one third of cases, which seems to be a good justification for the effort.The results of our INFORM pilot phase show that actionable targets can be identified in roughly half of the patients. The INFORM registry study has now opened (www.dkfz.de/en/INFORMaiming for collecting all molecular information and establishing the required infrastructure for a prospective clinical trial on personalized pediatric oncology.



HUMAN GLIOMA INFILTRATION OF AN ADULT NEURAL STEM CELL NICHE

Yael Kusne, Ph.D., Ning Su, Ph.D., Sandy Hemdan, Ph.D., Zaman Mirzadeh, M.D., Fu-Dong Shi, M.D, Ph.D.,Nader Sanai, M.D.
Barrow Neurological Institute, Phoenix, Arizona

Background: Mounting evidence suggests a facilitative relationship between gliomas and the subventricular zone (SVZ), a germinal niche that supports proliferation and migration of newborn neurons in humans. Although glioma contact with the SVZ has been offered as evidence for a stem cell origin of the tumor, here, we explore an alternative interpretation – that the SVZ is a preferred migratory route for tumor invasion and a reservoir for glioma stem cells (GSCs). Methods: Using intraoperatively-derived human tissue, we employ a combination of cell culture, FACS-sorting, and immunohistochemistry techniques to characterize human glioma and GSC homing to the SVZ, as well as identify new, targetable cytokine pathways relevant to this niche. Results: Our analysis identifies glioma cells homing to human SVZ and co-opting the gap layer for tangential migration. Interestingly, we find that human SVZ-invasive glioma cells are 50-fold more likely to function as glioma stem cells. Organotypic slice culture and co-culture assays also identify chemotactic effects, associated integrins, and related extracellular matrix proteins of 3 SVZ-enriched ligands (EGF, PDGF-BB, and SDF1) known to drive pro-migratory glioma pathways. Conclusions: Despite its quiescence, the adult human SVZ retains the signaling machinery to support cell migration and these mechanisms may be co-opted by glioma stem cells during subependymal spread in humans.

GLIOMA: A „NEUROCENTRIC" PERSPECTIVE ON CANCER

Harald Sontheimer
Center for Glial Biology in Medicine & Department of Neurobiology, University of Alabama Birmingham

Glioma arise from the malignant transformation of neural stem cells, glial cells, or their progenitors. they share many genetic mutations in tumor suppressor and oncogenes with other systemic cancers. However, Glioma cells may have even more in common with the brain cells they originate from. For example, gliomas never leave the nervous system but form secondary tumors almost exclusively within the brain and spinal cord. They do so through active cell migration rather than passive hematogenous spread which is common in systemic cancers. Invading Glioma cells utilize the same extracellular routes navigated by neural and glial stem cells. Dynamic regulation of cell volume through the channel mediated secretion of ions facilitates cell movement through the narrow extracellular brain spaces. As is the case with neural stem cells, migration of cells frequently occurs along blood vessels. Such perivascular invasion causes a displacement of astrocytic endfeet from blood vessels which is associated with a loss of tight junction proteins and a break down of the blood brain barrier. This in turn permits leakage of blood born molecules, toxins and immune cells, culminates in recruitment of microglia and significant brain inflammation and edema. Gliomas ultimately expand at vessel branch points, and their growth within a dense tissue mass is enabled by assiduous glutamate release which causes overactivation of neuronal Glutamate receptors that manifest as seizures and extensive excitotoxic neuronal cells death. Taken together, the progression of Glioma from mutated stem cell to deadly diseases is akin to other neurodegenerative diseases in that gliomas inflict progressive neurodegeneration, seizures, inflammation, vascular changes and edema, the hallmarks of neurodegenerative disease.

BAI1 IS A BRAIN-SPECIFIC TUMOR SUPPRESSOR AND REGULATES SPATIAL LEARNING AND MEMORY

Erwin G. Van Meir
Departments of Neurosurgery and Hematology and Medical Oncology, Winship Cancer Institute and School of Medicine, Emory University, Atlanta, Georgia, USA

Brain-specific Angiogenesis Inhibitor 1 (BAI1) is a seven transmembrane G protein-coupled receptor (GPCR) with potent anti-angiogenic and anti-tumorigenic properties in gliomas.1-6We now found that BAI1 expression is reduced in human medulloblastoma (MB) by epigenetic mechanisms,involving methylated DNA binding protein MBD2 and histone methylaseEZH2. Restoration of BAI1 expression reduced MB cell proliferation and tumor growth in mice xenografts. Targeting MBD2 and EZH2 with small molecules reactivated BAI1 expression, and suppressed tumor growth, supporting the use of epigenetic therapeutics against MB. To more directly examine whether loss of BAI1 expression may favor tumor development during cerebellar development, we generated a Bai1 knockout (KO) mouse. We detected a thicker external granular layer (EGL) during early postnatal cerebellum development, which was accompanied by increased proliferation in cGNPs and aberrant activation of Sonic hedgehog signaling. Bai1 loss was not sufficient to initiate tumorigenesisper se, but dramatically accelerated MB tumorigenesis when crossed to mice heterozygous for patched 1 (ptc1+/-), and we are exploring the underlying mechanisms. Further characterization of the Bai1-/-mice showed that they have severe deficits in hippocampus-dependent spatial learning and memory, accompanied by enhanced long-term potentiation (LTP), impaired long-term depression (LTD), and a thinning of the postsynaptic density (PSD) at hippocampal synapses.7They exhibited reduced levels of PSD-95, a canonical PSD component, which stemmed from protein destabilization. We foundthat BAI1 interacted with MDM2, an E3 ubiquitin ligase that regulates PSD-95 stability, and preventeditspolyubiquitination and degradation. Adeno-associated viral gene transfer of PSD-95 was sufficient to normalize synaptic plasticity in hippocampal neurons of Bai1-/- mice, e.g. rescue their ability to modulate the strength of neuronal connections. Altogether, our findings provide insight into the physiological function of BAI1 in the brain, including neurobiological mechanisms underlying synaptic function and suppression of medulloblastoma formation in the cerebellum.

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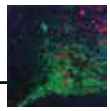
7.Zhu D, Li C, Swanson AM, et al. BAI1 regulates spatial learning and synaptic plasticity in the hippocampus. J Clin Invest. 2015;125:1497-1508.



List of Oral Presentations selected from Abstracts

Benveniste, Etty
Cell, Developmental and Integrative Biology, University of Alabama at Birmingham, 1900 University Blvd., 35294-0005 Birmingham, USA, tika@uab.edu
EXPLOITING THERAPEUTIC MACROPHAGES AGAINST GLIOBLASTOMA GROWTH
McFarland, B; Benveniste, E.N.
Keywords: macrophages; T-cells; GBM

Friedel, Roland
Department of Neuroscience, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, 10029 New York, USA, roland.friedel@mssm.edu
PLEXIN-B2 PROMOTES INVASIVE GROWTH OF MALIGNANT GLIOMA
Audrey P. Le 1, Yong Huang 1*, Sandeep C. Pingle4, SantoshKesari4, Huaien Wang 2,3, Raymund L. Yong 2,3, Hongyan Zou 1,2, Roland H. Friedel1,2*
Keywords: glioma invasion; Plexin; glioma vasculature

Hagemann, Carsten
Department of Neurosurgery, University of Würzburg, Josef-Schneider-Str. 11, 97080 Würzburg, Germany, hagemann_c@ukw.de
MACC1 REGULATES MIGRATION AND INVASION OF GLIOBLASTOMA CELLS
C. Hagemann, S. Fuchs, A. F. Kessler, P. Herrmann, J. Smith, T. Hohmann, U. Grabiec, N. Neuhaus, T. Linsenmann, M. Eyrich, F. Dehghani, R.-I. Ernestus, M. Löhr, U. Stein
Keywords: glioblastoma multiforme; MACC1; plasma marker

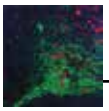
Kaminska, Bozena
Laboratory of Molecular Neurobiology, Neurobiology Center, Nencki Institute, Pasteur 3, 02-093 Warsaw, Poland, bozenakk@nencki.gov.pl
GLIOBLASTOMA MISUSE MACROPHAGE ACTIVATING SIGNALS TO SHAPE THE PROINVASIVE, IMMUNOSUPPRESSIVE MICROENVIRONMENT
Kaminska, B., Wisniewski, P., Ellert-Miklaszewska A., Kijewska M, Gajdanowicz, P., Przanowski P., Gieryng A., Pszczolkowska D.,
Keywords: tumor microenvironment; microglia re-programming; glioma secretome

Sevenich, Lisa
Memorial Sloan Kettering Cancer Center, 417 East 68th Street, 10065 New York, USA, sevenicl@mskcc.org
ANALYSIS OF TUMOR- AND STROMA-SUPPLIED PROTEOLYTIC NETWORKS REVEALS A BRAIN-METASTASIS-PROMOTING ROLE FOR CATHEPSIN S
Sevenich L.; Bowman R.; Mason S., Quail D.; Rapaport F., Brastianos P., Hahn W.; Holsinger L.; Massague J.; Leslie C.; Joyce J
Keywords: brain metastases; tumor microenvironment; proteases

Siebzehnrubl, Florian
European Cancer Stem Cell Research Institute, Cardiff University, Maindy Road, CF24 4HQ Cardiff, UK, fas@cardiff.ac.uk
DISPARATE RADIATION RESPONSE OF SLOW PROLIFERATING GLIOBLASTOMA INITIATING CELLS
Siebzehnrubl FA; Nabilsi N; Pasternack N; Rohaus M; Griffith B; Harding A; Kladde, MP; Reynolds BA; Steindler DA; Deleyrolle LP
Keywords: genomic instability; radiation

Swartling, Fredrik
Fredrik Swartling, Immunology, Genetics and Pathology, Uppsala University, Rudbeck Laboratory, SE-751 85 Uppsala, Sweden, fredrik.swartling@igp.uu.se
METASTATIC TUMOR RECURRENCE FROM RARE SOX9-POSITIVE CELLS IN MEDULLOBLASTOMA
Savov, V.; Cancer, M.; Fotaki, G.; Bolin, S.; Rosén, G.; Dubuc, A.; Remke, M.; Weishaupt, H.; Taylor, M.D.; Swartling, F.J.
Keywords: medulloblastoma; MYCN; recurrence

Tiberi, Luca
IRIBHM, ULB, route de Lennik 808, 1070 Brussels, Belgium, ltiberi@ulb.ac.be
A BCL6/BCOR/SIRT1 COMPLEX TRIGGERS NEUROGENESIS AND SUPPRESSES MEDULLOBLASTOMA BY REPRESSING SHH SIGNALLING
Luca Tiberi, Jérôme Bonnefont, Jelle van den Ameele, Serge-Daniel Le Bon, Adèle Herpoel, Angéline Bilheu, Beverly W. Baron, and Pierre Vanderhaeghen
Keywoards: medulloblastoma; neurogenesis; BCL6/BCOR/SIRT1



Abstracts of Oral Presentations

EXPLOITING THERAPEUTIC MACROPHAGES AGAINST GLIOBLASTOMA GROWTH

Etty (Tika) Benveniste and Braden C. McFarland
University of Alabama at Birmingham, Birmingham, AL 35294

Glioblastoma(GBM), a particularly devastating brain tumor, remains a challenging and difficult disease to treat. On a cellular level, GBM tumors are extremely heterogeneous, consisting of resident tumor cells, tumor initiating cells, infiltrating immune cells, endothelial cells, and other tumor associated stromal cells, which makes developing targeted therapies a challenge. Macrophages are the largest population of infiltrating cells in GBM (10-40% of tumor mass). Depending on the stimuli, macrophages are polarized to an M1 (pro-inflammatory) or M2 (immunosuppressive) phenotype, or can adopt a mixed M1/M2 phenotype. M1 macrophages produce soluble mediators such as IL-12, IL-6, IL-1, TNF-alpha, and iNOS, while M2 macrophages secrete IL-10 and TGF-beta. In the context of GBM, M2 macrophages aid in tumor growth through the secretion of immunosuppressive cytokines. We have generated a mouse model that exhibits a predominant M1 macrophage phenotype, which is due to conditional deletion of the SOCS3 gene in myeloid cells. Using this immunocompetent model, GL261 GBM cells were implanted intracranially, and survival evaluated. In this M1 model of GBM, tumor growth was delayed and increased survival of mice was observed, compared to control mice. This beneficial response was associated with increased numbers of CD8+ T-cells in the tumor, as well as a reduction in T regulatory (Tregs) cells. Further, the number of M2 macrophages infiltrating the tumor was diminished. These findings demonstrate a beneficial effect of M1 polarized macrophages on suppressing GBM tumor growth, and highlight the importance of immune cells in the tumor microenvironment.

PLEXIN-B2 PROMOTES INVASIVE GROWTH OF MALIGNANT GLIOMA

Audrey P. Le 1*, Yong Huang 1*, Sandeep C. Pingle4, SantoshKesari4, Huaien Wang 2,3, Raymund L. Yong 2,3, Hongyan Zou 1,2, Roland H. Friedel1,2
1 Department of Neuroscience, Friedman Brain Institute,2 Department of Neurosurgery, 3Comprehensive Brain Tumor Program,Icahn School of Medicine at Mount Sinai, New York, NY 10029
4 Translational Neuro-Oncology Laboratories, Moores UCSD Cancer Center and Department of Neurosciences, La Jolla, CA 92093

Invasive growth is a major determinant of the high lethality of malignant gliomas. Plexin-B2, an axon guidance receptor important for mediating neural progenitor cell migration during development, is upregulated in gliomas, but its function therein remains poorly understood. Combining bioinformatic analyses, immunoblotting and immunohistochemistry of patient samples, we demonstrate that Plexin-B2 is consistently upregulated in all types of human gliomas and that its expression levels correlate with glioma grade and poor survival. Activation of Plexin-B2 by Sema4C ligand in glioblastoma cells induced actin-based cytoskeletal dynamics and invasive migration in vitro. This proinvasive effect was associated with activation of the cell motility mediators RhoA and Rac1. Furthermore, costimulation of Plexin-B2 and the receptor tyrosine kinase Met led to synergistic Met phosphorylation. In intracranial glioblastoma transplants, Plexin-B2 knockdown hindered invasive growth and perivascular spreading, and resulted in decreased tumor vascularity. Our results demonstrate that Plexin-B2 promotes glioma invasion and vascularization, and they identify Plexin-B2 as a potential novel prognostic marker for glioma malignancy. Targeting the Plexin-B2 pathway may represent a novel therapeutic approach to curtail invasive growth of glioblastoma.

MACC1 REGULATES MIGRATION AND INVASION OF GLIOBLASTOMA CELLS

C. Hagemann1, S. Fuchs1, A. F. Kessler1, P. Herrmann2, J. Smith2, T. Hohmann3, U. Grabiec3, N. Neuhaus1, T. Linsenmann1, M. Eyrich4, F. Dehghani3, R.-I. Ernestus1, M. Löhr1, U. Stein2
1University of Würzburg, Department of Neurosurgery and 4Department of Pediatric Hematology/Oncology
2Experimental and Clinical Research Center, Charité University Medicine Berlin, and Max-Delbrück-Center for Molecular Medicine, Department of Translational Oncology of Solid Tumors
3Martin-Luther-University Halle-Wittenberg, Department of Anatomy and Cell Biology

Recently, we showed that mRNA- and proteinlevels of Metastasis-associated in colon cancer-1 (MACC1) were associated with the WHO grading of gliomas and allowed discrimination of dormant and recurrent low grade astrocytoma and of primary and secondary glioblastoma (GBM). We now confirm overexpression of MACC1 on large sample sets by datamining Oncomine microarray and The Cancer Genome Atlas databases. Endogenous expression of MACC1 was variable in primary cells derived from GBM tumors and the expression levels positively correlated with migration of these cells in a spheroid-assay. MACC1-transfected GBM cells were used for real-time measurements of migration and invasion in conjunction with the Met inhibitor crizotinib. Tumor formation capabilities were evaluated in organotypic hippocampal slice cultures of mice. In these assays MACC1 increased the migratory, invasive and tumor formation abilities of GBM cells, whereas crizotinib caused a reversion back to basal level. Importantly, we were able to detect MACC1 plasma levels by quantitative RT-PCR in GBM patients. The MACC1 concentrations correlated negatively with the prognosis of the patients. We conclude that MACC1 influences migration and invasion of GBM cells potentially by regulation of the hepatocyte growth factor (HGF) receptor Met. Inhibition of MACC1 may be a new therapeutic strategy for the inhibition of GBM cell migration and invasion. Moreover, MACC1 may be a new prognostic plasma marker for GBM patients.

GLIOBLASTOMA MISUSE MACROPHAGE ACTIVATING SIGNALS TO SHAPE THE PROINVASIVE, IMMUNOSUPPRESSIVE MICROENVIRONMENT

Kaminska, B.; Wisniewski, P.; Ellert-Miklaszewska A.; Kijewska, M.; Gajdanowicz, P.; Przanowski, P.; Gieryng, A.; Pszczolkowska, D.; Bocian, K.
Laboratory of Molecular Neurobiology, Nencki Institute of Experimental Biology

Malignant gliomas attract immune brain resident microglia and peripheral macrophages, and re-program these cells into pro-invasive, immunosuppressive cells. It results in formation of tumor supportive microenvironment and evasion of antitumor responses. The analysis of gene expression profiles in CD11b+ cells infiltrating experimental gliomas indicates their polarization to M2 phenotype, and contribution this immune subpopulation to glioma progression. Signals responsible for recruitment and polarization of immune cells in glioblastoma are poorly known. Proteomic analysis of glioma secretome combined with functional assay revealed osteopontin (SPP1) and lactadherin (MGF-E8) as activating factors. Both proteins stimulated primary microglia cultures via integrin signaling that results in activation of PI-3K/Akt and FAK, enhancement of microglial migration, phagocytosis and transcriptional responses. Ostepontin/SPP1, highly overexpressed in glioblastoma, was specifically processed in glioma cells by thrombin and metalloproteinases that results in losing a pro-inflammatory activity leaving intact its pro-tumorigenic activity. Knockdown of SPP1 in glioma cells strongly reduced growth of intracranial gliomas. Interestingly, infiltrating microglia/macrophages did not undergo M2 polarization and were infiltrated with interferon producing, T cytotoxic lymphocytes, while accumulation of T regulatory cells was significantly reduced. This is consistent with restoring anti-tumor responses. The expression of SPP1 was up-regulated in human glioblastoma and inversely correlated with patient's survival. Our findings define osteopontin/SPP1 as a new biomarker and target for glioma therapy, and show that targeting glioma-microglia interactions within the tumor microenvironment could be a promising strategy.

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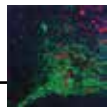


ANALYSIS OF TUMOR- AND STROMA-SUPPLIED PROTEOLYTIC NETWORKS REVEALS A BRAIN-METASTASIS-PROMOTING ROLE FOR CATHEPSIN S

Lisa Sevenich1, Robert L. Bowman1, Steven D. Mason1, Daniela F. Quail1, Franck Rapaport2, Benelita T. Elie1, Edi Brogi3, Priscilla K. Brastianos4,5, Willliam C. Hahn4, Leslie J. Holsinger6, Joan Massague1, Christina Leslie2 and Johanna A. Joyce1
1Cancer Biology and Genetics Program,2Computational Biology Program,3Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, USA, 4Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, USA, 5Division of Hematology/Oncology, Massachusetts General Hospital, Boston, USA, 6Virobay Inc., Menlo Park, USA

Metastasis remains the most common cause of death in most cancers, with limited therapies for combating disseminated disease. While the primary tumor microenvironment is an important regulator of cancer progression, it is less well understood how different tissue environments influence metastasis. We analyzed tumor-stroma interactions that modulate organ tropism of brain, bone and lung metastasis in xenograft models. We identified a number of potential modulators of site-specific metastasis, including cathepsin S as a regulator of breast-to-brain metastasis. High cathepsin S expression at the primary site correlated with decreased brain-metastasis-free survival in breast cancer patients. Both macrophages and tumor cells produce cathepsin S, and only the combined depletion significantly reduced brain metastasis in vivo. Cathepsin S specifically mediates blood-brain barrier transmigration through proteolytic processing of the junctional adhesion molecule, JAM-B. Pharmacological inhibition of cathepsin S significantly reduced experimental brain metastasis, supporting its consideration as a therapeutic target for this disease.

DISPARATE RADIATION RESPONSE OF SLOW PROLIFERATING GLIOBLASTOMA INITIATING CELLS

European Cancer Stem Cell Research Institute, Cardiff University, Maindy Road, CF24 4HQ Cardiff, UK, fas@cardiff.ac.uk
Siebzehnrubl FA, Nabilsi N, Pasternack N, Rohaus M, Griffith B, Harding A, Kladde MP, Reynolds BA, Steindler DA, Deleyrolle LP

Glioblastoma remains the most frequent and lethal of all adult brain tumors. Recurrence after radio- and chemotherapy particularly contributes to poor outcome. Cancer stem cells have been identified as a cellular source that is more resistant to anti-cancer therapy and capable of initiating new tumor growth. We have previously shown that isolating slow proliferating cells from glioblastoma enriches for a population with cancer stem cell properties. Here, we demonstrate that these slow proliferating cancer stem cells are more chemoresistant and invasive than the rest of the tumor population, but surprisingly slow proliferating cells are more sensitive to radiation damage. We find a significant overlap between the slow proliferating compartment and expression of the transcription factor ZEB1, which we have recently identified as a master regulator of stemness and chemoresistance in glioblastoma. Consequently, ZEB1-positive cells also exhibit greater radiosensitivity. Slow proliferating, ZEB1-positive cells accumulate genomic aberrations that result in G2/M retention of these cells, rendering them more sensitive to radiation damage. However, a fraction of cells that survive irradiation respond with a rebound proliferative burst that may result in recurrence of more aggressive tumors. This disparate effect of radiation on cancer stem cells points to a previously underappreciated heterogeneity within the cancer stem cell compartment and may open up new avenues of studying and targeting specific cancer stem cell sub-populations.

METASTATIC TUMOR RECURRENCE FROM RARE SOX9-POSITIVE CELLS IN MEDULLOBLASTOMA

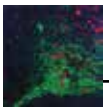
Vasil Savov1, Matko Čančer1, Grammatiki Fotaki1, Sara Bolin1, Gabriela Rosén1, Adrian Dubuc2, Marc Remke2, Vijay Ramaswamy2, Holger Weishaupt1, Michael D. Taylor2 and Fredrik J. Swartling1
1Rudbeck Laboratory, Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Sweden
2The Hospital for Sick Children, Toronto, Canada.

Medulloblastoma (MB) is the most common malignant brain tumor in children in where amplification of theMYCN oncogeneis a marker of poor prognosis. Tumor recurrence after treatment is the main cause of death in MB. Regional differences during relapseoccur within the four defined molecular MB subgroups - SHH tumors recur locally while Group 3 and 4 tumorsdevelop distant metastases. In order to study suchmetastatic recurrence, we used atransgenic mouse model of MYCN-driven Group 3 MB (GTML). The stem cell-associated transcription factor SOX9 is expressed infew scattered cells in GTML tumors and in MYCN-amplified human Group 3 MB.We combined Tet-ON and Tet-OFF inducible systems to target SOX9+ cellsin vivo. Following tumor removal by dox-inducible oncogene depletion, SOX9+cells were able to initiate distant tumor recurrences.Profiling relapsed tumorsusing RNA sequencing identified genes correlating with migration and metastasis but relapsed tumor did not changetheir molecular subgroup.We further showed that cells withincreased levels of SOX9 are more resistant to vincristine treatment and that SOX9 further promotes migration of MYCN-driven MB cells. A similar correlation was found in paired biopsies from Group 3 and Group 4 MB patients in where isolated recurrent metastases had consistently higher SOX9 levels as compared to the correspondingprimary tumor. To summarize,we developed a new model for MB recurrence and showed how rarepopulations of SOX9+ cells are capable of initiating recurrenceafter primary tumor removal. The relapsed MB has similar characteristics as the initial tumor butdevelops at a distant site in the brain, in line with recent data from patients.

A BCL6/BCOR/SIRT1 COMPLEX TRIGGERS NEUROGENESIS AND SUPPRESSES MEDULLOBLASTOMA BY REPRESSING SHH SIGNALLING

Luca Tiberi1, Jérôme Bonnefont1, Jelle van den Ameele1, Serge-Daniel Le Bon1, Adèle Herpoel1, Angéline Bilheu1, Beverly W. Baron2, and Pierre Vanderhaeghen1,3
1 Université Libre de Bruxelles (ULB), WELBIO, Institute for Interdisciplinary Research (IRIBHM), and ULB Institute of Neuroscience (UNI), 808 Route de Lennik, B-1070 Brussels, Belgium. 2 University of Chicago, Dept. of Pathology, Chicago IL 60637. 3 WELBIO, Université Libre de Bruxelles, 808 Route de Lennik, B-1070 Brussels, Belgium.

Disrupted differentiation during development can lead to oncogenesis, but the underlying mechanisms remain poorly understood. One striking example of the tight link between morphogenesis and oncogenesis is medulloblastoma (MB), the most prevalent malignant brain tumor in children. MB are thought to be caused in part by deregulation of WNT and SHH pathways in stem cells during brain development. The SHH medulloblastoma subtype accounts for approximately 25% of MB and are mainly caused by aberrant activation of the SHH pathway in granule neuron precursors (GNP). This cellular population was found to constitute the main cells of origin of SHH medulloblastoma in the mouse. We identified BCL6, a transcriptional repressor as a pivotal factor required for neurogenesis and tumor suppression of SHH MB:
a) BCL6 is required for neurogenesis of cerebellar granule neurons.
b) BCL6 is both necessary and sufficient to prevent the development of GNP-derived MB in the mouse and can block the growth of human MB cells in vitro.
c) BCL6 neurogenic and oncosuppressor effects rely on direct transcriptional repression of Gli1/2 effectors of the SHH pathway, through recruitment of BCOR co-repressor and SIRT1 deacetylase.
Our findings identify the BCL6/BCOR/SIRT1 complex as a potent repressor of the SHH pathway in normal and transformed stem cells, with direct diagnostic and/or therapeutic relevance for SHH medulloblastoma.



List of Poster Presentations

1. a Dzaye, Omar
Cellular Neurosciences, Max-Delbrück-Center for Molecular Medicine, Robert-Rössle-Str. 10, 13092 Berlin, Germany, omar.dzaye@mdc-berlin.de
INTRACELLULAR GLYCINE RECEPTOR FUNCTION FACILITATES GLIOMA FORMATION IN VIVO
Omar Dildar a Dzaye, Benjamin Förstera, Aline Winkelmann, Marcus Semtner, Bruno Benedetti, Ralf P. Friedrich, Darko S. Markovic, Carola Bernert, Michael Synowitz, Peter Wend, Michael Fähling, Erich E. Wanker, Marie-Pierre Junier, Rainer Glass, Helmut Kettenmann and Jochen C. Meier
Keywords: Glycine receptor; Gene regulation; Glioma

2. Alessandrini, Francesco
DIMES, University of Genoa, via Leonbattista Alberti, 16132 Genoa, Italy, francescoalessandrini89@gmail.com
LIVE MONITORING GLIOMA VIROTHERAPY
Alessandrini F.; Appolloni I.; Ceresa D., Menotti L.; Gatta V.; Campadelli G.; Malatesta P.
Keywords: Gliblastoma; Oncolytic virus; EGFRvIII

3. Bäsler, Nadine
EPO GmbH, Robert-Rössle-Str.10, 13125 Berlin, Deutschland, N.Baesler@epo-berlin.com
THERAPEUTIC RESPONSE TO CHEMOTHERAPEUTICS OF GLIOMA-PDX CAN NOT BE CORRELATED TO COMMON MUTATIONS IDENTIFIED BY PANEL SEQUENCING
Orthmann, A.; Hoffmann, A.; Zeisig, R.; Haybäck, J.; Jödicke, A.; Kuhn, S.; Linnebacher, M.; Hoffmann, J.; Fichtner, I.
Keywords: Glioma-PDX; PDX models; onco-mutations

4. Barciszewska, Anna-Maria
Department of Neurosurgery and Neurotraumatology, Poznan University of Medical Sciences, Przybyszewskiego 49, 60-355 Poznan, Poland, abarcisz@man.poznan.pl
BIMODAL ACTION OF TEMOZOLOMIDE IN BRAIN TUMOR CELLS
Barciszewska, A-M; Glodowicz, P; Piwecka, M; Nowak, S.
Keywords: temozolomide; glioma; DNA methylation

5. Barilari, Manuela
Cell biology (Growth and Signalling), INSERM, Bâtiment Leriche - 14 Rue Maria Helena Vieira, 75014 Paris, France, manuela.barilari@inserm.fr
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Barilari, M.; Castel, D.; Grill, J.; Puget, S.; Pende, M.; De Keyzer, Y.
Keywords: DIPG; mTOR signaling

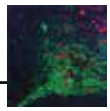
6. Bartsch, Jörg
Neurosurgery, Marburg University, Baldingerstr., 35033 Marburg, Germany, jbartsch@med.uni-marburg.de
THE METALLOPROTEASE-DISINTEGRIN ADAM8 MEDIATES BRAIN METASTASIS OF BREAST CANCER CELLS
Conrad, C; Schlomann, U.; Nimsky, C.; Preston, J.; Kamm, R.; Bartsch, J.W. ?
Keywords: Brain Metastasis; Blood-Brain Barrier; Metalloproteases

7. Baskaran, Sathishkumar
Immunology Genetics and Pathology, Uppsala University, C11:2 Rudbeck Laboratory, 75185 Uppsala, Sweden, sathishkumar.baskaran@igp.uu.se
SYSTEMATIC IDENTIFICATION OF GENE TARGETS IN A BIOBANK OF PATIENT DERIVED GLIOBLASTOMA-INITIATING CELLS
Sathishkumar Baskaran, Patrik Johansson, Caroline Hansson, Torbjörn Nordling, Ludmila Elfineh, Ulf Martens, Maria Häggblad, Bengt WestermarkLene Uhrbom, Karin Forsberg Nilsson, Bo Lundgren, Cecilia Krona, Sven Nelander
Keywords: GBM; RNA interference; High throughput screening

8. Blank, Anne
Institut für Neurochirurgie, Charité Universitätsmedizin Berlin, Charitéplatz 1/ Virchowweg 21, 10117 Berlin, anne.blank@charite.de
THE PRO-ANGIOGENIC PHENOTYPE OF CD11B+ CELLS DEPENDS ON THE CONSTITUTION OF THE MYELOID CELL POPULATION WITHIN HUMAN GLIOMA
Blank, A.; Brandenburg, S.; Schneider, U.; Vajkoczy, P.
Keywords: glioblastoma; microglia; angiogenesis

9. Bolin, Sara
Immunology Genetics and Pathology, Uppsala University, Dag Hammarskjolds vag 20, 75185 Uppsala, Sweden, sara.bolin@igp.uu.se
COMBINED BET-BROMODOMAIN AND CDK2 INHIBITION IN MYC-DRIVEN MEDULLOBLASTOMA
Bolin, S; Persson, C; Borgenvik, A; Qi, J; Weiss, WA; Cho, J-Y; Bradner, JE; Swartling, FJ
Keywords: Medulloblastoma; MYCN; CDK2

10. Brösicke, Nicole
Department of Cell Morphology & molecular Neurobiology, Ruhr-University Bochum, Universitätsstr. 150, 44801 Bochum, Germany, Nicole.Broesicke@rub.de
EXTRACELLULAR MATRIX GLYCOPROTEIN-DERIVED SYNTHETIC PEPTIDES DIFFERENTIALLY MODULATE GLIOMA AND SARCOMA CELL MIGRATION
Nicole Brösicke; Muhammad Sallouh; Lisa-Marie Prior; Albert Job; Ralf Weberskirch; Andreas Faissner
Keywords: Synthetic peptides; Extracellular matrix; Glioblastoma



11. Broggini, Thomas
Neurosurgery, Charité Universitätsmedizin, Charitéplatz 1, Berlin Berlin, Germany, thomas.broggini@charite.de
NDRG1 HIGH GLIOMA EXHIBIT REDUCED VESSEL DENSITY AND SUNITINIB RESISTANCE BY TNF-SF15 UPREGULATION
Thomas Broggini, Marie Wüstner, Lena Stange, Carina Thomé, Wolfgang Wick, Peter Vajkoczy, Marcus Czabanka
Keywords: Glioma angiogenesis; NDRG1; TNFSF15

