

CNSS CHAIR'S SELECT ABSTRACT PRESENTATIONS

C.01

CNSS K.G. McKenzie Prize in Basic Neuroscience Research

Developmental phosphoproteomics identifies Casein Kinase 2 as a therapeutic target in medulloblastoma

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Background: The hedgehog pathway (Hh) is an important developmental signaling pathway that is commonly dysregulated in brain tumors, most notably in medulloblastomas. To identify novel therapeutic targets within the Hh pathway, we performed the first quantitative proteome-wide evaluation of phosphorylation events resulting from in vitro SHH administration and occurring throughout Hh-driven cerebellar development in vivo. **Methods:** Multiplexed quantitative mass spectrometry was done using Tandem Mass Tags 10-plex reagents, TiO₂ phosphopeptide enrichment and HPLC-MS/MS/MS. **Results:** Motif analysis of 2-fold changing phosphorylation events suggested casein kinase 2 (CK2) was responsible for mediating 45% of all changes in phosphorylation. Epistasis studies revealed that CK2 activity is necessary for hedgehog signaling and affects terminal signaling components, thereby circumventing challenges of emergence of resistance and a priori resistance that are commonly encountered with existing small molecule inhibitors in medulloblastoma. In vivo, mice harboring MB allografts resistant to current therapies showed near-complete cessation of tumor growth in response to a CK2 inhibitor. **Conclusion:** Our use of developmental phosphoproteomics revealed casein kinase 2 as a key regulator of hedgehog signaling and therapeutic target in medulloblastoma. Our success establishes a foundation for us, and others, to apply a similar approach in different tumor initiating pathways.

C.02

CNSS K.G. McKenzie Prize in Basic Neuroscience Research

Early treatment of HER2-amplified brain tumours with targeted nk-92 cells and focused ultrasound improves survival

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Background: Malignant brain tumors have a dismal prognosis, with residual after surgery necessitating adjuvant chemoradiotherapy. We previously demonstrated that targeted Natural Killer (NK-92) cells could be delivered to the brain using a combination of MRI-guided focused ultrasound and Definity microbubbles. Once in the CNS, they can track to malignant tissues without inflicting collateral damage. The HER2 receptor is expressed by epithelial tumours including both breast and glioblastoma; breast tumors with HER2-amplification have a higher risk of CNS metastasis, and poorer prognosis. **Methods:** We investigated whether multiple combined treatments of targeted NK-92 cells and focused ultrasound with

microbubbles could slow tumour growth and improve survival in an orthotopic HER2-amplified rodent brain tumour model using a human breast cancer line as a prototype. **Results:** Early daily treatments with targeted NK-92 cells and ultrasound improved survival and decreased tumour volumes compared with bi-weekly treatments, or either treatment alone. The intensive treatment paradigm resulted in cure in 50% of subjects. **Conclusions:** Many tumour proteins could be exploited for targeted therapy with the NK-92 cell line, and combined with the mounting safety evidence for transcranial ultrasound, this may soon provide a non-invasive and highly targeted treatment option for patients with brain tumours.

C.03

CNSS K.G. McKenzie Prize in Clinical Neuroscience Research

Timing of resumption of antithrombotic agents following surgical evacuation of chronic subdural hematomas: a retrospective cohort study

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Background: Antithrombosis (AT), with antiplatelets or anticoagulants, is a significant risk factor for the development of chronic subdural hematomas (cSDH). Resumption of AT following hematoma evacuation is variable, with scant evidence for guidance. **Methods:** We retrospectively analyzed 479 patients with surgically-evacuated cSDH at St. Michael's Hospital from 2007-2012. Collected variables included type of AT, indication for AT, timing and type of postoperative complications, and restart intervals for AT agents. Postoperative complications were classified as major or minor hemorrhages, or thromboembolism. **Results:** Among all patients, 14.8% experienced major hemorrhage, 23.0% minor hemorrhage, and 1.67% thromboembolism. Patients on any preoperative AT were at higher risk of major hemorrhage (OR=1.93, p=0.014), experienced earlier major hemorrhage (mean 16.2 versus 26.5d, p=0.052) and earlier thromboembolism (mean 2.7 versus 51.5d, p=0.036). The type of agent did not affect complication frequency or timing. Patients restarted on any AT postoperatively were at decreased risk of major rebleed following resumption, than those not restarted (OR=0.06, p<0.01). **Conclusions:** Patients on preoperative AT experienced thromboembolism significantly earlier, at 3d postoperatively, with no increase in rebleed risk following AT resumption. We provide cursory evidence that resuming AT early, at 3d postoperatively, may be safe. Larger prospective studies are required for definitive recommendations.

C.04

Equestrian-related brain injuries presenting to emergency departments, Canada, 1990-2014

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Background: Horse riding is a hazardous activity with the potential for serious injury. Equestrian-related injuries account for a higher rate of injury per number of riding hours than motorcyclists and automobile racers. There is a lack of literature pertaining to equestrian-related brain injuries. The objectives of this study were to describe the incidence, characteristics, and mechanisms of equestrian-related