Combined risk stratification models were designed based on clinical and cytogenetic biomarkers identified by multivariate Cox proportional-hazards analyses. Identified biomarkers were tested using FISH on a non-overlapping medulloblastoma tissue microarray (n=453), with subsequent validation of the risk stratification models. Results: Subgroup information improves the predictive accuracy of a multivariate survival model compared to clinical biomarkers alone. Most previously published cytogenetic biomarkers are only prognostic within a single medulloblastoma subgroup. Profiling a six-pack of FISH biomarkers (GLI2, MYC, 11, 14, 17p, and 17q) on FFPE tissues, we can reliably and reproducibly identify very low-risk and very high-risk patients within each of SHH, Group3 and Group4 medulloblastomas. Conclusions: Combining subgroup and cytogenetic biomarkers with established clinical biomarkers substantially improves patient prognostication, even in the context of heterogeneous clinical therapies. The prognostic significance of most molecular biomarkers is restricted to a specific subgroup. We have identified a small panel of cytogenetic biomarkers that reliably identifies very high-risk, and very low-risk groups of patients, and which will make an excellent tool for selecting patients for therapy intensification and therapy de-escalation in future clinical trials.

S7 – Session1 1130-1145

Abstract withdrawn.

S8 – Session1 1145-1200

doi:10.1017/cjn.2014.51

An *in vitro* mouse model of GBM with abrupt and predictable onset

J DePetro[1, 2], C Binding[1, 2], M Blough[1, 2], J Kelly[1, 2], S Lawn[1, 2], J Chan[1, 2], S Weiss[3] and G Cairncross[1, 2, 3]

[1]Clark Smith Brain Tumour Centre, [2]Southern Alberta Cancer Research Institute and [3]Hotchkiss Brain Institute, [4]University of Calgary, Calgary, Alberta

Glioblastoma (GBM) is a fatal cancer which harbors multiple genetic alterations, many of which are thought to be passenger mutations. Those that involve receptor tyrosine kinase signaling and the p53 and RB pathways are found in most newly diagnosed GBMs and are thought to be 'drivers' of this cancer. Here we report a PDGF-A-linked *in vitro* mouse model of GBM in which malignant transformation appears to occur abruptly, and the responsible genetic events can be studied. Cells from the subventricular zone (SVZ) of p53-null, adult mice were dissected and cultured as spheres in serum-free media supplemented with either EGF/FGF or PDGF-A. p53-null SVZ cells cultured continuously in EGF/FGF proliferated rapidly but remained growth factor dependent and non-tumorigenic. In contrast, PDGF-A cultured SVZ cells grew poorly over 3-4 months until passage 8, whereupon sphere formation and size accelerated abruptly in multiple independent cultures. These transformed cells proliferated rapidly in the absence of PDGF-A, and unfailingly, generated tumors with a striking resemblance to GBMs when implanted into the striatum of immunocompetent, p53 wild-type mice. EGFR, PDGFRα, Olig2 and NG2 were expressed in EGF/FGF and PDGF-A cultures in early to late passages (≤P1-P15). Increased nestin expression was observed in PDGF-A transformed cultures only, whereas GFAP expression decreased in both. This model recapitulates other systems in which PDGF-A-driven glioma formation has been achieved *in vivo* in p53-null mice, but may have these advantages: low cost, easy accessibility to sequential molecular interrogation, and suitability for screening of libraries of potential inhibitors of gliomagenesis.

S9 – Session2 1400-1415

doi:10.1017/cjn.2014.52

Targeting oncofetal high mobility group A2 (HMGA2) to increase sensitivity to temozolomide (TMZ) in glioblastoma (GB) cells

Suchitra Natarajan[1], Thatchawan Thanasupawat1, Amy Rommel[2], Hugo Bergen1, Inder Verma[2], Marc Del Bigio[3], Marshall Pitz[4], Brian B. Hasinoff[5], Jerry Krcek1[6], Sabine Hombach-Klonisch[1], Thomas Klonisch1[6]*

Depts: [1]Human Anatomy and Cell Science, [3]Pathology, [4]CancerCare Manitoba, [5]Faculty of Pharmacy, [6]Surgery, University of Manitoba, Winnipeg, MB, Canada; [2]Laboratory of Genetics, Salk Institute, San Diego, USA

The Base Excision Repair (BER) pathway facilitates the removal of temozolomide (TMZ) induced alkylated DNA bases. We previously identified the non-histone chromatin binding protein and DNA minor groove binder HMGA2 as a novel member of BER that directly interacts with APE1, a key BER member. We showed that the AP/ dRP lyase activity, located within the AT-hook DNA binding domains of HMGA2, protects stem cells and cancer cells against alkylating drugs. The in-vivo interactions of HMGA2 with Ataxia telangiectasia and Rad3-related kinase (ATR) and checkpoint kinase 1 (CHK1) result in sustained activation of the ATR-CHK1 signaling pathway, prolonged G2/M

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

doi:10.1017/cjn.2014.53

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

J Hayes[1], H Thygesen[1], A Droop[1], M Boissinot[1], TA Hughes[1], D Westhead[1], S Short[#1], SE Lawler[2] ([#] joint PI's)

[1]Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, UK; [2]Harvey Cushing Neuro-oncology Laboratories, Department of Neurosurgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

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

doi:10.1017/cjn.2014.54

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

A Drapeau, MB Poirier, D Fortin

Department of Surgery, FMSS Universite de Sherbrooke, Quebec

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

doi:10.1017/cjn.2014.55

A role for matrix remodeling proteins in invasive and malignant meningiomas

S Jalali, S Singh, S Agnihotri, T Wataya, F Salehi, K Burrell, S Croul, KD Aldape and G Zadeh

Arthur and Sonia Labatt Brain Tumour Research Centre, The Hospital for Sick Children, Toronto, Ontario

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.