12. Busek, Petr
Institute of Biochemistry and Experimental Oncology, First Faculty of Medicine, Charles University in Prague, U Nemocnice 5, 12853 Prague 2, Czech Republic, busekpetr@seznam.cz
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Busek, P.; Trylcova, J.; Smetana, K.; Balaziova, E.; Dvorankova, B.; Sromova, L.; Sedo, A.
Keywords: Cancer-associated fibroblasts; Mesenchymal cells; Tumor microenvironment

13. Cancer, Matko
Department of Immunology, Genetics and Pathology, Uppsala University, Dag Hammarskjölds v 20, 751 85 Uppsala, Sweden, matko.cancer@igp.uu.se
A FAST FORWARD GENETICS SCREEN FOR RETROVIRUS-INDUCED BRAIN TUMOURS
Cancer, M.; Weishaupt, H.; Bunikis, I.; Jiang Y.; Bolin, S.; Häggqvist, S.; Gyllensten, U.; Uhrbom, L.; Ameur, A.;and Swartling, F. J.
Keywords: glioma; PDGF; insertional mutagenesis

14. Carro, Maria Stella
Neurosurgery, University of Freiburg, Breisacherstrasse 64, 79106 Freiburg, , maria.carro@uniklinik-freiburg.de
LINEAGE-SPECIFIC SPLICING OF AN ALTERNATIVE EXON OF ANXA7 PROMOTES EGFR SIGNALING ACTIVATION AND TUMOR PROGRESSION IN GLIOBLASTOMA
Carro, M.S.; Ferrarese, R.; Bug, E.; Maticzka, D.; Reichardt, W.; Bredel, M.
Keywords: splicing; angiogenesis; EGFR signaling

15. Chen, Daishi
Neurosurgery, , Schwabachanlage 6, 91054 Erlangen, Germany, cdsginqtbing@hotmail.com
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Chen DS; Fan Z; Buchfelder M; Eyüpoglu I; Savaskan NE
Keywords: CD44; gliomas; angiogenesis

16. Clement-Schatlo, Virginie
Stemergie Biotechnology SA, rue de la roseraie, 1205 Geneva, Switzerland, virginie.clement@stemergie.com
A CSC-PLATFORM FOR DRUG DISCOVERY AND TARGET VALIDATION IN GLIOMA
Vaslin, A.; Marino, D.; Teta, P.; Lembrez, N.; Fessard, T.; Carreira, E. and Clement-Schatlo, V.
Keywords: HTS; cancer stem cell; drug/target discovery

17. Combeau, Gaëlle
Cellular and Molecular Biology (CMB), Karolinska Institut, Nöbel väg 3, 17177 Stockholm, Sweden, gaelle.combeau@licr.ki.se
EXPRESSION LEVEL OF SOX2 IN CANCER STEM CELLS REGULATES GLIOBLASTOMA DEVELOPMENT
Combeau, G.; Karlèn, A.; Kurtsdotter, I.; Muhr, J.
Keywords: Sox2; glioblastoma development; transcription factor

18. Conde, Marina
Section Experimental Neurosurgery/ Tumor Immunology, Department of Neurosurgery. University Hospital Carl Gustav Carus, TU Dresden, marina.conde@uniklinikum-dresden.de
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Marina Conde; Ralf Wiedemuth; Isabell Düring; Gabriele Schackert; Hans Achim Temme
Keywords: Survivin overexpression; myc-N overexpression; nude mice

19. Costa, Barbara
Division of signal transduction and growth control, DKFZ (German Cancer Research Center), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany, b.costa@dkfz-heidelberg.de
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Costa B.; EisemannT.; Strelau J.; Spaan I.; Liu HK.; Angel P.; Peterziel H.
Keywords: Podoplanin; glioma; neural stem cell

20. Davila de Leon, David
Deparment of Biochemistry and Molecular Biology I, School of Biology, Complutense University, Calle José Antonio Nováis 2, 28040 Madrid, Spain, daviddav@ucm.es
TARGETING THE MIDKINE / ANAPLASTIC LYMPHOMA KINASE AXIS AS A THERAPEUTIC STRATEGY IN GBM
Dávila D; López-Valero I; Lorente M; Hernández-Tiedra S; Torres S; González J; Hernández A; Sánchez P; Sepúlpeda J; Velasco G
Keywords: Glioblastoma Multiforme; Midkine; Glioma Initiating Cells (GICs)

21. Eisemann, Tanja
Division of Signal Transduction and Growth Control, German Cancer Research Center (DKFZ), Im Neuenheimer Feld 280, 69120 Heidelberg, Germany, t.eisemann@dkfz.de
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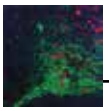
Eisemann T; Costa B; Martín-Villalba A; Mittelbronn M; Angel P; Peterziel



22. Felsenstein, Matthäus
Institute of Experimental Neurosurgery, Charité – Universitätsmedizin Berlin, Augustenburger Platz 1, 13353 Berlin, Germany, matthaeus.felsenstein@charite.de
CCR2-DEFICIENCY OF MICROGLIA/MACROPHAGES RESULTED IN ENHANCED GLIOMA PROGRESSION
Matthäus Felsenstein; Susan Brandenburg; Jonas Raggatz; Kati Turkowski; Peter Vajkoczy
Keywords: CCR2; Microglia; Glioma

23. Flüh, Charlotte
Klinik für Neurochirurgie, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Arnold-Heller-Straße 3, Haus 41, 24105 Kiel, Germany, charlotte.flueh@uksh.de
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Flüh, C.; Hattermann, K.; Mehdorn, H.M.; Mentlein, R.; Held-Feindt, J.
Keywords: Glioblastoma; stem cell markers; chemokinereceptors

24. Frenzel, Katrin
BioNTech AG, An der Goldgrube 12, 55131 Mainz, Germany, Katrin.Frenzel@biontech.de
GAPVAC: A NOVEL CONCEPT OF ACTIVELY PERSONALIZED CANCER IMMUNOTHERAPY FOR GLIOBLASTOMA
Frenzel K., Hilf N., Heesch S., Kuttruff-Coqui S., Lindner J., Admon A., Britten C.M. Bukur V., van der Burg S.H., Castle J., Diekmann J., Dorner S., Fritsche J., Gouttefangeas C., Kreiter S.,, Kroep J.R., Lassen U., Lewandrowski P., Löwer M., Martinez-Ricarte F., Maurer D., Mendrzyk R., Meyer M., Müllar S., Müller F., Okada H., Ottensmeier C., Paruzynski A., Pawlowski N., Piro J., Ponsati B., Poulsen H.S., Rössler B., Sahuquillo J., Al-Salihi O., Schoor O., Song C., Stevanovic S., Stevermann L., Tabatabai G. thor Straten P., Wagner C., Walter S., Weinschenk T., Huber C. Rammensee H.-G., Dietrich P.-Y., Wick W., Singh-Jasuja H., Sahin U.
Keywords: personalized cancer immunotherapy; glioblastoma; therapeutic vaccination

25. Ghoochani, Ali
Department of Neurosurgery, Universitätsklinikum Erlangen, Friedrich Alexander University of Erlangen-Nürnbe, Schwabachanlage 6, 91054 Erlangen, Germany, Ali.Ghoochani@uk-erlangen.de
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Keywords: Macrophage migration inhibitory factor; Glioma; angiogenesis

26. Grube, Susanne
Department of Neurosurgery, University Hospital Jena, Erlanger Allee 101, 7749 Jena, Deutschland, susanne.grube@med.uni-jena.de
TREATMENT WITH EPIGALLOCATECHIN GALLATE (EGCG) INDUCES OXIDATIVE STRESS IN HUMAN GLIOBLASTOMA CELLS
Grube, S.; Koegler, C.; Freitag, D.; Kalff, R.; Ewald C.
Keywords: green tea; oxidative stress; glioblastoma

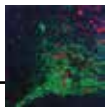
27. Hattermann, Kirsten
Institute of Anatomy, Christian-Albrechts-University Kiel, Olshausenstr. 40, 24098 Kiel, , k.hattermann@anat.uni-kiel.de
"INVERSE SIGNALING" OF THE TRANSMEMBRANE CHEMOKINE CXCL16 IN HUMAN MENINGIOMAS AS A NEW CONCEPT TO FAVOR TUMOR PROGRESSION
Hattermann, K; Bartsch, K; Gebhardt, H; Mehdorn, M; Mentlein, R; Held-Feindt, J
Keywords: inverse signaling; meningioma; chemokine

28. Heiland, Dieter Henrik
Department of Neurosurgery, University Medical Center Freiburg, Breisacherstr. 64, 79106 Freiburg, , dieter.henrik.heiland@uniklinik-freiburg.de
IDENTIFICATION AND CHARACTERIZATION OF C-JUN-N-TERMINAL PHOSPHORYLATION AS A REGULATOR OF DNA-METHYLTRANSFERASE 1 AND GENOME-WIDE METHYLATION IN GLIOBLASTOMA
Heiland,DH; Ferrarese,R; Claus,R; Weyerbrock,A; Nelander,S; Carro, MS
Keywords: epigenetic; c-Jun; genome-wide methylation

29. Johansson, Patrik
IGP, Uppsala University, Rudbecklab, Uppsala Uppsala, Sweden, patrik.johansson@igp.uu.se
INTERACTIVE PAN-CANCER NETWORKS USING GENERALIZED COVARIANCE SELECTION AND A CUSTOM WEB APPLICATION
Patrik Johansson, Teresia Kling, Jose Sanchez, Voichita D. Marinescu, Rebecka Jörnsten, Sven Nelander
Keywords: TCGA pan-cancer analysis; Network Models; Online Resource

30. Kahlert, Theresa
Department of Neurosurgery, University Hospital Jena, Friedrich-Schiller-University, Jena, Germany, theresakahlert@googlemail.com
THERAPEUTIC EFFICACY OF THE MULTI-RECEPTOR TYROSINE KINASE INHIBITOR AXITINIB IN AN INTRACRANIAL XENOGRAFT MOUSE MODEL OF HUMAN GLIOBLASTOMA
Kahlert, T.; Freitag, D.; Ewald, C.; Kalff, R.; Walter, J.
Keywords: glioblastoma; intracranial mouse model; axitinib

31. Kocyk, Marta
Department of Molecular Neurobiology, Nencki Institute of Experimental Biology, Pasteura 3, 02-093 Warsaw, Poland, m.kocyk@nencki.gov.pl
KNOCKDOWN OF OSTEOPONTIN IN C6 GLIOMA CELLS INFLUENCES MICROGLIA M2 RE-PROGRAMMING AND IMPAIRS TUMOR SPHERE FORMATION
Marta Kocyk, Anna Gieryng, Karolina Stepniak, Bozena Kaminska
Keywords: glioblastoma; microglia; stem-cells



32. Koglin, Norman
Clinical R&D, Piramal Imaging GmbH, Tegeler Str. 6, 13353 Berlin, , norman.koglin@piramal.com
PILOT (PRE)CLINICAL EVALUATION OF (4S)-4-(3-[18F]FLUOROPROPYL)-L-GLUTAMATE FOR PET/CT IMAGING OF INTRACRANIAL MALIGNANCIES
Koglin, N.; Mittra, E.; Mueller, A.; Berndt, M.; Friebe,M.; Gekeler, V.; Stephens, A.; Hoehne, A.; Chin, F.; Gambhir, S.
Keywords: glutamate; system xC-; PET

33. Krenzlin, Harald
Klinik für Neurochirurgie, HSK Wiesbaden, Ludwig-Erhard-Strasse 100, 65199 Wiesbaden, h.krenzlin@t-online.de
ATYPICAL TERATOID/RHABDOID TUMORS OF THE CENTRAL NERVOUS SYSTEM IN YOUNG CHILDREN
Harald Krenzlin, Manfred Schwarz, Peter Horn

34. Kübler, Ulrich
Labor-Praxisklinik GbR, , Siebertstr. 6, 81675 München, , info@labor-praxisklinik.de
CELLULAR DIAGNOSTICS AND MOLECULAR THERAPY OF DISEASES AND FUNCTION DISORDERS OF THE BRAIN
Kübler, U.; Schnepel, J.
Keywords: diagnostic gliapheresis; liquid biopsy; molecular classification of glioma

35. Kundu, Soumi
Immunology Genetics and Pathology, Uppsala University, Rudbecklaboratoriet C11:3 Dag Hammerskjölds v, 751 85 Uppsala, Sweden, soumi.kundu@igp.uu.se
HEPARANASE PROMOTES GLIOMA GROWTH AND CORRELATES TO PATIENT SURVIVAL
Soumi Kundu, Anqi Xiong, Grzegorz Wicher, Per-Henrik Edqvist, Argyris Spyrou, Lei Zhang, Magnus Essand,Anna Dimberg, Anja Smits, Neta Ilan, Israel Vlodavsky, Jin-Ping Li and Karin Forsberg-Nilsson
Keywords: Glioma; heparanase; tumor microenvironment

36. López Valero, Israel
Biochemistry and Molecular Biology, School of Biology, Complutense University, Madrid, Jose Antonio Novais, 12, 28040 Madrid, Spain, ilvalero@hotmail.com
A COMBINED PRECLINICAL THERAPY OF CANNABINOIDS AND TEMOZOLOMIDE AGAINST GLIOMA
López-Valero I; Lorente M; Torres S; Salazar M; Dávila D; Hernán D; Guzmán M; Hernández-Laín A; Sepúlveda J; Velasco, G
Keywords: Glioma; Cannabinoids; Combined preclinical therapy

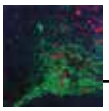
37. Lavon, Iris
Gaffin Center For Neuorooncology, Hadassah Hebrew University Medical Center, Ein-Kerem, 12000 Jerusalem, Israel, Irisl@hadassah.org.il
CIRCULATING MIRNASREFLECT THE ANTIANGIOGENIC EFFECT OF BEVACIZUMABTREATMENT IN PATIENTS WITH GLIOBLASTOMA (GBM)
Iris Lavon, Anat Mordechai, Hanna Charbit, Idd Paldor, Bracha Zelikovitch, Tamar Canello, Yigal Shoshan, Arriel Benis, Michael Wong, Lucy Paradiso, Andrew Morokoff,, Kate Drummond,, Andrew H. Kaye,and Tali Siegal
Keywords: Circulating MiRNAs; bevacizumab treatment; High grade glioma

38. Lewczuk, Ewa
Nencki Institute of Experimental Biology, Pasteur Street, 02-093 Warsaw, Polska, ewalewczuk92@gmail.com
THE ROLE OF LACTADHERIN IN GLIOMA-INDUCED MICROGLIA TRANSFORMATION
Lewczuk, E.; Gerigk, M.; Kaminska, B.; Ellert-Miklaszewska, A.
Keywords: LACTADHERIN; MICROGLIA;

39. Loebel, Franziska
Neurosurgery, Charité University Hospital Berlin, Augustenburger Platz 1, 13353 Berlin, Germany, franziska.loebel@charite.de
ASSESSMENT OF TREATMENT RESPONSE IN AN ORTHOTOPIC IDH1-MUTANT GLIOMA MODEL USING IN-VIVO MAGNETIC RESONANCE SPECTROSCOPY – A FEASIBILITY STUDY
Loebel, F., Tateishi, K., Wakimoto, H., Huber, P., Chi, A., Cahill, D.
Keywords: Glioma; IDH1 mutation; Magnetic Resonance Spectroscopy

40. Maire, Cecile
Neurosurgery, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany, c.maire@uke.de
PROFILING OF GBM PATIENT DERIVED CELL LINES IDENTIFIES CELL-INTRINSIC DIFFERENTIAL RADIATION RESPONSE WHICH CORRELATES WITH TP53 MUTATIONS
Maire C.L.; Abazeed M.; Lam F.; Pelton K.; Knoff D.; Koridеck H.; Adams D.; Pinnell N.; Ramkissoon S.; Wen P.; Ligon A.H.; Schreiber S., Floyd S., Ligon K.L., and Alexander B.M.
Keywords: Irradiation; Glioma stem cells; TP53

41. Maleszewska, Marta
Laboratory of Molecular Neurobiology, Nencki Institute of Experimental Biology, 3, Pasteur str, 02 093 Warsaw, Poland, m.maleszewska@nencki.gov.pl
PROFILING OF EPIGENETIC ENZYMES EXPRESSION IN GLIOBLASTOMA CELLS REVEALS TRANSCRIPTIONAL DOWNREGULATION OF EPIGENETIC MODULATORS
Maleszewska, M.; Wojtas, B.; Krol, S.K.; Gielniewski, B.; Kaminska, B.
Keywords: epigenetic enzyme; glioblastoma; histone modification



42.Michen, Susanne
Dep artment of Neurosurgery, University Hospital Carl Gustav Carus, TU Dresden, Fetscherstr. 74, 1307 Dresden, Germany, susanne.michen@uniklinikum-dresden.de
EGFRVIII-SPECIFIC AND CXCR4-OVEREXPRESSING NK CELLS IMPROVE IMMUNOTHERAPY OF CXCL12/SDF-1ALPHA-SECRETING GLIOBLASTOMA
Müller, N.; Michen, S.; Tietze, S.; Töpfer, K.; Schulte, A.; Lamszus K.; Schmitz, M.; Schackert, G.; Pastan, I.; Temme, A.
Keywords: adoptive immunotherapy; chimeric antigen receptor; engineered NK cell chemotaxis

43. Möckel, Sylvia
Department of Neurology, Regensburg University Hospital, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany, sylvia.moeckel@ukr.de
ATF4 AS A MEDIATOR OF RESISTANCE TO TARGETED THERAPY IN HIGH-GRADE GLIOMAS
Moeckel, S.; Neyns, B.; Pan, E.; Riemenschneider, MJ.; Bosserhoff, AK.; Vollmann-Zwerenz, A.; Meyer, K.; Spang, R.; Hau, P.
Keywords: Glioma stem cells; targeted therapy; therapy resistance

44. Nelander, Sven
Immunology, Genetics and Pathology, Uppsala University, Rudbeck Laboratory, SE-75185 Uppsla, Sweden, sven.nelander@igp.uu.se
SYSTEMS SCALE ANALYSIS AND PROSPECTIVE MODELING OF DRUG VULNERABILITIES IN 96 GLIOBLASTOMA INITIATING CELL CULTURES
Schmidt, L;Johansson, P;Baskaran, S;Elfineh, L.; Westermark,B; Uhrbom,L;Forsberg-Nilsson, K; Lundgren,B; Krona C;Nelander, S.
Keywords: systems biology of patient-derived glioblastoma in; large scale prediction of drug vulnerabilities; chemical genomics

45. Olimpico, Francesco
Neuroscience, CNR, via Moruzzi, 56124 Pisa, Italy, francesco.olimpico@in.cnr.it
GLIOMA: CELLULAR CHANGES AND MOLECULAR PATHWAYS FOLLOWING CNF1 TREATMENT.
Francesco Olimpico; Eleonora Vannini; Anna Panighini; Matteo Caleo; Mario Costa
Keywords: Glioma; Bacterial toxin; Senescence

46. O hAilin, Darren
Neuroscience Center, Universitätsklinikum Freiburg, Breisacher Str. 64, 79106 Freiburg, darren.ohailin@uniklinik-freiburg.de
A NOVEL INTEGRATIVE NETWORK MODEL IDENTIFIES ANXA2 AS AN EPIGENETICALLY REGULATED DRIVER OF MESENCHYMAL PROFILE IN GLIOBLASTOMA
Ó hAilín, D.; Ferrarese, R.; Kling, T.; Johansson, P.; Nelander, S.; Carro, M.S
Keywords: Glioblastoma; Bioinformatics; Epigenetics

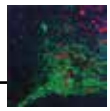
47. Proescholdt, Martin
Neurosurgery, University Regensburg Medical Center, Franz Josef Strauß Allee 11, 93053 Regensburg, Germany, martin.proescholdt@ukr.de
CAIX REGULATES EXTRACELLULAR PH AND INVASION IN GLIOBLASTOMA
Proescholdt M.A; Störr E-M; Lohmeier A; Merrill MJ., Brawanski A.
Keywords: http://www.braintumor-berlin.de/sites/braintumor-b; pH regulation; invasion

48. Reinartz, Roman
Institute of Reconstructive Neurobiology, University of Bonn, Sigmund Freud Staße 25, 53127 Bonn, Germany, roman.reinartz@uni-bonn.de
FUNCTIONAL ANALYSIS OF GLIOBLASTOMA SUBCLONES ENABLES PREDICTIONS ON THERAPY-RELATED ALTERATIONS TO THE TUMOR CELL COMPOSITION
Reinartz, R; Wang, S; Kebir, S; Wieland, A; Rauschenbach, L; Glas, M; Pincus, D; Simon, M; Brüstle, O; Steindler, D; Scheffler,B
Keywords: glioblastoma; intratumor heterogeneity; functional analysis

49. Riedel, Helene
Klinik und Poliklinik für Neurochirurgie, Universitätsklinikum Leipzig, Liebigstraße 20, 4103 Leipzig, Deutschland, helene.riedel@medizin.uni-leipzig.de
CARNOSINE INHIBITS THE GROWTH OF GLIOBLASTOMA CELLS INDEPENDENT FROM PI3K AND MTOR SIGNALING
Helene Riedel, Lutz Schnabel, Henry Oppermann, Ulrike Letzien, Jürgen Meixensberger, Frank Gaunitz
Keywords: glioblastoma; carnosine; mTOR

50. Ritter, Steffi
Department of Neurosurgery, Section Experimental Neurosurgery/Tumor Immunology, University Hospital Carl Gustav Carus, TU Dresden, Fetscherstr. 74, 1307 Dresden, Germany, steffi.ritter@uniklinikum-dresden.de
MODIFIED E-CADHERIN PROTEIN INFLUENCES MIGRATION AND INVASION BEHAVIOR OF GLIOMA CELL LINE U343-MG
Ritter, S.; Stirnnagel K., Schackert G., Temme A.
Keywords: E-cadherin; glioma; EMT

51. Sachkova, Aleksandra
Neurochirurgie, Universitätsmedizin Göttingen, Christophorusweg 12 App.828, 37075 Göttingen, Niedersachsen, sashasachkova@mail.ru
CIRCULATING BIOMARKERS FOR GLIOMA
AA. Sachkova, A. Eger, K. Schaller, V. Rohde, P.-P. Panciani, A.-R. Fathi, V. Clement-Schatlo, B. Schatlo
Keywords: Circulating biomarkers; Glioma; Clinical evidence grade



52. Sassi, Felipe
Cellular Neurosciences, Max-Delbrück-Center (MDC), Robert-Rössle-Strasse 10, 13125 Berlin, Felipe.deAlmeidaSassi@mdc-berlin.de
THE NOVEL ROLE OF VGF IN THE GLIOMA MICROENVIRONMENT
Sassi, F.; Mersch, M.; Tamagno, I.; Virk, S.; Wolf, S.; Hambardzumyan, D.; Kettenmann, H.
Keywords: Glioblastoma; Astrocytes; Vgf

53. Savaskan, Nic
Neurosurgery, FAU- University of erlangen-Nürnberg, Schwabachanlage 6, 91054 Erlangen, Germany, nicolai.savaskan@uk-erlangen.de
DISTINCT THRESHOLDS OF PRG3 AMPLIFY ONCOGENESIS IN GLIAL BRAIN TUMORS
Nic Savaskan, Zheng Fan, Gökce Hatipoglu, Marc Schwarz, Thomas Broggini, Tina Sehm, Michael Buchfelder and Ilker Eyüpoglu
Keywords: oncogenic threshold; plasticity related genes; tumor progression

54.Savov, Vasil
Upp sala University, Dag Hammarskjölds väg 20, 75185 Uppsala, Sweden, vasil.savov@igp.uu.se
METASTATIC TUMOR RECURRENCE FROM RARE SOX9 CELLS IN MYCN-DRIVEN SHH-INDEPENDENT MEDULLOBLASTOMA
Savov, V.; ?an?er, M.; Fotaki, G.; Bolin, S.; Rosén, G.; Dubuc, A.; Remke, M.; Weishaupt, H.; Taylor, MD.; Swartling, FJ.
Keywords: medulloblastoma; MYCN; tumor recurrence

55. Schatlo, Bawarjan
Neurosurgery, University Hospital Göttingen, Robert Koch Str 40, 37075 Göttingen, Germany, schatlo@gmail.com
COMBINED USE OF INTRAOPERATIVE MRI AND 5-AMINOLAEVULINIC ACID IN HIGH-GRADE GLIOMA SURGERY
Schatlo, B.; Fandino, J; Smoll, NR; Rohde, V; Remonda, L; Marbacher, S; Perrig, W; Landolt, H; Fathi, AR
Keywords: 5-aminolevulinic acid; intraoperative imaging; gross total resection

56. Schmidt, Linnea
Uppsala University, Immunology, Genetics and Pathology, Dag Hammarskjölds väg 20, SE-751 85 Uppsala, Sweden, linnea.schmidt@igp.uu.se
MULTIDIMENSIONAL AND IMAGE-BASED PROFILING OF PATIENT-DERIVED GLIOBLASTOMA INITIATING CELLS REVEALS EFFECTIVE AND PHENOTYPICALLY DISTINCT DRUG CANDIDATES
Linnéa Schmidt, Patrik Johansson, Sathishkumar Baskaran, Teresia Kling, Ludmila Elfineh, Maria Häggblad, Ulf Martens, Cecilia Krona, Bo Lundgren, Sven Nelander
Keywords: Glioblastoma; Stem cells;

57. Schnabel, Lutz
Klinik und Poliklinik für Neurochirurgie, Universitätsklinikum Leipzig, Liebigstraße 20, 4103 Leipzig, Germany, lutz.schnabel@medizin.uni-leipzig.de
CARNOSINE AND THE ENERGY METABOLISM OF GLIOBLASTOMA CELLS
Schnabel, L.; Riedel, H.; Meixensberger, J.; Gaunitz, F.; Oppermann, H.
Keywords: carnosine; glioblastoma; metabolism

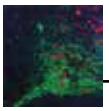
58. Schulte, Alexander
Neurosurgery, University Hospital Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany, aschulte@uke.de
ORAL ADMINISTRATION OF THE AXL TYROSINE KINASE INHIBITOR BGB324 PROLONGS SURVIVAL OF GLIOBLASTOMA-BEARING MICE
Schulte, A.; Kolbe, K.; Ben-Batalla, I.; Wroblewski, M.; Westphal, M.; Loges, S.; Lamszus, K.
Keywords: Axl; BGB324; targeted therapy

59. Simon, Michèle
Department of Neurosurgery, University Hospital, Friedrich-Schiller-University, Erlanger Allee 101, 7747 Jena, michele.simon@med.uni-jena.de
SPECIFYING THE ROLE OF MTOR SIGNALING IN MENINGIOMAS AND GLIOMAS
Simon M.; Freitag D.; Steinbach T.; Kalff R.; Walter J.
Keywords: mTOR; meningiomas; gliomas

60. Spyrou, Argyris
Immunology, Genetics and Pathology (IGP), Uppsala University, Dag Hammarskjölds v 20, 751 85 Uppsala, Sweden, argyris.spyrou@igp.uu.se
HEPARANASE IN PEDIATRIC BRAIN TUMORS
Argyris Spyrou, Soumi Kundu, Lulu Haseeb, Matyas Molnar, Di Yu, Magnus Essand, Neta Ilan, Israel Vlodavsky, Jin-Ping Li and Karin Forsberg-Nilsson
Keywords: Heparanase

61. Stec, Karol
MicroDiscovery GmbH, Marienburger str. 1, 10405 Berlin, Germany, karol.stec@microdiscovery.de
ANALYSIS OF INTERACTION OF GLIOBLASTOMA AND STEM CELL LINES
Karol Stec, Chris Bauer, Helena Motaln, Tamara Lah Turnšek, Joachim Selbig and Johannes Schuchhardt
Keywords: Glioblastoma; Deconvolution; Transcriptomic

62. Szulzewsky, Frank
Cellular Neurosciences, MDC Berlin, Robert Rössle Strasse 10, 13125 Berlin, Germany, frank.szulzewsky@mdc-berlin.de
IDENTIFICATION OF REGULATED GENES IN GLIOMA-ASSOCIATED MICROGLIA/MACROPHAGES USING MICROARRAY
Szulzewsky F; Pelz A; Synowitz M; Holtman IR; Boddeke HWGM; Wolf S; Kettenmann H
Keywords: Glioma; Microglia/Macrophages; GAMs



63. Uckermann, Ortrud
Klinik und Poliklinik für Neurochirurgie, Uniklinikum Dresden, Fetscherstr. 74, 1307 Dresden, ortrud.uckermann@uniklinikum-dresden.de
ANALYSIS OF THE BIOCHEMICAL PROFILE OF LOW GRADE GLIOMA WITH DIFFERENT IDH1 MUTATION STATUS USING VIBRATIONAL SPECTROSCOPY
Uckermann, O.; Juratli, T.; Conde, M.; Galli, R.; Krex, D.; Geiger, K.; Schackert, G.; Temme, A.; Steiner, G.; Kirsch,
Keywords: IDH1; low grade glioma; Fourier-transform infrared spectroscopy

64. Unterkircher, Thomas
Neurozentrum, Universitätsklinikum Freiburg im Breisgau, Breisacher Str. 64, 79106 Freiburg im Breisgau, Deutschland, Thomas.Unterkircher@uniklinik-freiburg.de
REGULATION OF MESENCHYMAL GENE EXPRESSION BY NF1 IN GLIOBLASTOMA
Unterkircher, T.; Franco, P.; Carro, MS
Keywords: Glioblastoma; NF1; Mesenchymal Signature

65. Vannini, Eleonora
CNR Pisa, Institute of Neuroscience, via G Moruzzi 1, 56126 Pisa, Italy, eleonora.vannini@in.cnr.it
ACTIVATION OF RHO GTPASES PREVENTS TUMOR GROWTH AND PRESERVES NEURONAL FUNCTIONS IN A MOUSE MODEL OF GLIOMA
Vannini, E.; Olimpico, F.; Costa, M.; Caleo, M.
Keywords: GL261 cells; bacterial toxin CNF1; electrophysiology

66. Wiedemuth, Ralf
Klinik und Poliklinik für Neurochirurgie, TU Dresden, Fetscherstr. 74, 1307 Dresden, , Ralf.Wiedemuth@uniklinikum-dresden.de
CHEMICAL AURORA B INHIBITION INCREASES SUSCEPTIBILITY OF GLIOBLASTOMA CELLS TO ALLOGENEIC NK CELLS BY UPREGULATION OF MIC A/B AND DEATH RECEPTORS
Wiedemuth R.; Conde M.; Schackert G.; Temme A.
Keywords: Aurora B; p53; NK cells

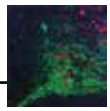
67. Winkler, Lars
FMP Leibniz-Institut fuer molekulare Pharmakologie, Robert-Roessle-Str. 10, 13125 Berlin, lars.winkler@live.de
PEPTIDES USED AS POTENTIAL DRUG ENHANCER FOR CYTOSTATIC DRUGS TO IMPROVE BRAIN TUMOR TREATMENT
Winkler, L.; Staat C.; Dabrowski. S.; Wolburg, H.; Engelhardt, B.; Campbell, M.; Deli, M.; Blasig, I.E
Keywords: Blood brain barrier; peptids; drug delivery

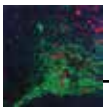
68. Xie, Yuan
Department of Immunology, Genetics and Pathology, Uppsala University, Dag Hammarskjölds v 20, 75185 Uppsala, Sweden, yuan.xie@igp.uu.se
THE HUMAN GLIOBLASTOMA CELL CULTURE (HGCC) RESOURCE: VALIDATED CELL MODELS REPRESENTING ALL MOLECULAR SUBTYPES
Yuan Xie,, Tobias Bergström,, Yiwen Jiang,, Patrik Johansson,, Voichita Dana Marinescu, Nanna Lindberg, Anna Segerman, Grzegorz Wicher, Mia Niklasson, Satishkumar Baskaran, Smitha Sreedharan, Isabelle Everlien,, Marianne Kastemar, Annika Hermansson, Lioudmila Elfineh, Sylwia Libard, Eric Charles Holland, Göran Hesselager, Irina Alafuzoff, Bengt Westermark,, Sven Nelander, Karin Forsberg-Nilsson, and Lene Uhrbom
Keywords: Glioblastoma; Stem cell culture conditions; Cancer cell panel for precision medicine

69. Xiong, Anqi
Department of Immunology, Genetics and Pathology, Uppsala University, Dag Hammarskjölds väg 20, 75185 Uppsala, Sweden, anqi.xiong@igp.uu.se
NUCLEAR RECEPTOR BINDING PROTEIN 2 (NRBP2): A PUTATIVE TUMOR SUPPRESSOR GENE IN MEDULLOBLASTOMA
Xiong, A.; Spyrou, A.; Weishaupt, H.; Alemayehu, G.; Swartling, FJ.; Olofsson, T.; Forsberg- Nilsson, K.
Keywords: medulloblastoma; tumor suppressor gene;

70. Yakubov, Eduard
Neurosurgery, Friedrich-Alexander University Erlangen-Nuremberg, Schwabachanlage 6, 91054 Erlangen, Germany, eduard.yakubov@uk-erlangen.de
CEREBRAL SELENIUM LEVELS CONTROL PROGRESSION OF MALIGNANT BRAIN TUMOURS
Yakubov, E.; Ghoochani, A.; Buchfelder, M.; Eyüpoglu, I.Y.; Savaskan, N.E.
Keywords: Glioblastoma; Selenium; Apoptosis

71. Zou, Hongyan
Neuroscience and Neurosurgery, Mount Sinai School of Medicine, 1425 Madison Ave, New York New York, United States, hongyan.zou@mountsinai.org
DOUBLE MINUTE AMPLIFICATION OF MUTANT PDGF RECEPTOR ALPHA IN A NOVEL MOUSE GLIOMA MODEL
Hongyan Zou, Rui Feng, Yong Huang, Joseph Tripodi, Vesna Najfeld, Nadejda M. Tsankova, Maryam Jahanshahi, Lo
Keywords: Double minute amplication; PDGF receptor alpha; mouse glioma model





Abstracts of Poster Presentations

(in alphabetical order of presenting author as in list of poster presentations)

INTRACELLULAR GLYCINE RECEPTOR FUNCTION FACILITATES GLIOMA FORMATION IN VIVO

Omar Dildar a Dzaye1, Benjamin Förstera1, Aline Winkelmann1, Marcus Semtner1, Bruno Benedetti2, Ralf P. Friedrich1, Darko S. Markovic3, Carola Bernert1, Michael Synowitz4, Peter Wend5, Michael Fähling4, Erich E. Wanker1, Marie-Pierre Junier6, Rainer Glass7, Helmut Kettenmann1 and Jochen C. Meier1
Max Delbrück Center Berlin1, Innsbruck Medical University2, Helios Clinical Center Berlin3, CharitéUniversitätsmedizin Berlin4, UCLA Jonsson Comprehensive Cancer Center5, Psychiatry and Neuroscience Center Paris6, University Clinics Munich7

The neuronal function of Cys-loop neurotransmitter receptors is established; however, their role in non-neuronal cells is poorly defined. As brain tumors are enriched in the neurotransmitter glycine, we studied the expression and function of glycine receptors. (GlyRs) in glioma cells. Human brain tumor biopsies selectively expressed the GlyR a1 and a3 subunits, which have nuclear localization signals (NLSs). The mouse glioma cell line GL261 expressed GlyR a1, and knockdown of GlyR a1 protein expression impaired the self-renewal capacity and tumorigenicity of GL261 glioma cells, as shown by a neurosphere assay and GL261 cell inoculation in vivo, respectively. We furthermore showed that the pronounced tumorigenic effect of GlyR a1 relies on a new intracellular signaling function that depends on the NLS region in the large cytosolic loop and impacts on GL261 glioma cell gene regulation. Stable expression of GlyR a1 and a3 loops rescued the self-renewal capacity of GlyR a1 knockdown cells, which demonstrates their functional equivalence. The new intracellular signaling function identified here goes beyond the well-established role of GlyRs as neuronal ligand-gated ion channels and defines NLS-containing GlyRs as new potential targets for brain tumor therapies.

