THURSDAY, SEPTEMBER 14, 2017

SPECIAL SESSION:
THE FUTURE OF PRIMARY BRAIN TUMOR TREATMENT

7:35 – 7:45

SURGICAL TREATMENT OF GLIOMAS

Mitchel S. Berger, MD, University of California, San Francisco

7:45 – 7:55

ADJUVANT TREATMENT OF GLIOMAS

Frederick M. Lang, MD, The University of Texas MD Anderson Cancer Center

7:55 – 8:05

IMMUNOTHERAPY OF GLIOMAS

Linda Liau, MD, PhD, MBA, The University of California, Los Angeles School of Medicine

ABSTRACT SESSION: TUMORS

8:05 – 8:15

THE PROGNOSTIC VALUE OF A NOVEL QUANTITATIVE MGMT PROMOTER METHYLATION SCORE FOR PATIENTS WITH GLIOBLASTOMA

Mitchel S. Berger, MD, Seunggu Jude Han, MD, Susan Chang, MD, Jennifer Clarke, MD, Annette Molinaro, MA, PhD, Nancy Oberheim-Bush, MD, PhD, Jennie Taylor, MD, MPH, Nicholas Butowski, MD; University of California, San Francisco

Evidence continues to solidify the central role molecular markers play in gliomas. Methylation status of MGMT promoter has been shown as a key marker in glioblastoma, predicting response to temozolomide. Traditional testing of MGMT promoter methylation, performed using a methylation specific PCR, yields a binary result; however it fails to consider the multiple potential methylation sites in MGMT's promoter region. A novel quantitative bisulfite Sanger DNA sequencing assay evaluates methylation status at each of the 17 potential methylation sites in the promoter, resulting in a methylation score of 0-17. This novel assay was evaluated for its prognostic role in a cohort of 180 consecutive patients undergoing treatment for newly diagnosed glioblastoma at UCSF from April 2014 to August 2015. All patients received concurrent chemoradiation with temozolomide. Univariate and multivariate models for overall survival were built along with other established prognostic variables such as age, KPS and extent of resection. Increasing methylation score was predictive of more favorable overall survival in a multivariate model (HR 0.89 per unit, 95% Cl 0.82- 0.96). Stratification into partition groups revealed most significant split in survival at methylation score of >= 8. Brier score revealed lower predictive error for the methylation score compared to the traditional binary MGMT promoter methylation assessment, suggesting the methylation score is a more reliable model predicting survival. The methylation score, derived from the bisulfite sequencing analysis, provides a quantitative representation of the degree of methylation in the MGMT promoter. Survival models and partitioning results support its role as a robust prognostic marker for overall survival, and the methylation score being superior to the traditional MGMT promoter methylation analysis in predicting survival in patients with newly diagnosed glioblastoma.

8:15 – 8:25

Reversible Opening Of The Blood-Brain Barrier By Targeted Suppression Of Claudin-5 To Enhance Drug Delivery To Brain Tumors

Gerald Grant, MD, FACS, Stanford University

Inadequate delivery of targeted therapeutics across the blood-brain barrier (BBB) to treat malignant brain tumors is a significant factor contributing to poor survival. We employed a novel strategy of using small interfering RNA (siRNA) targeting claudin 5, a tight junction protein highly enriched at the BBB, to reversibly open the BBB in a mouse orthotopic brain tumor model. Human xenograft tumor-bearing and non-tumor bearing control mice received either claudin-5 targeted siRNA or non-targeted siRNA administered systemically. There was a significant increase in permeability in both tumor and non-tumor bearing mice as measured by MRI and intravital microscopy to fluorescent dextran following systemic delivery of claudin 5 targeted siRNA. This effect peaked at 48 hours post injection and correlated with a significant decrease in claudin 5 expression on the microvasculature at the molecular level in the tumor and normal brain. We have also determined that delivering siRNA-targeting claudin 5 in primates at human relevant doses are safe. This novel translational BBB modulation strategy has the potential of improving survival by increasing the delivery of targeted tumor therapy into the brain in a tumor-selective fashion.

8:25 – 8:35

Single-Cell RNA-SEQ Identifies Glioblastoma Migrating Within Normal Brain

Sypros Darmanis, PhD, Steven Sloan, PhD, Ben Barres, MD, PhD, Steve Quake, PhD,
Melanie Hayden Gephart, MD, MAS
Stanford University Departments of Neurosurgery, Developmental Biology, Applied Physics, Bioengineering.
Dr. Quake is the co-President and Dr. Darmanis is an investigator for the Chan-Zuckerberg Initiative.

Introduction: Even when no microscopic or radiographic glioblastoma can be detected after surgical resection, migrating glioblastoma persist in the surrounding brain, ultimately recurring and killing the patient. Therapeutic advances depend on targeting migrating glioblastoma in normal brain, yet no one had yet isolated and analyzed the single cell transcriptome of migrating glioblastoma as compared to normal brain cells. Prior studies

relied on bulk glioblastoma and peritumoral samples in which more numerous non-tumor or bystander cells drowned out the migrating glioblastoma gene signature.

Methodology: We developed a single brain cell isolation technique and RNA sequencing (RNA-seq) analysis that allow us to define the transcriptomes of individual migrating glioblastoma and their peritumoral neighbors. Through immunopanning of fresh surgical specimens, we isolated single brain and tumor cells from matched glioblastoma and surrounding normal brain in four patients. We then performed high coverage single-cell RNA sequencing (RNA-seq) on 3589 cells. Having previously performed single-cell RNA-seq on normal brain at different stages of development, we were then able to compare the inter- and intra-tumoral heterogeneity, as well as comparing to the normal brain single cell gene expression profile.

Results: In addition to providing information about cell to cell variation in the tumor's gene expression and genome, we also identified neoplastic cells migrating in surrounding normal brain. Despite significant intra- and inter-tumoral heterogeneity among neoplastic cells in the glioblastoma, we found that glioblastoma migrating in normal brain share a consistent gene signature between patients, suggesting a common mechanism of dissemination.

Conclusion: Glioblastoma, the most common and deadly primary brain tumor, disseminates widely throughout the brain by hijacking cell migration pathways used by normal neural stem cells. Our data identify for the first time the single cell gene expression profiles of migrating glioblastoma within normal brain. The similarities of migrating glioblastoma within normal brain despite inter- and intra-tumoral heterogeneity suggest the importance of therapeutic targeting of these molecular pathways.

8:35 – 8:45

Deep Convolutional Neural Networks Provide Rapid Diagnosis Of Fresh Brain Tumor Specimens Imaged With Stimulated Raman Histology

Todd Hollon, MD and Daniel Orringer, MD, University of Michigan

Intraoperative diagnosis is essential in the surgical management of brain tumors. Conventional intraoperative histology is time- and labor-intensive, depletes scant specimens and is prone to artifact. Stimulated Raman histology (SRH) uses the intrinsic biochemical properties of fresh, unprocessed surgical specimens to provide label-free digital histologic images. We have previously shown that SRH is an ideal imaging modality to implement

machine-learning strategies for tissue diagnosis due to the robust histochemical information encoded in pixel data. Here, we develop and validate a deep convolutional neural network (CNN) for rapid and standardized diagnosis of fresh brain tumor specimens with minimal tissue requirement using SRH. For CNN training, 153,000 400x400μm SRH fields of view (FOV) from 70 patients across 12 common diagnostic classes of CNS tumors were used. Our deep neural network was developed from the GoogleNet InceptionV3 CNN architecture, which includes 23.8 million trainable parameters. Model validation was completed on 1,635 FOVs from 30 patients. The model was evaluated on its ability to differentiate 1) nonlesional versus lesional tissue, 2) glial versus nonglial tumors and 3) provide the correct histopathologic diagnosis. The CNN differentiated lesional from non-lesional FOV with 98.4% accuracy, glial from non-glial tumor FOVs with 96.4% accuracy and correctly classified FOV based on histologic subtype with 83.5% accuracy. By compiling FOV data from each specimen, the CNN predicted accurate diagnosis in 96.7% (29/30) of cases in the validation set. The only error by the CNN was a misclassification of a WHO grade III ependymoma as a WHO grade IV glioblastoma. We present the first application of a deep CNN for the intraoperative diagnosis of brain tumors. Our study demonstrates the feasibility of applying deep machine learning to brain tumor diagnosis and has the potential to guide brain tumor resection via rapid identification of residual tumor burden. Our results justify a more extensive study on combining automated diagnosis and residual tumor identification with SRH to improve the surgical care of brain tumor patients.

8:45 – 8:55

MSC-DERIVED EXOSOMES CARRYING MIR-124A: A NOVEL TREATMENT OF HUMAN GLIOMAS

Frederick M. Lang, University of Texas, Anwar Hossain, PhD, Mount Sinai Hospital and **Frederick M. Lang, MD,** University of Texas, MD Anderson Cancer Center

A promising new therapeutic approach for GBMs is treatment with microRNAs (miRs), which are small, noncoding RNAs that are powerful regulators of gene expression. However, which miRs will be most effective against GBMs and how these miRs should be delivered to GBMs are major unresolved problems in the application of miRs to GBMs. To identify effective miRs for treating GBMs, we selected eight miRs (miR-27a, miR-100, miR-124a, miR-122, miR-133, miR-138, miR-145, Let-7b) based on a literature search, and screened these miRs for their antiglioma effects against five glioma stem cell lines (GSCs), representing all TCGA-defined GBM subtypes (GSC267, GSC6-27, GSC8-11, GSC2-14,

GSC20). MiR-124a resulted in the greatest decrease in viability in all GSCs ($P<0.010$), identifying miR-124a as a highly effective anti-GBM miR. To address the delivery problem, we exploited the fact that human mesenchymal stem cells (MSCs) secrete exosomes, which are nanoscale vesicles that are stable in blood. We hypothesized that ex vivo cultured MSCs could be engineered to package miR-124a into exosomes, and that these exosomes could be collected and used to systemically deliver miR-124a to GBMs. To test this hypothesis, we transduced MSCs with a lentivirus containing miR-124a, and isolated exosomes (Exos-miR-124) from the supernatant. Electron microscopy, western blotting, and Nanosight™ all proved that the isolated vesicles were exosomes. qPCR revealed that miR-124a levels in Exos-miR-124 were 60-fold greater than control exosomes, which contained no miR-124a ($P<0.0001$). To demonstrate that Exos-miR-124a were capable of inhibiting the growth of GSCs, we treated five GSCs with Exos-miR-124a, Exos-miR-Ctrl, or Exos-empty (106/cell) and showed a significant reduction in viability and clonogenicity of all GSCs only after treatment with Exos-miR-124a ($p<0.001$). Immunoblotting of protein lysates showed that Exos-miR-124 were capable of down regulating FoxA2, a known miR-124 target gene. To assess efficacy of Exos-miR-124 in vivo, GSC267 was implanted into the brains of mice (N=8/group) and animals were treated intraperitoneally with Exos-miR-124, Exos-miR-Ctrl, or PBS (10^{10} Exos/100μl) every other day. Whereas all controls died by 60 days after tumor implantation (median survival Exos-miR-Ctrl=54 days; PBS=55 days), 50% of animals treated with Exos-miR-124 were alive >100 days ($P<0.0001$). Taken together, these data indicate that miR-124a is a highly effective anti-GBM therapeutic and that MSC-derived exosomes can be used to systemically delivery miR-124a to achieve cures of intracranial GBMs.

8:55 – 9:05

TARGETING MYELOID DERIVED SUPPRESSOR CELLS AS AN IMMUNOSTIMULATORY STRATEGY IN GBM: PRELIMINARY RESULTS OF A CLINICAL/TRANSLATIONAL TRIAL

Michael A. Vogelbaum MD, PhD, David M. Peereboom MD, Tyler Alban, Balint Otvos MD, PhD, Justin Lathia PhD; Cleveland Clinic

Introduction: Myeloid Derived Suppressor Cells (MDSCs) are premature leukocytes released from the bone marrow in a number of pathological conditions, including cancer. MDSCs have a profoundly immunosuppressive effect, particularly impacting T cell number and function. We have shown previously that systemic MDSC levels are higher in patients with glioblastoma (GBM) than in any other cancer studied to date, and that they impact on T-cell numbers and functions systemically and in brain tumor tissue. We have developed

an MDSC depletion strategy in a preclinical model of GBM that is currently being evaluated in a phase 0/I clinical trial.

Methodology: We created orthotopic brain tumors in immunocompetent mice and characterized their immunophenotype (blood and tumor) with respect to MDSCs, Tregs, and cytotoxic T-cells over the course of tumor growth. A separate group of tumor-bearing mice were treated with low dose (20% of conventional antineoplastic dose) 5-FU to evaluate its impact on immunophenotype and survival. Subsequently we launched a prospective phase 0/I clinical trial for patients with recurrent GBM undergoing a surgical resection. Patients have been treated with low dose capecitabine (oral 5-FU precursor) prior to and following surgery, and with bevacizumab following surgery. Blood and tumor samples have been evaluated for their immunophenotypes.

Results: Growth of orthotopic GBM tumors in mice produces consistent elevations in MDSCs in blood and tumor, which are associated with reductions in circulating and tumor infiltrating T-cells. Treatment with low dose 5-FU reduced MDSCs, and restored T-cell numbers and function in blood and tumor. Six patients have been enrolled in the clinical trial to date. We characterized the blood and tumor immunophenotypes in 4 of these patients so far, and observed MDSC reductions of approximately 12-28% from baseline. This decrease was associated with significant increases in cytotoxic T-cell concentrations (5, 28, 86, and 93%). No patient has experienced grade 3 or higher toxicity.

Conclusions: We have developed a potential strategy for selectively depleting immunosuppressive MDSCs in patients with recurrent GBM.

