arrest and reduced apoptosis. In addition, we recently identified in human stem cells a novel protective role of HMGA2 at replication forks, a function high jacked in cancer (stem) cells. Here, we identified HMGA2 in primary human GB cells and at the migrating front in a mouse model of primary GB. Oncofetal HMGA2 is a new nuclear factor impacting on TMZ resistance. We show that knockdown (kd) of HMGA2 in GB cells increases significantly the sensitivity of GB cells to alkylating agents, as determined by the detection of gamma H2AX nuclear foci, a marker of double DNA breakage, and increased caspase 3/7 activity upon TMZ treatment. We utilized the ability of DNA minor groove binding drugs to compete with HMGA2 for DNA binding and developed a new combinatorial therapeutic strategy that significantly enhanced the ability of TMZ to induce GB cell death.

S10 – Session2 1415-1430

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A ten-microRNA signature for robust prediction of clinical outcome in glioblastoma

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In this study we investigated the potential of microRNA expression to predict survival in adult glioblastoma. MicroRNA and mRNA expression data were accessed from The Cancer Genome Atlas. LASSO regression models were used to identify a prognostic microRNA signature. Functionally relevant targets of microRNAs were determined using bioinformatic microRNA target prediction, experimental validation and correlation of microRNA and mRNA expression data. A 10-microRNA prognostic signature was identified with a combined risk score strongly associated with overall survival. The signature optimally delineated prognosis groups in the proneural and temozolomide-treated cohorts. The statistical significance of the microRNA signature was at least as effective as MGMT methylation in this dataset. The 10-microRNA risk score was validated in an independent dataset where it also significantly predicted survival in lower grade glioma. The majority of the 10 microRNAs have been previously linked to glioblastoma biology or treatment response. Targets of the signature microRNAs were predicted and expression pattern correlation revealed a number of relevant microRNA/target pairs, which were validated in vitro. We have developed a novel, biologically relevant microRNA signature that stratifies high- and low-risk patients in glioblastoma. MicroRNA/target interactions identified within the signature point to novel regulatory networks and indicate a robust and functionally relevant signature, which may be effective alone or in combination with MGMT methylation.

S11 – Session2 1430-1445

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The effect of intra-arterial delivery of temozolomide with or without osmotic blood-brain barrier disruption and combined to radiotherapy

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The effect of intra-arterial delivery of temozolomide with or without osmotic blood-brain barrier disruption and combined to radiotherapy Temozolomide (TMZ) is the chemotherapeutic agent used in combination with radiotherapy as part of the standard treatment of glioblastoma. Only 20% of the dose administered orally reaches the cerebrospinal fluid. The intra-arterial (IA) administration of drugs following an osmotic blood-brain barrier disruption (OBBBD) allows a greater delivery of these drugs to the central nervous system (CNS). The IA delivery of TMZ, with and without OBBBD, has never been studied to this day. We hypothesize that the IA delivery of TMZ, with or without OBBBD, will increase its concentration in the CNS. Also, its delivery by these methods and its combination to radiotherapy will intensify its anti-neoplastic activity. In the Fischer-F98 model, the Kaplan-Meier survival curves show a decreased survival with increasing doses of TMZ (IA group). Against all odds, no differences in survival were shown between the IA with/without OBBBD versus IV/control groups. For each method of delivery, the addition of radiotherapy increased survival. Only the groups receiving TMZ intra-arterially (with/without OBBBD) demonstrated adverse effects. The combination of TMZ to radiotherapy seems to increase survival in the Fischer-F98 model. However, TMZ looks to be toxic when administered intra-arterially, most likely due to greater effects during its first passage through the cerebral circulation. Despite available data that TMZ is well tolerated clinically (oral administration), predicting its toxicity and its anti-neoplastic activity when delivered by alternative methods in this animal model is difficult.

S12 – Session2 1445-1500

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A role for matrix remodeling proteins in invasive and malignant meningiomas

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Aims: Meningiomas are one of the most common brain tumors in adults. Invasive and malignant meningiomas present a significant therapeutic challenge due to high recurrence rates and invasion into surrounding bone, brain, neural and soft tissues.