LIVE MONITORING GLIOMA VIROTHERAPY

Alessandrini F.1; Appolloni I.2;CeresaD.1, MenottiL.3;GattaV.4; CampadelliG. 4;MalatestaP.1,2
1 DIMES - University of Genoa, Italy; 2 IRCCS –AOU S.Martino IST, Genoa, Italy; 3 FaBiT, University of Bologna, Italy. 4DIMES, University of Bologna, Italy.

Glioblastoma is the most common and deadly malignant brain tumor. Whole resection of in□ltrative growing gliomas is often impossible, and new strategies for specifically targeting and eliminating cells migrated out of the main tumor mass into normal brain tissue might enhance the therapeutic response. For this purpose, the virotherapy seems to be a valuable and promising tool. We are testingthe efficiency of anoncolytic herpes simplex virusretargetedagainstcells expressingEGFRvIIIgene (R-LM613). EGFRvIII is a functional and permanently activated mutation of the epidermal growth factor receptor EGFR, expressed in about 40% of glioblastomas. To test in vivo R-LM613, we take advantage of a murine model of HGG, based on the overexpression of EGFRvIII in p16/p19 KO mice, and glioblastoma initiating cells derived from patient and expressing EGFRvIII. Besides, we engineered these cells to express the Gaussia Luciferase enzyme, that is producedandreleased into bloodby tumor cells, allowing us tomonitortumor growthfrequently andnon-invasively. Immunosuppressed NOD/SCID mice injected with engineered human glioma cell cultures mixed with a small percentage of the same cells pre-infected with R-LM613 showed a reduced concentration of luciferase in the blood from early times after transplant. The inhibition in tumor growth persisted after a long time from injection. Mice showed a remarkable improvement in their median survival compared to that of mice injected with controls. Moreover, in BALB/C mousemodel the local delivery of R-LM613 at a specific stage of tumor growth leads to reduction oftumor cell number, as shown by the reduced presence of Gaussia Luciferase, suggesting the effective action of the oncolytic virus in vivo.

THERAPEUTIC RESPONSE TO CHEMOTHERAPEUTICS OF GLIOMA-PDX CAN NOT BE CORRELATED TO COMMON MUTATIONS IDENTIFIED BY PANEL SEQUENCING

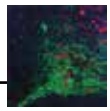
Orthmann, A.1; Hoffmann, A.1; Zeisig, R.1; Haybäck, J.2; Jödicke, A.3; Kuhn, S.4; Linnebacher, M.5; Hoffmann, J.1; Fichtner, I.1
1. EPO GmbH Berlin, 2. Dept. Pathology, Medical University of Graz; 3. Clinic for Neurosurgery, Vivantes Klinikum; 4. Clinic for Neurosurgery, Potsdam; 5. Molecular Oncology und Immunotherapy, Medical University of Rostock

The most common malignant brain tumor in adults is glioblastoma multiforme (GBM) showing a very heterogeneous, diffuse infiltrative and aggressive growth with a mean survival time between 8 and 18 months. Because efficient standard therapies for glioma are limited, translational research is focusing on the molecular mechanisms of glioma formation and development of resistance to identify new therapeutic targets. We transplanted more than 50 glioma tissue samples to immunodeficient mice and were able to establish and characterize 13 PDX models (engraftment rate 25%). Glioma PDX models were screened for sensitivity towards selected drugs (everolimus, sorafenib, bevacicumab, irinotecan, salinomycin, temozolomide). A strong treatment response was observed for bevacicumab (7 sensitive PDX/13), irinotecan (7/13) and temozolomide (10/13), while the other drugs investigated mostly had no activity. The frequency of common "oncomutations" was analyzed using the Illumina TrueSeq Cancer panel sequencing. Although some frequent mutations were detected, i.e. in KDR, FGFR3, PIK3CA, PTEN, P53 and NOTCH1, no correlation with drug sensitivity have be identified. Extended correlation between drug sensitivity, gene expression profiles, and further mutations are still under analysis. The available data demonstrate that our glioma PDX model panel has retained the original tumor biology and reflect the heterogeneity of the disease, ensuring a high similarity to the clinical situation. Our approach can not only be used for testing of established and new drugs, but also offers an individualized treatment of patients.

BIMODAL ACTION OF TEMOZOLOMIDE IN BRAIN TUMOR CELLS

Anna-Maria Barciszewska1,3, Pawel Glodowicz2, Monika Piwecka2, and Stanislaw Nowak1,3
1Department of Neurosurgery and Neurotraumatology, Karol Marcinkowski University of Medical Sciences, Przybyszewskiego 49, 60-355 Poznan, Poland, 2Institute of Bioorganic Chemistry of the Polish Academy of Sciences, Noskowskiego 12, 61-704 Poznan, Poland, 3Division of Neurosurgery and Neurotraumatology, Heliodor Swiecicki Clinical Hospital, Przybyszewskiego 49, 60-355 Poznan, Poland

Malignant gliomas are most aggressive brain tumors with a dismal prognosis despite optimal treatment. The gold standard treatment of glioblastoma, the most lethal glioma subtype, includes surgery followed by the combination of radiotherapy and chemotherapy with temozolomide (TMZ). The active metabolite of TMZ methylates DNA bases in several positions, from which methylation of the O6 position of guanine is regarded as the lethal lesion. However, the effect of TMZ appears to be limited by the occurrence of chmoresistance. Therefore there's an urgent need to adequately elucidate the mechanisms of TMZ action and the pathways by which glioma cells escape from death. We present the other possible point of TMZ action at the different, epigenetic level of the genome. We've showed that in addition to O6 methylation of guanines, TMZ induces methylation of cytosine at short times and then causes demethylation of DNA through reactive oxygen species (ROS) induced damage of 5-methylcytosine (m5C). The observed global hypomethylation of the genome contributes to regulation of gene expression on epigenetic level. The aim of our study was to evaluate the molecular mechanism of temozolomide action, the drug of choice in glioblastoma treatment. We have treated the C6, glioblastoma and HeLa (as a control) cell lines with TMZ dissolved in DMSO with different time. DNA from cultured cells was isolated with commercially available DNA isolation kit, hydrolysed into nucleotides and separated after labelling with 32P-ATP and T4-polynucleotide kinase. Separation of 32P-labelled nucleotides was done on cellulose thin layer chromatography (TLC) plates in two dimensions. Chromatograms were then evaluated using phosphoimager and the amounts of m5C calculated as a ratio (R) of spot intensities of m5C to m5C+C+T. Thymine and cytosine were included in the formula because they are also products of damage of m5C. We've showed that TMZ treatment affects m5C formation in DNA. m5C amount in gliomas' DNA increased significantly after short treatment with TMZ, whereas longer



treatment caused demethylation. The results of the study put a new light on the mechanism of action of TMZ situating it as an epigenetic modificator that acts not only as an directly destroying agent, but also indirectly by influencing the gene expression regulation.

IN VIVO MODELING OF PEDIATRIC BRAINSTEM GLIOMA

Barilari, M1,2; Castel, D3;Grill, J3; Puget, S1,2; Pende, M1,2; De Keyzer, Y1,2
1 Inserm U1151, Paris, France, 2University Paris Descartes, Sorbonne Paris Cité, Paris, France, 3Gustave Roussy, University Paris Sud, Villejuif, France

Diffuse Intrinsic Pontine Glioma (DIPG) is the most severe form of pediatric brain cancer, killing all affected children in the two years after diagnosis. Neither chemotherapy nor targeted agentsshowed substantial survival benefit. In addition, due to the location in a critical brain region and invasive properties these lesions are not amenable to surgery. The development of new therapies has been hampered by the lack of biological information on DIPG and the absence of relevant preclinical models. Recent studies performed on stereotactic biopsies have revealed DIPG to be driven by a unique pattern of alterations different from adult gliomas and from other pediatric gliomas arising in other brain regions:unique heterozygous mutations of histone H3 variants and unique activating mutations of ACVR1 receptors1. Other major alterations comprise mutations in p53, activation of PDGFR-alpha and PI3K/mTOR signaling pathway1,2. To better understand the role of these alterations in tumor formation and progression, we aredeveloping new murine models of DIPG recapitulating these main genetic modifications and also DIPG invasive properties. The alterations areintroduced in the brainstem of genetically modified newborn immunocompetent mice,in precise combinations based on their natural occurrence in patients. The recent developments on the project will be presented. Our studies should provide insights on the main players in DIPG tumorigenesis and on the mechanisms underlying highly infiltrating capacity of DIPG cells. This preclinical model should eventually help identifyingnew therapeutic targets.

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THE METALLOPROTEASE-DISINTEGRIN ADAM8 MEDIATES BRAIN METASTASIS OF BREAST CANCER CELLS

Catharina Conrad1, Uwe Schlomann1, Christopher Nimsky1, Jane Preston2, Roger Kamm3, Jörg W. Bartsch1
1, Klinik für Neurochirurgie, Philipps-Universität Marburg, Baldingerstr., 35033 Marburg, 2King's College London, Blood-Brain Barrier Group, IPS, London SE1 9NH, 3 MIT, Department of Bioengineering, Cambridge, MA, USA

Brain metastases outnumber primary neoplasms ten-fold, and are associated with a poor prognosis. Patients with metastatic, triple negative breast cancers are at high risk (25-46%) of developing brain metastases at some point in the course of their disease. Recently we demonstrated that high ADAM8 expression in breast tumors lead to increased numbers of circulating tumor cells and a higher frequency of brain metastasis in mouse tumor models. We evaluated the mechanistic role of ADAM8, a metalloprotease-disintegrin, in facilitating trans-endothelial migration and in the formation of brain metastases. To model brain metastasis of breast cancer cells, stable shRNA ADAM8 knock-down clones of the breast cancer cell line MDA-MB-231 (shA8) and control (shCtrl) cells were generated andsubjected to functional assays assessing migration, sphere formation and transmigration through a Blood Brain Barrier model consisting of endothelial cells and astrocytes. A significant increase in ADAM8 expression was identified in 34% of primary site tumors, and was found to be 2-fold higher in brain metastases of different origins, including breast cancer. In transendothelial migration assays, MDA-MB-231 ADAM8knock-down cells showed a reduced endothelial adhesion as well as a reduced transmigratory capacity both in serum-induced transmigration and in transmigration triggered by the chemokine SDF-1, a mediator of metastasis. This was further supported by the blood-brain barrier in vitro model as well as in matrigel invasion assays. ADAM8 knockdown caused reduced ERK1/2 and CREB phosphorylation and affected expression levels of MMP9 specifically. Our results suggest that ADAM8 is an important mediator for brain metastasis of breast cancer by affecting transendothelial migration and may offer an attractive target for therapeutic intervention.

SYSTEMATIC IDENTIFICATION OF GENE TARGETS IN A BIOBANK OF PATIENT DERIVED GLIOBLASTOMA-INITIATING CELLS.

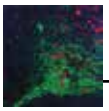
Sathishkumar Baskaran1, Patrik Johansson1, Caroline Hansson2, Torbjörn Nordling1, Ludmila Elfineh1, Ulf Martens3, Maria Häggblad3, Bengt Westermark1Lene Uhrbom1, Karin Forsberg Nilsson1, Bo Lundgren3, Cecilia Krona1, Sven Nelander1
1Department of Immunology, Genetics and Pathology and Science for Life Laboratory Uppsala, SE-751 85 Uppsala, Sweden, 2Sahlgrenska Cancer Center, Institute of Medicine, Box 425, SE-415 30 Gothenburg, Sweden, 3Cell screening facility, Science for Life Laboratory Stockholm, Department of Biochemistry and Biophysics, Stockholm University, Solna, Sweden

Glioblastoma, a devastating cancer type with dismal patient prognosis needs exploration of new therapeutic targets to complement the existing treatment strategies. Here, we report large-scale gene knockdown (KD) using a tailored short interfering RNA library to identify essential gene targets across a panel of GBM cells from the Human Glioma Cell Cultures (HGCC) biobank. The HGCC material represents functionally validated and characterized tumor initiating cells consisting of all molecular subtypes isolated from grade IV astrocytoma patients. In a primary screen, we individually knocked down 1200 genes across six HGCCs and measured cell viability after 72hours. Of the 1200 genes studied, 30 candidate genes that produced at-least 25% reduction in cell viability were chosen for further analysis. The targets, some of which are druggable, fall into three major functional classes: cell cycle regulation, DNA repair, and protein degradation. To define biomarkers of vulnerability, we are currently performing a secondary screen on the identified 30 genes across a broader panel of well-characterized HGCC lines and a control human astrocytic cell line. In the extended screen, the viability assay is complemented with cytoskeleton staining to record the phenotypic change of the cells induced by target knockdown. The candidate genes validated by the secondary screen will be further functionally studied using both in vitro studies of glioma initiating cells and in vivo modeling using zebrafish to identify their possible role as a therapeutic target.

THE PRO-ANGIOGENIC PHENOTYPE OF CD11B+ CELLS DEPENDS ON THE CONSTITUTION OF THE MYELOID CELL POPULATION WITHIN HUMAN GLIOMA

Anne Blank, Susan Brandenburg, Ulf Schneider, Peter Vajkoczy
Charité - Universitätsmedizin Berlin, Institut für Neurochirurgie

Glioblastoma multiforme (GBM), one of the most malignant brain tumors, is characterized by the accumulation of myeloid cells (CD11b+) and a high angiogenic activity. Therefore, we investigate the contribution of immune cells from the myeloid lineage to glioma vascularization. Brain tissue samples from 65 patients with astrocytomas (WHO°III and °IV) or epilepsy (control group) were obtained during surgical treatment, homogenized and CD11b+ cells were analyzed by FACS. Furthermore, myeloid cells were purified by MACS technology, RNA was isolated and qRT-PCRs regarding pro-angiogenic factors were performed. Frozen sections were used for immunofluorescence stainings. Based on FACS-analyses different subfractions of CD11b+ cells were defined. In controls and °III astrocytomas only a CD11b+CD45low population (microglia) was observed, whereas all GBM-patients displayed an additional CD11b+CD45high fraction (macrophages). Approximately 50% of them showed a third CD11b+ population, identified as granulocytes. We found increased levels of several pro-angiogenic factors (e.g. VEGF, CXCL8, CXCL2) within the CD11b+ isolated cells in GBM samples, highest in those who exhibit all three mentioned cell fractions. Beside the angiogenic activity of CD11b+ cells, microglia/macrophages showed an association with tumor blood vessels especially in GBM tissues. Furthermore, expression of MHCI, MHCII and CD86 on myeloid cells differed between tissue samples, while activation status of CD11b+ cells depends on the tumor grade. Here, upregulation of surface markers was correlated with a higher grade of glioma. Our data indicate, that cells of the myeloid lineage are able to support vascularization in human GBM by secretion of pro-angiogenic factors, and thus these cells have the opportunity to contribute to tumor progression.



COMBINED BET-BROMODOMAIN AND CDK2 INHIBITION IN MYC-DRIVEN MEDULLOBLASTOMA

Bolin S1, Persson C1*, Borgenvik A1*, Weishaupt H1, Qi J2, Weiss WA3, Cho J-Y4, Bradner JE2, Swartling FJ1
1Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Rudbeck Laboratory, Uppsala University, Uppsala, Sweden, 2Department of Medicine, Harvard Medical School; Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA USA, 3Departments of Neurology, Pediatrics and Neurosurgery, University of California, San Francisco, CA USA ,4Department of Neurology and Neurological sciences, Stanford University, CA USA
**Authors contributed equally to the work*

The embryonal brain tumor medulloblastoma (MB) is the most common malignant solid tumor in children. MYC proteins (like c-MYC or MYCN) are often overexpressed in MB correlating with poor prognosis. We previously used a medulloblastoma model to show that brain tumors become addicted to the oncoprotein MYCN and that MYCN stabilization is required for MB development. We now show how suppression of MYC expression by targeting Bromodomains in MB and how MYC protein destabilization by using CDK2 inhibition can reduce MB proliferation and promote cell death. MYC levels and proliferation of murine and human MB could be effectively reduced by a combination of specific CDK2-inhibition by Milciclib and by using the bromodomain inhibitor JQ1. Importantly, a sustained combination treatment over 7-10 days was needed in order to effectively abolish tumor cell proliferation. Both treatment strategies induced various levels of tumor cell senescence in combination with increased apoptosis. In addition, JQ1 together with Milciclib reduced tumor growth in orthotopical MB transplants and prolonged survival as compared to JQ1 alone. Our data suggest that dual inhibition of CDK2 and bromodomains could be a novel treatment approach in suppressing medulloblastoma by targeting MYC proteins.

EXTRACELLULAR MATRIX GLYCOPROTEIN-DERIVED SYNTHETIC PEPTIDES DIFFERENTIALLY MODULATE GLIOMA AND SARCOMA CELL MIGRATION

Nicole Brösicke1, Muhammad Sallouh2, Lisa-Marie Prior1*, Albert Job1#, Ralf Weberskirch2 and Andreas Faissner1
*1 Department of Cell Morphology and molecular Neurobiology, Ruhr-University Bochum, Bochum, Germany, 2Department of Chemistry and Chemical Biology, Technical University of Dortmund, Germany, * Present address: Max Planck Institute for molecular physiology, Dortmund, Germany, #Present address:Center for Tumor Biology and Immunology (ZTI), Clinic for Internal Medicine - Gastroenterology, Endocrinology and Metabolism, Phlipps-University Marburg, Marburg, Germany*

The class of glioma with an incidence of 5/100,000 patients is the most diagnosed type of primary brain tumors. Despite intensive research andimproved therapy strategies the prognosis of high-grade glioma remains shattering.For high-grade glioma the survival time still averages 15months whereas 3 years are common for low-grade glioma, both dependingon the grade of malignancy which is categorized by the World Health Organization (WHO). Glioblastoma multiforme correspond to the WHO class IV and represents the most malignant form of glial tumours. Histologically thesetumors are characterized by widespread angiogenesis and the generation of pseudopalisades around necrotic areas within the tumor mass. On protein level thetumors show a prominent overexpression of the glycoprotein tenascin-c (TN-C). TN-C displays a multimodular conformation and the potential of alternative splicing of FN III domains leads to a variety of functional properties that have been described for its domains. In general, glycoproteins of the extracellular matrix (ECM) are involved in regulationof proliferation, migration and differentiation in numerous cell lineages. The functions of the ECM are initiated by small peptide sequences inserted in large constituents recognized by specific cellular receptors. In this study, we have investigated the biological effects of peptides derived from the ECM-molecules tenascin-C and collagen type IV. We compared these effects to the well-known RGD-peptide originally discovered in fibronectin. For the study of the influence of glycoproteins and corresponding peptides on the migration we used the glioma cell lines U-251-MG and U-373-MG and the sarcoma line S-117.Testing the cell lines in a modified Boyden chamber assay on filters coated with the ECM glycoproteins, glioma cells showed a strong migration response on tenascin-C and the basal lamina constituent collagen IV, in contrast to S-117 cells. To identify correlatedstimulatory motifs, synthetic peptides derived from fibronectin (6NHX-GRGDSF), tenascin-C (TN-C, VSWRAPTA) and collagen type IV (MNYYSNS) were compared. Therefore we applied the peptides either in solution in combination with ECM glycoprotein substrates, in solution in the presence of untreated membranes, or coated on the filters of the Boyden chambers. We could identify the novel tenascin-C–derived peptide motif VSWRAPTA as a migration stimulus for glioma cells. Furthermore, though kin peptides blocked the effects of the corresponding ECM proteins, unexpected effects were detected in heterologous situations. Ina number of cases theadding of peptides in soluble formintenselyimproved the response to the coated ECM proteins. We conclude that peptides might synergize or antagonize each other by stimulating different signaling pathways.

NDRG1 HIGH GLIOMA EXHIBIT REDUCED VESSEL DENSITY AND SUNITINIB RESISTANCE BY TNF-SF15 UPREGULATION.

Thomas Broggini, Marie Wüstner, Lena Stange, Carina Thomé, Wolfgang Wick, Peter Vajkoczy, Marcus Czabanka
Neurosurgery, Charité Universitätsmedizin, Charitéplatz 1, Berlin Berlin, Germany, thomas.broggini@charite.de

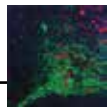
Hypoxia-regulated molecules play an important role in vascular resistance to antiangiogenic treatment. N-myc downstream-regulated-gene 1 (NDRG1) is significantly upregulated during hypoxia in glioma. It was the aim to analyse the role of NDRG1 on glioma angiogenesis and on antiangiogenic treatment. In vitro analysis included HUVEC proliferation, migration and tube formationassay under stimulation with supernatant from NDRG1transfected U87MG glioma cells and TNFSF15 promoter activity analysis. NDRG1 and control (empty vector) U87MG glioma cells were orthotopically implanted in mice (N=8 per group). Tumor growth was analyzed using repetitive MRI. Histological analysis included PECAM/Desmin staining. Genetic expression of various angiogenesis targets was performed. Sunitinib (80 mg/kg body weight, N=4-6 per group) was applied and tumor volume and vessel density were analyzed. NDRG1 supernatant resulted in reduced HUVEC proliferation, migration and angiogenic response in tube formation assays in vitro. NDRG1glioma showed reduced tumor growth (Control:61 ± 43 mm3; NDRG1:34 ± 35 mm3) and vessel density (Control:116 ± 15 n/ROI; NDRG1:79 ± 14 n/ROI) compared to controls. Molecular analysis revealed 30-fold overexpression of TNFSF15. Mutations in NF-kB and AP-1 promoter response elements suppressed TNFSF15 promoter activity. Sunitinib reduced tumor volume and vessel density in controls; in NDRG1 overexpressing cells no reduction of tumor volume (Control/Su:24 ± 24). Conclusion: NDRG1 expression in glioma reduced vascular density via increased TNFSF15 secretion. The remaining tumor blood vessels resisted anti-angiogenicSunitinib therapy.

GROWTH PROMOTING AND PRO-MIGRATORY EFFECTS OF CANCER-ASSOCIATED FIBROBLASTS ON GLIOMA CELLS IN VITRO

Petr Busek*, Jana Trylcova*, Karel Smetana Jr.‡, Eva Balaziova*, Barbora Dvorankova‡, Lucie Sromova*, AleksiSedo*
**Institute of Biochemistry and Experimental Oncology and ‡ Institute of Anatomy, First Faculty of Medicine, Charles University in Prague*

The behavior of transformed cells in epithelial cancers is significantly influenced by the cancer-associated fibroblasts (CAFs). The role of analogous mesenchymal cells is also anticipated in human gliomas. In order to determine whether CAF-like cells are present in human glioblastomas, the expression of markers typical for CAFs was evaluated by immunohistochemistry in 20 patients with newly diagnosed glioblastoma. This analysis revealed regular presence of mesenchymal cells expressing characteristic CAF markers alpha-smooth muscle actin and TE-7 in the tumor tissue.

To examine the possible role of CAFs in glioblastoma, we tested the effect of CAF conditioned media on the proliferation and chemotaxis of glioma cells. The growth of glioma cells was stimulated by CAF conditioned media, which was associated with an increase in the proportion of the Ki67 positive cells. Quantitatively similar growth enhancement was observed with the conditioned media from normal fibroblasts.Nevertheless, the CAF conditioned media significantly more potently promoted the chemotactic migration of glioma cells than the media from normal fibroblasts.



In summary, our observations confirm that stromal cells with mesenchymal characteristics are an integral component of the human glioblastoma microenvironment and suggest that these mesenchymal cells may promote glioma cell growth and migration by soluble factor(s).
Grant support:GAUK 44214, IGA 12237-5/2011, UNCE 204013, PRVOUK P27/LF1/1

A FAST FORWARD GENETICS SCREEN FOR RETROVIRUS-INDUCED BRAIN TUMOURS

Cancer M, Weishaupt H, Bunikis I, Jiang Y, Bolin S, Häggqvist S, Gyllensten U, Uhrbom L, Ameur Aand Swartling FJ
Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Sweden

Gliomas are the most common malignant brain tumours in adults,characterised by various genetic alterations. Grade IV gliomas(GBMs) have a very dismal prognosis and poor outcome. We have useda cell-type specific retroviral (Platelet-Derived Growth Factor B) PDGFB-driven murine model that closely resembles human high grade gliomas. Retroviral integration into the host genome presents a risk for insertional mutagenesis, which can alter the expression of proximate genes, thereby giving a particular tumour cell malignant advantage over the other cells during tumorigenesis. We have used whole genome sequencing (WGS) to identify genes that, together with the proto-oncogene PDGFB, contribute to tumour development. For this purpose we have developed a streamlined analysis pipeline called Integration Site DetectoR (InSiDeR) for the detection of viral integrations and their specific locations in the genome. So far, we have analysed 15PDGFB-driven gliomas and identified 22 novelcommon integration sites (CISs), sites containing that are repeatedly found in tumours and thus are more likely to collaborate with PDGFB in tumour formation. Some of the novel CISs contain loci of well-established cancer genes such as Pik3ca, commonly mutated in human glioma. Moreover, we have confirmed already published CISs in miR29and in Ppfibp1, but we also established new CISs in the Gas2, Nfic, Nrxn2, Ntrk2 and Ppp2r5b genes. In conclusion, we successfully used a novel WGS approach followed by a newly implemented analysis pipeline to identify a valuable list of potential cancer-causing genes for retrovirus-induced gliomas. We will now analyse more tumours, allowing us to reliably map novel cancer driver genes and further functionally characterise their importance in malignant brain tumour development.

LINEAGE-SPECIFIC SPLICING OF AN ALTERNATIVE EXON OF ANXA7 PROMOTES EGFR SIGNALING ACTIVATION AND TUMOR PROGRESSION IN GLIOBLASTOMA

Carro, M.S.1;Ferrarese, R.1; Bug, E.1; Maticzka, D.2; Reichardt, W.3; Bredel, M.4
1Department of Neurosurgery, Neurocenter, and Comprehensive Cancer Center, University of Freiburg, D-79106 Freiburg, Germany, 2Department of Computer Science and BIOSS Centre for Biological Signalling Studies, University of Freiburg, D-79110 Freiburg, Germany, 3Medical Physics, Department of Radiology, and Comprehensive Cancer Center, University of Freiburg, D-79106 Freiburg, Germany, 4Department of Radiation Oncology, UAB Comprehensive Cancer Center, University of Alabama at Birmingham School of Medicine, Birmingham, AL 35249, USA

Alternative splicing of pre-mRNA is crucial to increase the diversity of protein function. Splice variants may be tissue specific and, in some cancers, their transcription may contribute to the transformed phenotype. In the brain, the membrane-binding tumor suppressor Annexin A7 (ANXA7) isoform 1 (ANXA7-I1) is exclusively expressed in mature neurons, while isoform 2 (ANXA7-I2) in which exon 6 is skipped, is expressed in glial and progenitor cells. In our recent work (Ferrarese et al., 2014), we show that lineage-specific splicing of ANXA7 exon 6 diminishes endosomal targeting and consequent signal termination of the EGFR oncoprotein during brain tumor progression. Our study shows that splicing of this exon is mediated by Polypyrimidine Tract-Binding Protein 1 (PTBP1), a ribonucleoprotein normally repressed during neuronal development but which we found to be highly expressed in Glioblastoma (GBM) through loss of a brain-enriched microRNA, miR-124 and gene amplification.In vivo, intracranial injection of GBM cells upon PTBP1 knockdown leads to the formation of small, finger-shaped clusters of tumor cells around vessels, referred to as satellites, which are associated with inhibition of neovascularization; a phenotype previously observed upon treatment with a monoclonal antibody against VEGFR-2. We further confirmed the role for PTBP1 in tumor angiogenesis using patient-derived BTSCs with high endogenous PTBP1 expression. Overall, our data illustrate how lineage-specific splicing of a tissue-regulated alternative exon eliminates its tumor suppressor function and promotes glioblastoma progression. The observation that PTBP1 controls angiogenesis in vivo indicates that PTBP1 could represent a new potential target for brain tumor treatment.
Reference
Ferrarese et al. J Clin Invest. 2014 Jul;124(7):2861-76

CD44 VARIANT REGULATES XCT AND PROMOTES ANGIOGENESIS IN GLIOMA CELLS

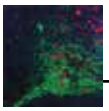
Daishi Chen, Zheng Fan, Michael Buchfelder, Ilker Eyüpoglu, Nicolai E. Savaskan
Department of Neurosurgery, Medical Faculty of the Friedrich Alexander University of Erlangen-Nürnberg (FAU)

Introduction:The cell surface glycoprotein CD44,especially its variant isoform v8-10, is thought to play important roles in tumor growth, metastasis, angiogenesis and therapy-resistance. However, the functional relevance of CD44 in glioma cells remains elusive. Thereforewe carried outthis study to determine the function and mechanism of CD44vin glioma cells. Further, we tested CD44v regulated xCT. Methods: Glioma cells were transfected with human CD44v8-10 and CD44 specific shRNA and stable cell lines were generated. CD44 wasquantitated by qRT-PCR. We determined the amino acidsecretion in glioma cells.Cell viability was assessed with MTT assay andpropidium iodide (PI) staining. CD44 overexpression and knockdown glioma cells were implanted in mouse brain (P5) sections for 7 days to analyze cell death in tumor zone II and tumor angiogenesis. Result:RT-PCR revealed that CD44 variant (CD44v8-10) regulatedxCT, a glutamate-cystine transporter, and controlled the level of glutamate uptake and cystine release. CD44 knockdown induced loss of xCT in glioma cells and suppressed tumor angiogenesis ex vivo. CD44v8-10 expressing glioma cells wereresistance to sorafenib anderastin-induced cytotoxicity. Conversely, CD44 knockdown sensitizes glioma cells to sorafenib anderastin-induced apoptosis. Notably, DFO prevented sorafenib anderastin-induced growth inhibition in CD44 knockdown gliomas, whereas overexpression of CD44 inhibits sorafenib anderastinferroptosis. Conclusion:These findings suggest that CD44v8-10-xCTregulates the glioma progression and CD44 is a potentialtherapeutic target of glioma.