9:05 – 9:15

IL11 Secretion By Glioblastoma Microglia Defines "Exceptional Responders"

Clark C. Chen, MD, PhD, UC San Diego Health

Despite aggressive treatment, most glioblastoma patients succumb to the disease within two years of diagnosis. The molecular basis for the rare patients who exhibit "exceptional response" and survive beyond expectation remains poorly understood. Using three independent patient cohorts, we showed that decreased expression of an inflammation gene signature consistently associated with "exceptional response".

Integrated cell-based analysis suggests glioblastoma-associated microglia as the principle mediator of this inflammation signature. Co-culturing of freshly isolated murine microglia

derived from GL261 glioblastoma enhanced glioblastoma tumorigenicity and resistance to temozolomide (TMZ), the standard-of-care therapy. Such effects were not observed with microglia isolated from normal murine brain, the pro-tumorgenic and -TMZ resistance effects of microglia were recapitulated using conditioned media from microglia. Proteomic analysis of microglia conditioned media revealed IL11 as the critical mediator. IL11 was both necessary and sufficient to induce glioblastoma tumorigenicity and TMZ resistance. These effects were mediated through IL11 receptor mediated STAT3-MYC signaling.

PI3Kγ activation in myeloid-derived cells, including microglia, is essential for its trafficking into the tumor microenvironment. We hypothesized that PI3Kγ inhibition should impede microglia accumulation in the glioblastoma microenvironment and reduce glioblastoma tumorigenicity. Supporting our hypothesis, treatment with a PI3Kγ inhibitor, TG100-115, suppressed glioblastoma tumorigenicity in vivo by reduced microglia density and IL11 release. These effects were recapitulated when murine glioblastoma GL261 were implanted into transgenic mice in which PI3Kγ were genetically inactivated ($p110\gamma^{-/-}$ mice). Importantly, ectopic expression IL11 in GL261 reversed the tumor-suppressive effect of TG100-115, supporting IL11 as a key mediator of these effects.

PI3Kγ inhibition through TG100-115 augmented the anti-neoplastic effects of TMZ, suggesting that TG100-115 transformed the glioblastoma microenvironment from one associated with poor TMZ response to one mimicking the microenvironment of "exceptional responders". Further supporting this hypothesis, TG100-105 treatment of GL261 decreased the expression of the poor-clinical response associated, inflammation gene signature. In contrast, ectopic IL11 expression or microglia induce the expression of this signature.

In aggregate, our study suggests microglia-glioblastoma interaction as a determinant of clinical response and translational potential for therapies targeting microglia-mediated inflammation.

9:15 – 9:25

Is There A Genetic Explanation For The Apparent Phenotypic Differences In Vestibular Schwannomas?

Michael J. Link, MD, Matthew L. Carlson, MD, James B. Smadbeck PhD, Eric W. Klee, PhD, Lisa Schimmenti MD, George Vasmatzis PhD, Mayo Clinic, Rochester, Minnesota.

Objectives: The purpose of this analysis was to: 1) Describe the genetic alterations discovered in a series of sporadic vestibular schwannomas (VS). 2) Identify if more clinically aggressive variants possessed different genetic alterations compared to more indolent behaving VS.

Methods: Fresh frozen tumor and matched leukocytes from 23 cases of sporadic VS were analyzed using whole-exome sequencing, whole transcriptome expression profiling (mRNA-Seq) of tumor and mate-pair sequencing of tumor. Source cases included tumors with fast preoperative growth, giant tumors in young patients, tumors with macrocystic change, recurrent tumors following radiation or microsurgery, and indolent small tumors with minimal or no growth prior to surgery. Somatic and germ-line alterations of the NF2 gene and outside the NF2 locus were identified and analyzed.

Results: A double hit to the NF2 gene was discovered in all specimens and none of these mutations occurred in the peripheral blood. 13 tumors had complete loss of one chromosome 22 (ch22). 4 tumors had loss of heterozygosity of ch22. 31 unique mutations in the NF2 gene were discovered: 10 were essential splice site, 11 frame shift, 6 stop gain, 2 nonsynonymous and 2 in-frame mutations. 14 were deletion, 16 were substitution and 1 was an insertion mutation. No other common gene mutations were found. However, several other chromosomal aberrations were discovered including 2 tumors also had loss of a ch21, 3 had loss of an X or Y chromosome, 1 lost a ch15 and 1 had loss of ch18p and ch16q. All of these other major chromosomal abnormalities only occurred in tumors demonstrating a more aggressive phenotype.

Conclusions: To date, few studies have utilized whole-exome sequencing to profile genome wide alterations in sporadic VS. Using high-throughput sequencing, "two-hit" alterations in the NF2 gene were identified in all cases. Type of NF2 gene alteration and accessory mutations outside the NF2 locus may predict phenotypic expression.

9:25 – 9:30

GENOTYPE-BASED LOCAL TARGETING OF METABOLIC VULNERABILITIES IN GLIOMA

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Introduction: Precision medicine pairs accurate molecular diagnosis with targeted therapies. The WHO 2016 molecular classification of gliomas holds substantial promise in this regard, as most tumors are characterized by recurrent mutations in IDH1/2, TERT promoter, H3F3A or BRAF. Emerging evidence also indicates that IDH1 mutant gliomas are exquisitely sensitive to metabolism-altering agents. We prototyped this pairing in IDH1 mutant astrocytoma, to establish a modern paradigm for delivering genotype-directed local therapy during neurosurgical resection.

Methods: We engineered an intraoperative (<30min) genotyping assay sensitive to hotspot mutations at 1% tumor allele fraction and validated this on 87 clinically annotated brain tumor specimens. To minimize the systemic toxicity noted with IDH1-directed nicotinamide phosphoribosyl transferase (NAMPT) inhibitors, we developed microparticles to provide sustained local delivery of these compounds. Microparticles were tested for in vitro activity in cell culture and in vivo efficacy on tumor growth and survival in murine orthotopic glioma models.

Results: We noted progression was characterized by local failure in 82% of patients with IDH mutant astrocytomas. We sought to improve this natural history with NAMPT inhibitors, but found that enteral administration of the brain permeable compound GMX-1778 resulted in significant systemic toxicity in adult mice. GMX-1778 microparticles resulted in local intracerebral therapeutic concentration without systemic toxicity. These microparticles decreased cell viability of IDH mutated cancer cells in a time-dependent manner. We then assessed the in vivo efficacy of genotype-directed local therapy. While GMX-1778 microparticles did not affect tumor volume in an IDH wildtype orthotopic

model, intratumoral implantation resulted in 160-fold decreased tumor volume in an IDH1 mutant glioma model.

Conclusions: IDH mutant diffuse astrocytomas serve as a prototypic tumor in which genotype-directed targeted therapy can improve local control and ultimately the natural history. To facilitate intraoperative precision medicine we developed a rapid method for assessing the status of recurrent glioma-specific mutants. Local delivery of targeted therapies can be directed against the additional mutants captured on this assay panel, such as H3F3A K27M and BRAF V600E, for glioma and other tumors bearing actionable hotspot mutations.

9:30 – 9:35

GENOMIC SEQUENCING OF MENINGIOMAS IDENTIFIES THREE MOLECULAR SUBGROUPS

Akash J. Patel, MD, Baylor College of Medicine

Background: The most common primary intracranial tumors, meningiomas, also happen to be most commonly benign. Their perceived benignity has resulted in them being relatively understudied. Approximately 20% of all meningiomas are high-grade (WHO grade II and III). With a recurrence rate of up to 41% within 5 years and a 5-year survival rate as low as 35%, they have no effective treatments. Three studies utilizing next-generation DNA sequencing found recurrent somatic mutations in benign meningiomas. A recent study used DNA methylation to create a classification system.

Hypothesis: We hypothesize that meningiomas can be classified molecularly based on transcriptional profile and high-grade meningiomas bear specific alterations that make them malignant.

Methods: Using primary meningioma tissue (fresh frozen), we performed comprehensive molecular characterization of 62 benign meningiomas and 38 high-grade meningiomas (100 patients), using whole-exome sequencing, copy-number analysis, and RNA sequencing. All patients provided written informed consent and studies done under an IRB approved protocol.

Results: We identified three molecular subgroups based on gene expression and exome mutation data. High-grade and benign meningiomas have some overlap but also distinct differences, supporting the notion that benign tumors must accumulate certain mutations to progress to higher grade. We found that genes identified from previous sequencing

studies fell into subgroup 1, comprised almost entirely of grade I tumors, suggesting that these mutations may act via a common downstream mechanism. Subgroups 2 and 3 were enriched in NF2 or chromosome 22 loss. Subgroup 3, which was composed of mostly high-grade tumors, showed an increased incidence of mutations in genes involved in chromatin remodeling complex.

Conclusions: Our data show that meningiomas can be classified into three molecularly distinct subgroups. Alterations in chromatin remodeling genes was seen more frequently with high grade meningiomas, and might explain the recently published findings that meningiomas can be divided into 2 major groups based on methylation pattern. Chromatin structural rearrangements and its molecular consequences should be explored further as a mechanism for the formation of high-grade meningiomas.

9:35 – 9:40

MYXOPAPILLARY EPENDYMOMA: REDUCING RECURRENCE; A 27 YEAR EXPERIENCE

Vijay Yanamadala, MD, JI Kumar, Lawrence Borges, MD, Massachusetts General Hospital

Myxopapillary ependymoma (MPE) is an uncommon intradural spinal tumor with a prevalence of 0.04-0.08 persons per 100,000. It is a benign tumor that should be curable by surgical resection. It is also an unusual intradural tumor, in that it can seed the subarachnoid space and therefore recur after surgical resection. In fact, numerous series in the literature report 5 year recurrence rates for these tumors ranging from 19-32%. Here we present an experience of the surgical treatment of myxopapillary ependymoma over 27 years (1988-2015), with no documented tumor recurrence. This presentation will focus on the surgical techniques of aggressive resection accompanied by the concept of "en bloc" subarachnoid tumor resection that has helped to achieve this outcome.

We retrospectively analyzed all patients treated by the senior author between 1988 and 2015 undergoing resection of myxopapillary ependymoma. 31 patients were identified with a mean age of 41 years (17 men and 14 women). Low back pain (74%) was the most common presenting symptom, followed by numbness (29%), weakness (16%), urinary retention (16%) and gait anomalies (16%). En bloc gross total resection was carried out in 27 cases. In three patients, gross total resection was performed through intralesional debulking with subarachnoid sequestration. In one patient, subtotal resection was performed. Complications were minimal and will be discussed. One month after surgery, all symptoms were improved. Bladder and bowel symptoms were minimal. Weakness and

gait anomalies had improved in all. With a mean follow up of 15 years, no patients demonstrated recurrence of the tumor including the one patient with sub-total resection. Clinical improvement was maintained in all patients at one year and beyond.
Surgery was performed in a manner to emphasize tumor resection with minimal tumor cell contamination of the subarachnoid space. The techniques used will be discussed and illustrated. We think that this attention to avoiding tumor cell contamination may have helped in achieving these results.

9:40 – 9:45 | SPECIAL LECTURE INTRODUCTION

Linda Liau, MD, PhD, MBA, UCLA School of Medicine

9:45 – 10:15 | SPECIAL LECTURE I

Byron Scott & Charlie Norris, authors of
"Slam-Dunk Success: Leading from Every Position on Life's Court"

10:15 – 10:30 | BREAK & BOOK SIGNING

ABSTRACT SESSION: SELECTED ABSTRACTS

10:30 – 10:40

CONTRALESIONAL BRAIN-COMPUTER INTERFACE CONTROL OF A POWERED EXOSKELETON FOR MOTOR RECOVERY IN CHRONIC STROKE SURVIVORS

David T. Bundy PhD[1,2], Lauren Souders MOT[3], Kelly Baranyai MOT[3], Laura Leonard MOT[3],Gerwin Schalk PhD[5], Robert Coker MS[2], Daniel W. Moran PhD[2], Thy Huskey MD[3]*, **Eric C. Leuthardt MD[2,4]***

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**Contributed equally*

Background and Purpose: There are few effective therapies to achieve functional recovery from motor-related disabilities affecting the upper limb after stroke. This proof-of-concept study tested whether a powered exoskeleton driven by a brain-computer interface (BCI), utilizing neural activity from the unaffected cortical hemisphere, could affect motor recovery in chronic hemiparetic stroke survivors. This novel system was designed and configured for a home-based setting to test the proof-of-concept of BCI-driven neurorehabilitation in outpatient environments.

Methods: Ten chronic hemiparetic stroke survivors with moderate to severe upper-limb motor impairment (mean Action Research Arm Test (ARAT)=13.4) used a powered exoskeleton that opened and closed the affected hand using spectral power from electroencephalographic (EEG) signals from the unaffected hemisphere associated with imagined hand movements of the paretic limb. Patients used the system at home for 12 weeks. Motor function was evaluated before, during, and after the treatment.

Results: Across patients, our BCI-driven approach resulted in a statistically significant average increase of 6.2 points in the Action Research Arm Test (ARAT). This behavioral improvement significantly correlated with improvements in BCI control. Secondary outcomes of grasp strength, Motricity Index, and the Canadian Occupational Performance Measure also significantly improved.

Conclusions: The findings demonstrate the therapeutic potential of a BCI-driven neurorehabilitation approach using the unaffected hemisphere in this sample of chronic

stroke survivors. They also demonstrate that BCI-driven neurorehabilitation can be effectively delivered in the home environment, thus increasing the probability of future clinical translation.

10:40 – 10:50

A Phase 0/II Trial For Precision Neurosurgical Oncology In Recurrent Glioblastoma Patients

An-Chi Tien, PhD[1], Xun Bao, PhD[2], Alanna Derogatis, PhD[1], Shwetal Mehta, PhD[1], Jing Li, PhD[2], **Nader Sanai, MD[1]**

1. Barrow Neurological Institute
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Introduction: CDK4/6-dependent cell-cycle regulation is disrupted in 78% of glioblastoma (GBM) patients and novel CDK4/6 inhibitors have shown anti-tumor activity in animal models of glioma. However, 40% of early-phase trials fail due to unfavorable drug properties not predicted by preclinical studies. As a paradigm for precision neurosurgical oncology, we conducted a Phase 0/II clinical trial of ribociclib, a selective CDK4/6-inhibitor, measuring it's *in vivo* effects following microdosing and then therapeutically-dosing patients with demonstrable pharmacokinetic (PK) and pharmacodynamic (PD) drug response.