Understanding the molecular mechanism of invasion could help in designing novel therapeutic approaches in order to prevent the need for repeat surgery, decrease morbidity and improve patient survival. The aim of this study was to identify the key factors and underlying mechanisms which govern invasive properties of meningiomas. Methods: Towards this end, we performed gene expression profiling of invasive and non-invasive meningioma tumors. Matrix metalloproteinases (MMPs) 16 and 19 were among the genes associated with cell movement and invasion. Results & Discussion: We establish that the expression level of MMP16 was significantly elevated in both bone-invasive and brain invasive meningiomas. Gain- and loss-of-function experiments indicated a role for MMP16 in meningioma cell movement, invasion and tumor cell growth. Furthermore, MMP16 was shown to positively regulate MMP2, suggesting this mechanism may modulate meningioma invasion in invasive meningiomas. Conclusions: Overall, the results support a role for MMP16 in promoting invasive properties of the meningioma tumors. Further studies to explore the potential value for clinical use of matrix metalloproteinases inhibitors, perhaps specifically targeting MMP16 are warranted.

P1 – Session3 1615-1625

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Neural derivatives from human embryonic stem cells: modelling early cellular and molecular events contributing to Depediatric brain tumorigenesis

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Malignant brain tumors are among the most prevalent forms of childhood cancers. The extensive genetic, molecular and clinical heterogeneity within subtypes has made it difficult to assess the functional relevance of genes to malignant progression. For example, medulloblastoma is classified into four molecular subgroups; Wnt, Sonic hedgehog, Group 3 and Group 4, based on genetic alterations and molecular signatures. Among these molecular signatures, a homeodomain transcription factor, Orthodenticle homeobox2 (Otx2), is frequently amplified and overexpressed in medulloblastoma; however, the functional relevance of Otx2 may indeed be subtype-specific. We recently demonstrated that neural precursors derived from neoplastic human embryonic stem cells (hESCs), but not their normal counterparts, model pediatric brain tumors in vivo and exhibit high Otx2 expression. Here, we used this hESC-based model system to further delineate the role of Otx2 in normal human neurodevelopment and medulloblastoma progression using gain and loss of function studies. Parallel experiments with well-established brain tumor cell lines support the subtype-dependent tumor suppressive or oncogenic role of Otx2 in medulloblastoma. Otx2 overexpression resulted in an overall repressive effect on cellular functions such as cell proliferation, migration and self-renewal and this was accompanied by global downregulation of hESC pluripotency genes. While knockdown of Otx2 also suppressed cellular functions, this appears to be less dependent on hESC gene regulation. Our study reveals a novel link between Otx2 and hESC genes that may contribute to both human neurodevelopment and medulloblastoma progression and validates our hESC-derived system as an alternative model for studying the mechanisms underlying pediatric neural tumorigenesis.

P2 – Session3 1625-1635

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Targeting the base excision repair pathway to overcome therapeutic resistance to alkylating agents in pediatric glioblastoma

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Alkylating agents are a common frontline therapy for the treatment of several cancers including pediatric glioblastoma (pGBM), a devastating lethal tumor in children. Unfortunately, many tumors are resistant to this therapy and traditional mechanisms of resistance including MGMT promoter methylation fail to fully explain treatment resistance in pGBM. We sought to identify ways of sensitizing tumor cells to alkylating agents while leaving normal glia and neural stem cells unharmed; increasing therapeutic response while minimizing toxicity. An siRNA screen targeting over 240 DNA damage response genes identified novel sensitizers to alkylating agents, namely temozolomide. In particular the base excision repair (BER) pathway, including DNA-3-methyladenine glycosylase (MPG), as well as ataxia telangiectasia mutated (ATM) were identified in our screen. ATM, MPG and BER were required for allowing tumour cells to repair damaged DNA and survive exposure to temozolomide. Patients with high expression of MPG had poorer overall survival compared to MPG low expressing patients and that MPG was one the most commonly amplified genes of the BER pathway in pGBM. Combined inhibition or loss of MPG and ATM resulted in increased alkylating agent-induced cytotoxicity in vitro and prolonged survival in vivo using several orthotopic mouse models of pGBM. Further, we identified, several small molecule inhibitors of BER that effectively sensitized pGBM cells to clinically relevant doses of TMZ and prolonged survival in vivo. Inhibition of ATM and BER cooperate to sensitize tumour cells to alkylating agents, impairing tumour