A CSC-PLATFORM FOR DRUG DISCOVERY AND TARGET VALIDATION IN GLIOMA

Vaslin A1, Marino D1,2, Teta P1,2, Lembrez N1, Fessard T3, Carrera E3 and Clément-Schatlo V1,2
1Stemergie Biotechnology SA, rue de la roseraie 64, 1205 Geneva, Switzerland, 2University of Geneva, rue Michel-Servet 1, 1211 Geneva, Switzerland, 3ETH Zurich, Wolfgang-Pauli Strasse 10, 8039 Zurich, Switzerland

Glioblastoma multiforme (GBM) are among the most devastating of cancers, often with a mean survival period of 15 months following diagnosis. The current choice of drug is temozolomide, which at best prolongs survival by a few months, and nevertheless has annual sales of U.S.$1 billion in United States. Consequently, new therapeutic strategies that effectively target the lethal aspect of this cancer are in great demand.GBM tumors are highly infiltrative and can arise from cells with extensive self-renewal capability, tumorigenic capacity and chemoresistance, frequently termed glioma-initiating cells (GICs) or Cancer Stem Cell (CSC). GICs are thus the plausible culprits of tumor recurrence. Treatment strategies such as the one we are developing at Stemergie that target GICs, and therefore focus on eradicating the cause of tumor reccurence, will greatly improve disease outcome. Such findings support the use of GICs as in vitro cellular systems for small-molecule screening. Nevertheless, the use of those primary GICs in cellular screening platform is not trivial for the following reasons: i) These slow-growing cells are typically cultured as suspension, spheroid structures in serum-free condition supplemented with growth factors. Consequently, replenishment of growth factors throughout the screening period must occur to maintain cells in their undifferentiated state. ii) GICs have frequently been associated with several marker profiles. However, such marker expression has generated conflicting data. iii) Conventional tumor cell screening typically involves short-term viability



readouts of adherent monolayer cells upon drug treatment. When working with GICs, the bona fide self-renewal propertiy of slow-growing cells cannot be accurately detected in short-term viability assays as the latter also measure other transient-amplifying progenitors in the heterogeneous spheres. iv) GICs express MDR channels (multidrug resistant channels) that pump out drugs. Taking into considerations these critical points, we focused on designing and implementing a specific CSC_platform, which articulates into 3 modules and which most closely replicates the physiological nature of GBM.

EXPRESSION LEVEL OF SOX2 IN CANCER STEM CELLS REGULATES GLIOBLASTOMA DEVELOPMENT

Combeau G., Karlèn A., Kurstdotter I., Muhr J.
Cellular and Molecular Biology (CMB), Karolinska Institut, Nöbel väg 3, 17177 Stockholm, eMail: gaelle.combeau@licr.ki.se

Glioblastoma is the most common and lethal primary brain tumor in adults. During the last century, the Cancer Stem Cells (CSC) theory suggested that some cells within the tumor might drive cancer formation. Such CSCs have been isolated from human glioblastomas (1) and are characterized by their self-renewal capacity, expression of stem cells markers and a high tumorigenicity potential. Among the stem cell markers expressed, the transcription factor Sox2 has been detected in the cell fraction displaying properties of CSC (2). We have recently demonstrated that high expression levels of Sox2 are restricted to slow cycling cells in the embryonic and adult brain (3). Interestingly, a cancer data-base shows that glioblastoma patients expressing high levels of Sox2 survive longer than those expressing lower levels of this protein. In this study, we investigate the link between Sox2 expression levels and glioblastoma development. The overexpression of Sox2 in glioblastoma cell lines decreases their proliferation capacity and tumor-forming potential in NOD-SCID mice, compared to those cells expressing lower levels of Sox2. Together, these data suggest that high levels of Sox2 are sufficient to induce a slow self-renewing state in glioblastoma cells, a key trait of CSCs.

(1) Galli et al (2004) Isolation and Characterization of Tumorigenic, Stem-like Neural Precursors from Human Glioblastoma. Cancer Research 64, 7011–7021 (2) Favaro et al (2014). Sox2 is required to maintain cancer stem cells in a mouse model of high-grade oligodendroglioma. Cancer Res. 2014 Mar 15;74(6):1833-44. doi: 10.1158/0008-5472. (3) Hagey and Muhr (2014) Sox2 Acts in a Dose-Dependent Fashion to Regulate Proliferation of Cortical Progenitors Cell report, Volume 9, Issue 5, 11 December 2014, Pages 1908–1920

SURVIVIN AND MYC-N OVEREXPRESSION INCREASES TUMORIGENIC PROPERTIES OF U373-MG CELLS IN NMRI-FOXN1NU /FOXN1NU MICE

Marina Conde; Ralf Wiedemuth; Isabell Düring; Gabriele Schackert; Hans Achim Temme
Section Experimental Neurosurgery/ Tumor Immunology, Department of Neurosurgery. University Hospital Carl Gustav Carus, TU Dresden

Survivin, which belongs to the family of inhibitor of apoptosis proteins (IAPs), assembles with the chromosomal passenger complex and regulates chromosomal segregation and cytokinesis. Together with its molecular partners INCENP, Aurora B and Borealin it safeguards bi-orientated sister chromatid segregation and cytokinesis. Overexpression of Survivin has originally been described to inhibit apoptosis. Yet, our in vitro studies discovered mitotic defects, aneuploidy, chromosomal instability and DNA damage in glioma cells overexpressing Survivin. Further in vivo studies using U373-MG cells subsequently transduced with lentiviral vectors encoding for Survivin and myc-N, or transduced with Survivin and myc-N alone, respectively, revealed enhanced proliferation of Survivin/myc-N-transduced tumors when compared to tumors expressing myc-N alone. Noteworthy, Survivin-transduced U373-MG and mock controls failed to induce tumors. Histology of U373Survivin/myc-N tumours showed pronounced nuclear polymorphism, numerous atypical mitoses and an increased nuclear-to-cytoplasmic ratio. To determine the mechanisms by which the combined overexpression of Survivin and myc N led to a more aggressive tumour growth in vivo, tumors were stained for Ki67. Apoptosis was assessed using TUNEL staining. The proliferation index of Survivin/myc-N tumours was similar when compared to myc-N tumors, whereas apoptosis was significantly decreased. In conclusion, these data indicate that Survivin, in collaboration with myc-N, facilitates tumorigenic properties of cancer cells including decreased latency, enhanced growth and decreased apoptosis.

PODOPLANIN IN A NEURAL STEM CELL-SPECIFIC GLIOMA MODEL

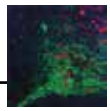
Barbara Costa1, Tanja Eisemann1,Jens Strelau2, Ingrid Spaan1, Hai-kun Liu3, Peter Angel1, Heike Peterziel1
1.Transduction and Growth Control, DKFZ/ZMBH Alliance, Heidelberg, Germany, 2. Functional Anatomy, University of Heidelberg, Heidelberg, Germany, 3. Normal and Neoplastic CNS Stem Cells, DKFZ/ZMBH Alliance, Heidelberg, Germany

High expression of podoplanin (PDPN), a mucin-type transmembrane protein,is associated with shorter overall survival in primary glioblastoma (GB).We showed previously that mutation or deletion of PTEN,as frequently observed in human glioma, leads to Pdpn promoter activation. Consistently, in a novel genetic mouse model of glioma where neural stem cell-specific deletion of Pten- and p53-floxed alleles is achieved by tamoxifen-inducible Cre-recombinase under control of the orphan nuclear receptor tailless (Tlx)–promoter($p53^{flox/flox}$,$Pten^{flox/flox}$,Tlx-CreERT2), PDPN expression is strongly increasedboth atearly pre-malignant stages as well as in the established tumors. To assess PDPNcontribution to glioma formation we ablated its expression by introducing Pdpnconditional alleles into the $p53^{flox/flox}$,$Pten^{flox/flox}$,Tlx-CreERT2 glioma model, obtaining mice that are $p53^{flox/flox}$,$Pten^{flox/flox}$,$Pdpn^{flox/flox}$,Tlx-CreERT2. For simplicitymice lacking Pten and p53 are hence called double knock out (DKO) and mice additionally deleted for Pdpntriple knock out (TKO). Our preliminary studies show that neural stem cells (NSC) isolated from TKO mice proliferate less and have lower levels of c-Myc expression compared to DKO cells. Characterizationof the histopathology of glioma tumors arising from DKO and TKO mice, complemented by analyses of thein vitroclonogenic ability, chemotherapy resistance and differentiation and migration capacity of DKO and TKO NSC in vitrowill elucidate the role of PDPN in glioma formation and progression. Furthermore, our studies will clarify whether interference with PDPN may constitute a promising therapeutic strategy for the treatment of GB.

TARGETING THE MIDKINE / ANAPLASTIC LYMPHOMA KINASE AXIS AS A THERAPEUTIC STRATEGY IN GBM

David Dávila1, Israel López-Valero1,2, Mar Lorente1, Sonia Hernández-Tiedra1, Sofía Torres3, José González1, Aurelio Hernández Laín4, Pilar Sánchez-Gómez5, Juan Sepúlveda4 and Guillermo Velasco1,2.
1Deparment of Biochemistry and Molecular Biology I, School of Biology, Complutense University. 2Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC). 3Department of Cellular and Molecular Medicine, Centro de Investigaciones Biológicas (CIB-CSIC). 4Instituto de Investigación i+12, Hospital Universitario 12 de Octubre, Madrid, Spain. 5Neuro-Oncology Unit, Instituto de Salud Carlos III-UFIEC, Madrid, Spain.

Glioblastoma Multiforme (GBM) is the most frequent and aggressive class of malignant primary brain tumor. Important characteristics of GBMs are their high resistance to radio- / chemo-therapy and their recurrence, which occurs in practically all GBM patients. These features could be explained by the presence within the tumour mass of a small subpopulation of cells termed Glioma Stem-like Cells (GSCs) or Glioma Initiating Cells (GICs), due to their similarity with the normal Stem Cells and to their capacity to initiate and maintain tumour growth. Therefore, GICs elimination is considered a priority to fight GBM. Our group had previously found that increased expression of the growth factor Midkine (MK) correlates with a decreased survival of GBM patients, suggesting a possible role of MK in GBM initiation and growth. Likewise, we had found that MK promotes resistance to the anticancer action of Cannabinoids (a family of antineoplastic agents derived from Cannabis Sativa) via activation of the Anaplasic Lymphoma Kinase tyrosine kinase receptor (ALK). In this work we investigated the role of the MK/ALK axis in GICs. We found that MK levels are strikingly increased in the GIC population and that this event contributes to maintain their stem cell features. Moreover, both the pharmacologic and the genetic inhibition of the MK/ALK axis prevented the growth of GICs-derived tumour xenografts in mice. Furthermore, enhanced MK expression in neuronal stem cells and pro



genitors cellular functions that are associated with glioma malignancy. (Nestin+ cells) facilitated the growth of Platelet-derived growth factor B (PDGFB)-induced gliomas in Tg-nestin TVA mice. We also found that the combined administration of Cannabinoids and inhibitors of the MK/ALK axis leads to sustained activation of autophagy and the subsequent activation apoptotic death of GICs, which in turn leads to the almost complete elimination of GICs in vitro. Taken together, our findings support that the MK/ALK axis plays a prominent role in the regulation of GICs and that blockade of this axis could be a potential therapeutic strategy to target GIC population in GBM.

THE ROLE OF PODOPLANIN IN A PATIENT-DERIVED MOUSE MODEL OF GLIOMA

Tanja Eisemann1, Barbara Costa1, Ana Martín-Villalba2, Michel Mittelbronn3, Peter Angel1, Heike Peterziel1
Divisions of 1Signaltransduction and Growth Control and 2Molecular Neurobiology, DKFZ/ZMBH Alliance, Heidelberg, Germany; 3Institute of Neurology (Edinger Institute), Goethe University, Frankfurt, Germany

Glioblastoma (GB) is the most frequentand most malignant primary brain tumor in humans with a median survival of 12 months. Despite extensive surgical resection, chemo- and radiotherapy GB is still considered incurable. The infiltrative growth of GB cells along distinct anatomic structures results in incomplete surgical resection and eventual repopulation of the tumor representing the major hurdle in GB therapy. The transmembrane protein PDPN is expressed in a variety of human tissues including the brain. Whilephysiologic expression of PDPN in the brain is restricted to the choroid plexus and to the ependymal layer of the lateral ventricles, PDPN has been shown to be strongly expressed in primary glioma correlating with shorter overall survival. PDPN is predominantly present at the invasive edge of tumors. We have shown that knock-down of PDPN expression in established glioma cell lines results in decreased proliferation and migration in vitro and in a reduction of growth of intracranial tumor xenograftsindicating a malignant role of PDPN in GB invasion and progression. This study aims to investigate the functional roleof PDPN in GBusing primary human tumor material.In vitro and ex vivo analyses will address the functional consequences and the molecular mechanisms of CRISPR-mediated PDPN deletion ontumor cell proliferation, migration and therapy resistance.Moreover, patient-derived xenograft models will serve to assess the effect of PDPN-depletion ontumor growth, invasionand survival. Taken together, this study will give insight into the functional role of PDPN in GBprogression and clarify whether targeting PDPN could be a promising strategy for the treatment of GB patients.

CCR2-DEFICIENCY OF MICROGLIA/MACROPHAGES RESULTED IN ENHANCED GLIOMA PROGRESSION

Matthäus Felsenstein, Susan Brandenburg, Jonas Raggatz, Kati Turkowski, Peter Vajkoczy
Charité – Universitätsmedizin Berlin, Institute of Experimental Neurosurgery

Glioblastoma multiforme belongs to highly malignant brain tumors with particularly aggressive and invasive properties. An additional feature is the accumulation of microglia/macrophages within these tumors. Previously we found an up-regulation of CCR2 in microglia/macrophages of glioma-bearing mice. Therefore, we focused on the function of CCR2-signaling for migration of myeloid cells to glioma tissue and its role in glioma progression. Glioma cells (GL261) were implanted stereotactically into the brain parenchyma of transgenic CCR2ko and wildtype BL6/J mice. Infiltrated microglia/macrophages and tumor vascularization were analyzed by immunofluorescence stainings or FACS. Moreover, magnetic resonance imaging (MRI) was used to measure tumor volumes. Investigating the myeloid cell distribution, a reduced infiltration of microglia/macrophages intratumoral was observed within CCR2ko mice, while remaining myeloid cells express characteristic microglia/macrophage marker and antigen-presenting molecules (MHCI/II). Remarkably, at all analyzed time points of tumor growth, we observed increased glioma sizes in CCR2-deficient animals, whereas at day 21 volumes were doubled based on a highly amplified proliferative activity of tumor cells. Surprisingly, here the vessel density in the tumor tissue was unchanged but detailed analyses of the vasculature revealed an angiogenic phenotype. Here, the vessels showed remodeling and a higher maturation level within the tumor of transgenic mice. Infiltration of microglia/macrophages into the tumor tissue of CCR2ko mice is significantly decreased and accompanied by accelerated tumor growth implying that myeloid cells have potential anti-tumoral functions. Thus, our data demonstrate the CCR2-CCL2 pathway as a crucial signal in the context of microglia/macrophage accumulation and glioma progression.

STEM CELL MARKERS IN GLIOBLASTOMAS: COMPARATIVE ANALYSIS OF MATCHED PRIMARY AND RECURRENT TUMORS

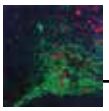
Flüh, C.1; Hattermann, K.2; Mehdorn, H.M.1; Mentlein, R.2; Held-Feindt, J.1
1Klinik fürNeurochirurgie, UKSH, Campus Kiel, Arnold-Heller-Str. 3, Haus 41, 24105 Kiel, Germany; 2Anatomisches Institut, CAU zu Kiel, Olshausenstr. 40, 24118 Kiel, Germany

Glioblastomas (GBMs) show a variety of cells with many differentiation levels. Since cells with stem cell properties have a major influence on tumor malignancy and progression and comparative studies of stem cell markers on primary WHO grade IV GBMs versus relapses are currently not available, here 14 matched pairs of primary and recurrent GBMs were analyzed by qPCR for expression of Sox2, Nanog, Klf4, Oct4, Musashi-1, c-Myc, and the chemokine receptors CXCR4 and CXCR7. Double-immunofluorescence staining for all markers was performed on 3 matched tumor samples. The number of cells positively stained for Oct4, Klf4 and Sox2 was counted in samples costained for CXCR4 and CXCR7 in situ. In addition, the influence of temozolomide and camptothecin on neural stem cell marker expression was examined by qPCR. We showed that the expression of c-Myc ($p<0.01$) and CXCR7 ($p<0.05$) decreased in recurrent GBMs compared to primary tumors. No alteration was seen for Musashi-1, Oct4, Klf4, Sox2, Nanog, and CXCR4. Additionally, we observed an upregulation of expression of Klf4 ($p24h<0.01$, $p48h<0.001$) and Oct4 ($p48h<0.01$) by temozolomide and camptothecin (Klf4: p24h, $48h<0.01$) in T98G cells, whereas Oct4 was downregulated after camptothecin treatment ($p24h<0.01$). Similar effects were seen in A172 cells (Klf4: $p48h<0.01$). We conclude that neural stem cell markers are complexly involved in tumor progression of GBMs and that chemotherapy has an effect on their transcriptional regulation. As neural stem cell markers are key structures for differentiation in GBM cells, this implies a potential role concerning prognosis and receptivity for chemotherapy in practice.

GAPVAC: A NOVEL CONCEPT OF ACTIVELY PERSONALIZED CANCER IMMUNOTHERAPY FOR GLIOBLASTOMA

Frenzel K.1, Hilf N.2, Heesch S.1, Kuttruff-Coqui S.2, Lindner J.2, Admon A.3, Britten C.M.4, Bukur V.1, van der Burg S.H.4,5, Castle J.6, Diekmann J.1, Dorner S.2, Fritsche J.2, Gouttefangeas C.4,7, Kreiter S.1,6, Kroep J.R.5, Lassen U.8, Lewandrowski P.2, Löwer M.6, Martinez-Ricarte F.9, Maurer D.2, Mendrzyk R.2, Meyer M.2, Müllar S.2, Müller F.1, Okada H.10, Ottensmeier C.11, Paruzynski A.1, Pawlowski N.2, Piro J.12, Ponsati B.12, Poulsen H.S.8, Rössler B.2, Sahuquillo J.9, Al-Salihi O.13, Schoor O.2, Song C.2, Stevanovic S.7, Stevermann L.2, Tabatabai G.14, thor Straten P.8, Wagner C.2, Walter S.2, Weinschenk T.2, Huber C.4, Rammensee H.-G.7, Dietrich P.-Y.15, Wick W.16, Singh-Jasuja H.2, Sahin U.1
1BioNTech Group, Mainz, Germany, 2immatics biotechnologies GmbH, Tuebingen, Germany, 3TECHNION - Israel Institute of Technology, Haifa, Israel, 4CIMT - Association for Cancer Immunotherapy, Mainz, Germany, 5Leiden University Medical Center, Leiden, Netherlands, 6TRON -Translational Oncology at the University Medical Center Mainz, Mainz, Germany, 7Eberhard Karls University Tuebingen, Tuebingen, Germany, 8Copenhagen University Hospital, Herlev, Denmark, 9Vall d'Hebron University Hospital, UniversitatAutònoma de Barcelona, Barcelona, Spain, 10University of California San Francisco, Department of Neurological Surgery, San Francisco, United States, 11University of Southampton, Southampton, United Kingdom, 12BCN Peptides S.A, Barcelona, Spain, 13Southampton General Hospital, Southampton, United Kingdom, 14University Hospital Tübingen, Interdisciplinary Division of Neurooncology, Tuebingen, Germany, 15Université de Genève, Genève, Switzerland, 16University Hospital Heidelberg, Heidelberg, Germany

The Glioma Actively Personalized Vaccine Consortium (GAPVAC) is a European consortium aiming to introduce a new concept of immunotherapy in a multicenter first-in-human trial in patients with glioblastoma (GB). GAPVAC takes personalization to the next level by engaging multiple independent methodologies (NGS, HLA peptido



mics, transcriptomics, immunogenicity screening) to characterize the individual disease and patient's immune system in depth and to guide the manufacturing of a unique therapeutic cancer vaccine for every patient. For every patient two actively personalized vaccines (termed APVACs) will be subsequently administered and up to 30 patients with newly diagnosed, fully resectable GB will be enrolled. The first vaccine will consist of a tailored selection of 5 to 10 peptides chosen from a pre-manufactured warehouse. Peptides containing tumor-specific mutations and non-mutated, individually over-presented peptides not contained in the warehouse may be selected into the second vaccine and be produced de novo for every patient. This innovative project will be introduced to the community and firstpreclinical and clinical data are presented:(i) Feasibility tests of the multi-disciplinary process for the APVAC drug development were successful.In all test runs, the peptide compositions of both APVACs were defined within the predetermined ambitious time. (ii) A huge effort was undertaken to establish the logistics of sample and data transfer. In addition, manufacturing of approx. 70 warehouse peptides has been completed.(iii) In a joint effort, the CTA documents were finalized and the German national authority approved the start of GAPVAC-101 trial.Opening of sites in Spain, Switzerland, Denmark, Netherlands, UK and the USA is ongoing. (iv) With the enrollment of the first patients the novel and ambitious concept of actively personalized cancer immunotherapy has been realized in the clinical setting.

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MIF IS A NOVEL ANGIOGENIC REGULATOR FOR GLIOMAS

Ali Ghoochani1, Eduard Yakubov1,Michael Buchfelder1,Ilker Y. Eyüpoglu1, Nicolai E. Savaskan1

1Department of Neurosurgery, Universitätsklinikum Erlangen, Medical Faculty of the Friedrich Alexander University of Erlangen-Nürnberg (FAU), D-91054 Erlangen, Germany.

Introduction: Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine which is secreted by different tumor cells to modify tumor microenvironment. Recent studies propose that MIF cytokine enablesto recruit endothelial cells as an angiogenic factor. Therefore, we investigated the role of MIF in tumor induced angiogenesis. Methods: Vascular glioma invasion ex vivo method (VOGIM) was facilitated to evaluate glioma induced angiogenesis. We implanted MIF overexpression or knockdown glioma cells into rodent brainsand analyzed angiogenesis. Furthermore, we used MIF-knockout mice and C57BL/6 mice as wild type (WT)to observe direct influence of MIF on vascularization during CNS development. Total vessels length, number of branch points, endothelial tip number and characterization of sprouting activity (e.g., filopedia number and length) were measured to evaluate retinal and brain vascularization. Results:MIF overexpression in glioma cells significantly increased vessels migration into tumor area while MIF knockdowndisplayed reduced angiogenesis. In addition, treatment of tumor cells with recombinant MIF induced more angiogenesis in tumor area.Conversely, blocking of CD74 as MIF receptor reduced vascularization. Furthermore, analysis of ERK signaling pathway as angiogenic regulator demonstrated MIF treatment did not only increased ERK activation but also induced VEGF A and B expression in endothelial cells. In second line of experiment, MIF-knockout mice revealed reduced brain vessel density in postnatal mice. Retinal vascularization also confirmedfilopedia length shortly formed in MIF-knockout mice which means less vascular radial migration rate. Conclusion: Our results evidencedMIF cytokine is an angiogenic regulator secreted by glioma cells. Furthermore, we found that MIF is a modulator of angiogenesis during CNS development.

TREATMENT WITH EPIGALLOCATECHIN GALLATE (EGCG) INDUCES OXIDATIVE STRESS IN HUMAN GLIOBLASTOMA CELLS

Susanne Grube, Christine Kögler, Diana Freitag, Rolf Kalff, Christian Ewald

Department of Neurosurgery, Section of Experimental Neurooncology, University Hospital Jena, Friedrich Schiller University Jena

The anti-proliferative effects of the green tea main constituent epigallocatechin gallate (EGCG) are the result of regulation of the cell cycle, inhibition of cell proliferation,andinduction of oxidative stress in tumor cells. In prior experiments we showed a slight time dependent decrease in viability of primary glioblastoma cells under the influence of EGCGin physiologically reachable concentrations.Here weanalyseits influence on the redox state of these cells. Aprimaryglioblastoma cell culture was incubated with of 100nM of EGCG over six hours. By detection of reactive oxygen species (ROS, Cell-ROX), lipid peroxidation (TBARS) and nitrogen species (NO, DAF FM-DA) the oxidative effects of EGCG were determined. Additionally the expression of iNOS, NOX4, and-SOD1 was measured by qPCR. In the cultured cells, ROS production and lipidperoxidation wereinduced (33% and 11%) within 6h of treatment.As qPCR revealed, the NADPH oxidase NOX4was 5.7 fold up-regulated to produce superoxide, whereas the superoxide dismutase SOD1 was 1.27 fold down-regulated. Large amounts of reactive NO are generated, shown by the two fold increase in the microscopic determination of NO production and a 2.6 fold up-regulation of the inducible NO synthase (iNOS). Our data show that in a physiological concentration EGCG induces strong oxidative stressinglioblastoma cells. NO will react readily with superoxide, produced by SOD1 and produce large amounts of peroxynitrite, which will cause protein nitration deleterious to the tumor cells. Large amounts of NO damage DNA strands directly by deamination, leading to apoptosis.According to our data, drinking green tea or taking green tea concentrate as nutritional supplement can be anti-proliferative even for intracranial tumors.

"INVERSE SIGNALING" OF THE TRANSMEMBRANE CHEMOKINE CXCL16 IN HUMAN MENINGIOMAS AS A NEW CONCEPT TO FAVOR TUMOR PROGRESSION

Kirsten Hattermann,1Kareen Bartsch,2Henrike Gebhardt,1 Maximilian Mehdorn, 2Rolf Mentlein,1Janka Held-Feindt 2

1Institute of Anatomy, University Kiel, 24098 Kiel, Germany, 2Department of Neurosurgery, University Medical Center Schleswig-Holstein UKSH, Campus Kiel, 24105 Kiel, Germany

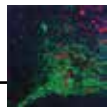
Meningiomas are slowly growing benign tumors, however, anaplastic meningiomas(WHO grade III) have an aggressive biological and clinical behavior. Since recent investigations have suggested a possible role of chemokines in tumor biology, the aim of the study was to investigate the expression and functional role of the transmembrane chemokine CXCL16 and its receptor CXCR6 in human meningiomas. Quantitative RT-PCR revealed a distinct expression in solid human meningioma samples, and double-immunostainingshowed a predominant expression of the chemokine/-receptor pairin the tumor cells themselves, in infiltrating microglia cells/macrophages and endothelial cells of blood vessels. Interestingly, cultured human meningioma cells were characterized only by the expression of the chemokine ligand CXCL16, lackingthe corresponding receptor. Nevertheless, cultured human CXCL16-positive meningiomas bound soluble CXCL16 and responded after stimulation with the chemokine by phosphorylation of the kinasesERK and Akt in a time-dependent manner. Same results were observed when using a CXCL16-specific antibody. Additionally, enhanced proliferation and rescue from apoptosis were measuredin CXCL16-positive meningioma cells after stimulation withsoluble CXCL16. Since intracellular signaling effects and binding experiments were repressed afterCXCL16 silencing (RNAi), we concluded that the transmembrane ligand itself acts as a receptor and generates auto-/paracrine signals ("inverse signaling"). In this view, our results provide an interesting basis for further investigations on the functional roles of chemokines/-receptors in human meningiomas.

IDENTIFICATION AND CHARACTERIZATION OF C-JUN-N-TERMINAL PHOSPHORYLATION AS A REGULATOR OF DNA-METHYLTRANSFERASE 1 AND GENOME-WIDE METHYLATION IN GLIOBLASTOMA

Heiland D.H.1, Ferrarese R. 1, Claus, R.2, Weyerbrock A. 1, Sven Nelander 3, Carro M.S. 1

1Department of Neurosurgery, University Medical Center Freiburg, Freiburg, Germany, 2Department of Hematology, Oncology, and Stem Cell Transplantation, University of Freiburg Medical Center, Freiburg, Germany, 3Department of Immunology, Genetics and Pathology and Science for Life Laboratories, University of Uppsala, Uppsala, Sweden

Objective: High-grade gliomas (HGG) are the most common brain tumors with an average survival of 14 months. A large number of highly methylated gene loci (G-CIMP) are associated with the proneural subgroup and better clinical outcome. Our aim was to identify and characterize putative transcription factors, which are involved in the regulation of genome-wide methylation in glioblastoma (GBM). Method: Analysis of the The Cancer Proteome Atlas (TCPA; http://bioinformatics.mdanderson.org/main/TCPA:Overview) was perfor-



med to detect protein modification specifically associated to GBM subclasses. We found that phosphorylated c-Jun (serine 73) was significantly inversely associated to the mesenchymal group of GBM. Different patient-derived GBM cells, characterized as mesenchymal or proneural, were used to validate the TCPA results. Cell behaviour was evaluated using a scratch assay and invasions assay in two proneural and one mesenchymal cell lines treated with an activator (Anisomycin) or inhibitor (SP600125) of the JNK pathway. The methylation status of treated cells was detected by Infinium Human Methylation 450k and analysed with R-software (RnBeads and additional packages). Chromatin-bound phosphorylated c-Jun was immunoprecipitated to evaluate the enrichment on the DNMT1 promoter. The expression of 3 key mesenchymal markers (CHI3L1, MMP9 and CD44) was analysed by western blot, immunostaining and quantitative real-time PCR (qRT-PCR). Results: Analysis of the TCGA (The Cancer Genome Atlas) database showed that phosphorylated c-Jun (serine 73) was significantly inversely associated to the mesenchymal group of GBM. By influencing the JNK pathway and consequently the phosphorylation of c-Jun we detected significant changes in cell behavior and expression of mesenchymal signature genes (CHI3L1, MMP9 and CD44). An increase of phosphorylated c-Jun resulted in a less aggressive cell behavior with significant lower expression of genes connected to the mesenchymal subtype and increased expression of DNA methylatransferase-1 (DNMT1) whereas reduction in phosphorylation had the opposite effect. The methylation array detected an increase in global DNA methylation upon increase of phosphorylated c-Jun and a loss of DNA methylation in JNK-inhibited cells. Chromatin immunoprecipitation showed a significant enrichment of phosphorylated c-Jun binding to the DNMT1 promoter. Conclusion: We show that the phosphorylation status of c-Jun influences the genome-wide methylation status by directly regulation DNMT1 expression. These data suggest that the JNK pathway plays an important role in the development of GBM methylated phenotype and the associated less aggressive behavior. This pathway might therefore be a potential target for personalized GBM treatment.

INTERACTIVE PAN-CANCER NETWORKS USING GENERALIZED COVARIANCE SELECTION AND A CUSTOM WEB APPLICATION

Teresia Kling*1,2, Patrik Johansson*1, Jose Sanchez3, Voichita D. Marinescu1, Rebecka Jörnsten3, Sven Nelander1

(1) IGP and Science for Life Laboratory, Uppsala University, Rudbecklaboratoriet, SE-751 85 Uppsala, Sweden, (2) Sahlgrenska Cancer Center and Dept of Molecular and Clinical Medicine, University of Gothenburg, Box 425, SE-40530, Sweden, (3) Mathematical Sciences, University of Gothenburg and Chalmers University of Technology, SE-412 96 Gothenburg, Sweden

Statistical network modeling techniques are increasingly useful tools for analyzing cancer genomics data. Comprehensive pan-cancer datasets such as The Cancer Genome Atlas (TCGA) actualize the need for techniques and tools working across multiple platforms and diagnoses. Cancer Landscapes is a data driven network modeling technique combined with a publicly accessible tool for exploring pan-cancer networks (cancerlandscapes.org), linked to several pathway and pharmacological databases. The network inference method, based on generalized sparse inverse covariance selection (SICS), was evaluated on a set of 3900 TCGA cancers spanning 8 cancers. The method rediscovered known mechanisms and contained promising predictions. Possible applications of this approach include prediction of regulatory relationships, comparison of network modules across multiple forms of cancer, and identification of drug targets.