Methodology: Recurrent GBM patients enrolled in the phase 0 component were treated with ribociclib (900 mg) for 5 days prior to plan tumor resection. Patient selection was based on intact Rb expression and CDKN2A deletion or CDK4/6 amplification. Plasma, tumor, and CSF samples were collected at predefined timepoints, and drug concentrations were determined by validated LC-MS/MS methods. PD effects were compared to matched archival tissue. Patients with positive PK and PD outcomes were enrolled into the phase II component to evaluate clinical efficacy with a primary endpoint of progression-free survival.

Results: 12 recurrent GBM patients were enrolled into the phase 0 component and no drug-related adverse events were observed. Ribociclib penetrated both contrast- and non-enhancing tumor regions, with median concentrations of 48.4 and 12.7 nmol/g, respectively, and median tumor-to-plasma partition ratios of 10.2 and 3.5, respectively. The median CSF concentration (*i.e.*, pharmacologically-active, unbound drug) was 0.58 nmol/mL, exceeding the *in vitro* IC_{50} for inhibition of CDK4/6 (<0.04 nmol/mL). CDK4/6-inhibition was evident in microdosed patients ($p<0.001$) and cell-cycle arrest was

intensified after drug exposure (p<0.001). Based of PK and PD effects, 67% of phase 0 patients were enrolled into the phase II component.

Conclusions: This Phase 0/II study demonstrates therapeutic concentrations of ribociclib in human GBM and provides direct evidence of its molecular effects. Within 6 months of study activation, we identified *in vivo* biological activity of a targeted inhibitor and confirmed the utility of Phase 0/II trials as part of an accelerated, neurosurgery-led paradigm for brain tumor drug development.

10:50 – 11:00

WHO BENEFITS FROM THROMBOLYSIS FOR INTRAVENTRICULAR HEMORRHAGE AND HOW? PRE-SPECIFIED SUBGROUP AND PER-PROTOCOL (MEDIATION) ANALYSES IN THE CLEAR III TRIAL

Issam Awad, MD, MSc, The University of Chicago

Introduction/Hypothesis: CLEAR III, a randomized, double-blinded, placebo controlled trial, demonstrated benefits of rt-PA over current "best care" in mortality and other clinical parameters in severe IVH with small ICH. Pre-specified subgroup analyses addressed hypotheses regarding who might/or not benefit per intention-to-treat assignment, and if any treatments rendered per-protocol mediated favorable outcome.

Methodology: Enrolled patients were randomized to receive rt-PA or saline via external ventricular drain (EVD) placed per pragmatic indications. End of treatment (EOT) was considered when at least the 3rd & 4th ventricles cleared, while sites were encouraged to attempt >80% clot removal with protocolized options for multiple catheters and further dosing up to 12 doses.

Results: Treatment groups were balanced with respect to epidemiologic, medical presentation, severity factors, IVH size, ICH size, and clot location. Use of rt-PA led to greater EOT clot removal (62% vs 44%, p<0.001). Utilization of guidelines and study protocol achieved >80% clot removal in only 33% of subjects receiving rt-PA and 10% of saline patients. When efficiency of IVH removal was substituted for treatment assignment, mRS 0-3 correlated directly with extent of clot removal (AOR=0.96/ml time-averaged IVH, p < 0.001). AORs were consistent within IVH size (<20 vs ≥20, p=0.019 and <0.001) and ICH location (thalamic vs non-thalamic, p=0.002 and <0.001) subgroups. Treatment fidelity analysis of IVH volume reduction showed the absence of IVH removal difference and any clinical benefit for IVH <20 ml (n=216, AOR=0.62, NS); conversely, for IVH ≥20

ml (n=274), rt-PA demonstrated a benefit in mRS 0-3 (AOR=1.84, p=0.046). Where rt-PA achieved ≥ 90% removal, odds of mRS 0-3 were greater (AOR=2.25, p=0.05). Among patients receiving rt-PA, EVD use ipsilateral to dominant lateral ventricle IVH (ipsi vs contra, p=0.004), multiple EVD catheters (dual vs single p=0.005) and greater number of doses (per dose p=0.01) achieved greater IVH removal.

Conclusion: Treatment of cases with larger IVH, and more complete blood removal must be pursued, if good mRS status is to be optimized with intraventricular rt-PA.

11:00 – 11:10

NON-SURGICAL TREATMENT OF SYMPTOMATIC POST-HEMORRHAGIC HYDROCEPHALUS OF PREMATURITY

Shenandoah Robinson, MD, John Hopkins Medicine and Lauren Jantzie, PhD, University of New Mexico

Introduction: Post-hemorrhagic hydrocephalus of prematurity (PHHP) remains a vexing problem. The most common intervention, ventricular shunts, are prone lifelong to complications. Shunt-related hospitalizations are a leading cause of US pediatric health-resource utilization. Importantly, millions of children globally do not have access to timely surgery. Motile ependymal cilia (Ecil) propel cerebrospinal fluid, and genetic mutants with impaired Ecil maturation develop symptomatic hydrocephalus with both ventriculomegaly and progressive macrocephaly. We predict that prenatal injury plus early postnatal intraventricular hemorrhage (IVH) impairs Ecil maturation via microglial-mediated calpain-degradation of Ecil, leading to symptomatic hydrocephalus. We hypothesize that neuroreparative agents erythropoietin (EPO) plus melatonin (MLT) can restore Ecil maturation and prevent symptomatic hydrocephalus.

Methods: We developed a novel rat PHHP model. Following prenatal injury on E18 that mimics chorioamnionitis, the most common cause of prematurity, pups are born at term (E22). On postnatal day 1 (P1), pups are randomized to intraventricular injection with vehicle (veh-sterile PBS) or littermate lysed red blood cells (IVH). Injury pups are randomized to treatment with EPO+MLT or veh. Intra-aural measurement (IAM-surrogate for head circumference) was obtained daily. MRI was performed on P21. P5 and P21 samples were used for histological and biochemical analyses. Groups were compared with t-test or two-way ANOVA with Bonferroni-correction with $p<0.05$ significant.

Results: Injury-IVH rats had larger IAM at P21 than sham-veh, sham-IVH or injury-veh rats (n=11-30, two-way, $p<0.01$). Stereological measurement of ventricular volumes (VV) at P5 show mild increases in sham-IVH or injury-veh rats, while injury-IVH rats exhibited a 7-fold increase (n=3-4). P5 injury-IVH rats had dramatic alterations in periventricular microglia. P21 MRI show VV remain larger in injury-IVH rats (n=4,22±7μm^3) than sham-IVH rats (n=3,6±1). After EPO+MLT treatment, P21 IAM for injury-IVH rats normalized compared to vehicle-treated injury-IVH rats (n=10-15,$p<0.001$), consistent with no ventriculomegaly observed on MRI in four treated injury-IVH rats. Corpus callosum fractional-anisotropy normalized after treatment, compared to vehicle-treated injury-IVH rats (n=4,$p=0.038$).

Conclusions: These initial results suggest that early treatment with clinically-available, safe agents can potentially restore Ecil function and prevent symptomatic hydrocephalus

11:10 – 11:20

GENETIC INFLUENCE OF LUMBAR DISK HERNIATION IN YOUNG PATIENTS

Nicholas Theodore, MD[1], A. Karim Ahmed, BS[1], Travis Fulton, MS[1], C. Rory Goodwin, MD, PhD[2], Daniel M. Sciubba, MD[1]

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Introduction: Intervertebral disk disease (IVDD) is one of the most common causes of low back pain and can substantially impact patient quality of life. Lumbar disk herniation has traditionally thought to be attributed to natural 'wear and tear' and mechanical insult. However, studies in the past two decades, have demonstrated the role for genetic influence instead of solely environmental factors.

Methods: A cohort of patients with definitively diagnosed lumbar intervertebral disk disease was compiled. The cohort was younger than the average age of presentation and excluded based on environmental risk factors for IVDD. A genome-wide association study (GWAS) was performed to characterize the genetic influences that may predispose IVDD.

Results: Missense mutations in collagen encoding genes were observed in 13 out of 15 patients in the cohort with intervertebral disk disease. Moreover, the odds ratios of key variants in Collagen 9A2 (COL9A2) and Collagen 11A1 (COL11A1) were greater than 1. The IVDD cohort also demonstrated statistical significance for 2 variants in the gene encoding for aggrecan—which facilitates load-bearing properties in the cartilaginous end plate.

Conclusions: These results support the previously published work describing genetic variants in the gene encoding collagen as a genetic risk factor for intervertebral disk disease. However, the present study sheds new light on the role for genetic variants in the aggrecan gene, the primary proteoglycan of the intervertebral disk, which sustains the cartilaginous end plate. Genetic predisposition to IVDD, therefore, may be a multimodal combination of mutations in the nucleus pulposus, annulus fibrosus, as well as cartilaginous end plates.

11:20 – 11:30

THE DEVELOPMENT OF AN ENDOVASCULAR CSF SHUNT

Carl B. Heilman MD, Adel Malek MD, PhD, Tufts Medical Center, Tufts University School of Medicine

Introduction: There has been minimal progress in the treatment of communicating hydrocephalus over the last 50 years. We sought to develop a novel approach for the treatment of communicating hydrocephalus that would replace the function of arachnoid granulations.

Methodology: A patent was obtained for the placement of an endovascular CSF shunt device into the wall of the sigmoid sinus. A company, CereVasc LLC, was formed to develop an endovascular CSF shunt (eShunt) that could be delivered via a transfemoral venous approach to establish a one way path for CSF drainage.

Results: Analysis of cisternal anatomy around the lateral cerebellum on thin slice axial MRI images in 36 patients aged 20 – 80 years revealed a larger CSF volume in the CP angle cistern immediately adjacent to the inferior petrosal sinus (IPS) than next to the sigmoid sinus. 3-D printed high resolution models were generated based on patient-based MRI anatomy of the IPS and CP angle cisterns incorporating a dural substitute membrane. These enabled rapid development of multiple eShunt prototypes that could be delivered on benchtop through a 3 French catheter into the IPS and penetrate the sinus wall into the CP angle cistern, thus establishing a CSF venous shunt. Design of the eShunt prototypes

was further refined by deployment into the IPS and CP angle cistern in 12 cadaver head specimens in the angiography suite using biplane and 3D fluoroscopic imaging and conventional endovascular tools. Additional work was performed on valve design, device coatings, and blood flow loops to mitigate the risk of clotting. The eShunt prototype is currently undergoing testing in live animals in preparation for application towards a "First in Human" Trial.

Conclusion: The development of a minimally invasive CSF shunt inserted through a transfemoral endovascular approach in the Neuroendovascular suite offers a novel method for the treatment of communicating hydrocephalus which could possibly revolutionize CSF diversion care. The development of an eShunt system has moved beyond the proof of principle to a prototype stage that is being tested in animals.

11:30 – 11:40

NEUROSURGERY RESEARCH & EDUCATION FOUNDATION (NREF) UPDATE

Regis W. Haid, Jr., MD, Chair, NREF

11:40 – 11:50

In Vivo Femtosecond Laser Sub-Surface Supragranular Cortical Microtransections Attenuate Initiation and Propagation of Acute Focal Epileptic Seizures In Rodent Model

Mingrui Zhao PhD, Hongtao Ma PhD, Chris B. Schaffer PhD, **Theodore H. Schwartz MD**
Department of Biomedical Engineering, Cornell University, Departments of Neurosurgery, Otolaryngology and Neuroscience, Weill Cornell Medical College

Introduction: Focal cortical epilepsy can be treated effectively with surgical removal of the epileptic focus but if the focus lies within or adjacent to important brain tissue neurologic deficits can occur. Recent evidence shows that seizures may spread preferentially through supragranular layers.

Tightly-focused, femtosecond infrared laser pulses can produce precise cuts only micrometers in neocortex limited to individual cortical layers.

Methods: An epileptic focus was created using injection of 4-AP into rat neocortex *in vivo*. We used a femtosecond infrared "laser scalpel" to produce sub-surface cortical incisions selectively to supragranular layers surrounding an epileptic focus.

Results: Microtransections completely blocked all seizures in 20% of animals and ictal propagation in another 15%. In the remaining animals, seizure frequency was reduced by 2/3 and seizure propagation reduced by 1/3. In those seizures that still propagated, it was delayed and reduced in amplitude. Somatosensory responses were maintained but with reduced amplitude.

Conclusions: Our data shows that just a single enclosing wall of laser cuts limited led to a marked reduction in seizure initiation and propagation with preserved cortical function. It may be a useful treatment for human epilepsy.

11:50 – 12:00

MUTANT GLYCINE CHANNEL CHEMOGENETIC NEUROMODULATION

Nicholas Boulis, MD, PhD, Emory University School of Medicine

The standard of care for neuromodulation treatments of pain, epilepsy, and movement disorders utilizes an array of neurostimulators that require an implanted prosthetic dependent on either an internal or external power source. These devices are prone to infection, lead fracture, and migration. The cumulative cost of these therapies includes the device and surgery for initial implantations, battery changes, and complications throughout the life of the patient. Moreover, the mode of therapy, electric current, is fundamentally nonspecific affecting both white and gray matter, leading to off target effects which usually prove dose limiting. To overcome these limitations, a glycine gated channel was mutated to reduce its capacity to induce a glycine mediated chloride conductance. The channel was further mutated to increase the receptor's inherent responsiveness to the FDA approved antihelminthic drug ivermectin. The gene for this mutant ligand gated channel (GlyRM) was then cloned into herpes simplex (HSV) and adeno-associated virus serotype 6 (AAV6) vectors. Next, thermal and mechanical allodynia were measured in mice with a model of postherpetic neuralgia. Wildtype animals were compared to groups of mice treated with subcutaneous HSV containing either the reporter gene or GlyRM. Treatment with ivermectin reduced both types of allodynia in a dose dependent manner in the HSV.GlyRM treated animals but not controls. Using the spared nerve injury model of pain in the mouse, the impact of dorsal horn expression of GlyRM was tested. AA V6 vectors

for GlyRM or a reporter gene were injected into the dorsal horn using a DREZ approach. The GlyRM gene was expressed in the dorsal horn but not surrounding white matter. Ivermectin completely abolished allodynia in GlyRM expressing animals but not control animals. Analgesia wore off on the expected time course for ivermectin clearance and was reinstated with redosing of ivermectin. These data provide proof of concept for chemogenetic pain neuromodulation using an FDA approved drug together with expression of the GlyRM ligand gated channel in either DRG or dorsal horn neurons.

12:00 – 12:10

MOTOR CORTEX AND PALLIDOCORTICAL DESYNCHRONIZATION AS THERAPEUTIC MECHANISMS OF PALLIDAL DEEP BRAIN STIMULATION

Nader Pouratian, MD PhD[1], Mahsa Malekmohammadi, PhD[1], Yalda Shahriari, PhD[2], Nicholas Au Yong, MD PhD, Xiao Hu, PhD[3]

1. University of California Los Angeles
2. University of Rhode Island
3. University of California San Francisco

Introduction: Subthalamic nucleus (STN) and globus pallidus internus (GPi) brain stimulation (DBS) are both efficacious therapies for Parkinson disease (PD). The majority of studies have focused on understating the mechanisms of STN-DBS and suggest that STN-DBS exerts its effect by modulating local (low) beta power at STN, STN-cortical (high) beta coherence, and cortical beta (13-35 Hz) to broadband gamma phase-amplitude coupling (PAC). To further delineate the role of low and high beta local and cross-site coupling in PD pathophysiology, we examine the effect of GPi-DBS to uncover the generalizability of findings with STN DBS, which have generally pointed to the hyperdirect pathway as a therapeutic mediator.

Methods: We recorded simultaneous right GPi local field potentials (LFPs) and sensorimotor LFPs via an electrocorticography strip in 10 PD patients undergoing pallidal DBS. Data was recorded during 30-second blocks of rest with eyes open OFF-DBS and ON-DBS. We examined effect of GPi-DBS on local beta power, cortical beta-gamma PAC as well as cross-site pallidocortical coherence.

Results: We found that acute therapeutic pallidal stimulation improved motor symptoms and resulted in: (1) local pallidal power suppression in low beta band (13-20 Hz) despite no significant sensorimotor cortical beta power modulation or any of the sub beta bands. (2) Suppression of pallidocortical high beta coherence (20-35 Hz) and, (3) significant

modulation of motor cortical high beta-gamma PAC ($P<0.05$). Regression analysis also revealed that improvement in clinical scores for rigidity and bradykinesia were positively correlated with (1) pallidcortical high beta coherence and (2) cortical highbeta-gamma PAC.

Conclusions: Our results show that GPi-DBS, like STN DBS, affects pallidcortical functional connectivity coupling. Suppression of motor cortical beta-gamma PAC is a common "fingerprint" of the therapeutic stimulation regardless of target. Our findings therefore suggest that DBS acts by reducing the "pathological" coupling across basal ganglia-thalamocortical motor network. Given that no monosynaptic connectivity exists between GPi and motor cortex, such phenomenon might not be solely mediated via modulation of the hyperdirect pathway.

12:10 – 12:20

CYBERPHYSICAL SYSTEMS TO RESTORE SOMATOSENSATION TO PARALYZED PATIENTS

Tim Lucas, MD and Andrew Richardson, MD, University of Pennsylvania

The dexterous hand is a defining feature of human existence. Regaining basic hand function is a principal concern for paralyzed patients. Toward this aim, the neuroscience community has witnessed significant advances in motor-or efferent-brain-machine interfaces (BMIs) in recent years. Several groups have demonstrated the capacity to transform cortical signals into motor commands that actuate robotic systems or evoke muscle contraction in paralyzed limbs. By comparison, the development of sensory-or afferent-BMIs has lagged behind. The absence of sensory feedback constitutes a critical barrier to wide-spread clinical implementation of BMI technology. Observations from patients with the selective loss of somatosensation reveals that real-time somatosensory feedback is essential to guide even the most basic of hand movements, like the continuous grip-hold of a cup. To address this unmet need, we are developing cyberphysical systems that integrate a suite of implantable sensors with neural stimulators. This Body Area Network wirelessly links miniature compressive force sensors, micro-electro-mechanical sensors (MEMS) and electrogoniometers with custom wearable computer circuits worn like an Apple® watch. Radiofrequency coupled implanted receivers permit efficient powering and data read-out of subdermal implants without the need of percutaneous wires, making the sensors fully passive and free of the requirement of a battery. In parallel, we are developing novel neural stimulator circuits and targets to receive finger sensor data and

encode information back into the brain. We have demonstrated the feasibility of this system in rodents and nonhuman primates. Once fully implemented, this closed-loop sensor-brain interface system will permit bidirectional BMI functionality by integrating existing efferent BMI systems. Such systems could enable basic hand functionality in paralyzed patients without the requirement of external robotic systems.

12:20 – 12:30

A "Precision Medicine" Approach To Limbic System Surgery For Psychiatric Disorders

Sameer Sheth, MD, PhD, Pranav Nanda, BA, Garrett Banks, MD, Columbia University

Introduction: 20-30% of patients with OCD or depression remain refractory to conventional treatment and are potential neurosurgical candidates. Although outcomes continue to improve, there is still significant response heterogeneity. We suggest that a significant barrier is our still rudimentary understanding of the involved circuits.

Methods: We identified 26 patients with OCD treated with stereotactic radiosurgical (SRS) capsulotomy. We used a statistical model to test for voxel-wise relationships between lesion location and outcome. We then used DTI data from 842 control subjects in the Human Connectome Project database to segment the anterior limb of the internal capsule (ALIC) based on prefrontal cortical connectivity. Finally, we combined this information to identify cortical regions mostly commonly affected by capsulotomy.

Results: Twenty-one of the 26 patients (81%) were responders. A region in the bilateral anteromedial ALIC demonstrated a significant relationship to symptom reduction, suggesting that inclusion of this region within the target was statistically associated with response. The ALIC segmentation demonstrated a corticotopic axis of organization, with fibers to OFC arranged ventromedially, and fibers to lateral PFC arranged dorsolaterally. Similarity indices demonstrated significant inter-individual variability, with only 66.2% average consistency. The SRS "hotspot" corresponded to fibers traveling to medial OFC.

Conclusions: This analysis demonstrates the power of combining multi-institutional data with national imaging repositories to improve circuit-level understanding. We conclude: 1) SRS capsulotomy remains an effective treatment for refractory OCD; 2) Inter-individual variability in ALIC organization demands personalized targeting; 3) Modulation of fibers to medial OFC is critical to therapeutic outcome. Finally, we use these insights to propose a fundamentally novel way of studying individual limbic networks. We describe a proposal

recently funded by the NIH BRAIN Initiative in which we use individualized intracranial recordings and "steerable" DBS systems to study and modulate limbic circuitry. We propose that this "precision medicine" approach to psychiatric neurosurgery will lead to better understanding of the involved circuitry and improved outcomes.

12:30 – 12:40

Deep Brain Stimulation For The Control Of Fat Metabolism: A Potential Therapy For Morbid Obesity

Kim Burchiel, MD, Chris Madden PhD, Shaun Morrison, PhD, Department of Neurological Surgery, Oregon Health & Science University

Obesity (BMI>30) now affects 40% of the US population, and is associated with significant medical co-morbidities (Type 2 Diabetes, heart disease, hypertension, etc.). It is expected to cost US healthcare $500 Billion dollars annually by 2030. The combination of "eat less, move more" has never been proven to be an effective approach to obesity, and bariatric surgery (gastroplasty or "duodenal switch" procedures remains the only treatments proven effective for this population.

Brown adipose tissue (BAT) represents only 5-7% of total body fat stores, but it is highly metabolically active, and it is densely innervated by sympathetic efferents. The role of BAT is strictly for thermogenesis (cold environments, fever). We have developed a potentially new treatment for refractory obesity which involves deep brain stimulation (DBS) of the hypothalamus to drive the metabolism of brown adipose tissue (BAT) through a polysynaptic pathway (Fig. 1) which stimulates neurons in the intermediolateral column of the upper thoracic spinal cord, producing increased sympathetic nerve activity (SNA) which drives BAT metabolism. In an experimental model of obesity, the high-fat diet (HFD) rat, we have shown that: (1) DBS electrodes can be localized to the paraventricular nucleus (PVN) by continuous monitoring of BAT temperature while stimulating the electrode; (2) BAT metabolism can be immediately increased by DBS producing increased BAT temperature, and expired CO2 production (3) PVN stimulation produces no sustained change in systemic arterial blood pressure (SAP) (Fig. 2).

Figure 1

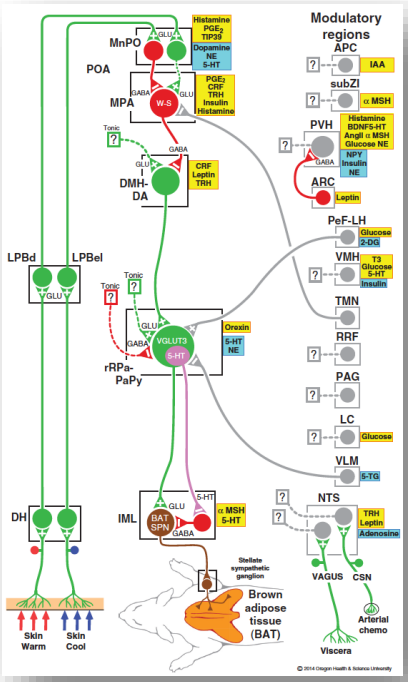
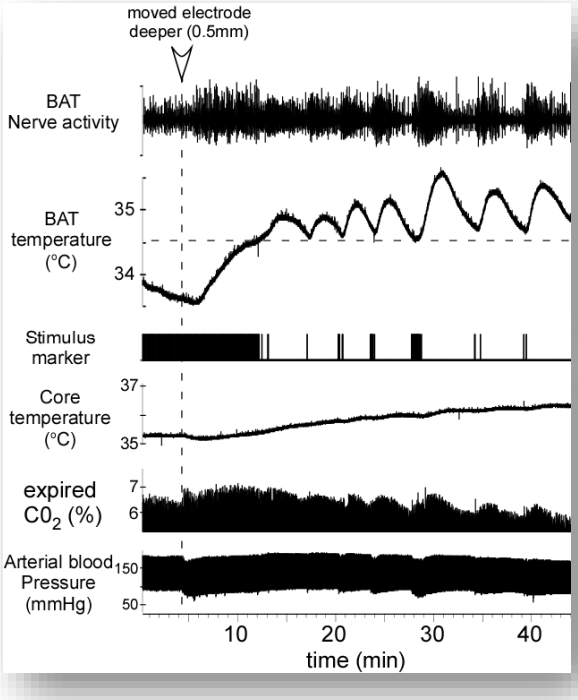


Figure 2



These results suggest that DBS of the PVN may prove to be an effective stimulus to increase BAT metabolism, and to potentially mobilize other fat stores ("beigeing" of white fat) to become metabolically active. This represents a new approach to the use of DBS as a treatment for obesity.

SPECIAL SESSION: THE FUTURE OF CEREBROVASCULAR TREATMENT

7:35 – 7:45

OPEN SURGERY

Daniel L. Barrow, MD, Emory University School of Medicine

7:45– 7:55

ENDOVASCULAR TECHNIQUES

Howard Riina, MD, NYU Langone

7:55 – 8:05

VASOSPASM

R. Loch Macdonald, MD, University of Toronto

ABSTRACT SESSION: VASCULAR

8:05 – 8:15

BLOOD PROTEOMIC BIOMARKERS OF ATHEROSCLEROSIS AND STROKE SYMPTOMOLOGY

Robert Dempsey, MD, University of Wisconsin School of Medicine and Public Health

Background: Biomarkers have become increasingly important in the diagnosis and treatment of disease. Therapeutic targets for treatment may also serve as such biomarkers. The incidence of atherosclerosis and stroke has become a worldwide health concern. Thus, to discover and validate biomarkers that alert physicians to identify individuals at increased risk for stroke is of clinical importance. Secreted proteins including dipeptidyl peptidase (DPPIV) and Lipocalin 2 (LCN2) in plasma may serve as reliable blood biomarkers for plaque rupture and stroke as they regulate inflammation and apoptosis. Many clinical and pre-clinical studies provide evidence for involvement of DPP4 and LCN2 in cerebro-vascular diseases. In this study, we examined if asymptomatic and symptomatic patients show distinct circulating proteomic signatures that serve as blood biomarkers of stroke symptomology.

Methods: Blood samples were collected from consented control subjects, and patients, and plasma was isolated. In global approach, nano-Liquid Chromatography-Mass Spectrometry was used to examine the differential levels of proteins in the plasma. The data was analyzed using Scaffold V4 software. Since obesity and glucose metabolism play critical roles in atherosclerosis and stroke, we examined the differential adipokine levels in plasma using a targeted proteome profiler adipokine array.

Results: In a global approach, we identified 237 differentially expressed proteins involved in inflammation and tissue remodeling. Adipokine array profiling showed altered serum levels. DPPIV was significantly increased in both asymptomatic and symptomatic patients. LCN2 was substantially increased in symptomatic carotid artery (CA) patients. Enzyme-linked immunosorbent assay (ELISA) validated these observations. DPPIV was increased in more than 75% of all CA patients, and LCN2 levels were increased in over 50% of symptomatic patients. In a pre-clinical animal model we found significantly increased levels of both DPPIV and LCN2 in the post-stroke brain.