THERAPEUTIC EFFICACY OF THE MULTI-RECEPTOR TYROSINE KINASE INHIBITOR AXITINIB IN AN INTRACRANIAL XENOGRAFT MOUSE MODEL OF HUMAN GLIOBLASTOMA

Theresa Kahlert, Diana Freitag, Christian Ewald, Rolf Kalff, Jan Walter

Department of Neurosurgery, University Hospital Jena, Friedrich-Schiller-University, Jena, Germany

Objective:Multi-receptor-tyrosine kinase (RTK) inhibition in general and anti-angiogenic therapy in particular are promising strategies in treatment of glioblastoma. The effect of axitinib, a small molecule multi-tyrosine kinase inhibitor, is based on the selective inhibition of VEGRF-1,-2 and -3 as well as c-KIT (CD117) and in parts PDGFR-alpha,-beta which are very much involved in vascularisation and tumour growth. Its efficacy was already proven clinically in treatment of lung cancer (NSCLC), thyroid and renal cell cancer. Therefor we show its efficacy in an intracranial xenograft mouse model of human GBM. Methods: For intracranial tumour establishment 1x10^6 LN229 tumour cells were stereotactically injected in 22 8-10 weeks old female immunodeficient SCID mice. Thereafter mice were randomly divided in three groups and tumour growth was demonstrated using 3T-MRI (t0, FLAIR, T1+/- Gd) after two weeks. In treatment group 1 (11mice) orally application with axitinib (25mg/kg) and in group 2 (5mice) vehicle solution was undertaken twice a day for another two weeks. A second MRI (t1) was performed after treatment completion. Group 1 and 2 were compared to untreated mice (n=6) in control group 3 in terms of tumour size and oedema volume, together with overall survival, health status, body weight and neurological symptoms. Animals were sacrificed when showing significant deterioration or neurological deficits. After death rodent brains were dissected and analysed histopathologically. Results: The anti-angiocenic effect of axitinib was shown in all treated mice. Animals of group 1 presented with distinct deceleration in further tumour growth as well as decreased FLAIR and tumour-signal compared to group 2 and 3. Additionally, contrast-agent took several minutes longer to spread in the tumour after treatment with axitinib was performed. Moreover, untreated mice exposed obvious tumour progression associated symptoms like seizures, hydrocephalus, hemiparesisand changes in behaviour than the treatment arm. Reduced vessel density and fewer vascular abnormalities in group 1 were revealed by morphological and histopathological analysis. On top of that axitinib-treated mice showed prolonged overall survival. Conclusion: This in-vivo study demonstrates that the multi-RTK inhibitor axitinib exhibits anti-tumour and anti-angiogenic activity, resulting in a modestly prolonged survival of mice bearing orthotopic intracranial GBMs. The results support further investigation of axitinib as targeted anti-angiogenic and anti-proliferative agent GBM treatment.

KNOCKDOWN OF OSTEOPONTIN IN C6 GLIOMA CELLS INFLUENCES MICROGLIA M2 RE-PROGRAMMING AND IMPAIRS TUMOR SPHERE FORMATION

Marta Kocyk1,2, Anna Gieryng1, Karolina Stepniak1, Bozena Kaminska1

1Laboratory of Molecular Neurobiology, Nencki Institute of Experimental Biology, Warsaw, Poland, 2Postgraduate School of Molecular Medicine

Microglia are the myeloid cells residing in the central nervous system (CNS) and the first cells to respond to infection, injury or pathological alterations. Microglia participate in the initiation of inflammatory and anti-tumor responses.In gliomas a number of infiltrating microglia and blood derived macrophages positively correlates with tumor grade and invasiveness as documented by clinical and animal studies. Glioma cells secrete soluble factors which convert microglia and infiltrating macrophages into amoeboid cells with attenuated inflammatory responses and the switch to a pro-invasive phenotype. One of tumor secreted factors activating microglia is osteopontin, a small phosphoglycoprotein(encoded by the SPP1 gene),which is overexpressed in malignant gliomas. Knockdown of osteopontin with lentivirally-delivered shRNA in C6 rat glioma cells reduced the pro-invasive re-programming of primary rat microglia cultures as evidenced by the reduced expression of M2 markers. Moreover, Spp1was over-expressed in C6 glioma sphere cultures enriched in the stem like cells. Knockdown of Spp1affected glioma stem cell self- renewal and reduced the number of tumor spheres and the expression of stemness markers. Rescue experiments with Spp1 variants devoid of specific functional domains demonstrated that the CD44 binding domain of osteopontin is necessary for a sphere forming activity, while mutations in a thrombin cleavage site and a integrin binding site affect interactions with microglia. Our findings demonstrate that tumor derived osteopontin is required for both glioma stem cell self-renewal and glioma interactions with microenvironment.

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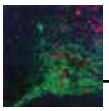
PILOT (PRE)CLINICAL EVALUATION OF (4S)-4-(3-[18F] FLUOROPROPYL)-L-GLUTAMATE FOR PET/CT IMAGING OF INTRACRANIAL MALIGNANCIES



Koglin, N.; Mittra, E.; Mueller, A.; Berndt, M.; Friebe,M.; Gekeler, V.; Stephens, A.; Hoehne, A.; Chin, F.; Gambhir, S.
Clinical R&D, Piramal Imaging GmbH, Tegeler Str. 6, 13353 Berlin, norman.koglin@piramal.com

(S)-4-(3-[18F]Fluoropropyl)-L-glutamic acid (FSPG) is a novelradiopharmaceutical for PET imaging of tumors. It is a glutamate analogue that can be used to non-invasively measurethe activity of system xC-, a SLC7A11/SLC3A2 heterodimer.1,2Data of this new imaging agent are presented from small animals with orthotopic brain tumors andthe human subjects with intracranial malignancies. Experimental Design: For the small animal study, GS9L glioblastoma cells were implantedinto brains of Fischer rats and studied with FSPG, 18F-2-fluoro-2-deoxy-D-glucose (FDG) and O-(2-18F-fluoroethyl)-L-tyrosine(FET). For a humanpilot study, five subjects with either primary or metastatic brain cancer were recruited (mean age50.4 years). After injection of 300 MBq of FSPG, 3 PET/CT scans were obtained. The three subjects with brain metastases from NSCLC also hadan FDG PET/CT scan. Quantitative and qualitative comparison of the scans wasperformed to assess kinetics, biodistribution, and relative efficacy of the tracers. Results: In the small animals, the orthotopic brain tumors were well visualized with FSPG.The high tumor uptake of FSPG in the GS9L model and the absence of backgroundsignal led to good tumor visualization with high contrast (T/brain: 32.8). For comparison, FDG and FETshowed T/brain ratios in this model of 1.7 and 2.8, respectively. In the human study, FSPGwas well tolerated and there was similar whole body distribution in all patients.All malignant lesions were positive with FSPG except for one low-grade brain tumor. Inthe FSPG-PET-positive tumors similar T/brain ratio were observed as in the animalmodel. Conclusions: FSPG is a novel PET radiopharmaceutical that demonstrates good uptake inboth small animal and human studies of intracranial malignancies. Future studies on larger numbers ofsubjects and a wider array of brain tumors are ongoing.

References: 1) Koglin et al. ClinCanc Res 2011; 2)Baek et al. ClinCanc Res 2012

ATYPICAL TERATOID/RHABDOID TUMORS OF THE CENTRAL NERVOUS SYSTEM IN YOUNG CHILDREN

Harald Krenzlin, Manfred Schwarz, Peter Horn
Department of Neurosurgery, HSK, Dr. Horst Schmidt Kliniken Klinikum der Landeshauptstadt Wiesbaden und der HELIOS Kliniken Gruppe, Wiesbaden

Objective: Atypical teratoid/rhabdoid tumors (AT/RT) are highly malignant, extremely rare neoplasms of the central nervous system. Patients are usually younger than 2 years at the time of onset of symptoms. Despite very aggressive treatment regiments the course of the disease is still fatal. AT/RT is the first paediatric brain tumour for which a candidate tumour suppressor gene, a mutation or deletion in the INI1 gene, has been identified. Efforts have been made to standardize and optimize different treatment regiments introducing the RHABDOID 2007 prospective study and setting up the EURHAB register. We report about the clinical course of patients treated in our hospital. Methods:
Patients with AT/RT requiring surgical treatment due to space-occupying supra- or infratentorial lesions from 2006 to 2012 were included in our case series. Baseline parameters are age, localization and preoperative paediatric GLASGOW COMA SCALE (PGCS). Co-primary outcome parameters were extent of surgical removal according to postinterventional MRI, additional necessary surgical procedures and PGCS at discharge from hospital. Secondary outcome parameters included time until tumour recurrence, PGCS at time of recurrence and time of survival. Results: In our case series 4 patients (2 male, 2 female; mean age at time of diagnosis: 28,5 + 22; mths; 3 supratentorial, 1 infratentorial). Initial focal neurological deficits (strabismus, ataxia)
were present in 1 patient, signs of mild to moderate elevated intracranial pressure (nausea, vomiting and fatigue) were present in 3 patients. Initial PGCS was 15 in 3 patients, 14 in 1 patient (Lansky score 90 or higher). INI 1 gene mutations were found in 1 out of two patients.
Microsurgical resection was performed in 3 cases, primary inoperable conditions were found in one case. Cerebrospinal fluid drainage and ventricular-peritoneal shunt (VP-shunt) insertion became necessary in all 4 cases. Postoperative PGCS was 15 in 3 patients, 3 in 1 patient. No residual tumour was visible in MRI scans after first resection in 3 patients.. All patients received chemotherapy (3 patients according to EURHAB –ie.: Doxorubicin (DOX), Ifosfamide, Carboplatinum, Etoposide (ICE) and Vincristin + Actinomycin-D + Cyclophosphamid (VCA) + intrathecal Methotrexate (MTX) protocols; 1 according to GPOH protocol- i.e.—Radition theray (Rtx) and Temozolmid). Tumour recurrence and progression occurred in all patients. Mean duration until tumour recurrence was 11+1 mths. Revision surgery was performed in none of the patients (2 because of disseminated disease, 1 due to near fatal first operation and 1 lost to follow-up). Conclusion: All four children were treated with initial surgery whenever possible and subsequent chemotherapy according to current guidelines (GPOH or EURHAB). Our cases fall in line with the findings published in the RHABDOID 2007 study and demonstrate the fast and devastating progression of this rare disease. So far no solid individual predictor influencing the course of the disease has been established. This case series underlines the devastating course of this disease and suggest a fatal outcome despite all therapeutic efforts.

CELLULAR DIAGNOSTICS AND MOLECULAR THERAPY OF DISEASES AND FUNCTION DISORDERS OF THE BRAIN

Ulrich Kübler, Jörn Schnepel
Labor-Praxisklinik Dr. Kübler & Partner GbR, Siebertstr. 6, 81675 München, www.labor-praxisklinik.de

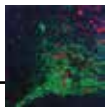
Glial cells perform many functions in the Central Nervous System (CNS), e.g. providing structural support and defining brain architecture. They are also indispensable for neurogenesis and development of the CNS. Diagnostic gliapheresis (EP1486787B1*) is a patented cell collecting system, which enables the isolation, quantification and molecular characterization of circulating glial cells emitted from the brain into the bloodstream. This is not only possible with malignancies but also with multisystem atrophies, Alzheimer's disease and not yet understood glial disorders. With this method the pathophysiology of glial disorders can be examined for the first time in vitro without biopsy. Thus target-specific, diagnostic and therapeutic consequences became possible. Glial cells are the immune cells of the central nervous system (CNS). They communicate as sensors with the neurons and the environment and respond to endogenous and exogenous transcription factors, for example, PDGF from platelets. Using diagnostic gliapheresis, the influence of different substances and drugs on the number and the molecular expression profile of circulating glial cells can be examined.In this way, diseases and disorders of the brain can be decrypted and the response on therapies can be studied without side effects in patients. Diagnostic Apheresis enables a quantitative extraction of GFAP expressing cells from the bloodstream and their complete molecular-pathological characterization without biopsy. In addition biomarkers like c-Met, Oct-3/4, GFAP, EGFR, erb/B2, erb/B3, myc, ras, p53m, MDR, CD44v5/v6, VEGF, Akt/mTOR, IDO, Survivin, or uPA can provide information about metastasis initiating Cancer Stem Cells (MICs) .

*Process for the in vitro diagnosis of a glioma or an astrocytoma and a pharmaceutical mixture for the treatment, Kübler, U., 2011, EP1486787B1

PROFILING OF GBM PATIENT DERIVED CELL LINES IDENTIFIES CELL-INTRINSIC DIFFERENTIAL RADIATION RESPONSE WHICH CORRELATES WITH TP53 MUTATIONS

Maire C.L.1,2, Abazeed M.1,4, Lam F.4, Pelton K.1, Knoff D.1,Korideck H.1, Adams D.1,Pinnell N.3, Ramkissoon S.1,3, Wen P.3, Ligon A.H.3, Schreiber S.5, Floyd S.6, Ligon K.L.1,3, and Alexander B.M.3
1Dana-Farber Cancer Institute, Boston; 2University Medical Center Hamburg-Eppendorf; 3Dana-Farber/Brigham & Women Cancer Center, Boston;4Cleveland Clinic, Cleveland;5Broad Institute, Cambridge;6Koch Institute, MIT, Cambridge

We tested whether 35 GBM patients(newly diagnosed and recurrent) derived cell lines (PDCL),established as part of the Living Tissue Bank at the DF/BWCC respond differently to radiation treatment. Genomic alterations and expression profile were performed on all 35PDCL by whole exome sequencing, aCGH and microarray. These lines were then irradiated as single cells and assessed for growth rate/survival. Quantification by mean area under the curve (AUC) value from survival fraction show a broad continuous normal distribution of radiosensitivity across patients. The most sensitive lines exhibited80% loss at 4Gy while the most resistant lines exhibited10-20% loss at 10Gy. Moreover resistant lines do not correlate with high proliferation rate or stem/progenitor markers CD133 and OLIG2. More strikingly, PDCL derived from recurrent patients previously treated with standard of care therapy were not more radioresistant than the de novo. The radiosensitivity



observed in vitro also did not correlate with clinical outcome for their corresponding patient, however these are not fully conclusive due to sample size. Examination of whole exomedata for genomic predictors of responsiveness demonstrated that TP53 mutant lines were significantly more resistant to irradiation but not other common genomic. In conclusion our data suggest that GBM PDCLand likely patients harbor intrinsic differences in response to radiation that TP53 should be further explored as a potential biomarker of response.

HEPARANASE PROMOTES GLIOMA GROWTH AND CORRELATES TO PATIENT SURVIVAL

Soumi Kundu1, Anqi Xiong1, Grzegorz Wicher1, Per-Henrik Edqvist1, Argyris Spyrou1, Lei Zhang1,Magnus Essand1,Anna Dimberg1, Anja Smits2, Neta Ilan3, Israel Vlodavsky3, Jin-Ping Li4 and Karin Forsberg-Nilsson1

1Department of Immunology, Genetics and Pathology, and 2Department of Neuroscience, Uppsala University, Sweden, 3Cancer and Vascular Biology Research Center, Bruce Rappaport Faculty of Medicine, Israel, 4Department of Medical Biochemistry and Microbiology, Uppsala University.

Malignant gliomais characterized by rapid growth and invasion of neoplastic cells into healthy brain tissue.Heparan sulfate, which is a vital part of the ECMis mainly cleaved byheparanase (HPSE). We hypothesize that glioma progression depends partly on HPSE, mediating its role in more than one way.Here, we show that human glioma cells express high levels of HPSE and its downregulationreduced cell growth. Gliomatissue microarrays showed that HPSE is highly expressed, and high grade glioma had higher HPSEintensity in the neuropil.Mining the TCGA database we found that HPSE expression in correlated to shorter patient survival.Overexpression of HPSE in the mouse brain resulted in larger tumors upon intracranial grafting of glioma cells, compared to wildtype mice, while HPSE knockout (KO) mice had reduced tumor growth rate. In the peritumoral area ofHPSE-KO brain, we found less reactive gliosis and less blood vessel density, compared to HPSE-Tg brains. The ERK and Akt signaling pathways in human and mouse glioma cell were stimulated by recombinant HPSE, which also enhanced their growth and viability. Additionally, HPSE inhibition dramatically reduced the growth and viability of glioma cells, both in vitro and in vivo. Our data therefore suggest that HPSE influence glioma progressionand that it would be clinically relevant to target HPSE for therapeutic purposes.

A COMBINED PRECLINICAL THERAPY OF CANNABINOIDS AND TEMOZOLOMIDE AGAINST GLIOMA

Israel López-Valero1, Mar Lorente1,2, Sofía Torres1,2, María Salazar1,2, Sonia Hernández-Tiedra, David Dávila1,2, Dolores Hernán3, Ana Isabel Torres Suárez3, Manuel Guzmán1, Aurelio Hernández Laín4, Juan Sepúlveda4 and Guillermo Velasco1,2

1Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, 28040 Madrid, Spain, 2 Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain, 3Department of Pharmacy and Pharmaceutical Technology, School of Pharmacy, Complutense University, 28040 Madrid, Spain, 4Instituto de Investigación Sanitaria del Hospital 12 de Octubre (i+12)

Introduction: Cannabinoids, the active components of marijuana and their derivatives, are currently investigated due to their potential therapeutic application for the management of cancer. Specifically, Δ9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) - the two major ingredients of marijuana – have been shown to inhibit tumor growth in a number of animal models of cancer, including glioma. The antitumoral effect of THC relies, at least in part, on the stimulation of autophagy-mediated apoptosis in tumor cells. Objectives: Optimizing cannabinoid-based anticancer therapies in preclinical models of glioma. Methods: Tumor xenografts were induced in nude mice by subcutaneous injection of 5 x 106 U87 cells.Orthotopic mouse model of glioma was generated injecting 3 x 105 U87 cells into the striatum of nude mice. Animals were treated using different routes of administration. Results: (i) intraperitoneal or oral administration of THC or THC + CBD reduces the growth of glioma xenografts with similar efficacy than the local administration of these agents. (ii) administration of THC, CBD or THC+CBD-loaded microparticles reduced tumour growth with the same efficacy than a daily local administration of the equivalent cannabinoids in solution. (iii) local or oral delivery of THC or THC+CBDin combination with temozolomide produced a very strong synergic reduction in tumour growth in subcutaneous and intracranial glioma xenografts. Conclusion: The combined treatment of cannabinoids and temozolomideusing different vias of administration produces a strong anticancer activity in animal models of glioma.

CIRCULATING MIRNASREFLECT THE ANTIANGIOGENIC EFFECT OF BEVACIZUMABTREATMENT IN PATIENTS WITH GLIOBLASTOMA (GBM)

Iris Lavon1, AnatMordechai1, Hanna Charbit1, Iddo Paldor2, Bracha Zelikovitch1, Tamar Canello1, Yigal Shoshan2, Arriel Benis1, Michael Wong3, Lucy Paradiso4, Andrew Morokoff3,4, Kate Drummond3,4, Andrew H Kaye3,4andTali Siegal5.

1Gaffin Center for Neuro-Oncology Center for Neuro-Oncology, 2department of Neurosurgery, Hadassah Hebrew University Medical Center, Jerusalem, Israel.3The Department of Neurosurgery, The Royal Melbourne Hospital, Parkville VIC 3050, Australia, 4Department of Surgery, The University of Melbourne, 5Center for Neuro-Oncology, Rabin Medical Center, PetachTikva, Israel.

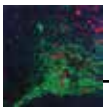
INTRODUCTION: Therapeutic modalities for GBM, the most malignant brain tumor, include surgical resection, radiation, chemotherapy, and recently also antiangiogenic therapy such as bevacizumab. Antiangiogenic therapy can produce early marked decrease in contrast enhancement in imaging studies and consequently results in high rate of radiologic response.We previously demonstrated that among others, four of the hypoxia-mediated-miRNAs, are up-regulated in gliomas as compared to normal brain. We hypothesized that the regulation and expression of those miRNAs will be altered in response to treatment with bevacizumab and that analysis of the relevant circulating miRNAs might reflect tumor dynamics.AIM: to perform a longitudinal monitoring of the circulating microRNAs in patients exposed to bevacizumab treatment and to correlate it with tumor response. METHODES:55 serum samples were prospectively collected from 15 GBM patients prior to bevacizumabtreatment and longitudinally during treatment. The expression of4 miRNAswas evaluated by real-time-RT-PCR using total RNA that was extracted from the serum.Tumor response was assessed on MRI using fluid-attenuated inversion recovery (FLAIR) sequences and contrast enhanced T1-weighted images to measure cross sectional tumor diameters. RESULTS:The expression of miR-Xand miR-Ynegativelyand significantly correlatedwith changes in enhancing tumor diameters ($R= -0.51$, $p=0.002$; $R= -0.568$, $p<0.0001$respectively) with higher correlation observed for average expression of both miRNAs($R=-0.648$, $p<0.0001$).CONCLUSIONS: This non-invasive monitoring of circulating miRNAsmightserve as an adjunctive objective measure of anti-angiogeniceffectof therapy.

THE ROLE OF LACTADHERIN IN GLIOMA-INDUCED MICROGLIA TRANSFORMATION

Ewa Lewczuk1,2, Magda Gerigk1, Bozena Kaminska1, Aleksandra Ellert-Miklaszewska1

1 Laboratory of Molecular Neurobiology, Neurobiology Center, Nencki Institute of Experimental Biology, Warsaw, Poland, 2 Faculty of Biology, University of Warsaw, Poland

Experimental and clinical studies show an important role of microglia in glioma pathogenesis. Using rat microglial cultures exposed to glioma conditioned medium (GCM) or lipopolysaccharide (LPS), we demonstrated that microglia adapt different fates and polarize into pro-inflammatory or alternatively activated cells (Ellert-Miklaszewska et al. Glia 2013). Lactadherin – milk fat globule-epidermal factor 8 (MFG-E8, SED1) was identified by us in GCM fraction activating rat microglia. MFG-E8 contains a phosphatidylserine (PS)-binding domain and integrins-binding RGD (Arginine-Glycine-Aspartate) motif, which enable it to act as a bridging molecule between the phagocyte and the engulfed apoptotic cell. Genetic depletion of lactadherin in glioma cells as well as a recombinant lactadherin were used to evaluate the role of this protein in glioma-induced microglia transformation and stimulation of angiogenesis. We produced a recombinant His-tagged wild type rat lactadherin and two non-functional mutant proteins: with PS-binding domain deletion and with mutated RGD motif. We tested the impact of lactadherin-depleted glioma cells or recombinant proteins on gene expression in microglia and evaluated their activity on angiogenesis of rat brain microendothelial cells. Knockdown of MFG-E8 in glioma affected the induced expression of some M2 genes. Although, a recombinant MFG-E8 stimulated angiogenesis of brain microendothelial cells, MFG-E8 knockdown in glioma had no effect, suggesting compensation by other factors. Altogether, our results demonstrate that MFG-E8 is partly



responsible for tumor-induced microglia re-education and in consequence for setting-up of microenvironment favorable for glioma growth. Supported by Foundation for Polish Science grant POMOST 2012-5/4.

ASSESSMENT OF TREATMENT RESPONSE IN AN ORTHOTOPIC IDH1-MUTANT GLIOMA MODEL USING IN-VIVO MAGNETIC RESONANCE SPECTROSCOPY - A FEASIBILITY STUDY

Loebel, F., Tateishi, K., Wakimoto, H., Huber, P., Chi, A., Cahill, D.
Neurosurgery, Charité University Hospital Berlin, Augustenburger Platz 1, 13353 Berlin, Germany, franziska.loebel@charite.de

Objective: Recurrent IDH1-mutations in a distinct subset of human gliomas cause marked elevation of 2-hydroxyglutarate (2HG) [1,2], which can be specifically detected using in-vivo Magnetic Resonance Spectroscopy (MRS) [4]. IDH1 targeted therapies are currently in development and show promising preliminary results [5]. The present study demonstrates the use of in-vivo MRS in an orthotopic IDH1-mutant glioma model for assessment of treatment response to IDH1-targeted therapies. Methods: Patient-derived IDH-mutant glioma stem cells were implanted stereotactically into the right frontal lobes of 26 SCID mice. Tumor formation was confirmed in T2-weighted MRI-scans using a 15T small-bore animal scanner with conventional spectroscopic imaging software. 1-dimensional unedited and spectral-edited multivoxel spectroscopic measurements of 2HG were performed in mice with detectable tumors. The mice were re-scanned following treatment with small molecule inhibitors of IDH1. Results: Tumor formation was confirmed by T2-weighted imaging in 19/26 mice (73.1%). Detectable levels of 2HG were found in the majority of T2-confirmed gliomas. Significantly decreased levels of 2HG were found in post-treatment scans following targeted therapy with IDH1-inhibitors when compared to their corresponding baseline scans, confirming the feasibility of our method. Conclusions: Our results show that assessment of treatment response is feasible in an orthotopic IDH1-mutant glioma model by assessment of 2HG with in-vivo MRS. This non-invasive, objective method has the potential to serve as diagnostic tool for pre-clinical testing of novel targeted therapies of IDH1-mutant gliomas. Further studies are needed to test and evaluate the potential of these novel therapies. References: [1] Parsons et al, Science 2008; 321:1807-12., [2] Yan et al, NEJM 2009; 360(8):765-73, [4] Andronesi et al., STM 2012; 4:116, [5] Rohle et al., Science 2013; 340(6132):626-30.

PROFILING OF GBM PATIENT DERIVED CELL LINES IDENTIFIES CELL-INTRINSIC DIFFERENTIAL RADIATION RESPONSE WHICH CORRELATES WITH TP53 MUTATIONS

Maire C.L.1,2, Abazeed M.1,4, Lam F.4, Pelton K.1, Knoff D.1,Koridek H.1, Adams D.1,Pinnell N.3, Ramkissoon S.1,3, Wen P.3, Ligon A.H.3, Schreiber S.5, Floyd S.6, Ligon K.L.1,3, and Alexander B.M.3
1Dana-Farber Cancer Institute, Boston; 2University Medical Center Hamburg-Eppendorf; 3Dana-Farber/Brigham & Women Cancer Center, Boston;4Cleveland Clinic, Cleveland;5Broad Institute, Cambridge;6Koch Institute, MIT, Cambridge

We tested whether 35 GBM patients(newly diagnosed and recurrent) derived cell lines (PDCL),established as part of the Living Tissue Bank at the DF/BWCC respond differently to radiation treatment. Genomic alterations and expression profile were performed on all 35PDCL by whole exome sequencing, aCGH and microarray. These lines were then irradiated as single cells and assessed for growth rate/survival. Quantification by mean area under the curve (AUC) value from survival fraction show a broad continuous normal distribution of radiosensitivity across patients. The most sensitive lines exhibited80% loss at 4Gy while the most resistant lines exhibited10-20% loss at 10Gy. Moreover resistant lines do not correlate with high proliferation rate or stem/progenitor markers CD133 and OLIG2. More strikingly, PDCL derived from recurrent patients previously treated with standard of care therapy were not more radioresistant than the de novo. The radiosensitivity observed in vitro also did not correlate with clinical outcome for their corresponding patient, however these are not fully conclusive due to sample size. Examination of whole exomedata for genomic predictors of responsiveness demonstrated that TP53 mutant lines were significantly more resistant to irradiation but not other common genomic. In conclusion our data suggest that GBM PDCLand likely patients harbor intrinsic differences in response to radiation that TP53 should be further explored as a potential biomarker of response.

PROFILING OF EPIGENETIC ENZYMES EXPRESSION IN GLIOBLASTOMA CELLS REVEALS TRANSCRIPTIONAL DOWNREGULATION OF EPIGENETICS MODULATORS

Marta Maleszewska, Bartosz Wojtas, Sylwia K. Krol, Bartlomiej Gielniewski, Bozena Kaminska
Laboratory of Molecular Neurobiology, Nencki Institute of Experimental Biology, Warsaw, Poland

Growing evidence indicates thatthe state of chromatin iscrucial for making cell-fate decisionsin both normal and malignant cells. Oncogenic transformation may deeply alter the epigenetic information enclosed in the pattern of DNA methylation or histone modifications. Deregulation of the epigenetic landscape can occur due to malfunction of the enzymes that maintain and modify the epigenome. In fact, epigenetic enzymes are frequent targets for mutation in some types of cancer.Recent studies indicate that besides genetic alterations, epigenetic aberrations have been implicated in the development and progression of brain tumors. Glioblastoma (GBM) is the most aggressive brain tumor, highly resistant to current therapeutic modalities.. Established glioma cell lines are explored to pharmacological and biological studies, however, little is known about epigenetic enzyme expression in GBM cell lines. We performed profiling of epigenetic enzyme expression in 3 established and 2 primary GBM cell lines, and normal human astrocytes by a custom qRT-PCR profiler. The analysis of selected histone modifications in these cells has been performed using Western blot and immunofluorescence. Our data show that the patterns of epigenetic enzyme expression in primary glioma cell cultureswere more similar to astrocytes than established cell lines. Interestingly, the expression of epigenetic enzymes was globally downregulated in all tested glioma cell cultures compared to astrocytes. Histone modifications levels were notably changed in glioma cell cultures compared to non-transformed astrocytes. These results show that epigenetic mechanisms are significantly deregulated in GBM cells and may play an important role in GBM development.
This work was supported from National Science Center grant no 2013/09/B/NZ3/01402

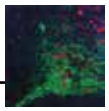
EGFRVIII-SPECIFIC AND CXCR4-OVEREXPRESSING NK CELLS IMPROVE IMMUNOTHERAPY OF CXCL12/SDF-1ALPHA-SECRETING GLIOBLASTOMA

Michen, S1; Müller, N1; Tietze, S1; Töpfer, K1; Schulte, A2; Lamszus K2; Schmitz, M3; Schackert, G1; Pastan, I4; Temme, A1
1Department of Neurosurgery, Section Experimental Neurosurgery and Tumor Immunology, University Hospital Carl Gustav Carus, TU Dresden, Fetscherstr. 74, 01307 Dresden, Germany, 2Laboratory for Brain Tumor Biology, Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany, 3Institute of Immunology, Medical Faculty Carl Gustav Carus, TU Dresden, Fetscherstr. 74, 01307 Dresden, Germany
4Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA

NK cells are promising effector cells for adjuvant immunotherapy of cancer. We reasoned that the efficiency of an immunotherapy using chimeric antigen receptor (CAR)-modified NK cells critically relies on efficient migration to the tumor site and might be improved by the engraftment of a receptor specific for a chemokine released by the tumor. Based on DAP12 we constructed an EGFRvIII-CAR, designated MR1.1-DAP12 which confers specific cytotoxicity of NK cell towards EGFRvIII+ glioblastoma cells in vitro and to established subcutaneous U87-MGEGFRvIII tumor xenografts. So far, infusion of NK cells with expression of MR1.1-DAP12 caused a moderate but significantly delayed tumor growth and increased median survival time when compared to NK cells transduced with control CAR. Notably, the further genetic engineering of these EGFRvIII-specific NK cells with the chemokine receptor CXCR4 conferred a specific chemotaxis to CXCL12/SDF-1alphasecreting U87-MG glioblastoma cells. Moreover, the administration of such NK cells resulted in complete tumor remission in a number of mice and a significantly increased survival. We conclude that chemokine receptor engineered NK cells with concomitant expression of a tumor-specific CAR are a promising tool to improve adoptive tumor immunotherapy.