Conclusion: Our studies suggest that blood/plasma proteins including DPPIV and LCN2 represent potential diagnostic biomarkers for development and progression of atherosclerosis and stroke. Taken together, these non-invasive proteomic approaches may identify biomarkers that are likely to provide a timely warning to prevent atherosclerosis progression and stroke.

8:15 – 8:25

GAMMA KNIFE RADIOSURGERY OF RABBIT MODEL SACCULAR ANEURYSMS

Mark D. Meadowcroft, PhD[1,2], Timothy K. Cooper, DVM, PhD, DACVP[3,4], Sebastian Rupprecht, BS[2], Thaddeus C. Wright BS[1], Elizabeth E. Neely, BS[1], Michele Ferenci, PhD[2], Robert E. Harbaugh, MD[1], James R. Connor, PhD[1] and **James McInerney, MD**

1. Department of Neurosurgery, The Pennsylvania State University – College of Medicine, Milton S. Hershey Medical Center
2. Department of Radiology (The Center for NMR Research), The Pennsylvania State University – College of Medicine, Milton S. Hershey Medical Center
3. Department of Comparative Medicine, The Pennsylvania State University – College of Medicine, Milton S. Hershey Medical Center
4. Department of Pathology, The Pennsylvania State University – College of Medicine, Milton S. Hershey Medical Center

Object: Intracranial aneurysms are vascular abnormalities associated with neurological morbidity and mortality due to risk of rupture. In addition, many aneurysm treatments have associated risk profiles that can preclude the prophylactic treatment of asymptomatic lesions. Gamma knife radiosurgery (GKRS) is a standard treatment for trigeminal neuralgia, tumors, and arteriovenous malformations (AVMs). Aneurysms associated with AVMs have been noted to resolve after treatment of the AVM. The aim of this study was to determine the efficacy of GKRS treatment in a saccular aneurysm animal model.

Methods: Aneurysms were surgically produced using an elastase-induced aneurysm model in the right common carotid artery (RCCA) of ten New Zealand White rabbits. Following initial observation of four years, each rabbit aneurysm was treated with a conformal GKRS isodose of 25 Gy to the 50% margin. Longitudinal MRI over two years and terminal measures obtained at multiple time points were used to track aneurysm size and shape index modifications.

Results: Aneurysms did not involute during the observation period prior to treatment and no aneurysm ruptured either before or after radiosurgery. Whole aneurysm and blood volume averages decreased with a linear trend at rates of 1.7% and 1.6% per month over twenty-four months, respectively, after GKRS. Aneurysm wall percent volume increased linearly at a rate of 0.3% per month indicating a relative thickening of the aneurysm wall during occlusion. Nonsphericity of the average volume, aspect ratio, and isoperimetric ratio of whole aneurysm

volume all remained constant. Histopathological samples demonstrated progressive reduction in aneurysm size and wall thickening with subintimal fibrosis. Consistent shape indices demonstrated stable aneurysm patency and maintenance of minimal rupture risk following treatment.

Conclusions: These data indicate that targeted GKRS to saccular aneurysms is associated with histopathological changes leading to increased aneurysm wall thickness and linear reduction of aneurysm size over time. The results suggest that GKRS may be a viable, minimally invasive treatment option for intracranial aneurysm obliteration.

8:25 – 8:35

REDUCTIONS IN BRAIN PERICYTES ARE ASSOCIATED WITH ARTERIOVENOUS MALFORMATION VASCULAR INSTABILITY

Ethan A. Winkler, MD, PhD[1], Jan-Karl Burkhardt, MD[1] and **Michael T. Lawton, MD**[1,2]

1. University of California, San Francisco
2. Barrow Neurological Institute

Introduction: Brain arteriovenous malformations (bAVMs) are a rupture-prone tangle of blood vessels with direct shunting between arterial and venous circulations. The molecular and/or cellular mechanisms contributing to brain AVM pathogenesis and/or destabilization in sporadic lesions remains elusive. Initial insights into AVM formation have been gained through models of genetic AVM syndromes. However, many studies have focused on endothelial cells and the contributions of other vascular cell types have yet to be systematically studied. Pericytes are multi-functional mural cells which regulate brain angiogenesis, blood-brain barrier integrity and vascular stability. Here, we analyze the abundance of brain pericytes and their association with vascular changes in sporadic human AVMs.

Methods: Human bAVMs and non-vascular lesion epilepsy tissue were surgically resected. Immunofluorescent staining with confocal microscopy was performed to quantify pericytes (platelet derived growth factor receptor beta (PDGFRβ) and N-aminopeptidase (CD13)) and extravascular hemoglobin. Iron-positive hemosiderin deposits were quantified with Prussian blue staining. Syngo-iFlow post-image processing was utilized to measure nidal blood flow on pre-intervention angiograms.

Results: Quantitative immunofluorescent analysis demonstrated a 68% reduction in vascular pericyte number in brain AVMs when compared to non-vascular lesion controls (NVLCs) ($p < 0.01$). Additional analysis demonstrated 52% and 50% reduction in the

vascular surface area covered by CD13- and PDGFRβ-positive pericyte cell processes, respectively, in bAVMs ($p < 0.01$). Reductions in pericyte coverage were statistically significantly greater in bAVMs with prior rupture ($p < 0.05$). Unruptured bAVMs had increased microhemorrhage as evidenced by a 15.5-fold increase in extravascular hemoglobin when compared to NVLCs ($p<0.01$). Within unruptured bAVM specimens, extravascular hemoglobin correlated negatively with pericyte coverage in brain AVMs (CD13: $r = -0.93$, $p<0.01$; PDGFRβ: $r = -0.87$, $p<0.01$). A similar negative correlation was observed with pericyte coverage and Prussian-blue positive hemosiderin deposits (CD13: $r = -0.90$, $p<0.01$; PDGFRβ: $r = -0.86$, $p<0.01$). Pericyte coverage correlated positively with the mean transit time of blood flow or the time circulating blood spends within the bAVM nidus (CD13: $r = 0.60$, $p < 0.05$; PDGFRβ: $r = 0.63$, $p < 0.05$). A greater reduction in pericyte coverage is therefore associated with a reduced mean transit time or faster rate of blood flow through the bAVM nidus. No correlations were observed with time-to-peak flow within feeding arteries or draining veins.

Conclusions: Brain pericyte number and coverage is reduced in sporadic bAVMs and is lowest in cases with prior rupture. In unruptured bAVMs, pericyte reductions correlate with severity of microhemorrhage. A loss of pericytes also correlates with a faster rate of blood flow through the bAVM nidus. This suggests that pericytes are associated with and may contribute to vascular fragility and hemodynamic changes in bAVMs. Future studies in animal models are needed to better characterize the role of pericytes in AVM pathogenesis.

8:35 – 8:45

IMMEDIATE HEMODYNAMIC CHANGES AFTER ANEURYSM TREATMENT PREDICT LONG-TERM OUTCOMES

Louis Kim MD, Michael Barbour PhD, Alberto Aliseda PhD, Cory Kelly BS, Michael Levitt MD, University of Washington School of Medicine

Background: Treatment failure after endovascular aneurysm embolization with coils or flow-diverting stents is thought to be dependent on changes in aneurysm hemodynamics, which can be calculated using computational fluid dynamics modeling (CFD). Immediate post-treatment aneurysm hemodynamics could predict embolization success or failure. Previous studies have not incorporated patient-specific blood flow measurements or accurate representation of the complex geometry of aneurysm coils into CFD models, reducing the accuracy of their outcome predictions.

Methods: Patients undergoing endovascular treatment for unruptured aneurysms were included. Blood flow velocity and pressure were measured in peri-aneurysmal locations using an intravascular dual-sensor pressure and Doppler velocity guidewire before and immediately after treatment. These measurements defined inflow and outflow boundary conditions for computational models, and coils were represented based on geometric approximations using synchrotron microtomography. Changes after treatment in intra-aneurysmal flow rates (Q), wall shear stress (WSS) and wall shear stress gradient (WSSG) were calculated. Treatment success was determined by radiographic outcome at least six months after initial treatment, and was correlated with immediate post-treatment hemodynamic changes.

Results: Forty patients were included in the study. Intravascular patient-specific physiological measurements were successful in all patients. Treatment success at follow-up (defined as no significant aneurysm residual or need for aneurysm retreatment) was seen in 33 patients, while treatment failure was seen in seven. The influence of immediate post-treatment hemodynamics (Q, WSS and WSSG) on long-term treatment outcome was analyzed to establish predictive thresholds.

Conclusions: Integration of patient-specific physiological measurements in the creation of accurate CFD models of aneurysm hemodynamics is safe and feasible. Immediate post-treatment changes in peri-aneurysmal hemodynamics can be used to predict long-term treatment outcome.

8:45 – 8:55

RESULTS OF DIRECT STA-MCA BYPASS FOR CEREBRAL ISCHEMIA AND MOYAMOYA DISEASE: A RECENT SINGLE SURGEON SERIES, WITH EMPHASIS ON OUTCOMES, COMPLICATIONS AND FLOW MEASUREMENTS.

Angela M. Richardson, MD, PhD, Brian M. Snelling, MD, Robert M. Starke, MD, **Jacques J. Morcos, MD,** Jackson Memorial Hospital, University of Miami

Introduction: The COSS trial has concluded that bypass surgery for atherosclerotic ischemia (ATH) is not beneficial, in spite of several non-randomized series demonstrating the contrary. In the setting of adult Moyamoya disease/syndrome (MMD), direct bypass is well-established. Additionally, little has been published on the use and interpretation of intraoperative blood flow measurements in either set of patients. We assessed our recent surgical series to address outcomes and blood flow results in both groups.

Methods: A retrospective chart review was performed to identify all patients undergoing EC-IC bypass at our institution, 2005-2016, (single surgeon, JJM). We included patients with evidence of hypoperfusion undergoing STA-MCA bypass for MMD or ATH, and excluded aneurysms and tumors. We analyzed: intraoperative blood flow data; bypass patency (traditional angiography, CTA, or MRA) prior to discharge and at 12 months; complications; patient symptoms (worsened/stable/mild improvement/major improvement/resolved); and Modified Rankin scale (mRS) (pre- and post-operatively).

Results: During the study period, 129 EC-IC bypass operations were performed; 91 of which met inclusion criteria. There were 72 patients/105 anastomoses. Patients presented primarily with ischemia (1 day – 5 years), mean mRS 2.2 (MMD 2.0; ATH 2.7). Perioperative infarcts occurred in 4 MMD (9%) and 2 ATH (6%) patients. Graft occlusion rates were: MMD 10.3% (1/4 asymptomatic, mean time-to-occlusion 189 days); ATH 10.8% (all asymptomatic, mean time-to-occlusion 45 days). 91.2 % of patients showed clinical improvement/no change, mean follow-up 335 days (MMD: 93.1%, ATH: 87.9%). mRS at final follow-up was: MMD 1.2; ATH 1.4. Cut Flow Index (CFI) (MMD 95.3%; ATH 106.5%) was not significantly different between occluded and patent grafts (p=0.7354). Further clinical, radiological, technical and blood flow data will be presented.

Conclusions: We can reasonably conclude that STA-MCA bypass remains highly beneficial in most Moyamoya patients, and a select group of atherosclerotic carotid occlusion patients, with respect to clinical outcomes and graft patency rates. We were unable to replicate the reported correlation between CFI and graft occlusion rates, details of which will be discussed during the presentation.

8:55 – 9:05

SIRT1 Activation: A Strategy for Harnessing Endogenous Protection Against SAH-induced Neurovascular Dysfunction

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Introduction: Delayed cerebral ischemia (DCI) is a major contributor to poor outcome after aneurysmal subarachnoid hemorrhage (SAH) and is multifactorial in etiology. Our prior proof-of-concept work demonstrated that hypoxic preconditioning (PC), a powerful

and pleiotropic phenomenon, is an effective multi-faceted strategy to combat DCI after SAH. In this study, we hypothesized that Sirtuin 1 (SIRT1) is a critical upstream inducer of PC-induced protection and may, therefore, represent an attractive therapeutic target.

Methods: Wild-type C57BL/6J mice were utilized in the study and subjected to normoxia or hypoxia (8% oxygen for 4 hours). Surgical procedures included induction of SAH via endovascular perforation or sham surgery. Multiple endpoints were assessed including cerebral vasospasm, neurobehavioral deficits, SIRT1 expression via quantitative real-time PCR for mRNA, and Western blot for protein quantification. Pharmacological agents utilized in the study include EX-527 (SIRT1 inhibitor), Resveratrol (SIRT1 activator), and L-NNA (nitric oxide synthase inhibitor).

Results: SIRT1 mRNA and protein expression was upregulated at 6, 12, 24, and 48 hours after PC. SIRT1 inhibition with EX-527 resulted in a loss of PC-induced protection against vasospasm and neurobehavioral deficits after SAH. Resveratrol increased SIRT1 protein expression and induced nitric oxidase synthase-dependent vasodilation in cerebral arterioles ex vivo. Resveratrol treatment resulted in a dose-dependent protection against vasospasm and neurobehavioral deficits after SAH. This Resveratrol-induced neurovascular protection in SAH was blocked by EX-527, indicating the protective effects of Resveratrol in SAH are SIRT1-mediated.

Conclusion: The multi-faceted protective effects of both physiologic and pharmacologic PC against SAH-induced neurovascular dysfunction are SIRT1-dependent. This suggests SIRT1 activation is a promising, novel, pleiotropic therapeutic strategy to combat DCI after SAH.

9:05 – 9:15

OUTCOME OF COMBINED ENDOVASCULAR AND SURGICAL TREATMENT OF UNRUPTURED ANTERIOR COMMUNICATING ARTERY ANEURYSMS: SHOULD MORE AGGRESSIVE TREATMENT BE OFFERED?

Philip G. R. Schmalz, MD[1,2], Gabriel Sneh, MHS[1], Roger B. Davis, ScD[3], Christopher J. Stapleton, MD[4], Abdulrahman Alturki, MBBS, MSc[1,5], Ajith J. Thomas, MD[1], **Christopher S. Ogilvy, MD[1]**

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Introduction: Natural history studies show anterior communicating artery aneurysms have a higher risk of rupture than other anterior circulation lesions, yet treatment of small unruptured aneurysms remains controversial. As treatment improves, risk may fall to levels which justify intervention for these aneurysms. With low treatment risk and a nuanced understanding of lesion risk, an aggressive treatment strategy may be justified.

Methods: 149 patients with unruptured aneurysms of the anterior communicating artery were treated by the senior authors over a five-year period. Treatment was performed by operators trained both in endovascular and surgical techniques. Treatment method was based on estimate of lowest risk/highest efficacy for each patient. Outcomes were recorded at three months and one year from treatment. The primary outcome was defined as a modified Rankin score (mRS) of >2 or persistent cognitive impairment.

Results: Age averaged 61, range 34-84 years. Aneurysm size averaged 6 mm, range 2-15 mm. 79% of aneurysms measured 7 mm or less. Clipping was performed in 98 patients (65.8%). Patients aged >60 years were more likely to be treated endovascularly (33/76, OR=2.55; 95% CI 1.26-5.14, p=0.0089). The primary outcome was met in 12 patients (8%). Of all poor outcomes, 11/12 occurred in patients >60. Size or treatment method did not predict poor outcome. Age >60 was the most significant predictor of poor outcome with a nearly 13-fold increased risk for older patients (OR=12.9; 95% CI 1.62-102.9, p=0.016). Only one patient under 60 had a poor outcome (cognitive dysfunction, 1.36%). No patient under 60 had an mRS>1.

Conclusions: The risk of treatment of unruptured anterior communicating artery aneurysms for patients under age 60 is low. Comparing treatment risk to natural history

studies, a patient treated under age 60 will outperform natural history within one to two years. Recognizing the lower risk of treatment for smaller anterior communicating artery aneurysms, an aggressive management strategy is supported.

9:15 – 9:25

NOVEL COMPOUNDS THAT REDUCE INTRACEREBRAL HEMORRHAGE AND BRAIN MICROHEMORRHAGES IN ZEBRAFISH AND MOUSE MODELS

R. Loch Macdonald, MD, PhD, University of Toronto

Background: Intracerebral hemorrhage (ICH) is a debilitating subtype of stroke, accounting for 10-15% of all stroke cases. Furthermore, brain microhemorrhages are an emerging form of brain hemorrhage associated with cerebrovascular disease and cognitive dysfunction. Injury to endothelial cells and their intercellular junctions may underlie the pathophysiology of these diseases as well as of cavernous malformations. There is no medical therapy for these diseases associated with vascular instability.

Methods: We developed several models of ICH and brain microhemorrhage using atorvastatin and reverse genetics or mutant strain selection and used these models for high throughput screening in zebrafish and efficacy testing in mice.

Results: Through a large-scale screening of two of the NIH compound libraries, we identified five compounds (coded as A, B, E, L and T) that can restore the vascular stability defect and prevent ICH and brain microhemorrhage in zebrafish with moderate to high potencies (with EC50 in the nanomolar to low micromolar range). Furthermore, the test of several derivatives of one of the compounds (A) showed that the whole family of compounds are active with high potency (with EC50 in the nanomolar range). Mechanistic studies of these compounds suggest enhancement of endothelial-mural cell adhesion molecules as the basis for the restoration of cerebrovascular stabilization in zebrafish. Compound A was studied in mouse models of ICH induced by lipopolysaccharide and in mouse embryos when the mother is treated with anti-integrin antibodies. Compound A reduced brain hemorrhage in both models as assessed by magnetic resonance imaging and histology. New chemical entities synthesized from compound A determined some structural elements critical to the vascular stabilization effect.

Conclusions: These studies form the basis for further preclinical studies and new chemical entity synthesis to develop drugs that stabilize the cerebral vasculature and prevent brain hemorrhage possibly due to multiple different diseases through a common mechanism.

9:25 – 9:35

BRAINSTEM ARTERIOVENOUS MALFORMATIONS: LESION CHARACTERISTICS AND TREATMENT OUTCOMES

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Introduction: Brainstem arteriovenous malformations (AVMs) are rare lesions that are difficult to diagnose and treat. They are often more aggressive in their behavior when compared with their supratentorial counterparts. The consequence of a brainstem hemorrhage is often devastating, and many patients are in poor neurological status at presentation. The authors examine the factors associated with angiographically confirmed cure and those affecting management outcomes for these complex lesions.

Methods: This was a retrospective analysis of data gathered from the prospectively maintained Stanford AVM database. Lesions were grouped based on their location in the brainstem (medulla, pons, or midbrain) and the quadrant they occupied. Angiographic cure was dichotomized as completely obliterated or not, and functional outcomes was dichotomized as either independent or not independent at last follow-up.

Results: Between 1994 – 2016, 39 lesions were treated. Of these, 3 were located in the medulla, 14 in the pons, and 22 in the midbrain. At presentation, 92% of the patients had hemorrhage, and only 43.6% were functionally independent. Surgery resulted in the best radiographic cure rates, with a morbidity rate of 12.5%. In all, 53% of patients either improved or remained stable after surgery. Absence of residual nidus and female sex correlated with better outcomes.

Conclusions: Brainstem AVMs usually present with hemorrhage. Surgery offers the best chance of cure, either in isolation or in combination with other modalities as appropriate.

9:35 – 9:40

DIFFERENTIAL TRANSCRIPTOME WITH CEREBRAL CAVERNOUS MALFORMATION GENE LOSS IN MODEL SYSTEMS (CULTURED CELLS, WORM AND MOUSE) AND IN HUMAN LESIONAL ENDOTHELIUM REFLECT POSTULATED DISEASE MECHANISMS

Sean Polster, MD and Issam Awad, MD, MSc, The University of Chicago

Introduction: Mechanistic studies have correlated CCM gene loss with signaling aberrations of MEKK3-KLF2/4, Rho/ROCK, angiogenesis activity, disruption of junctional proteins and EC-mesenchymal transition. Other studies demonstrated a robust antigen driven clonally expanded pathogenetic B-cell immune response, and more recently microbiome mediated innate immune response driving lesion genesis. We hypothesize that the transcriptome of cultured endothelial cells (ECs) with *Ccm* loss, Caenorhabditis (C.) Elegans mutants, and laser microdissected ECs from murine and human lesions reflect postulated disease mechanisms.

Methodology: Resected human CCMs were harvested at surgery, snap frozen, embedded in OCT and stored at -80 °C and normal brain tissue was acquired at autopsy. ECs from these lesions, and from murine lesions in *Ccm+/-* and postnatal *Ccm flx-/-* models, and normal capillaries were collected using laser-captured microdissection. RNA was extracted using the TRIzol protocol from these ECs, from homozygous C. Elegans mutants for *Ccm* homologous genes and wild worms, as well as cultured brain microvascular ECs with and without *Ccm flx* gene loss. RNA libraries, generated using low-input strand specific RNA-Seq kit (Clontech), were multiplexed and sequenced with 50 basepair (bp) single end reads (SR 50 bp), and mapped using STAR v2.4.0g1 alignment. Differentially expressed (DE) genes between CCM and normal ECs were identified with DESeq2. Functional enrichment analysis (FEA) on DE genes was performed using QIAGEN's Ingenuity®, defining differentially activated canonical pathways.

Results: Gene ontology revealed significant DE of immune system and the regulation of response to stress across all models (23 homologous DE genes across 3 species). Across cultured ECs, murine and human lesional ECs, there were 73 homologous DE genes, reflecting canonical pathways related to cytoskeletal/extracellular matrix, inflammation/immune response, cell growth/apoptosis, and coagulation/angiogenesis interactions.

Conclusions: Common molecular processes occur in CCM across species and model systems, the first such homology demonstrated in any disease. These validate postulated disease mechanisms and identify specific targets within canonical pathways for future investigation. They allow the interrogation of genes mediating differences across genotypes, with different lesion maturity, hemorrhage, or with putative therapies.

9:40 – 9:45

TRIAL DESIGN, METHODS, AND RATIONALE FOR THE EARLY MINIMALLY INVASIVE REMOVAL OF INTRACEREBRAL HEMORRHAGE (ENRICH) CLINICAL TRIAL

Jonathan J. Ratcliff, MD, MPH[1], Alex J. Hall, MS[1], Benjamin R. Saville, PhD[6], Victoria L. Phillips, DPhil[5], Roger J. Lewis, MD, PhD[6], Scott Berry[6], PhD, Jason W. Allen, MD, PhD[3], Michael Frankel, MD[2], David W. Wright, MD[1], Daniel Barrow, MD[4], **Gustavo Pradilla, MD[4]**

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6. Berry Statistical Consulting

Introduction: Spontaneous intracerebral hemorrhage (ICH) is a common form of stroke that often results in severe morbidity or death. For most ICH, there are no proven therapies for acute management. Evidence suggests minimally invasive surgical evacuation of ICH may result in improved patient outcomes. The ENRICH clinical trial is designed to determine the efficacy and economic impact of early ICH evacuation using minimally invasive, transulcal, parafascicular surgery (MIPS) compared to standard guideline-based management. In this abstract we present the trial design and rationale at the foundation of the ENRICH clinical trial.

Methods: ENRICH is an adaptive, prospective, multi-center clinical trial designed to enroll up to 300 patients with acute ICH. Patients are block-randomized based on hemorrhage location (lobar vs basal ganglia) 1:1 to MIPS or standard management. Included patients are 18 - 80 years, GCS 5-14, baseline mRS < 1, and NIHSS > 6, presenting within 24 hours from last known well and found to have a spontaneous, CTA-negative, supratentorial ICH (30-80 mL). Primary efficacy will be determined by demonstrating significant improvement in the mean utility-weighted mRS at 180 days after

enrollment. Economic effect of MIPS will be determined by quantifying the cost per quality-adjusted life-years gained at pre-determined time points.

Results: The rationale for early intervention is to interrupt the time-dependent ICH related pathophysiology caused by mechanical pressures and the pro-inflammatory secondary cascade that leads to worsened cellular injury and edema formation. The planned enrichment strategy acknowledges that hemorrhages in varied locations may have a differential response to MIPS. Study adaptation, in the form of enrichment, may occur if pre-determined futility rules are met for the primary outcome in either of the two locations.

Conclusion: ENRICH is designed to establish the clinical and economic value of early MIPS in the treatment of ICH. Enrollment was initiated in December 2016.

9:45 – 9:50

Optimized Reversible Von Willebrand Factor Inhibitor Demonstrates Superior Arterial Recanalization Compared To rTPA In Murine And Canine Arterial Occlusion

Shahid M. Nimjee, MD, PhD, David Dornbos III, MD, Debra Wheeler, BS, Nicholas Venetos, BS, Allyson Huttinger, BS, Nicholas Musgrave, BS, Spencer Talentino, Cheyenne Jones, BS, Matthew E. Joseph, BS, Jay Zweier, MD, Bruce A. Sullenger, PhD, The Ohio State University Medical Center

Introduction: Recombinant tissue plasminogen activator (rTPA) treatment of ischemic stroke is limited by a non-specific thrombolytic effect, a narrow therapeutic window, poor rates of recanalization and associated risk of hemorrhage. Aptamers are RNA-based compounds that can selectively inhibit biologic pathways in a potent and reversible manner. Aptamer targeting von Willebrand Factor (vWF), which is the basis for stroke-associated platelet aggregation and thrombus stabilization, could provide a new method to specifically lyse stroke-associated thrombosis in a reversible manner.

Hypothesis: An RNA aptamer can be developed to selectively inhibit vWF and lyse cerebrovascular arterial occlusion in a reversible manner (using an antidote oligonucleotide).

Methodology: We developed a targeted RNA aptamer (9.14T79-VR7) to inhibit vWF using systematic evolution of ligands by exponential enrichment. Aptamer specificity and effective inhibition were assessed via in vitro binding and activity assays. Murine (n=24)

and canine (n=9) models (FeCl3) of carotid artery occlusion were used to assess the feasibility, safety and effectiveness of the thrombolytic aptamer in vivo. Antidote reversibility using a targeted oligonucleotide (designed by Watson-Crick base pairing) was assessed in vitro and in a murine tail vein model (n=55). Laboratory, angiographic and histologic assessments were performed.

Results: Aptamer bound to vWF with high affinity and specificity (nitrocellulose binding assay; Kd=8.8 nM). Aptamer inhibited platelet aggregation in a dose-dependent manner (logIC50=1.86; 72.5nM). While vWF aptamer (dose, 0.5 mg/kg) successfully restored carotid blood flow after aptamer administration following carotid occlusion in the murine and canine models, flow was not restored in any vehicle and rTPA controls ($P<0.05$). Oligonucleotide reversed aptamer activity in vitro and in vivo in less than 2 minutes ($P<0.01$). Histopathology in aptamer treated animals confirmed arterial patency and lack of intracranial hemorrhage or thromboembolism.

Conclusions: Targeted aptamer inhibition of VWF provides superior arterial recanalization to rTPA. vWF aptamer effect can be rapidly and completely reversed using an antidote oligonucleotide. These findings indicate using an aptamer drug-antidote combination targeting vWF in stroke may represent a safer and more effective treatment than rTPA.

9:50 – 10:05 | Break

10:05 – 10:10 | Special Lecture Introduction

Frederick Barker, MD, Harvard Medical School

10:10 – 10:40 | Special Lecture II

Ted Schilowitz, Futurist at Paramount Pictures.

Working with studio leadership and technology teams, he spends his time exploring forms of next generation immersive cinema experiences with an emphasis on Virtual Reality and Augmented Reality. His past work includes the advancement of interactive visual storytelling for 20th Century Fox and the initial product development of the RED digital cinema camera, in wide use in today's motion picture industry.