ATF4 AS A MEDIATOR OF RESISTANCE TO TARGETED THERAPY IN HIGH-GRADE GLIOMAS

Sylvia Moeckel1, Bart Neyns2, Edward Pan3, Markus J. Riemenschneider4, Anja-Katrin Bosserhoff5, Arabel Vollmann-Zwerenz1,



Katharina Meyer6, Rainer Spang6, Peter Hau1
1Wilhelm Sander-NeuroOncology Unit and Department of Neurology, 4Department of Neuropathology, 5Institute of Pathology, Regensburg University Hospital, 6Institute of Functional Genomics, University of Regensburg, Regensburg, Germany, 2Medical Oncology, UZ Brussel, Brussel, Belgium, 3Department of Neuro-Oncology, H. Lee Moffitt Cancer Center, Tampa, USA

Small molecule inhibitors have been investigated in a large set of clinical trials in high-grade gliomas (HGG). Despite promising preclinical studies, results of pilot trials have been generally disappointing.A deeper understanding of the complex biology of malignant glioma cells, and their adaptation to targeted agents is therefore critical for further therapy development. We performed microarray analysis in 18 short-term serum-free cultures of high-grade gliomas enhanced for brain tumor initiating cells (BTIC) before and after in vitro treatment with the tyrosine kinase inhibitor Sunitinib.Based on the observation of gene network analysis we hypothesize that the central mediator of the integrated stress response ATF4 (activating transcription factor 4) plays an important role in the regulation of the Sunitinib induced expression profiles and probably in the adaptation to treatment conditions.ATF4 is involved in metabolism and nutrient uptake, antioxidation, and regulation of apoptosis and autophagy. Interestingly, ATF4 has been associated with multidrug resistance in different cancer models. We analyzed the expression of ATF4 in paraffin embedded tissue blocks from HGG patients treated with Sunitinib by immunohistochemistry. Interestingly, ATF4 significantly correlated with shorter overall survival from the beginning of Sunitinib treatment. In vitro studies confirmed a dose dependent induction of ATF4 protein expression in Sunitinib treated BTICs. Furthermore weobserved an intracellular accumulation of autophagosomes. Co-administration of the autophagy inhibitor-Chloroquinecould enhance the sensitivity to Sunitinib treatment. In summary our data suggest that ATF4 expression may be predictive for response to Sunitinib and might also be involved in general resistance mechanisms in HGGs. Further studies are ongoing to elucidate the induction of apoptosis and autophagy in dependence of ATF4 expression and its contribution to therapy response.

SYSTEMS SCALE ANALYSIS AND PROSPECTIVE MODELING OF DRUG VULNERABILITIES IN 96 GLIOBLASTOMA INITIATING CELL CULTURES.

Linnéa Schmidt1,2, Patrik Johansson2, Sathishkumar Baskaran2, Teresia Kling 1,2, Ludmila Elfineh2, Maria Häggblad3, Ulf Martens3, Bengt Westermark2, Lene Uhrbom2, Karin Forsberg Nilsson2, Cecilia Krona2, Bo Lundgren3, Sven Nelander2
1Sahlgrenska Cancer Center, Institute of Medicine, Box 425, SE-415 30 Gothenburg, Sweden (auxiliary affiliation of SN), 2Department of Immunology, Genetics and Pathology and Science for Life Laboratory Uppsala, SE-751 85 Uppsala, Sweden (main affiliation of SN), 3Cell screening facility, Science for Life Laboratory Stockholm, Department of Biochemistry and Biophysics, Stockholm University, Solna, Sweden

A key challenge for current cancer research is to enable personalized targeting of the cancer stem cell (CSC) compart¬ment in solid tumors. However, drug vulnerabilities of the cancer stem cell population have been hard to explore by chemical genomic methods, due to the absence of appropriate cell biobanks.Here, we perform a large-scale integrated study of drug vulnerabilities, molecular- andhigh throughput image-based profiling of a panel of cancer stem-like cell cultures from the Uppsala University Human Glioma Cell Culture (HGCC) project. From a library of 1600 chemical inhibitors, we performed screens to define a focus set of 248 compounds, which was subsequently profiled by detailed measurements of dose-response characteristics and imaging in each of 96 cell cultures. Statistical modeling of the data thus obtained, reveals that drugs with similar mechanism of action form correlating groups of drugs that tend to share common targets. Analyses show that particular classes of drugs have high potency but also display characteristic patterns of variation across HGCCs. DNA copy number aberrations and transcript profiles of the HGCC cell lines both contained information to accurately capture the global variability in drug response (R square of 0.7). While good predictive accuracy was obtained, the established transcriptional subtypes were, by contrast, surprisingly poor predictors of drug response, strongly warranting alternative classification systems. Ahigh-resolution compendium of drug vulnerabilities in glioblastoma stem-like cell cultures from well-defined patient cases will facilitate the develop-ment of CSC-targeted therapies, and integration of chemical genomic information from imaging adds an additional dimension to pinpoint promising candidates.

GLIOMA: CELLULAR CHANGES AND MOLECULAR PATHWAYS FOLLOWING CNF1 TREATMENT.

Francesco Olimpico1, Eleonora Vannini1, Anna Panighini1, Matteo Caleo1, Mario Costa1
1CNR Institute of Neuroscience Pisa, Italy

Glioblastomas are primary central nervous system tumors and are largely unresponsive to all available treatments.There is therefore an urgent need for novel therapeutics. Here we have probed the antineoplastic effects of a bacterial protein toxin, namely cytotoxic necrotizing factor 1 (CNF1). CNF1 causes a long-lasting activation of Rho GTPases and displays a double action: (i) it leads to actin stabilization, blockade of cytodieresis, multinucleation and eventually cell death in proliferating glioma cells; (ii) it promotes neuron health and plasticity, with an increase in dendritic and spine growth. In view of these striking effects of CNF1 on proliferating cells and neurons, we have exploited this toxin for the treatment of glioma in the syngenic GL261 cellularmodel. GL261 cells treated with CNF1 (3 nM) showed acell proliferation arrest and a senescent morphology (enlargement and flattening of cells, increase in size of nuclei and nucleoli). There was no clear evidence for apoptotic cell death (annexin V labelling), whereaswe found a little increase inpropidium iodide labelling (a marker of necrosis).Moreover, CNF1 dramatically decreased the motility of GL261, thus limiting their migration capabilities (wound migration assay). Large scale gene profiling (Agilent Mouse G4122F microarray) of CNF1-treated cells vs untreated cells, identified 5447 genes up regulated and 5531 which were down-regulated ($p<0.05$).Bioinformatic tools (Pathway Express Analysis and David) have been used to find, among the expressed genes, enriched biological themes identifying pathways connected to cell cycle, cell adhesion, MAPK signaling, adherens junction and migration. Finally, we focused our attention on a set of key candidate genes whose differential expression could explain molecular pathways that play a role in CNF1 treated cells.

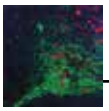
A NOVEL INTEGRATIVE NETWORK MODEL IDENTIFIES ANXA2 AS AN EPIGENETICALLY REGULATED DRIVER OF THE MESENCHYMAL SIGNATURE IN GLIOBLASTOMA.

Darren Ó hAilín1, Roberto Ferrarese1, Teresia Kling2, Patrik Johansson3, Sven Nelander3, Maria Stella Carro1.
1 Freiburg University Medical Centre, Germany, 2 University of Gothenburg, Sweden, 3 Uppsala University, Sweden

An integrative network model was used to analyse multi-faceted genetic, epigenetic, and clinical data collected from the GBM databases, revealing ANXA2 expression as a robust node in a mesenchymal profile and patient survival nexus. We found that ANXA2 expression was positively linked to the mesenchymal signature and ANXA2 promoter methylation to patient survival, with ANXA2 promoter methylation negatively correlated with its expression.We validated this model using primary material cultured from GBM patient samples collected on site, and further elucidated ANXA2's role in mesenchymal signature maintenance using patient-derived cancer stem cells (CSC). ANXA2 knockdown in CSCs attenuated their capacity for proliferation and invasion, and induced a global transcriptional shift, downregulating the expression of a number of mesenchymal marker genes and invasion-associated transcription factors.Although no effect on global DNA methylation was observed, CSCsexhibited an enriched expression of genes characteristically expressed in tumours harbouring the G-CIMP phenotypeupon ANXA2 knockdown, suggesting that ANXA2 silencing might transcriptionally mimic IDH1 mutation-driven hypermethylator phenotype, which is associated with more favourablepatient prognosis. Our preliminary findings support the model proposed by our bioinformatic network approach that ANXA2 serves as a major epigenetically regulated mediator of the aggressive mesenchymal phenotype, warranting further investigation of its underlying molecular mechanisms and methylation dynamics.

CAIX REGULATES EXTRACELLULAR PH AND INVASION IN GLIOBLASTOM

Proescholdt M.A; Störr E-M; Lohmeier A; Merrill MJ., Brawanski A.
Neurosurgery, University Regensburg Medical Center, Franz Josef Strauß Allee 11, 93053 Regensburg, Germany, martin.proescholdt@ukr.de



Objective: Malignant gliomas are highly invasive tumors that are metabolically characterized by glycolysis leading to increased levels of lactic acid. Carbonic anhydrase (CA) IX modulates proton transfer to the extracellular space, which may lead to tumor cell invasion due to activation of lysosomal proteolytic enzymes such as cathepsin B. We investigated the interrelationship between glycolytic metabolism, extracellular pH, expression of (CA) IX as well as subcellular distribution and secretion of cathepsin B with regard to the invasive behavior of glioblastoma cells. Methods: U251 glioblastoma cells were transfected with a CAIX siRNA. Cathepsin B expression and localization was investigated by quantitative RTPCR, Western blot and immunofluorescence staining respectively. The pH-dependent lysosome trafficking was analyzed by horseradish peroxidase labeling. For invasion assays, a Matrigel invasion chamber was used. The chambers were incubated in a 5% CO2 modular with either 21% oxygen and 25 mM glucose in the culture medium (ctrl.) or 0% oxygen plus 125 mM glucose (glycolysis). Extracellular acidification was investigated by pH measurement of the supernatant. Results: In vitro glycolysis caused a significant drop of extracellular pH (pHe) combined with massive invasion of glioblastoma cells, which was antagonized by CAIX knockdown. The cathepsin B expression was induced under glycolytic conditions, which was not influenced by CAIX interference. In contrast, CAIX knockdown reduced the subcellular distribution change of cathepsin B towards the cell periphery, which was induced by glycolysis. Also, the secretion of cathepsin B, which was strongly increased under glycolysis, was significantly reduced by CAIX knockdown. Lysosome labeling revealed the identical pattern of bidirectional, pH-dependent movement indicating the possible mechanism of subcellular cathepsin B transport. Conclusion: Our data demonstrate that CAIX moderates invasion in glycolytic glioma cells via acidification of the extracellular milieu and enhanced secretion of cathepsin B.

FUNCTIONAL ANALYSIS OF GLIOBLASTOMA SUBCLONES ENABLES PREDICTIONS ON THERAPY-RELATED ALTERATIONS TO THE TUMOR CELL COMPOSITION

Roman Reinartz1,2*, Shanshan Wang3, Sied Kebir1,2, Anja Wieland1,2, Laurèl Rauschenbach1,2, Martin Glas1,2,4, David W. Pincus3, Mathias Simon5, Oliver Brüstle2,4,6, Dennis A. Steindler3, and Björn Scheffler1,2,4

1Stem Cell Pathologies, 2Inst Reconstructive Neurobiology, University Bonn Med Ctr, Germany. 3Dept Neurosurgery, University of Florida, Gainesville, FL, USA. 4LIFE & BRAIN GmbH, Bonn, Germany. 5Clinic for Neurosurgery, University Bonn Med Ctr, Germany. 6DZNE – German Center for Neurodegenerative Disease, Bonn, Germany

The malignant brain tumor glioblastoma is a prime example for the examination of intra-tumor heterogeneity. Recent studies have revealed a substantial degree of intra-tumor cellular diversity on a genetic and non-genetic level. However, little is known on the consequences of this heterogeneity in respect to pharmacological intervention. Investigation of drug-related changes to the clonal diversity may be key to understanding mechanisms of therapeutic failure in human cancer. In this study, we used 33 single cell-derived subclones generated from five clinical glioblastoma specimens for exploring intra- and inter-individual spectra of drug resistance profiles. Subclones from individual tumors exhibited a remarkable heterogeneity of endogenous resistance to a compound library of potential anti-glioblastoma drugs. In a personalized setting, stable genetic and phenotypic characteristics of co-existing subclone identities could be correlated with distinct drug sensitivity profiles. The data obtained from differential drug response analysis could further be employed to predict clonal population shifts within the naïve parental tumor in vitro and in vivo. Together, our data provide a previously unrecognized strategy for revealing functional consequences of intra-tumor heterogeneity by enabling predictive modeling of treatment-related subclone dynamics in human glioblastoma.

CARNOSINE INHIBITS THE GROWTH OF GLIOBLASTOMA CELLS INDEPENDENT FROM PI3K AND MTOR SIGNALING

Helene Riedel, Lutz Schnabel, Henry Oppermann, Ulrike Letzien, Jürgen Meixensbergerand Frank Gaunitz

Klinik und Poliklinik für Neurochirurgie, Universitätsklinikum Leipzig, Liebigstraße 20, 4103 Leipzig, Gemrany, helene.riedel@medizin.uni-leipzig.de

Previous experiments indicated that the anti-neoplastic effect of the dipeptide carnosine on cells derived from glioblastoma is accompanied byenhanced transcription of the pyruvate dehydrogenase kinase 4(PDK4) gene. AsPDK4 mRNA expression is known to be regulated by PI3K/PKB/mTOR signaling which is frequently aberrantly regulated in tumors we wondered whether carnosine does interfere with this signaling axis. Therefore, cells from the line U87 were cultivated in the absence and presence of carnosine (50 mM), the mTOR inhibitor rapamycin (25 nM) and the PI3K inhibitor LY-294,002 (5 μM). After treatment the expression of PDK4 was determined by qRT-PCR and changes in viability were determined by cell based assays. In the presence of rapamycin and LY-294,002 the expression of PDK4 was significantly enhanced (5.7$\pm$0.3 fold, and 6$\pm$1.1 fold, respectively), comparable to the effect observed under the influence of 50 mMcarnosine (15$\pm$3.8). Additionally, carnosine was able to further enhance expression of PDK4 in the presence of rapamycin or LY-294,002. However, transfection experiments using a reporter gene containing the secreted luciferase from Gaussiaprinceps under the control of the $\sim$4000 bp 5'-region from the human PDK4 gene, clearly demonstrated an effect of rapamycin and Ly-294,002 on the PDK4 promoter constructwhereas there was no response to the presence of carnosine. In addition, ATP and dehydrogenase assays neither demonstrated an effect of rapamycin nor of LY-294,002 on viability of U87 cells which strongly responded to the presence of carnosine with reduced viability. Therefore, we conclude that carnosine's antineoplastic effect is not mediated by an influence on PI3K/PKB/mTOR signaling. This observation should encourage further studies to investigate whether carnosine may be a therapeutic option for such tumors that cannot be targeted via the PI3K/PKB/mTOR axis.

MODIFIED E-CADHERIN PROTEIN INFLUENCES MIGRATION AND INVASION BEHAVIOR OF GLIOMA CELL LINE U343-MG

Steffi Ritter, Kristin Stirnnagel,Gabriele Schackert, Achim Temme

1Department of Neurosurgery, Section Experimental Neurosurgery/ Tumor Immunology, University Hospital Carl Gustav Carus, TU Dresden

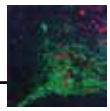
Glioma cells are known to be highly aggressive tumor cells that are able to deeply penetrate the surrounding brain tissue. Since many years numerous cell lines were used to study specifically thisinfiltrativebehavior. Recently published datademonstrated significant differences in migration and invasion capacity of commonly used U87-MG and U343-MGglioma cells (Pei et al., 2014). We found that, among different primary cultures and established glial cell lines, solely U343-MG cells expressed E-cadherin (ECAD). To investigate its functional relevance, we stably knocked down (KD)ECAD by retroviral transduction of shRNA-vectors in U343-MG.The resulting phenotype was analyzed for survival, proliferation, apoptosis as well as tumorigenicity. Since RNA analysis indicates modifications in ECAD 5'-region, in particular its propetide sequence, subcellular protein localization was performed. Noteworthy, this modified ECAD lacking wildtype membrane anchoragedomains was mainly detected inthe membrane fraction. Dependent on KD efficiency,ECAD silencingled to decreased overall clonogenic survival, inhibited proliferation, and clearly increased apoptosis. Partial ECAD KD enabled U343-MG cells to undergo epithelial-mesenchymal transition accompanied by changes in cell morphology and significant increased migration and invasion capacity in 2- and 3-dimensional cultures. Interestingly,contrary results were observed for abrupt total silencing of ECAD.RNA deep sequencing analysis is already under investigation to determine genetic alterations andto find potential pathways leading to those individual phenotypes. (Pei Jet al. Proteomic Analysis between U87MG and U343MG-A Cell Lines: Searching for Candidate Proteins for Glioma Invasion. Brain Tumor Res Treat 2014;2:22-8).

CIRCULATING BIOMARKERS FOR GLIOMA

Aleksandra Sachkova1, Antoine Eger2, Karl Schaller2, Veit Rohde1, Pier-Paolo Panciani3, Ali-Reza Fathi4, Virginie Clement-Schatlo2, Bawarjan Schatlo1

1) Dpt of Neurosurgery, University Medicine Göttingen, Germany, 2) Dpt of Neurosurgery, University Hospital Geneva, Switzerland, 3) Dpt of Neurosurgery, University Hospital Brescia, Italy, 4) Dpt of Neurosurgery, Kantonsspital Aarau, Switzerland

Introduction: Biomarkers for solid tumors can potentially facilitate diagnosis, stratification and follow-up of patients in a non-invasive and cost-effective manner. Despite regular publications on circulating tumor markers of glioma, none appears to have gained widespread



acceptance in the neuro-oncological community. Our aim is to provide a systematic, authoritative review of the available literature on the subject by performing a grading of the present studies to identify the most promising candidates for a putative clinical use. Methods: We performed a systematic literature search for the terms glioma, glioblastoma, glial tumor, brain tumor, marker, biomarker, serum marker, blood marker, CSF marker, and urine marker. Articles were then included in a database listing biological, radiological, histological and clinical variables of each biomarker. By using the Tumor Marker Utility Grading System (TMUGS, Hayes 1996), each article was graded for its level of evidence and clinical utility by two independent reviewers. The markers were categorized according to their use, i.e. screening, differential diagnosis, follow-up and prognosis. Results: A total of 361 articles were retrieved after excluding articles addressing histological markers. One hundred eighty five articlesremained for analysis after application of exclusion criteria. Biomarkers were mostly described in serum (n=131), plasma (n=38) and CSF (n=58). The majority of the studies evaluated biomarkers for differential diagnosis (n=165). For studies concerning differential diagnosis, median level of evidence and clinical utility scores were 4 and 1, respectively. For papers investigating prognosis, median level of evidence and clinical utility scores were 3 and 1, respectively. Finally, for studies concerning follow-up, median level of evidence and clinical utility scores were 4 and 0. Conclusion: Among the 185 articles which were evaluated and graded, a minority reached high levels of evidence and clinical utility. While no single marker has sufficient predictive power to guide management in differential diagnosis, efforts are under way to combine biomarkers which may result in improved utility scales. Future research into a combined panel of markers including among others GFAP, VEGF, alpha2-HS-glycoprotein, MMPs and YKL-40.Further avenues of potential value include among others novel biomarker types as miRNA, exosome proteins and methylation status of such prognostic genes as MGMT in peripheral blood.

THE NOVEL ROLE OF VGF IN THE GLIOMA MICROENVIRONMENT.

Sassi, F. 1, 2; Mersch, M. 1; Tamagno, I. 2; Virk, S .2; Wolf, S. 1; Hambardzumyan, D. 2; Kettenmann, H. 1
1 Max-Delbrueck-Center of Molecular Medicine, Cellular Neuroscience, Berlin, Germany, 2 Department of Neurosciences, Lerner Research Institute, Cleveland, USA

The cellular compartment of the glioblastoma (GBM)-associated microenvironment is emerging as a promising therapeutic target. We therefore sought to investigate the biological role of a top candidate signaling molecule that was selected by RNAseq of sorted tumor-associated astrocytes from a proneural animal model of GBM. Vgf was selected due to its very prominent upregulation in astrocytes and its unknown function in the cancer context and known function as a neuropeptide precursor that regulates neurogenesis. We confirmed Vgf upregulation by RT-qPCR of freshly isolated glioma-associated astrocytes and also detected the protein in astrocytes and glioma cells by IHC in vivo; neither of the techniques showed increased Vgf expression in the tumor-associated microglia population. The RNA levels of Vgf and GFAP positively correlated in 30 mouse samples of GBM while Vgf expression did not significantly correlate with the fractalkine receptor CX_3CR1 or the CD44 expression. Treatment with Vgf-derived peptides increased in vitro proliferation of primary cultured GBM cells. Furthermore, freshly isolated microglia presented functional receptors to Vgf-derived peptides when using calcium imaging as readout. Cultured primary microglia cells significantly increased their migratory and chemotactic activity with Vgf application when analyzed in the scratch and agarose-spot assays. We conclude that Vgf participates in the crosstalk between glioma and stromal and is able to modulate cellular functions that are associated with glioma malignancy.

DISTINCT THRESHOLDS OF PRG3 AMPLIFY ONCOGENESIS IN GLIAL BRAIN TUMORS

Nic Savaskan1,#,*Zheng Fan1, Philipp Rummel1, Gökce Hatipoglu1, Stefan W. Hock1, Marc Schwarz2, Thomas Broggini3, Tina Sehm1, Arnd Doerfler2, Michael Buchfelder1, Ilker Y. Eyupoglu1#
1Department of Neurosurgery, University Hospital Erlangen, Friedrich-Alexander University of Erlangen-Nuremberg, D-91054 Erlangen, Germany;2Department of Neuroradiology, University Hospital Erlangen, Friedrich-Alexander University of Erlangen-Nuremberg, Erlangen, Germany;3Department of Neurosurgery, Charité - Universitätsmedizin Berlin, D-10015 Berlin, Germany.

Malignant gliomas are one of the most devastating cancersin humans. One characteristic hallmark of malignant gliomas is their cellular heterogeneity with frequent genetic lesions and disturbed gene expression levels conferring selective growth advantage. Here, we report on the neuronal-associated growth promoting gene PRG3 executing oncogenic cooperation in gliomas. We have identified perturbed PRG3 levels in human malignant brain tumors displaying either elevated or down-regulated PRG3 levels compared to non-transformed specimens. We hypothesized that imbalances of PRG3 levels bear the capacity to transform cells by facilitating similar downstream effects. To test this we analyzed wild-type gliomas and gliomas with distinct PRG3 levels. Perturbation of PRG3 levels in gliomas accelerates anchor-independent proliferation and migration, indicating amplified oncogenic signaling. In vivo dis-equilibrated PRG3 gliomas show aggravated proliferation, invasion, and deteriorate clinical outcome, whereas tumor angiogenesis remained unaffected. Hence, PRG3 interacts with RasGEF1 and activates oncogenic Ras via its C-terminal domain whereas PRG3 with deleted C-terminal tail inhibits Ras activation. Moreover, PRG3 disrupts the lipid second messenger phosphatidylinositol-(4,5)-bisphosphate (PIP2) from the plasma membrane. Restoration of PIP2 levels via phosphatidylinositol 4-phosphate 5-kinase (PIP5K) attenuated PRG3-induced transformation and reverted the phenotype. In conclusion, these results show that PRG3 acts dosage and context-dependent in cells, and interference with the PRG3 homeostasis amplifies oncogenic signaling events.

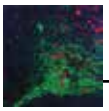
METASTATIC TUMOR RECURRENCE FROM RARE SOX9 CELLS IN MYCN-DRIVEN SHH-INDEPENDENT MEDULLOBLASTOMA

Vasil Savov1, Matko Čančer1, Grammatiki Fotaki1, Sara Bolin1, Gabriela Rosén1, Adrian Dubuc2, Marc Remke2, Vijay Ramaswamy2, Holger Weishaupt1, Michael D. Taylor2 and Fredrik J. Swartling1
1Rudbeck Laboratory, Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Sweden, 2The Hospital for Sick Children, Toronto, Canada.

Medulloblastoma (MB) is the most common malignant childhood brain tumor. Amplification ofMYCN in MB is a marker for poor prognosis. Tumor recurrence after treatment is the main cause of death in childrenwith MB. Recent findings suggesttemporal differences within the four molecular MB subgroups - SHH tumors tend to recur locally while SHH-independent Group 3 and 4 tumorsdevelop distant metastases. In order to study this, we used atransgenic mouse model of MYCN-driven SHH-independent MB (GTML) to recreate metastatic recurrence of such brain tumorsin vivo. The stem cell associated transcription factor SOX9 is expressed infew scattered cells in SHH-independent GTML tumors and in MYCN/MYC amplified human MB.We used a combination of Tet-ON and Tet-OFF inducible systems to target these cellsin vivo. Following tumor removal by using dox-inducible onco-gene depletion, SOX9+cells were able to initiate distant recurrences which were similar to the primary GTML tumors.Profiling using RNA sequencing identified genes correlating with metastasis but no change in molecular subgroup. We also overexpressed SOX9 in cerebellar NSCs transfected with a mutationallystabilized MYCNT58A and injected them into the cerebellum of adult mice. Interestingly,the MB-like tumors developed in the forebrain in contrast to the cerebellar tumors induced bythe same cells transfected with MYCNT58Aonly. The findings suggest that increased levelsof SOX9 drives migration of MYCN-driven MB cells. A similar correlation was found in Group 4MB patients where isolated metastases had consistently higher SOX9 levels as compared to thecorresponding primary tumor. To summarize,we have developed a new mouse model for MB recurrence and showed how a rarepopulation of SOX9-positive cells is capable of initiating recurrenceafter primary tumor removal. The relapsed MB has similar characteristics as the initial tumor butdevelops at a distant site in the brain, in line with recent data from human tumors.

COMBINED USE OF INTRAOPERATIVE MRI AND 5-AMINOLAEVULINIC ACID IN HIGH-GRADE GLIOMA SURGERY

Bawarjan Schatlo, M.D.; Javier Fandino, M.D.; Nicolas R. Smoll, M.D.; Oliver Wetzel, M.D.; Veit Rohde, M.D.; Luca Remonda, M.D.; Serge Marbacher, M.D., MSc; Wolfgang Perrig,M.D.; Hans Landolt, M.D.; Ali-Reza Fathi, M.D.
1. Department of Neurosurgery, University Hospital Göttingen, Robert Koch Str. 40, 37075 Göttingen (BS, VR), 2. Kantonsspital Aarau,



Tellstrasse, 5001 Aarau, Switzerland (BS)(JF)(OW)(SM)(WP)(HL) (ARF), 3. Department of Radiology, Division of Neuroradiology, Kantonsspital Aarau, Tellstrasse, 5001 Aarau, Switzerland (LR), 4. Department of Surgery, Frankston Hospital, 2 Hastings Rd, Frankston VIC 3199, Australia (NRS)

Background: Previous studies have shown the individual benefits of 5-aminolaevulinic acid (5-ALA) and intraoperative magnetic resonance imaging (iMRI) in enhancing survival for patients with high-grade glioma. In this retrospective study, we compare rates of progression-free and overall survival between patients who underwent surgical resection with the combination of 5-ALA and iMRI and a control group without iMRI. Methods: In 200 consecutive patients with high-grade gliomas, we recorded age, sex, World Health Organization (WHO) grade of the tumor and pre- and postoperative Karnofsky performance status (good $\geq$80 and poor $<$80). A 0.15 Tesla magnet was used for iMRI; all patients operated with iMRI received 5-ALA. Overall and progression-free survival rates were compared using multivariable regression analysis. Results:Median overall survival (OS) was 13.8 months in the non-iMRI group and 17.9 months in the iMRI group (p=0.043). However, on identifying confounding variables (i.e. KPS and resection status) in this univariate analysis, we then adjusted for these cofounders in multivariate analysis and eliminated this distinction in overall survival (HR 1.23, p=0.34, 95%CI 0.81, 1.86). Although 5-ALA enhanced the achievement of gross total resection (OR 3.19, p=0.01) (95%CI 1.28, 7.93), it offered no effect on overall or progression-free survival when adjusted for resection status. Conclusions: Gross total resection is the key surgical variable that influences progression and survival in patients with high-grade glioma and more likely when surgical adjuncts, such as iMRI in combination with 5-ALA, are used to enhance resection.

MULTIDIMENSIONAL AND IMAGE-BASED PROFILING OF PATIENT-DERIVED GLIOBLASTOMA INITIATING CELLS REVEALS EFFECTIVE AND PHENOTYPICALLY DISTINCT DRUG CANDIDATES

Linnéa Schmidt1,2, Patrik Johansson2, Sathishkumar Baskaran2, Teresia Kling 1,2, Ludmila Elfineh2, Maria Häggblad3, Ulf Martens3, Cecilia Krona2, Bo Lundgren3, Sven Nelander1,2
1Sahlgrenska Cancer Center, Institute of Medicine, Box 425, SE-415 30 Gothenburg, Sweden (auxiliary affiliation of SN), 2Department of Immunology, Genetics and Pathology and Science for Life Laboratory Uppsala, SE-751 85 Uppsala, Sweden (main affiliation of SN), 3Cell screening facility, Science for Life Laboratory Stockholm, Department of Biochemistry and Biophysics, Stockholm University, Solna, Sweden

A key challenge for current cancer research is to enable personalized targeting of the cancer stem cell (CSC) compartment in solid tumors. However, drug vulnerabilities of the cancer stem cell population have been hard to explore by chemical genomic methods, due to the absence of appropriate cell biobanks. Here, we perform a large-scale integrated study of drug vulnerabilities, molecular- and high throughput image-based profiling of a panel of cancer stem-like cell cultures from the Uppsala University Human Glioma Cell Culture (HGCC) project. From a large library of drugs, we defined a focus set of drug candidates, which was subsequently profiled by detailed measurements of dose-response characteristics and imaging in each cell culture. Statistical modeling of the data thus obtained, reveals that drugs with similar mechanism of action form correlating groups of drugs that tend to share common targets. Analyses show that particular classes of drugs have high potency but also display characteristic patterns of variation across HGCCs. In addition, the image-based profiles revealed distinct features for one specific drug characterized by "pearls-on-a-string" phenotype. Thus, the chemical compendium of drug effects in glioblastoma stem-like cell cultures from well-defined patient cases will facilitate the development of CSC-targeted therapies, where the integrated imaging platform forms an additional dimension to pinpoint promising candidates.

CARNOSINE AND THE ENERGY METABOLISM OF GLIOBLASTOMA CELLS

Lutz Schnabel, Helene Riedel, Jürgen Meixensberger, Frank Gaunitz and Henry Oppermann
Klinik und Poliklinik für Neurochirurgie, Universitätsklinikum Leipzig, Liebigstraße 20, 4103 Leipzig, Germany, lutz.schnabel@medizin.uni-leipzig.de

Previous experiments demonstrated an anti-neoplastic effect of the dipeptide carnosine on cells derived from glioblastoma. Several investigations indicated that carnosine may affect glycolytic ATP production but the primary targets are still unknown. As a high variation of the magnitude of carnosine's effect on viability from experiment to experiment was impeding a detailed further analysis of the dipeptide's effect on metabolism a highly reproducible protocol was established which allowed the analysis of glioblastoma cell viability under the influence of carnosine in the presence of different carbon sources. Using cells from different glioblastoma lines a protocol was established in which the cells were starved for 20 hours in a medium without a carbon source before receiving fresh medium with carnosine. With this protocol it was demonstrated that pre-starved U87 cells cultivated for 24 hours in the presence of glucose or galactose were completely depleted of ATP in the presence of carnosine whereas in the presence of pyruvate no effect on the production of ATP was observed. In fact, cells treated with carnosine in the absence of pyruvate exhibited a high rate of necrotic cell death as detected by release of LDH into the culture medium. Using the fluorescent dye calcein AM which specifically stains viable cells and propidium iodide for the detection of necrotic cell death, the cytotoxic effect of carnosine and also the ability of pyruvate to rescue cells from carnosine induced cell death was confirmed. This clearly demonstrates that glioblastoma cells are able to produce ATP via oxidative phosphorylation. However, experiments with the pyruvate dehydrogenase inhibitor CPI-613 revealed that the cells do not seem to use this pathway to produce ATP as long as glucose is abundant. Our experiments clearly confirmed the hypothesis that carnosine inhibits glycolytic ATP production but also demonstrates that glioblastoma cells are able to produce ATP via oxidative phosphorylation in the absence of glucose.