ABSTRACT SESSION: PEDIATRIC, SPINE & GENERAL

10:40 – 10:50

HOSPITAL AND HEALTH SYSTEM CONSOLIDATION: IMPACT UPON QUALITY AND PRICE

Marc Mayberg, MD, University of Washington

An unintended consequence of the Affordable Care Act has been the rapid consolidation of hospital systems in the U.S. through mergers and acquisitions (M&A). Approximately two-thirds of U.S hospitals are currently consolidated with nearly 1 million employed physicians; there are projected to be no independent hospitals remaining within 5 years. Consolidation has been caused in part by significant capital expenditures in response to Affordable Care Act regulations (EHR, ICD-10, meaningful use), lack of patient loyalty due to network constraints, and persistent low net margins, which limit access to capital. Acquisition of physician practices (vertical consolidation) has been especially notable for neurosurgery, with projected continuing inpatient growth and high inpatient margins. The proliferation of hospital M&A has resulted in several for-profit and not-for profit systems with total revenue in the upper quartile of the U.S. Fortune 500. Hospital system market concentration is monitored by the DOJ and FTC, using the Herfindahl-Hirschman Index (HHI). Highly concentrated hospital markets (HHI>2500), which might trigger antitrust litigation, have been increasing for several years in all regions of the U.S. Many hospital systems carry debt in excess of $1 billion, and downgraded hospital bond ratings due to poor margins result in higher interest rates, which in turn have a negative impact on profitability. There is ample data that consolidated systems have increased utilization of technologies such as EHR and amalgamation of high-volume services with better outcomes (e.g. comprehensive stroke centers), but little evidence that overall quality is improved. Importantly, hospital charges are directly related to market power - consolidated hospitals have >40% higher insurance charges despite equivalent costs. Consequently, there is a spiral of hospital M&A resulting in increased costs to the public - hospitals employ neurosurgeons and incentivize procedures to augment margins, which improve bond ratings and lower interest rates, which helps the bottom line and enables further M&A. Simultaneously, increased hospital market power enables consolidated systems to increase charges to commercial insurers, which pass cost increases to patients through higher premiums and co-pays. The hospital consolidation spiral might be mitigated by value-based

reimbursement and assumed risk contracts, although the future of such changes remain uncertain.

10:50 – 11:00

A Randomized Trial Of Endoscopic Third Ventriculostomy With Choroid Plexus Cauterization Compared To Ventriculoperitoneal Shunt For The Treatment Of Post-Infectious Hydrocephalus In Ugandan Infants

Abhaya V. Kulkarni, MD, PhD, The Hospital for Sick Children, Department of Neurosurgery, University of Toronto; **Steven J. Schiff, MD, PhD**, Center for Neural Engineering, Department of Neurosurgery, Engineering Science and Mechanics, and Physics, Penn State University; Benjamin C. Warf, MD, Department of Neurosurgery, Boston Children's Hospital, Harvard University

Background: Post-infectious hydrocephalus (PIH) in infants is a major health burden in sub-Saharan Africa. Recently, treatment by endoscopic third ventriculostomy with choroid plexus cauterization (ETV/CPC) has shown some advantages over the current standard of care, ventriculoperitoneal shunt (VPS), with respect to late failure rates. VPS, however, is better at reducing ventricle size than ETV/CPC, and this might result in superior cognitive outcome and brain growth.

Methods: We conducted a randomized trial to determine if a protocol of primary treatment with VPS results in superior cognitive outcome in Ugandan infants (<180 days old) with PIH compared to treatment with ETV/CPC. The primary outcome was Bayley Scales of Infant Development (BSID-3) Cognitive scaled score at 12 months after surgery, measured by blinded evaluators. Brain volume from CT scan was assessed by evaluators blinded to patient outcome. Analyses were by intention-to-treat.

Results: Fifty-one eligible infants were randomized to ETV/CPC and 49 to VPS. There was no significant difference in 12 month BSID-3 Cognitive score (p=0.35, estimated difference 0 [-2, 0]), change in BSID-3 Cognitive score (p=0.66, estimated difference 0 [-2, 1]), or in any other BSID-3 score or change in score. There were no significant differences in treatment failure (p=0.24, log–rank, hazard ratio 1.4 [0.7, 3.0]) or achieving normal brain volume (volume larger than 1 SD below the age- and sex-corrected mean, 21.3% ETV/CPC, 27.7% VPS, p=0.63). Only 10.1% of infants had normal brain volume at baseline, but 26.6% demonstrated a substantial increase, with 24.4% achieving normal volume at 12 months. The proportion of patients achieving normal brain volume and of

those demonstrating substantial brain growth was not significantly different between treatment arms. Those with substantial brain growth at 12 months demonstrated higher median BSID Fine Motor scores and also significantly better improvement from baseline in BSID Cognitive, Gross Motor, and Fine Motor. Brain volume, but not CSF volume, at 12 months correlated with all BSID-3 scores.

Conclusions: For infants with PIH in Uganda, a protocol of primary treatment with VPS was not shown to result in superior cognitive outcome compared to a protocol of primary treatment with ETV/CPC, despite greater reduction in CSF volume.

11:00 – 11:10

MANAGEMENT OF BOTTOM OF SULCUS DYSPLASIA USING NEURONAVIGATED EEG DEPTH ELECTRODE PLACEMENT

James T Rutka, MD, PhD, The Hospital for Sick Children, University of Toronto

Bottom of sulcus dysplasia (BOSD) is a recently described source of intractable epilepsy. Since the advent of high field (3T – 7T) MRI, the diagnosis of BOSD has become relatively routine. Depth electrodes placed into BOSD frequently demonstrate this region as the ictal onset zone in many cases. The challenges associated with resecting BOSD to achieve seizure freedom are three-fold:

1. BOSD lesions are frequently small and subtle.
2. Localization of the BOSD at the time of resection can be difficult even with neuronavigation given problems associated with brain shift, and distinguishing lesional from non-lesional tissue.
3. BOSD lesions are often found in the peri-Rolandic region making surgical approaches to avoid neurological deficits somewhat challenging.

In this study, we treated 12 patients with BOSD in efforts to control their seizure disorders. All patients had pre-operative assessments with prolonged video-EEG recordings, high field MRI scans, CT-PET scans, magnetoencephalography (MEG), and neuropsychological tests. Nine of the 12 patients were found to have peri-Rolandic BOSD lesions. All patients underwent craniotomy for placement of subdural grids and depth electrodes into the BOSDs. Accurate placement of the depth electrodes was performed with image guidance. All patients had extra-operative EEG assessments to capture seizure onset zones. All patients returned to surgery for repeat craniotomy and resection of their BOSDs. Complete excision of their BOSDs was facilitated by suturing the depth

electrodes to the pial surface, and following the electrodes to the target sites using microneurosurgical techniques and intra-operative neuromonitoring and neuronavigation. At this time, 10 patients are seizure free (Engel I) and 2 patients are Engel II with a range in follow up from 6 – 24 months. Post-operative imaging has verified the complete removal of the BOSDs. No patient suffered a serious, permanent neurological deficit.

BOSDs are a relatively recently described source for intractable epilepsy. The surgical management of BOSD is aided by the technique we describe of tracking the depth electrodes to the active sites of epileptogenesis. Video demonstration will be provided.

11:10 – 11:20

THE INFLAMMATORY MILIEU OF PEDIATRIC ADAMANTINOMATOUS CRANIOPHARYNGIOMA INCLUDES AN IMMUNOSUPPRESSIVE PHENOTYPE

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Introduction: Adamantinomatous Craniopharyngioma (ACP) is associated with considerable short and long-term morbidity but lacks biologically-directed therapies. Through development of a multicenter consortium and international collaboration, we have demonstrated that inflammatory mechanisms play a critical role in pediatric ACP pathogenesis and that paracrine mechanisms, directed from a minority of tumor stem cells, may drive growth and infiltration. To further explore the balance between tumorigenic inflammation and immunoediting in pediatric ACP, we explored the immunosuppressive characteristics of human tumor tissue.

Methodology: Milliplex cytokine and gene expression analyses were used to compare ACP with other common pediatric brain tumors and normal tissue. Immunohistochemistry and fluorescence-activated cell sorting (FACS) were used to characterize the tumor infiltrating immune cell phenotype. Next-generation techniques were used to explore gene expression.

Results: Myeloid cells from the ACP cyst compartment demonstrated low levels of CD64 and HLA-DR expression, combined with high levels of CD163 expression. Both CD4 and CD8(+) T-cells demonstrated high levels of Programmed Cell Death Protein 1 (PD-1). ACP

tissue also demonstrated higher levels of Programmed Death-Ligand 1 (PD-L1) than any pediatric brain tumor other than some classes of low grade glioma. This pattern is most consistent with an immunosuppressive milieu. ACP further demonstrated highly elevated levels of IDO-1 (FC 9.43 versus all other tumor/tissue types, p=1.4x10-28), confirmed by IHC staining for IDO-1 in the epithelial tumor compartment. Elevated levels of IL-10 were demonstrated in the cyst fluid and solid tumor compartments of ACP.

Conclusions: In addition to the previously described pro-inflammatory phenotype, pediatric ACP is characterized by immunosuppressive factors in both the solid and cyst fluid compartments, and an exhausted infiltrating T-cell phenotype. This may be consistent with a failure of immune-mediated tumor suppressive function, in the face of chronic tumor-induced inflammation. Further advancement of these data through small animal models and clinical translation through the inclusion of ACP patients in trials of immune-directed therapies, such as checkpoint inhibitors, is now under consideration.

11:20 – 11:30

A NOVEL BRACHYURY-YAP REGULATORY AXIS DRIVES CANCER STEMNESS AND GROWTH

Sagar R. Shah, MS, PhD, Johns Hopkins University School of Medicine and **Alfredo Quinones-Hinojosa, MD,** Mayo Clinic, Florida

Malignant neoplasms exhibit uninhibited and dysregulated growth coupled with acquisition of stem-like properties that are integral to the development and progression of disease. Hence, it is imperative to identify the transcriptional drivers of cancer stemness. Here, we demonstrate a critical role of Brachyury, an embryonic transcriptional factor, in regulating stemness in cancer by activating YAP, a key regulator of tissue growth and homeostasis. We found that brachyury-based regulation of YAP can occur through direct transcriptional or post-transcriptional mechanisms leading to enhanced YAP-dependent oncogenic activity in various cancers where it correlates with tumor aggressiveness. This regulatory mechanism can shed further light on phenotypic plasticity in various cancers and inform new directions for treatment of chordoma and more common aggressive cancers.

11:30 – 11:40

THE PREVENTABLE SHUNT REVISION RATE - A MULTICENTER ANALYSIS

Paul Klimo Jr., MD, MPH, Semmes Murphey

Introduction: Several metrics have been proposed to gauge quality in shunt surgery. In July 2016 we introduced the Preventable Shunt Revision Rate (PSRR) in an attempt to identify shunt revision operations that were felt to be due to potentially preventable causes. We reported the PSRR at our institution to be 33%. We then expanded our efforts to determine the PSRR at other pediatric institutions.

Methods: All institutions were asked to review at least 2 years of shunt operations (de novo or revision surgery) and record specific demographic and procedural information per index surgery. There were two outcomes. The first was the need for further shunt surgery within 90 days of the index procedure (90-day revision rate or "early revision"). The second calculated rate was the PSRR, "Preventable" was defined as inaccurate proximal or distal catheter placement, infection or wound breakdown, or inadequately secured or assembled shunt apparatus. In addition to updating our own PSRR, 6 other institutions provided their overall 90-day shunt revision rate, PSRR, and reasons for failure.

Results: In addition to our own institution, 6 other pediatric neurosurgical groups from the United States (n=5), and Canada (n=1) provided data for this study. Data collection time periods were 2-years for 5 institutions, 3-years for one and 6.75-years for ours. Total number of revisions performed within 90 days ranged from 11.7% to 20.4% (16.9% overall). Among these institutions, the PSRR ranged from 5% to 34.5% (23.1% overall). Within the preventable malfunction group infection was the most common preventable cause (45.1%), followed by malposition of the proximal catheter (32.6%), malposition of the distal catheter (10.9%), and wound breakdown (10.3%).

Conclusions: Although the range of 90-day revision rates across institutions was fairly narrow, the range of PSRRs provided was quite broad. This represents an opportunity to find ways to reduce early shunt failures. As a quality metric, the strength of the PSRR lies in its high specificity, but may lack acceptable sensitivity**.**

11:40 – 11:50

LUMBAR FUSION VERSUS LAMINECTOMY FOR SPONDYLOLISTHESIS: READMISSION, REOPERATION, AND PATIENT REPORTED OUTCOMES FROM THE QOD REGISTRY

Erica F. Bisson, MD, MPH[2]; Panagiotis Kerezoudis, MD[3]; Steven Glassman, MD[4]; Kevin Foley, MD[5]; Jonathan Slotkin, MD[6]; Eric Potts, MD[7]; Mark Shaffrey, MD[8]; John Knightly, MD[10]; Paul Park, MD[11]; Kai-Ming Fu, MD[12], PhD; Silky Chotai, MD[13]; Andrew K. Chan, MD[1]; Michael Virk, MD[1], PhD; Mohamad Bydon, MD[3]; Anthony L. Asher, MD[9]; Praveen V. Mummaneni, MD[1]

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10. Atlantic Neurosurgical specialists, Morristown
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12. Department of Neurologic Surgery, Weill Cornell Medical
13. Department of Orthopedic Surgery, Vanderbilt University

Objective: Patient reported outcomes (PROs) play a pivotal role in defining the value of surgical interventions for spinal disease. The concept of minimum clinically important difference (MCID) is considered the new standard for determining the effectiveness of a given treatment and describing patient satisfaction in response to that treatment. Herein, we sought to determine the MCID associated with surgical treatment for lumbar spondylolisthesis.

Methods: We queried the Quality Outcomes Database registry from July 2014 through December 2015 for patients undergoing posterior lumbar surgery for grade I degenerative spondylolisthesis. Recorded patient reported outcomes included Oswestry Disability Index (ODI), EQ-5D, numeric rating scale (NRS)-leg pain and -back pain. Anchor-based and distribution-based methods were used to calculate the MCID for each PRO.