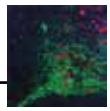
ORAL ADMINISTRATION OF THE AXL TYROSINE KINASE INHIBITOR BGB324 PROLONGS SURVIVAL OF GLIOBLASTOMA-BEARING MICE

Alexander Schulte1, Katharina Kolbe1, Isabel Ben-Batalla2, Mark Wroblewski2, Manfred Westphal1, Sonja Loges2, Katrin Lamszus1
1Klinik und Poliklinik für Neurochirurgie, 1Labor für Hirntumorbiologie und 2Institut für Tumorbiologie, Universitätsklinikum Hamburg-Eppendorf, Martinistraße 52, 20246 Hamburg, Deutschland

Overexpression of the Axl receptor tyrosine kinase is associated with a bad prognosis in glioblastoma (GBM) patients. The aim of this study was to evaluate the efficacy of the specific Axl-inhibitor BGB324 on GBM cell proliferation, migration and tumor initiating capacity in vitro and tumor growth in an orthotopic glioblastoma model in vivo. Axl was strongly expressed in GBM cells with a differentiated phenotype such as G55 and U87 at the mRNA as determined by microarray analysis and quantitative PCR and at the protein level as analyzed by Western blot and flow cytometry, while its expression was weak in stem-like GBM cells. Full length Axl protein was present at the cell surface, while its soluble form sAxl was detectable in conditioned media of GBM cells along with its natural ligand Gas 6, indicating the presence of an autocrine stimulation loop. Notably, full length Axl was also found in conditioned media, suggesting an association of Axl with GBM-derived exosomes. Erk 1/2 and Akt phosphorylation induced by recombinant Gas 6 was abrogated by interfering with Axl tyrosine kinase function using BGB324, resulting in a dose-dependent decrease in proliferation and cell migration at inhibitor concentrations above 1 μM. Most importantly, oral administration of 25mg/kg BGB324 to tumor-bearing mice twice daily significantly increased the median survival of treated animals compared to vehicle controls of both G55 (23 vs. 19 days, p$<$0.0001) and U87 (26.5 vs. 24 days, p$<$0.001). In summary, targeting Axl by oral administration of BGB324 appears a promising strategy for the Axl-overexpressing, differentiated compartment of glioblastoma in vitro and in vivo. However, the impact of Axl inhibition on the stem-like compartment of glioblastoma remains to be elucidated.

SPECIFYING THE ROLE OF MTOR SIGNALING IN MENINGIOMAS AND GLIOMAS

Simon M., Freitag D., Steinbach T., Kalff R., Walter J.
Department of Neurosurgery, University Hospital, Friedrich-Schiller-University, Jena, Germany



Objective: During the last 20 years strong effort has been made to understand the complexity of the mTOR network in different human pathologies. Identified as critical effector, the subsequent implementation of targeted pharmacological inhibition of mTOR to treat brain tumors is due to inconsistent results in various clinical trials still debatable. Being aware of that, the aim of our analysis was to illustrate the expression patterns of the key components of both mTOR complexes- RAPTOR and RICTOR- in the two most common adult brain tumor entities, gliomas and meningiomas. Methods: The gene expression of mTORC1 associated RAPTOR and mTORC2 associated RICTOR were quantitatively analyzed in 50 glioma specimens of WHO grades II-IV and in 50 surgical specimens of all three WHO grades of meningiomas using real-time polymerase chain reaction (qPCR) and subsequently evaluated applying the comparative delta-delta Ct method against normal brain or non pathological dural tissue respectively. Results: In gliomas the gene expression level of RAPTOR decreased, whereas the expression of RICTOR increased concerning WHO grades II and III, but exhibited no significant alteration for glioblastomas compared to normal brain tissue. In meningiomas we detected a rising overexpression of RAPTOR within all three WHO grades compared to dural tissue. In contrast RICTOR showed a decreased gene expression level in all three WHO grades of meningiomas. Conclusions: Analyzing mRNA of gliomas (WHO II°-IV°) and meningiomas (WHO I°-III°) by quantitative RT-PCR with regard to the gene expression of key components of both mTOR complexes we detected a statistically significant different expression profile between the neuroectodermal glial and mesodermal meningeal tumor types on the one hand as well as intriguing differences between the WHO grades within each tumor entity on the other hand.

HEPARANASE IN PEDIATRIC BRAIN TUMORS

Argyris Spyrou1, Soumi Kundu1, Lulu Haseeb1, Matyas Molnar1, Di Yu1, Magnus Essand1, Neta Ilan2, Israel Vlodavsky2, Jin-Ping Li3 and Karin Forsberg-Nilsson1
1Department of Immunology, Genetics and Pathology, Uppsala University, Sweden, 2Cancer and Vascular Biology Research Center, Bruce Rappaport Faculty of Medicine, Haifa, Israel, 3Department of Medical Biochemistry and Microbiology, Uppsala University.

Heparanase (HPSE) is an endo-ß-D-glucuronidase, which cleaves heparan sulfate chains at a specific number of sites, thus yielding fragments of 5-7 kDa. Overexpression of HPSE has been detected in a wide cohort of tumors1. We have recent data of its involvement in glioma (Kundu et al, manuscript), as well as Medulloblastoma (MB) and supratentorial PNET brain tumors (this study). Robust phosphorylation of Erk, Akt and Src was shown after addition of recombinant HPSE (rHPSE), as well as cell proliferation advantage, thus showing clearly that HPSE has many functions besides its enzymatic activity. By introducing shRNA, we investigated various aspects in vitro, showing thus that reduced levels of HPSE attenuated the invasion capacity of the cells in collagen matrix, proliferation and migration. We furthermore investigated the role of HPSE in pediatric brain tumors by using a HPSE inhibitor. A small molecule which has the capacity to block the activity of HPSE reduced tumor cell proliferation, migration but also invasion in a 2D and 3D collagen matrix. Furthermore, HPSE inhibitor affects the activation of signaling pathways and most recently, we found a significant reduction of the growth of subcutaneous sPNET and MB tumors in vivo after treatment with the HPSE inhibitor. Heparanase has been associated to increased cancer metastasis, angiogenesis and significantly reduced post-operation survival of patients, thus providing a putative diagnostic biomarker for the detection of malignancy, and a possible target for drug development.

1. Ilan N., Elkin M., Vlodavsky I. (2006), Int J Biochem Cell Biol., 2018–39.

ANALYSIS OF INTERACTION OF GLIOBLASTOMA AND STEM CELL LINES

Karol Stec[1], Chris Bauer[1], Helena Motaln[2], Tamara Lah Turnšek[2], Joachim Selbig[3] and Johannes Schuchhardt[1]
[1]MicroDiscovery GmbH, Marienburgerstr. 1, 10405 Berlin, Germany, [2]National Institute of Biology, Ljubljana, Slovenia , [3]Institute of Biochemistry and Biology, University of Potsdam, Potsdam, Germany

Tumours are not alone in their cellular environment, as with every other cell in the human body their physiology is not only dictated by their intrinsic properties but by the cellular and extracellular environment they participate in. In order to gain a better understanding of Glioblastoma multiforme, it is essential to gain insight into the cellular interaction, in which it is involved. To shed light on these relationships, coculture experiments of Glioblastoma (U87 and U373) with mesenchymial stem cell lines (MSC1 and MSC4) have been performed. The transcriptomic expression profile of the cell cultures was measured afterwards via an Illumina BeadChip. So as to interpret these results we have developed and applied a deconvolution algorithm along with a method of identifying interaction targets, altered in their expression by cellular interaction. These interaction targets have been found to be mostly involved in the extracellular space as well as cell-cell communication. Indicating that the extracellular environment becomes severely altered in the presence of glioblastoma and mesenchymial stem cells.

IDENTIFICATION OF REGULATED GENES IN GLIOMA-ASSOCIATED MICROGLIA/MACROPHAGES USING MICROARRAY

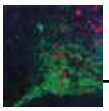
Szulzewsky F; Pelz A; Synowitz M; Holtman IR; Boddeke HWGM; Wolf S; Kettenmann H
Cellular Neurosciences, MDC Berlin, Robert Rössle Strasse 10, 13125 Berlin, Germany, frank.szulzewsky@mdc-berlin.de

Malignant glioma belong to the most aggressive neoplasms in humans with no successful treatment available. Patients suffering from glioblastoma multiforme (GBM), the highest-grade glioma, have an average survival time of only around one year after diagnosis. Both microglia and peripheral macrophages/monocytes accumulate within and around glioma, but fail to exert effective anti-tumor activity and even support tumor growth. Here we use microarray analysis to compare the expression profiles of glioma-associated microglia/macrophages and naive control cells. Samples were generated from CD11b+ MACS-isolated cells from naïve and GL261-implanted C57BL/6 mouse brains. Around 1000 genes were more than 2-fold up- or downregulated in glioma-associated microglia/macrophages when compared to control cells. Comparison to published data sets of M1, M2a,b,c-polarized macrophages revealed a gene expression pattern that has only partial overlap with any of the M1 or M2 gene expression patterns. Samples for the qRT-PCR validation of selected M1 and M2a,b,c-specific genes were generated from two different glioma mouse models and isolated by flow cytometry to distinguish between resident microglia and invading macrophages. We confirmed in both models the unique glioma-associated microglia/macrophage phenotype including a mixture of M1 and M2a,b,c-specific genes. To validate the expression of these genes in human we MACS-isolated CD11b+ microglia/macrophages from GBM, lower grade brain tumors and control specimens. Apart from the M1/M2 gene analysis, we demonstrate that the expression of Gpnmb and Spp1 is highly upregulated in both murine and human glioma-associated microglia/macrophages. High expression of these genes has been associated with poor prognosis in human GBM, as indicated by patient survival data linked to gene expression data. We also show that microglia/macrophages are the predominant source of these transcripts in murine and human GBM. Our findings provide new potential targets for future anti-glioma therapy.

ANALYSIS OF THE BIOCHEMICAL PROFILE OF LOW GRADE GLIOMA WITH DIFFERENT IDH1 MUTATION STATUS USING VIBRATIONAL SPECTROSCOPY

Uckermann, O.1; Juratli, T.1; Conde, M.1;Galli, R.2;Krex, D.1; Geiger, K.3;Schackert, G.1;Temme, A.1; Steiner, G.2; Kirsch, M.1
1 Neurosurgery, 2 Clinical Sensoring and Monitoring, Department of Anesthesiology and Intensive Care Medicine, 3 Neuropathology, University Hospital Carl Gustav Carus, TechnischeUniversität Dresden, Germany

Mutations in human cytosolic isocitrate dehydrogenases 1 (IDH1) are a common feature of low grade gliomas (LGG) and cause profound changes of the metabolites of the Krebs cycle. We used label-free-fourier-transform infrared (FT-IR) spectroscopy thatprobes molecular composition in order to determine the IDH1-mutation status in cell culture systems and human brain tumor samples. Permanent cell lines (U87-MG, SVG p12) and primary glioblastoma cell lines (HT7606, HT12346 and HT12347) were transduced with either IDH1 wild-type or mutated IDH1. Clusteranalysis and principal-component-analysis were able to detect differences in the respective FT-IR spectral datasets in regions assigned to saccharides (1050 and 1120 cm-1) and proteins (1236, 1545 and 1651 cm-1). The IDH1 mutation status of human LGG was determined by DNA sequencing (n=26). Difference spectra (IDH1-mut vs. IDH1-wt) showed changes in the region around



1100 cm-1 which is attributed to saccharidesand the band at 1740 cm-1 assigned to C=O stretching vibrations. Principal-component-analysis confirmed differences between the two groups. Supervised classification recognized relevant spectral regions at 1328, 1359, 1371, 1442, 1490, 1598 cm-1 related to proteins and lipids and was able to assign 24 of the 26 tumor samples to the correct group. On the basis of FT-IR spectroscopy samples of LGG carrying IDH1 mutations can be discerned from IDH1 wildtype tumors. Relevant spectral regions assigned to saccharides and C=O stretching vibrations can be explained by changes in the Krebs cycle.

REGULATION OF MESENCHYMAL GENE EXPRESSION BY NF1 IN GLIOBLASTOMA

Thomas Unterkircher, Pamela Franco Jimenez, Maria Stella Carro
Neurozentrum, Universitätsklinikum Freiburg im Breisgau, Breisacher Str. 64, 79106 Freiburg im Breisgau, Thomas.Unterkircher@uniklinik-freiburg.de

In recent years several landmark studies have identified gene expression signatures associated with clinical outcome and survival in GBM. Most importantly, the tumor subset characterized by expression of mesenchymal genes has been correlated with poor prognosis. In our previous work, STAT3 and C/EBPß were identified as master regulators of this signature. In the current study we investigated gene aberrations that might drive the expression of these master regulators, specifically NF1, EGFR and PTEN, as associated chromosomal aberrations have previously been correlated with mesenchymal signature. Using linear regression analysis of STAT3 and C/EBPß expression on EGFR, PTEN and NF1 expression in a set of GBM data available through The Cancer Genome Atlas, we found an inverse C/EBPß-NF1 correlation. Conversely, EGFR and PTEN levels were not associated with any master regulator. We therefore focused on characterizing the association between NF1, C/EBPß and mesenchymal GBM. In a set of NF1 wild type and NF1deleted GBM samples we found a strong enrichment of mesenchymal gene expression upon NF1 deletion. Using patient derived brain tumor stem cells (BTSCs), we found that knockdown of NF1 increased, while overexpression of NF1-GRD, the Ras-interacting domain of NF1, in turn reduced expression of mesenchymal signature, suggesting that NF1 strongly contributes to mesenchymal gene expression. NF1-GRD expression also decreased osteogenesis differentiation capacity and YKL40 expression in mesenchymal BTSCs. Unexpectedly, knockdown of NF1, though increasing mesenchymal expression profile, did not induce C/EBPß, suggesting that additional transcription factors might contribute to mesenchymal expression in GBM. Analyzing microarray data of NF1 knockdown and NF1 overexpressing cells, we identified a set of transcription factors that might contribute to changes in gene signature, which are under further investigation.

ACTIVATION OF RHO GTPASES PREVENTS TUMOR GROWTH AND PRESERVES NEURONAL FUNCTIONS IN A MOUSE MODEL OF GLIOMA

Vannini, E.; Olimpico, F.; Costa, M.; Caleo, M.
Institute of Neuroscience, CNR Pisa

Glioblastomais the most malignant form of gliomas andits treatment is one of the greatest challenges to oncologists.Here we probed the antineoplastic effects of a bacterial protein toxin, cytotoxic necrotizing factor 1 (CNF1). CNF1 causes a long-lasting activation of Rho GTPaseswhich leads to (i) actin stabilization, blockade of cytodieresis,multinucleation and eventually cell death in proliferating glioma cells; (ii) promotion of neuron health and plasticity, with an increase in dendritic spine growth. Due to CNF1 double effect, we exploited it for the treatment of glioma in the syngenic GL261 model. We injected GL261 cells into the adult mouse visual cortex and, 5 days later, we administered either a single intracerebral dose of CNF1 or vehicle. CNF1 (80 nM) resulted in a dramatic enhancement of survival of glioma-bearing mice with no obvious toxicity. Indeed, 57%of the CNF1-treated animals survived up to 60 days following GL261 glioma cell transplant, while the median survival time of glioma-bearing controls was 28 days.Neuroanatomical analysis conducted at day 21 showed that CNF1 treatment halved tumor volume and caused a significant increase in the density of astrocytes and microglial cells in peritumoralareas.Wealso assessed the physiology of peritumoral areas performing recordings of cell spiking activity and visual evoked potentials (VEP). Compared to naïve controls,in the visual cortex of glioma-bearing mice we found a significant increase in spontaneous spiking and a robust dampening of absolute VEP amplitudes and cell spiking following visual stimulation of cortical neurons. On the contrary, in CNF1-treated animals we observed a very significant preservation of visual responsiveness. In addition, the reliability of visual responses was reduced in vehicle-treated glioma-bearing mice and this parameter was completed restored by CNF1 delivery. All these data show thatthe activation of Rho GTPases by CNF1 reduces growth of the tumoral mass and spares the functionality of the cortical areassurrounding the glioma.

CHEMICAL AURORA B INHIBITION INCREASES SUSCEPTIBILITY OF GLIOBLASTOMA CELLS TO ALLOGENEIC NK CELLS BY UPREGULATION OF MIC A/B AND DEATH RECEPTORS

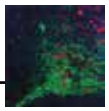
Ralf Wiedemuth, Marina Conde, Gabriele Schackert, AchimTemme
Section Experimental Neurosurgery/ Tumor Immunology, Department of Neurosurgery. University Hospital Carl Gustav Carus, TU Dresden

The „Chromosomal Passenger Complex" (CPC) is one of the key regulators of cell division involved in the coordination of chromosomal and cytoskeletal events. The enzymatically active member of the complex, the Aurora B kinase, is overexpressed in a variety of tumors including glioblastoma. Targeting Aurora B by RNAi or chemical inhibition overrides the spindle checkpoint and drives cells through an aberrant mitosis, followed by DNA endoreduplication and eventually cell death representing a promising target for anti-cancer therapy. In this study, we evaluated the biological effects of pharmacological Aurora B inhibition on wildtypeU87-MGwt, p53-deficient U87-MGshp53 and primary HT7606 glioma cells, in particular the upregulation of death receptors and NK cell ligands and analysed the susceptibility of treated glioma cells to allogeneic NK cells. Chemical Inhibition of Aurora B by barasertib (AZD 1152-hQPA) treatment induced in U87-MGwt cells a p53-dependent G1 arrest caused by DNA damage as indicated by γH2AX,activated ATM/CHK2 kinases and p53 phosphorylation. Furthermore Aurora B inhibition led to cell death and decreased clonal survival of U87-MG and HT7606 cells which was further augmented in p53-deficient U87-MGshp53 cells. Flow cytometry analysis of barasertib treated cells revealed a strong upregulation of the death receptors TRAIL R2, CD95 and the stress induced non-classical MHC molecule MIC A/B. Subsequent experiments showed an enhanced cytotoxic response of allogeneic human NK cells against barasertib-treated glioma cells. Therefore, combined Aurora B inhibition and a concomitant immunotherapy with NK cells might represent a promising avenue for adjuvant local treatment of gliomas.

PEPTIDES USED AS POTENTIAL DRUG ENHANCER FOR CYTOSTATIC DRUGS TO IMPROVE BRAIN TUMOR TREATMENT

Winkler, L.; Staat C.; Dabrowski. S.; Wolburg, H.;1 Engelhardt, B.;2 Campbell, M.;3 Deli, M.;4 Blasig, I.E.
FMP Berlin, Germany; 1Univ. Tübingen/Germany; 2Univ. Bern/Switzerland; 3Trinity Coll. Dublin/Ireland; 3Hung. Acad. Sci., Szeged/Hungary

Claudin (Cldn) peptidomimetics and ligands are potential modulators of the blood-brain barrier (BBB) formed by endothelial cells. Cldns constitute tight junctions (TJs) limiting permeation through the interendothelial space. The tightening is achieved via Cldns' extracellular loops (ECLs). Therefore, modulation of Cldn functions by peptidomimetics is a promising strategy to enhance drug delivery through the BBB. Peptides from ECLs of Cldn1 and -5 (C1C2, Pep5) were analyzed concerning their Cldn and barrier modulating properties. C1C2 transiently increased permeability in a murine BBB model, in Caco-2 and MDCK-II cell barriers. The barrier openings were accompanied by redistribution of different Cldns form cell contacts to cytosol suggesting interaction of C1C2 with Cldns. Analyses in TJ-free HEK cells transfected with Cldn1, -2, -3, -4 or -5-YFP identified Cldn1>Cldn5>Cldn3 as targets. Binding measurements at full-length Cldns and recombinant ECLs confirmed these findings. Freeze-fracture EM revealed alterations in Cldn5 TJ-architecture, i.e. drastic plasmatic fracture (P)- to exoplasmic fracture (E)-face transition, whereas the Cldn1 TJ network was altered, i.e. formation of parallel strands. C1C2 and Pep5 also increased small molecule permeability in a rat cell BBB. Transmission EM showed disappearance of interendothelial TJs. Pep5 revealed high affinity to Cldn5 and less to Cldn3; i.v. injection in mice



monitored by MRI resulted in concentration dependent opening of the BBB. Similarly, the blood-retina barrier exhibited enhanced permeability and down-regulation of Cldn5. Collectively, Cldn peptidomimetics enable transient drug release through Cldn1-, Cldn3- and/or Cldn5-expressing barriers by affecting composition, localization and structure of TJs.

THE HUMAN GLIOBLASTOMA CELL CULTURE (HGCC) RESOURCE: VALIDATED CELL MODELS REPRESENTING ALL MOLECULAR SUBTYPES

Yuan Xie1,5, Tobias Bergström1,5, Yiwen Jiang1,5, Patrik Johansson1,5, Voichita Dana Marinescu1, Nanna Lindberg2, Anna Segerman1, Grzegorz Wicher1, Mia Niklasson1, Satishkumar Baskaran1, Smitha Sreedharan1, Isabelle Everlien1,3, Marianne Kastemar1, Annika Hermansson1, Lioudmila Elfineh1, Sylwia Libard1, Eric Charles Holland2, Göran Hesselager4, Irina Alafuzoff1, Bengt Westermark1,6, Sven Nelander1,6,*, Karin Forsberg-Nilsson1,6 and Lene Uhrbom1,6,*

*1 Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Rudbeck Laboratory, Uppsala University, 751 85 Uppsala, Sweden, 2 Fred Hutchinson Cancer Research Center, 1100 Fairview Ave N., PO Box 19024, Seattle, WA 98109, 3 Department of Molecular Neurobiology, German Cancer Research Center (DKFZ) Heidelberg, 69120 Heidelberg, Germany, 4 Department of Neuroscience, Uppsala University, Uppsala University Hospital, SE-751 85 Uppsala, Sweden, 5 These authors contributed equally to this study, 6 These authors contributed equally to this study, * Correspondence: sven.nelander@igp.uu.se (S.N.), lene.uhrbom@igp.uu.se (L.U.)*

Glioblastoma (GBM), the most frequent and malignant form of primary brain tumor is essentially incurable and its resistance to currently available therapy has been attributed to a tumor-initiating subpopulation of cells referred to as glioma stem cells (GSCs). To address the present shortage of validated GSC lines representative of GBM diversity, we developed a panel of newly established, clinically annotated and experimentally validated cell lines derived from surgical samples of patient tumors. This collection, which we call the Human Glioblastoma Cell Culture (HGCC) resource, consists of both a biobank and an associated database containing high-resolution molecular data. The HGCC now includes 48 cell lines maintained under serum-free, defined neural stem cell conditions. We demonstrate here that these HGCC lines are tumorigenic, harbor genomic lesions characteristic of glioblastomas, and represent all four transcriptional subtypes. The HGCC models thus presents an open resource that will enable modeling of GBM diversity.

NUCLEAR RECEPTOR BINDING PROTEIN 2 (NRBP2): A PUTATIVE TUMOR SUPPRESSOR GENE IN MEDULLOBLASTOMA

Anqi Xiong1, Argyris Spyrou1, Holger Weishaupt1, Groom Alemayehu1, Fredrik J. Swartling1, Tommie Olofsson2, Karin Forsberg-Nilsson1

1Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, 751 85 Uppsala, Sweden, 2The Swedish National Board of Forensic Medicine, Uppsala, Sweden

We previously reported that malignant brain tumors and neural stem cells share a common transcriptional signature1. In addition to an increased understanding of regulation of normal stem cell division, further knowledge about novel identified genes may contribute to the improvement of brain tumor diagnosis and therapy. Nuclear receptor binding protein 2 (NRBP2 was selected for study based on the high level of regulation. In mouse brain development, NRBP2 was continuouslyexpressed in cerebellum. In medulloblastoma, NRBP2 was expressed in a subset of tumor cells, co-staining with neuronal markers, but never with astrocyte lineage markers2. To understand the role of NRBP2 in brain tumors, a human brain tumor tissue array was analyzed. We found that NRBP2 expression was low in the majority of tumors.Databasemining showed decreased expression of NRBP2 in human medulloblastoma samples, compared to healthy cerebellum tissue. In addition, NRBP2 expression was lowest in the medulloblastomas with poorer outcome. Recent studies indicate that medulloblastoma exhibit frequent epigenetic alternations. Therefore, we treated medulloblastoma cell lines withdrugs inhibiting DNA methylation or histone methylation.In all cell lines, these treatmentsled to the up-regulation of NRBP2 expression levels. Due to the possible link between low NRBP2 expression and poor prognosis, we overexpressed NRBP2 in a medulloblastoma cell line and found a decrease in cell proliferation, increased cell death and less cell migration in vitro. We are evaluating these effects on more cell lines, and planning to examine the function of NRBP2 in tumor growth in vivo.

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CEREBRAL SELENIUM LEVELS CONTROL PROGRESSION OF MALIGNANT BRAIN TUMOURS

Eduard Yakubov, Ali Ghoochani, Michael Buchfelder, Ilker Y. Eyüpoglu, Nic E. Savaskan

Department of Neurosurgery, Friedrich-Alexander University Erlangen-Nuremberg, 91054 Erlangen, Germany

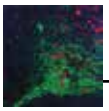
Glioblastoma (GBM)represents the most malignant primary brain tumour in adults.Even with aggressive multimodality treatments, outcome of patients with GBM still remains fatal.Therefore, we have investigated in agents that may be relevant for therapy. Selenium is an essential micronutrient with toxic properties.Higher selenium supplementation has been suggested to protect against several types of cancer. Inthis study, we showfor the first time in vivothe impact of micronutrient selenium in reducing glioma tumour growth in a dose-dependent manner.Interestingly, glioma xenograft models revealed that selenium deficiency is also associated with acceleration of glioma progression. Invitro, we show that the treatment with selenite resulted in a massive glioma cell reduction, while primary neuronal cells remained viable indicating that selenium toxicity is selective for glioma cells. Selenite counteracts glioma cells by inducing ROS and caspase-independent apoptosis. A significant increase in the expression and activity of the seleno-enzyme cytosolic glutathione peroxidase (cGPx) wasalso observed.Our study further demonstrates that selenium-induced cell death is PIP2 dependent and interferes with the cell cycle regulator p21.Moreover, we found in ex vivo brain slices thatselenite significantly inhibitsglioma cell invasion and prevents peritumoural cell death. The findings in this study provideinsight into the importance of selenium as a therapeutic option for glioblastoma therapy, atrace element that can be considered as a promising agent in neurooncology.

DOUBLE MINUTE AMPLIFICATION OF MUTANT PDGF RECEPTOR ALPHA IN A MOUSE GLIOMA MODEL

Hongyan Zou 1,2, RuiFeng1, Yong Huang 1, Joseph Tripodi3, VesnaNajfeld3, Nadejda M. Tsankova1,4, Maryam Jahanshahi 5,6, Lorin E. Olson 5, Philippe Soriano 5,6, Roland H. Friedel1,2,5

1Fishberg Department of Neuroscience, Friedman Brain Institute,, 2 Department of Neurosurgery,, 3 Tumor Cytogenomics Laboratory, 4 Department of Pathology, 5Department of Developmental and Regenerative Biology, 6 Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029

In primary brain tumors, oncogenes are frequently amplified and maintained on extrachromosomal DNA as double minutes (DM), but the underlying mechanismsand the oncogenic roles in the initiation and progression of glioma remain poorly understood. We have generated a mouse model of malignant glioma based on knock-in of a mutant PDGF receptor alpha (PDGFRalpha) that is expressed in oligodendrocyte precursor cells (OPCs) after activation by a Cre recombinase. In the tumor suppressor INK4/Arf-/- background, mutant animals frequently developed brain tumors resembling anaplastic human gliomas (WHO grade III). Importantly, in the brain tumors and cell lines derived from brain tumor tissues, we identified a high prevalence ofDM Pdgfra gene amplification, suggesting its occurrence as an early mutational event contributing to the malignant transformation of OPCs. Amplicons extended beyond the Pdgfra locus and included in some cases neighboring genes Kit and Kdr. Our genetically defined mouse brain tumor model therefore supports OPC as a cell of origin for malignant glioma and offers an example of a defined temporal sequence of mutational events, thus providing an entry point for a mechanistic understanding of DM gene amplification and its functionality in gliomagenesis.



Address List

a Dzaye, Omar
Cellular Neurosciences
Max-Delbrück-Center for Molecular Medicine
Robert-Rössle-Str. 10
13092 Berlin
Email: omar.dzaye@mdc-berlin.de

Aldape, Professor Kenneth D
Division of Pathology and Laboratory Medicine
University of Texas MD Anderson Cancer Center
151 Holcombe Boulevard
Houston TX 77030, USA
Email: kaldape@mdanderson.orgj

Alessandrini, Dr. Francesco
DIMES
University of Genoa
via Leonbattista Alberti
16132 Genoa, Italy
Email: francescoalessandrini89@gmail.com

Amend, Diana
Juliuspromenade
97070 Würzburg,
Email: amend.diana@web.de

ANJUM, Dr. Fahra
Neurosurgery
International Neuroscience Institute
Fehrsweg 26
30655 Hannover
Email: farhaanjum272@yahoo.com

Appolloni, Dr. Irene
Terapie oncologiche integrate
IRCCS San Martino - IST
Largo Rosanna Benzi 10
16132 Genova, Italy
Email: irene.appolloni@gmail.com

Arends, Max
Charité Berlin
Sprengelstr. 7
13353 Berlin
Email: christopher-maximilian.arends@charite.de

Bäsler, Nadine
EPO GmbH
Robert-Rössle-Str.10
13125 Berlin, Deutschland
Email: N.Baesler@epo-berlin.com

Balaziova, Dr Eva
Institute of Biochemistry and Experimental Oncology
Inst of Biochemistry and Experimental Oncology
U Nemocnice 5
12853 Prague 2, Czech Republic
Email: eva.balaziova@gmail.com

Barciszewska, Dr med. Anna-Maria
Department of Neurosurgery and Neurotraumatology
Poznan University of Medical Sciences
Przybyszewskiego 49
60-355 Poznan, Poland
Email: abarcisz@man.poznan.pl

Barilari, Dr Manuela
Cell biology (Growth and Signalling)
INSERM
Bâtiment Leriche - 14 Rue Maria Helena Vieira
75014 Paris, France
Email: manuela.barilari@inserm.fr

Baroncelli, Dr. Laura
CNR
Neuroscience Institute
via G. Moruzzi 1
56124 Pisa, Italy
Email: baroncelli@in.cnr.it

Bartsch, Prof. Jörg
Neurosurgery
Marburg University
Baldingerstraße
35033 Marburg
Email: jbartsch@med.uni-marburg.de

Baskara, Sathishkumar
Immunology Genetics and Pathology
Uppsala University
C11:2 Rudbeck Laboratory
75185 Uppsala, Sweden
Email: sathishkumar.baskaran@igp.uu.se

Bauer, Dr. Chris
MicroDiscovery GmbH
Marienburger Str. 1
10405 Berlin,
Email: chris.bauer@microdiscovery.de

Benveniste, Professor Etty (Tika)
Cell, Developmental and Integrative Biology
University of Alabama at Birmingham
1900 University Blvd.
Birmingham, AL 35294-0005, USA
Email: tika@uab.edu

Beyeler, Dr. Sarah
Universität Tübingen
Hertie Insitut für Klinische Hirnforschung
Otfried-Müller Strasse 27
72076 Tübingen
Email: sarah.beyeler@medizin.uni-tuebingen.de

Blank, Anne
Institut für Neurochirurgie
Charité Universitätsmedizin Berlin
Charitéplatz 1/ Virchowweg 21
10117 Berlin
Email: anne.blank@charite.de

Blasig, Ingolf
FMP
R.-Rössle-Str. 10
13125 Berlin
Email: iblasig@fmp-berlin.de

Blecharz, Dr. Kinga
Neurosurgery
Charité Universitätsmedizin
Charitéplatz 1, Virchowweg 21
10117 Berlin
Email: kinga.blecharz@charite.de

Bolin, MSc Sara
Immunology Genetics and Pathology
Uppsala University
Dag Hammarskjolds vag 20
75185 Uppsala, Sweden
Email: sara.bolin@igp.uu.se

Borgenvik, MSc Anna
Uppsala University
Immunology, genetics and pathology
Dag Hammarskjöldsväg 20
75185 Uppsala, Sweden
Email: anna.borgenvik@igp.uu.se

Bouazza, Boris
Biophysical Chemistry
Humboldt-Universität zu Berlin
Groninger Strasse 3
13347 Berlin
Email: 2b.a.boris@gmail.com

Brandenburg, Dr. Susan
Experimental Neurosurgery
Charite
Chariteplatz 1
10117 Berlin
Email: Susan.Brandenburg@charite.de

Brösicke, Dr. Nicole
Department of Cell Morphology & Molecular Neurobiology
Ruhr-University Bochum
Universitätsstr. 150
44801 Bochum
Email: Nicole.Broesicke@rub.de

Broggini, Thomas
Neurosurgery
Charité Universitätsmedizin
Charitéplatz 1
10117 Berlin
Email: thomas.broggini@charite.de

Bungert, Alexander
Experimentelle Neurochirurgie
Ackerstr. 120
13355 Berlin,
Email: alexander.bungert@charite.de

Buonfiglioli, Alice
Cellular Neuroscience
MDC
Robert-Roessle-str 10
13125 Berlin
Email: alice.buonfiglioli@mdc-berlin.de

Busek, Dr. Petr
Inst of Biochemistry and Experimental Oncology
1 Faculty of Medicine, Charles University in Prague
U Nemocnice 5
12853 Prague 2, Czech Republic
Email: busekpetr@seznam.cz

Calea, Dr. Matteo
CNR Neuroscience Institute
via G. Moruzzi 1
56124 Pisa, Italy
Email: caleo@in.cnr.it

Cancer, Matko
Department of Immunology, Genetics and Pathology
Uppsala University
Dag Hammarskjölds v 20
751 85 Uppsala, Sweden
Email: matko.cancer@igp.uu.se

Carro, Dr. Maria Stella
Neurosurgery
University of Freiburg
Breisacherstrasse 64
79106 Freiburg,
Email: maria.carro@uniklinik-freiburg.de

Chen, Daishi
Neurosurgery
Schwabachanlage 6
91054 Erlangen
Email: cdsginqtbing@hotmail.com

Clement-Schatlo, Dr. Virginie
Stemergie biotechnology SA
rue de la roseraie
1205 geneva, switzerland
Email: virginie.clement@stemergie.com

Combeau, Dr. Gaëlle
Cellular and Molecular Biology (CMB)
Karolinska Institut
Nöbel väg 3
17177 Stockholm, Sweden
Email: gaelle.combeau@licr.ki.se

Conde, Marina
Fetscherstraße 74
1309 Dresden,
Email: marina.conde@uniklinikum-dresden.de

Costa, Amanda
Max-Delbrück-Center
Robert-Rössle-Str 10
13125 Berlin,
Email: Amanda.Costa@mdc-berlin.de

Costa, PhD Barbara
Division of signal transduction and growth control
DKFZ (German Cancer Research Center)
Im Neuenheimer Feld 280
69120 Heidelberg
Email: b.costa@dkfz-heidelberg.de

Czarnecka, MSc Joanna
Laboratory of Molecular Neurobiology
Nencki Institute of Experimental Biology
Pasteur 3
02-093 Warsaw, Poland
Email: j.czarnecka@nencki.gov.pl.

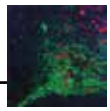
Davila de Leon, PhD David
Deparment of Biochemistry and Molecular Biology I
School of Biology, Complutense University
Calle José Antonio Nováis 2, 28040 Madrid
28040 MADRID, SPAIN
Email: daviddav@ucm.es

de Almeida Sassi, Felipe
Cellular neurosciences
Max-Delbrück-Center (MDC)
Robert-Rössle-Strasse 10
13125 Berlin
Email: Felipe.deAlmeidaSassi@mdc-berlin.de

Deumelandt, Katrin
CCU Neuroimmunology and Brain Tumor Immunology
DKFZ Heidelberg
Im Neuenheimer Feld 280
69120 Heidelberg
Email: k.deumelandt@dkfz.de

Dreihardt-Kübler, Leontine
Labor-Praxisklinik GbR Dr. Kübler & Partner
Siebertstr6
81675 München
Email: info@labor-praxisklinik.de

Düring, Isabell
Department of Neurosurgery, Section Experimental Neurosurgery and Tumorimmunolog
University Hospital Carl Gustav Carus TU Dresden
Fetscherstraße 74
1307 Dresden
Email: Isabell.Duering@uniklinikum-dresden.de



Eisemann, MSc Tanja
Division of Signal Transduction and Growth Control
German Cancer Research Center (DKFZ)
Im Neuenheimer Feld 280
69120 Heidelberg
Email: t.eisemann@dkfz.de

Ellert-Miklaszewska, Dr. Aleksandra
Laboratory of Molecular Neurobiology
Nencki Institute of Experimental Biology PAS
Pasteur 3
02-093 Warsaw, Poland
Email: aellert@nencki.gov.pl

Feenstra, Jennifer
Physiology and Pharmocology
Karolinska Institutet
Nanna Svartz väg 6A
171 77 Stockholm, Sweden
Email: jennifer.feenstra@ki.se

Fejfarova, MSc Edita
Inst of Biochemistry and Experimental Oncology
1 Faculty of Medicine, Charles University in Prague
U Nemocnice 5
12853 Prague 2, Czech Republic
Email: edfejfar@gmail.com

Feldheim, Jonas
Tumorbiologisches Labor der Neurochirurgischen Klinik
Julius-Maximilians-Universität Würzburg
Reiserstr. 3
97080 Würzburg
Email: jonas.feldheim@googlemail.com

Felsenstein, Matthäus
Institute of Experimental Neurosurgery
Charité – Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin,
Email: matthaeus.felsenstein@charite.de

Flüh, Dr. Charlotte
Klinik für Neurochirurgie
Universitätsklinikum Schleswig-Holstein, Campus Kiel
Arnold-Heller-Straße 3, Haus 41
24105 Kiel
Email: charlotte.flueh@uksh.de

Forsberg-Nilsson, Professor Karin
Immunology, Genetics and Pathology
Uppsala Universitet
Rudbeck Laboratory
75185 Uppsala, Sweden
Email: karin.nilsson@igp.uu.se

Frenzel, Dr. Katrin
BioNTech AG
An der Goldgrube 12
55131 Mainz
Email: Katrin.Frenzel@biontech.de

Friedel, Dr. Roland
Department of Neuroscience
Icahn School of Medicine at Mount Sinai
1425 madison Avenue
10029 New York, USA
Email: roland.friedel@mssm.edu

Fuchs, Steffen
University of Würzburg
Department of Neurosurgery
Dunzendorf 9
97996 Niederstetten
Email: steffen_fuchs@gmx.net

Gaunitz, Prof. Dr. Frank
Clinic for Neurosurgery
Medical Faculty / University of Leipzig
Liebigstraße 20
4103 Leipzig
Email: fgau@medizin.uni-leipzig.de

Gebhardt, Henrike
Anatomisches Institut
CAU zu Kiel
Otto-Hahn-Platz 8
24118 Kiel
Email: h.gebhardt@anat.uni-kiel.de

Ghoochani, Ali
Department of Neurosurgery
Universitätsklinikum Erlangen, Friedrich Alexander University of Erlangen-Nürnbe
Schwabachanlage 6
91054 Erlangen
Email: Ali.Ghoochani@uk-erlangen.de

Govindarajan, Parameswari
Hertie institute for clinical brain research
Hoppe-Seyler-Straße 3
72076 Tübingen
Email: parameshwari.govindarajan@gmail.com

Grasskamp, M.Sc. Andreas
NeuroCure
Braunschweiger Straße 75
12055 Berlin,
Email: andreas.grasskamp@charite.de

Green, Dr Edward
Neuroimmunologie und Hirntumorimmunologie
DKFZ
Im Neuenheimer Feld 280
69120 Heidelberg
Email: e.green@dkfz.de

Grube, Dr. Susanne
Department of Neurosurgery
University Hospital Jena
Erlanger Allee 101
7749 Jena, Deutschland
Email: susanne.grube@med.uni-jena.de

Gutmann, Donald O. Schnu David H.
Department of Neurology, Neurofirbromatosis Centermbeau
Washington University School of Medicine
660 S Euclid Avenue
St. Louis, 63110 Missouri, USA
Email: gutmannd@neuro.wustl.edu

Haack, Johannes
Cognitive Science
Universität Potsdam
Karl-Liebknecht-Strasse 24-25
14476 Potsdam,
Email: haack@uni-potsdam.de

Hagemann, Dr. Carsten
Department of Neurosurgery
University of Würzburg
Josef-Schneider-Str. 11
97080 Würzburg
Email: hagemann_c@ukw.de

Hagemeier, Prof. Dr. Christian
Prodekanat Forschung
Charité - Universitätsmedizin Berlin
Charitéplatz 1
10117 Berlin
Email: prodekan-forschung@charite.de

Hasselmann, Helge
Psychiatry
Clinic for Psychiatry and Psychotherapy
Liebenwalder Straße 43
13347 Berlin,
Email: helgehasselmann@googlemail.com

Hattermann, Dr. Kirsten
Institute of Anatomy
Christian-Albrechts-University Kiel
Olshausenstr. 40
24098 Kiel,
Email: k.hattermann@anat.uni-kiel.de

Heiland, Dieter Henrik
Department of Neurosurgery
University Medical Center Freiburg
Breisacherstr. 64
79106 Freiburg,
Email: dieter.henrik.heiland@uniklinik-freiburg.de

Held-Feindt, Prof. Dr. Dr. Janka
Neurosurgery
Arnold-Heller-Str.3, No.41
24105 Kiel
Email: held-feindtj@nch.uni-kiel.de

Hendel, Sarah
Hertie Institut
Universitätsklinikum Tübingen
Ottfried-Müller-Str.27
72076 Tübingen
Email: sarah.hendel@med.uni-tuebingen.de

Heppner, Prof. Dr. Frank
Charité Universitätsmedizin
Charitéplatz 1
10117 Berlin
Email: Frank.Heppner@charite.de

Hertenstein, Anne
Neuroonkologie
DKFZ Heidelberg
Im Neuenheimer Feld 280
69120 Heidelberg,
Email: a.hertenstein@dkfz-heidelberg.de

Hilser, Dr Marek
Inst of Biochemistry and Experimental Oncology
1 Faculty of Medicine, Charles University in Prague
U Nemocnice 5
12853 Prague 2, Czech Republic
Email: marek.hilser@email.cz

Hofmann, Philipp
Elberfelderstraße 5
10555 Berlin,
Email: philipp.hofmann@charite.de

Holzgreve, Adrian
Augustenstrasse 87
80798 Munich
Email: adrien@holzgreve.net

Jahani-Asl, Dr. Arezu
Cellular and Molecular Medicine
Ottawa Hospital Research Institute
501 Smyth Road
K1H 8L6 Ottawa, Canada
Email: arezu.jahaniasl@gmail.com

Jödicke, PD Dr. Andreas
Neurosurgery
Klinikum Neukölln
Rudower Str. 48
12351 Berlin
Email: andreas.joedicke@vivantes.de

Johansson, Patrik
IGP
Uppsala University
Rudbecklab
Uppsala Uppsala, Sweden
Email: patrik.johansson@igp.uu.se

Johnson, Dr. Derek
Neurology / Neuro-Oncology
Mayo Clinic
200 First St SW
Rochester, 55905 NY, USA
Email: johnson.derek1@mayo.edu

Kahlert, Theresa
Erlanger Allee 101
7747 Jena
Email: theresakahlert@googlemail.com

Kaminska, Professr Bozena
Laboratory of Molecular Neurobiology,
Neurobiology Center
Nnecki Institute
Pasteur 3
02-093 Warsaw, Poland
Email: bozenakk@nencki.gov.pl

Kessler, Dr. Almuth F.
Department of Neurosurgery
University Hospital of Würzburg
Josef-Schneider-STraße 11
97080 Würzburg
Email: kessler_a1@ukw.de

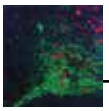
Kettenmann, Prof. Dr. Helmut
Zelluläre Neurowissenschaft
MDC
Robert-Rössle-Str. 10
13125 Berlin
Email: kettenmann@mdc-berlin.de

Kiwit, Prof. Dr. Jürgen
Neurochirurgische Klinik
Helios Klinikum Berlin-Buch
Schwanebecker Chaussee 50
13125 Berlin
Email: juergen.kiwit@helios-kliniken.de

Kocyk, Marta
Department of Molecular Neurobiology
Nencki Institute of Experimental Biology
Pasteura 3
02-093 Warsaw, Poland
Email: m.kocyk@nencki.gov.pl

Kögler, Christine
Klinik für Neurochirurgie
Universitätsklinikum Jena
Erlanger Allee 101
7747 Jena
Email: christine.kogler@yahoo.de

Koglin, Norman
Clinical R&D
Piramal Imaging GmbH
Tegeler Str. 6
13353 Berlin
Email: norman.koglin@piramal.com



Kovalchuk, Assistant Alina
Human Anatomy
Bogomolets National Medical University
Peremohy avenue
2000 Kiev, Ukraine
Email: alin.kovalchuk@gmail.com

Król, Sylwia Katarzyna
Laboratory of Molecular Neurobiology,
Neurobiology Center
Nencki Institute of Experimental Biology Polish Academy of Sciences
3 Pasteur
02-093 Warsaw, Poland
Email: s.krol@nencki.gov.pl

Kratzsch, Dr. med. M.Sc. Tobias
Department of Neurosurgery
Charité Berlin
Hindenburgdamm 30
12203 Berlin
Email: tobias.kratzsch@charite.de

Krenzlin, Dr. med. Harald
Klinik für Neurochirurgie
HSK Wiesbaden
Ludwig-Erhard-Strasse 100
65199 Wiesbaden
Email: h.krenzlin@t-online.de

Kuchelmeister, Prof. Dr. med. Klaus
Institut für Neuropathologie
Universitätsklinikum Bonn
Sigmund-Freud-Straße 25
53105 Bonn
Email: klaus.kuchelmeister@ukb.uni-bonn.de

Kübler, Dr. Ulrich
Labor-Praxisklinik GbR
Siebertstr. 6
81675 München
Email: info@labor-praxisklinik.de

Kübler, Dr. Janina
Siebertstr. 6
81827 München, Deutschland
Email: info@labor-praxisklinik.de

Kundu, Dr Soumi
Immunology Genetics and Pathology
Uppsala University
Rudbecklaboratoriet C11:3 Dag Hammerskjölds v
751 85 Uppsala, Sweden
Email: soumi.kundu@igp.uu.se

López Valero, Israel
Biochemistry and Molecular Biology
School of Biology, Complutense University, Madrid
Jose Antonio Novais, 12
28040 Madrid, Spain
Email: ilvalero@hotmail.com

Lavon, Dr. Iris
Gaffin Center For Neuorooncology
Hadassah Hebrew University Medical Center
Ein-Kerem
12000 Jerusalem, Israel
Email: Irisl@hadassah.org.Il

Lewczuk, Ewa
Nencki Institute of Experimental Biology
Pasteur Street
02-093 Warsaw, Polska
Email: ewalewczuk92@gmail.com

LI, Ting
Leipzigerstraße 44
39120 Magdeburg,
Email: ting.li@med.ovgu.de

Loebel, Dr. med. Franziska
Neurosurgery
Charité University Hospital Berlin
Augustenburger Platz 1
13353 Berlin
Email: franziska.loebel@charite.de

Lucía, del Valle Antón
Cellular Neurosciences
Max-Delbrück-Center for Molecular Medicine (MDC)
Robert-Rössle-Str. 10
13092 Berlin
Email: delvalleanton@gmail.com

Maire, Dr. Cecile
Neurosurgery
University Medical Center Hamburg-Eppendorf
Martinistrasse 52
20246 Hamburg
Email: c.maire@uke.de

Malatesta, Professor Paolo
DIMES
University of Genoa
Via L.Battista Alberti 2
16132 Genoa, Italy
Email: paolo.malatesta@unige.it

Maleszewska, Dr. Marta
Laboratory of Molecular Neurobiology
Nencki Institute of Experimental Biology
3, Pasteur str
02 093 Warsaw, Poland
Email: m.maleszewska@nencki.gov.pl

Maricos, Meron
Cellular Neurosciences
MDC
Robert-Rössle-Str. 10
13125 Berlin-Buch,
Email: Maricos.Meron@mdc-berlin.de

Marquina, Ruben
Experimental Neurology
Charite
Friedrichstrasse 172
10117 Berlin
Email: rimarquina@gmail.com

Marx, Dr. med. Sascha
Department of Neurosurgery
University medicine Greifswald
Sauerbruchstraße
17475 Greifswald
Email: marxs@uni-greifswald.de

Mersch, Martin
Hermannstraße 33
12049 Berlin
Email: martin.mersch@charite.de

Mesaric, Vita Andreja
Student
Charité Universitätsmedizin
Herschelstrasse 3a
10589 Berlin
Email: vita.mesaric@gmail.com

Michen, Susanne
Department of Neurosurgery
University Hospital Carl Gustav Carus, TU Dresden
Fetscherstr. 74
1307 Dresden
Email: susanne.michen@uniklinikum-dresden.de

Möckel, Dr. Sylvia
Department of Neurology
Regensburg University Hospital
Franz-Josef-Strauß-Allee 11
93053 Regensburg
Email: sylvia.moeckel@ukr.de

Mohme, Dr. Malte
Department of Neurosurgery
University Medical Center Hamburg-Eppendorf
Martinistr. 52
20246 Hamburg
Email: m.mohme@uke.de

Mordechai, MSc Anat
Gaffin Center For Neuorooncology
Hadassah Hebrew University Medical Center
Ein-Kerem
12000 Jerusalem, Israel
Email: Matan29@hadassah.org.il

Müller-Jensen, Leonie
Marienstraße 25
10117 Berlin, Deutschland
Email: leonie.mueller-jensen@charite.de

Nelander, Assoc Prof Sven
Immunology, Genetics and Pathology
Uppsala University
Rudbeck Laboratory
SE-75185 Uppsla, Sweden
Email: sven.nelander@igp.uu.se

Neuhaus, Nikolas
Huttenstraße 10a
97072 Würzburg,
Email: niko.neuhaus@gmail.com

Neumann, Dr. Manfred
Neurosurgery/-oncology
Hertie Institute for Clinical Brain Research,
University of Tübingen
Otfried-Müller-Straße 27
72076 Tübingen
Email: docmn@web.de

Nissen, Dr. Urs
Klinik für Neurochirurgie
WKK Heide
Esmarchstr.50
25746 Heide
Email: unissen@wkk-hei.de

Ó hAilín, Darren
Neuroscience Center
Universitätsklinikum Freiburg
Breisacher Str. 64
79106 Freiburg
Email: darren.ohailin@uniklinik-freiburg.de

Oezen, Dr. Iris
CCU Neuroimmunology and Brain Tumor Immunology
DKFZ Heidelberg
Im Neuenheimer Feld 280
69120 Heidelberg
Email: i.oezen@dkfz.de

Olimpico, Dr. Francesco
Neuroscience
CNR
via Moruzzi
56124 Pisa, Italy
Email: francesco.olimpico@in.cnr.it

Oppermann, Henry
Klinik und Poliklinik für Neurochirurgie
Universitätsklinikum Leipzig
Liebigstraße 20
4103 Leipzig
Email: henry.oppermann@medizin.uni-leipzig.de

Pagenstecher, Prof. Dr. Axel
Neuropathology
Universität Marburg
Baldingerstrasse
35043 Marburg
Email: pagenste@med.uni-marburg.de

Parrinello, Simona
MRC Clinical Sciences Centre
Imperial College London
Du Cane Rd
W12 0NN London, UK
Email: simona.parrinello@imperial.ac.uk

Pendekanti, Naga Prathyusha
Immunuology genetics and Pathology(IGP)
Uppsala University
Dag Hammarskjolds Vag v 20,
75185 Uppsala, Sweden
Email: naga_prathyusha.pendekanti@igp.uu.se

Peterziel, Dr. Heike
A100 - Signal Transduction and Growth Control
German Cancer Research Center (DKFZ)
Im Neuenheimer Feld 280
69120 Heidelberg
Email: h.peterziel@dkfz.de

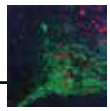
Petritsch, Dr. Claudia
Department of Neurological Surgery
University of California, San Francisco
505 Parnassus Avenue
San Francisco, CA 94143-0520 USA
Email: Claudia.Petritsch@ucsf.edu

Pfister, Professor Stefan
Pädiatrische Neuroonkologie
DKFZ
Im Neuenheimer Feld 280
69120 Heidelberg
Email: s.pfister@dkfz.de

Proescholdt, PD Dr. Martin
Neurosurgery
University Regensburg Medical Center
Franz Josef Strauß Allee 11
93053 Regensburg
Email: martin.proescholdt@ukr.de

Radke, Dr. Josefine
Neuropathology
Charité
Virchowweg 15
10117 Berlin
Email: josefine.radke@charite.de

Raggatz, Jonas
Charite - Universitätsmedizin Berlin
Wichurastraße 11
12249 Berlin
Email: sire2008@hotmail.de



Rajaraman, Srinath
Clinical and Experimental Neuro-Oncology
Hertie Institute for Clinical Brain Research
Otfried-Müller straße.27
72076 Tübingen
Email: srinath.rajaraman@med.uni-tuebingen.de

Rauschenbach, Katharina
CCU Neuroimmunology and Brain Tumor Immunology
DKFZ Heidelberg
Im Neuenheimer Feld 280
69120 Heidelberg
Email: k.rauschenbach@dkfz.de

REHMAN, Dr. Safi Ur
Department of Neurosurgery, Kwong Wah Hospital
25 Waterloo Road , Kowloon
0 Hong Kong, Ho ng Ko ng
Email: safiurrehman@hotmail.com

Reinartz, Roman
Institute of Reconstructive Neurobiology
University of Bonn
Sigmund Freud Staße 25
53127 Bonn
Email: roman.reinartz@uni-bonn.de

Renner, PD Dr. med. Christof
Klinik für Neurochirurgie
Städtisches Klinikum Dessau
Auenweg 38
6847 Dessau-Roßlau
Email: christof.renner@klinikum-dessau.de

Riedel, Helene
Klinik und Poliklinik für Neurochirurgie
Universitätsklinikum Leipzig
Liebigstraße 20
4103 Leipzig
Email: helene.riedel@medizin.uni-leipzig.de

Ritter, Steffi
Department of Neurosurgery
Section Experimental Neurosurgery/Tumor Immunology
University Hospital Carl Gustav Carus, TU Dresden
Fetscherstr. 74
1307 Dresden
Email: steffi.ritter@uniklinikum-dresden.de

Rosen, Gabriela
Dep. for Immunology, Genetics and Pathology (IGP)
Uppsala University
Dag Hammarskjölds väg 20
751 85 Uppsala, Sweden
Email: gabriela.rosen@igp.uu.se

Sachkova, Aleksandra
Universitätsmedizin Göttingen
Christophorusweg 12 App.828
37075 Göttingen, Niedersachsen
Email: sashasachkova@mail.ru

Sanai, Dr. Nader
Neurosurgical Oncology
Barrow Brain tumor Research Center
359 West Thomas Road
AZ 85013 Phoenix, USA
Email: nader.sanai@bnaneuro.net

Santaella, Anna
Medical Neuroscience
Charité
Luisenstr. 56
10117 Berlin,
Email: santaella.anna@gmail.com

Savaskan, PD Dr. Nic
Neurosurgery
FAU- University of Erlangen-Nürnberg
Schwabachanlage 6
91054 Erlangen
Email: nicolai.savaskan@uk-erlangen.de

Savov, Vasil
Uppsala University
Dag Hammarskjölds väg 20
75185 Uppsala, Sweden
Email: vasil.savov@igp.uu.se

Schatlo, Dr. Bawarjan
Neurosurgery
University Hospital Göttingen
Robert Koch Str 40
37075 Göttingen
Email: schatlo@gmail.com

Schmidt, Dr. Linnea
Uppsala University
Immunology, Genetics and Pathology
Dag hammarskjölds väg 20
SE-751 85 Uppsala, Sweden
Email: linnea.schmidt@igp.uu.se

Schnabel, Lutz
Klinik und Poliklinik für Neurochirurgie
Universitätsklinikum Leipzig
Liebigstraße 20
4103 Leipzig
Email: lutz.schnabel@medizin.uni-leipzig.de

Schuchhardt, Dr. Johannes
MicroDiscovery GmbH
Marienburger Str. 1
10405 Berlin,
Email: johannes.schuchhardt@microdiscovery.de

Schulte, Dr. Alexander
Neurosurgery
University Hospital Hamburg-Eppendorf
Martinistrasse 52
20246 Hamburg
Email: aschulte@uke.de

Schwendinger, Nina
MDC
Leberstraße 81
10829 Berlin,
Email: nina.schwendinger@charite.de

Sedo, Professor Aleksi
Inst of Biochemistry and Experimental Oncology
1 Faculty of Medicine, Charles University in Prague
U Nemocnice 5
12853 Prague 2, Czech Republic
Email: aleksi@cesnet.cz

Seifert, Dr. Stefanie
Institut für Neuropathologie
Charité Universitätsmedzin
Charitéplatz 1
10117 Berlin,
Email: stefanie.seifert@charite.de

Sevenich, Dr. Lisa
Memorial Sloan Kettering Cancer Center
417 East 68th Street
New York, 10065 NY, USA
Email: sevenicl@mskcc.org

Siebzehnrubl, Dr. Florian
European Cancer Stem Cell Research Institute
Cardiff University
Maindy Road
CF24 4HQ Cardiff, United Kingdom
Email: fas@cardiff.ac.uk

Simon, Michèle
Department of Neurosurgery
University Hospital, Friedrich-Schiller-University
Erlanger Allee 101
7747 Jena
Email: michele.simon@med.uni-jena.de

Soni, Mr. Himanshu
Molecular mechanisms of Tumor cell invasion
German Cancer Research Center
Im Neuenheimer Feld 581
69120 Heidelberg
Email: h.soni@dkfz-heidelberg.de

Sonner, Jana
CCU Neuroimmunology and Brain Tumor Immunology
DKFZ Heidelberg
Im Neuenheimer Feld 280
69120 Heidelberg
Email: j.sonner@dkfz.de

Sontheimer, Professor Harald W.
Neurobiology Research Center
Unviversity of Alabama at Brimingham
1119 6th Avenue S
Brimingham AL 35294, USA
Email: sontheimer@uab.edu

Spaan, Bsc Ingrid
Division of signal transduction and growth control
DKFZ (German Cancer Research Center)
Im Neuenheimer Feld 280
69120 Heidelberg
Email: i.spaan@dkfz-heidelberg.de

Spyrou, MSc Argyris
Immunology, Genetics and Pathology (IGP)
Uppsala University
Dag Hammarskjölds v 20
751 85 Uppsala, Sweden
Email: argyris.spyrou@igp.uu.se

Sromova, MSc Lucie
Inst of Biochemistry and Experimental Oncology
1 Faculty of Medicine, Charles University in Prague
U Nemocnice 5
12853 Prague 2, Czech Republic
Email: lucie.sromova@lf1.cuni.cz

Stange, Lena
Dept of Neurosurgery
Charité - Universitätsmedizin Berlin
Arndtstraße 5
10965 Berlin,
Email: lena.stange@charite.de

Stec, Karol
MicroDiscovery GmbH
Marienburger str. 1
10405 Berlin
Email: karol.stec@microdiscovery.de

Stepniak, MSc Karolina
Labolatory of molecular biology
Nencki Institute of Experimental Biology
Pasteura 3
02-093 Warsaw, Poland
Email: k.stepniak@nencki.gov.pl

Stoler, Iris
Rheinstr. 41
12161 Berlin, Deutschland
Email: stoler_p@yahoo.de

Swartling, Assistant Professor Fredrik
Immunology, Genetics and Pathology
Uppsala University
Rudbeck Laboratory
SE-751 85 Uppsala, Sweden
Email: fredrik.swartling@igp.uu.se

Synowitz, Prof. Dr. Michael
Neurochirurgische Klinik
Universitätsklinikum Schleswig-Holstein
Arnold Heller Str. 3
24105 Kiel
Email: Michael.Synowitz@uksh.de

Szulzewsky, Frank
Cellular Neurosciences
MDC Berlin
Robert Rössle Strasse 10
13125 Berlin
Email: frank.szulzewsky@mdc-berlin.de

Tabatabai, Prof. Ghazaleh
Division of Neuro-Oncology / Departments of Neurology & Neurosurgery
University Hospital Tübingen
Hoppe-Seyler Strasse 3
72076 Tübingen,
Email: ghazaleh.tabatabai@uni-tuebingen.de

Temme, Prof. Dr. Achim
Department of Neurosurgery, Section Exp. Neurosurgery/Tumor Immunology
University Hospital Carl Gustav Carus, TU Dresden
Fetscherstr. 74
1307 Dresden
Email: achim.temme@uniklinikum-dresden.de

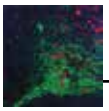
Tews, Dr. Björn
Molecular Mechanisms of Tumor Invasion
German Cancer Research Center
INF 581
69120 Heidelberg
Email: b.tews@dkfz.de

Thome, Carina
CCU Neurooncology
German Cancer Research Center
Im Neuenheimer Feld 280
69120 Heidelberg
Email: c.thome@dkfz.de

Tiberi, Dr. Luca
IRIBHM
ULB
route de Lennik 808
1070 Brussels, Belgium
Email: ltiberi@ulb.ac.be

Tugai, Alisa
Strenzfelder Allee 28
6406 Bernburg
Email: aliceiam1992@mail.ru

Tugai, Alisa
Strenzfelder Allee 28
6406 Bernburg
Email: aliceiam1992@mail.ru



Uckermann, Dr. Ortrud
Klinik und Poliklinik für Neurochirurgie
Uniklinikum Dresden
Fetscherstr. 74
1307 Dresden
Email: ortrud.uckermann@uniklinikum-dresden.de

Unterkircher, Dr. rer. nat. Thomas
Neurozentrum
Universitätsklinikum Freiburg im Breisgau
Breisacher Str. 64
79106 Freiburg im Breisgau
Email: Thomas.Unterkircher@uniklinik-freiburg.de

Vajkoczy, Prof. Dr. Peter
Klinik für Neurochirurgie
Charité Universitätsmedizin Berlin
Augustenburger Platz 1
13353 Berlin
Email: peter.vajkoczy@charite.de

Van Meir, Professor Erwin G
Departments of Neurosurgery, Hematology and Medical Oncology
Winship Cancer Institute of Emory University
1365 C Clifton Road NE
Atlanta GA 30322, USA
Email: evanmei@emory.edu

Vannini, PhD Eleonora
Institute of Neuroscience
via G Moruzzi 1
56126 Pisa, Italy
Email: eleonora.vannini@in.cnr.it

Wiedemuth, Ralf
Klinik und Poliklinik für Neurochirurgie
TU Dresden
Fetscherstr. 74
1307 Dresden
Email: Ralf.Wiedemuth@uniklinikum-dresden.de

Winkler, Dr. Lars
Leibniz-Institut für Molekulare Pharmakologie
Robert-Roessle-Str. 10
13125 Berlin
Email: lars.winkler@live.de

Wolf, Dr. Susanne
Zelluläre Neurowissenschaften
MDC
Robert-Rössle-Str. 10
13125 Berlin
Email: susanne.wolf@mdc-berlin.de

Wood, Carla
Charite Medical Neurosciences Master Program
Torfstrasse 11 c/o von Heymann
13353 Berlin
Email: carla.nicole.wood@gmail.com

Xie, Yuan
Department of Immunology, Genetics and Pathology
Uppsala University
Dag Hammarskjölds v 20
75185 Uppsala, Sweden
Email: yuan.xie@igp.uu.se

Xiong, Anqi
Dept. of immunology, genetics and pathology
Uppsala University
Dag Hammarskjölds v 20
75185 Uppsala, Sweden
Email: anqi.xiong@igp.uu.se

Xu, Li-Xin
Neurosurgery
Universität Leipzig
Tarostr. 12, Zimmer 0704
4103 Leipzig
Email: lixin.xv@gmail.com

Yakubov, Eduard
Neurosurgery
Friedrich-Alexander University Erlangen-Nuremberg
Schwabachanlage 6
91054 Erlangen
Email: eduard.yakubov@uk-erlangen.de

Zabiegalov, Oleksandr
Charité Universitätsmedizin
Sewanstraße, 211
10319 Berlin
Email: zabiegalov@icloud.com

Zelikovitch, Ms Bracha
Neuro-Oncology
Hadassah Hebrew University Medical Center
Ein Kerem
12000 Jerusalem, Israel
Email: Brach_cl3@hadassah.org.il

Zou, Dr. Hongyan
Neuroscience and Neurosurgery
Mount Sinai School of Medicine
1425 Madison Ave
New York New York, United States
Email: hongyan.zou@mountsinai.org

Berlin Liniennetz Routemap