Results: A total of 437 patients from 11 participating sites were included in the analysis. Change in functional outcomes scores between baseline and 1-year were 23.7 ± 17.3 points for ODI, 0.24 ± 0.23 for EQ-5D, 4.1 ± 3.5 for NRS-LP, and 3.7 ± 3.2 for NRS-BP. The different calculation methods generated a range of MCID values for each PRO: 3.3 to 26.6 points for ODI, 0.04 to 0.3 points for EQ-5D, 0.6 to 4.6 points for NRS-leg pain and 0.5

to 4.2 points for NRS-back pain. The MDC approach appeared to be the most appropriate for calculating MCID because it provided a threshold greater than the measurement error and was closest to the average change difference between the satisfied and not satisfied patients. On subgroup analysis, the MCID thresholds for laminectomy alone patients were comparable to those undergoing arthrodesis as well as the entire cohort.

Conclusions: The MCID for PROs is highly variable based on calculation technique. The MDC seems to be a statistically and clinically sound method for defining the appropriate MCID value for patients with grade I degenerative lumbar spondylolisthesis. Based on this method, the MCID values are 14.3 points for ODI, 0.2 points for EQ-5D, 1.7 points for leg pain, and 1.6 points for back pain.

11:50 – 11:55

USE OF OMENTAL FLAP IN EN-BLOC SACRECTOMIES DECREASES INTRA-ABDOMINAL PRESSURE AND BLOOD LOSS

Zoe Zhang, MD; Nguyen Hoang, MD; Ian Valerio, MD; Ehud Mendel, MD MBA

Introduction: En-bloc sacrectomy is the treatment of choice for rare tumors such as sacral chordomas and chondrosarcomas. These tumors are radio- and chemo-resistant, thus, wide surgical resection provides best local control and prevention of recurrence. These surgeries are often staged radical procedures that result in extensive blood loss and large defects requiring sacral reconstruction. While pedicled vertical rectus abdominis myocutaneous (VRAM) or rectus-only muscle flaps are often utilized in many sacral defect reconstructions, these flaps may be too bulky. Furthermore, when placed in the abdominal cavity in preparation for the pull-through reconstruction, the flap can cause elevation of intra-abdominal pressures leading to higher rates of blood loss during the posterior resection. We posit the use of omental flaps as an adjunctive choice in certain sacral reconstructions.

Methodology: Omental flaps have a long pedicle via the gastroepiploic artery and vein with a rich blood supply. When harvested, they cover a large surface area and also have angiogenic and immunologic properties. This intrinsic flap adds no additional intra-abdominal bulk and is tunneled posteriorly and adapted to certain sacral defects.

Results: The use of an omental flap in combination with local advancement flaps allow for wide coverage that can obliterate small dead spaces and form a great immunological barrier

without the necessity of a VRAM harvest. This decreases surgical time, intra-abdominal pressures, blood loss and incidence of secondary hernia rates.

Conclusions: En-bloc sacrectomy is a rare but invasive procedure associated with blood loss of 20-60 Liters. Even small decreases in transfusion can protect the patient from allergic reactions, acute immune hemolytic reactions, blood-borne infections including post-operative infections, transfusion related lung injuries, and pulmonary edema. Omental flaps have been used historically for reconstructions as distant as the thoracic cavity. Their flexibility makes for a good adjunct in reconstruction techniques of the pelvis.

11:55 – 12:00

TO FUSE OR NOT TO FUSE? READMISSION, REOPERATION, AND PATIENT REPORTED OUTCOMES AFTER SURGERY FOR GRADE 1 LUMBAR SPONDYLOLISTHESIS IN 332 PATIENTS FROM THE PROSPECTIVE QUALITY OUTCOMES DATABASE

Andrew K. Chan MD[1], Erica F. Bisson MD[2], MPH, Mohamad Bydon MD[3], Steven D. Glassman MD[4], Kevin T. Foley MD[5], Eric A. Potts MD[6], Christopher I. Shaffrey MD[7], Mark E. Shaffrey MD[7], Domagoj Coric MD[8], John J. Knightly MD[9], Paul Park MD[10], Kai-Ming Fu MD, PhD[11], Jonathan R. Slotkin MD[12], Anthony L. Asher MD[8], Michael S. Virk MD, PhD[1], Panagiotis Kerezoudis MD[3], Silky Chotai MD[13], Anthony M. DiGiorgio DO[1], Regis W. Haid MD[13], and Praveen V. Mummaneni MD[1]

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7. University of Virginia
8. Neuroscience Institute, Carolinas Healthcare System and Carolina Neurosurgery & Spine Associates
9. Atlantic Neurosurgical Specialists
10. University of Michigan
11. Weill Cornell Medical Center
12. Geisinger Health System
13. Atlanta Brain and Spine Care

Introduction: The Quality Outcomes Database (QOD) is a prospective longitudinal registry created to measure the quality of spinal surgery. In light of the differing findings of two recent randomized clinical trials, this registry can offer "real world" insights into the

utility of fusion in addition to decompressive surgery for degenerative lumbar spondylolisthesis (DLS). Using the QOD, we investigated the hypothesis that 12-month outcomes differ for patients undergoing fusion and those undergoing laminectomy alone for grade 1 DLS.

Methodology: Data from eleven top-enrolling sites was analyzed and we found 332 patients undergoing single-level surgery for grade 1 DLS. Baseline, 3-month, and 12-month follow-up data were collected and compared including baseline characteristics, readmission rates, reoperation rates, and patient reported outcomes (Oswestry Disability Index (ODI), back and leg pain Numeric Rating Scale (NRS), and EuroQol-5 Dimensions Questionnaire (EQ-5D).

Results: 278 (83.7%) patients underwent fusion with the remaining 54 (16.3%) undergoing decompression alone. The fusion cohort was younger (59.7 vs. 66.8 years, $p<0.001$), had higher mean BMI (31.0 vs. 28.2, $p=0.001$), and a greater proportion of patients presenting with back pain (85.3% vs. 53.7%, $p<0.001$). From 3 to 12 months following index surgery, the decompression alone cohort had a significantly higher proportion of patients requiring reoperation (7.4% vs. 2.2%, $p=0.04$). Two decompression only patients had a second decompression surgery and two underwent subsequent lumbar fusion. There were no significant differences for reoperation within 30 days, or readmission within 30 or 90 days. At 12 months, both cohorts improved significantly with regards to ODI, NRS back and leg pain, and EQ-5D ($p<0.001$, all comparisons). There was a trend toward greater ODI improvement in the fusion cohort at 12 months ($p=0.061$).

Conclusions: Surgery for grade 1 DLS—regardless of treatment strategy—was associated with significant improvements in disability, back and leg pain, and quality of life at 12 months. At 12 months, the decompression alone group had a significantly greater proportion of patients requiring reoperation. Longer-term study will assess the durability of either surgical strategy.

12:00 – 12:05

Reconstruction Of The Pelvis And Lumbar-Pelvic Junction Using Vascularized Autologous Bone Grafts After En Bloc Resection Of Primary Sacral Malignancies

Ahmed Mohyeldin MD, PhD, Zoe Zhang, MD, Ian Valerio, MD and Ehud Mendel, MD, MBA, 1Department of Neurological Surgery, The Ohio State University Wexner Medical Center, The James Cancer Hospital and Solove Research Institute

Introduction: Primary pelvic sarcomas remain challenging and complex surgical problems with significant potential for postoperative impairment of ambulation, as well as bowel, bladder, and sexual function. En bloc resection with negative tumor margins represents the best chance of control or cure as current adjuvant therapies remain ineffective. Tumor involvement of the sacrum with extension to the greater sciatic notch and ipsilateral ilium requires an external hemipelvectomy and sagittal sacrectomy with sacrifice of the lower extremity to achieve en bloc resection, followed by lumbar-pelvic reconstruction.

Methodology: Here we present our case series of iliosacral primary malignancies to illustrate a novel lumbarpelvic reconstruction technique, in which vascularized soft tissue and 2 vascularized bone grafts were harvested from the amputated lower extremity and transferred to the pelvis as composite flaps to restore pelvic ring integrity, augment lumbar-pelvic fusion, and close the soft-tissue defect.

Results: The biomechanical dynamics of this unique construct and early outcome experience from our institution are discussed.

Conclusion: We report on the use of a novel lumbarpelvic reconstruction technique in an early cases series of patients with patient with iliosacral primary malignancies, resulting in good functional outcome. This technique involved using a composite flap composed of vascularized soft tissue and 2 vascularized bone grafts harvested from the amputated lower extremity and transferred to the pelvis to restore pelvic ring integrity, augment lumbar-pelvic fusion, and close the soft tissue defect.

12:05 – 12:15 | Presidential Introduction

Daniel Fults III, MD, University of Utah

12:15 – 12:45 | Presidential Address

QUALITY, MINDFULNESS AND THE NEUROSURGEON

William T. Couldwell, MD, PhD, University of Utah

SPECIAL SESSION: ACADEMY AWARD WINNER & HONORABLE MENTION

7:35 – 7:45

DEVELOPMENTAL PHOSPHOPROTEOMICS IDENTIFIES CK2 AS A DRIVER OF HEDGEHOG SIGNAL TRANSDUCTION AND A THERAPEUTIC TARGET IN MEDULLOBLASTOMA

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5. Department of Biomedical Sciences, University of Padua, and CNR, Neuroscience Institute
6. Department of Neurology and Neurological Sciences, Oregon Health & Science University
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A major hurdle to targeted cancer therapy is rapid drug resistance due to the variability in mutations driving tumor growth. For example, medulloblastoma, the most common malignant pediatric brain tumor, develops from granule neuron precursors (GNPs) that are driven to proliferate due to retained over-active hedgehog pathway signaling. However, hedgehog inhibitors have been limited by both a priori and rapidly acquired mutations at or downstream of the drug target Smoothened. To discover drug targets less susceptible to rapid resistance, we evaluate changes in protein phosphorylation during GNP development through quantitative phosphoproteomics and identified Casein Kinase 2 (CK2) as a driver of multiple phosphorylation events which are critical to hedgehog-driven GNP proliferation. Not only does CK2 affect the Hedgehog signaling pathway directly, it also has several other substrates that are important to medulloblastoma growth and survival. Mice with smoothened-inhibitor resistant medulloblastomas had stable tumor regression when treated with CK2 inhibitors, suggesting a promising new therapeutic approach.

7:45 – 7:55

EXOME SEQUENCING UNCOVERS NOVEL GENETIC DETERMINANTS OF HUMAN CONGENITAL HYDROCEPHALUS

Charuta Furey, BS[1], Andrew Timberlake, PhD[1], Jungmin Choi, PhD[1], Xue Zeng, PhD[1], Daniel Duran[1], Mora, MD[1], Carol Nelson-Williams[1], MS[1], Arjun Khanna[2], Bermans J. Iskandar, MD[3], Yasar Bayri, MD[4], Yener Sahin, MD[4], William Butler, MD[2], Greg Heuer, MD[5], Charles Duncan, MD[1], Michael DiLuna, MD[1], Murat Gunel, MD[1], Richard P. Lifton, MD, PhD[1], and **Kristopher T. Kahle, MD, PhD**

1. Yale School of Medicine
2. Massachusetts General Hospital
3. University of Wisconsin School of Medicine
4. Marmara University, Turkey
5. Children's Hospital of Philadelphia

Introduction: Congenital hydrocephalus (CH) is the primary (idiopathic) accumulation of Cerebrospinal fluid (CSF) that results in pathologic expansion of the cerebral ventricles. CH affects ~1/1000 newborns, is empirically treated with unacceptably morbid surgical CSF Shunting, and is poorly understood. It is well established that CH has a strong genetic component; however, for the vast majority of cases, including sporadic forms, the underlying cause is unknown. Understanding critical genetic drivers underlying human CH Holds promise for the development of targeted therapies. Traditional genetic approaches have been limited in their ability to identify causative CH genes because kindreds are rare, small in size, or appear to have sporadic inheritance patterns. Whole exome sequencing (WES) can overcome these barriers to gene discovery.

Methods: We performed WES on DNA isolated from 125 patient-parent trios (affected patient and unaffected parents) and an additional 52 probands for a total of 177 CH patients with non-L1CAM, primary CH. Exome-sequencing data from these 447 individuals was then analyzed to identify rare, *de novo*, and transmitted mutations contributing to CH, and candidate mutations were subsequently confirmed by Sanger sequencing. We then utilized CRISPR/Cas9 gene editing in *Xenopus tropicalis*, coupled with quantitative Optical Coherence Tomography, to create "frog avatars" of human patients and assess the Functional impact of novel, discovered CH-causing mutations in vivo.

Results: Exome sequencing identified multiple novel and recurrent de novo and transmitted loss-of function gene mutations enriched in ciliogenesis and neurodevelopmental pathways. Binomial and case-control analyses confirmed exome-wide statistical significance of candidate genes, and functional modeling in Xenopus established gene causality by recapitulating the patient phenotype.

Conclusions: Our results demonstrate the utility of WES for discovering genetic determinants of CH; identify at least at ***four*** novel *bona fide non-syndromic* CH-causing genes; and implicate previously unrecognized cellular processes in the pathogenesis of CH. Our data support a paradigm that CH is heterogeneous, with clinical-radiographic CH subtypes arising from distinct genetic alterations that commonly impact ependymal cilia structure and function and subependymal neurogenesis. These findings provide new opportunities for improved prognostic assessment and non-invasive therapies.

ABSTRACT SESSION: TUMOR

7:55– 8:05

DUAL ROLE OF MITOCHONDRIA IN PRODUCING MELATONIN AND DRIVING GPCR SIGNALING TO BLOCK CYTOCHROME C RELEASE AND MODULATION OF CEREBRAL ISCHEMIC INJURY

Yalikun Suofu and **Robert M. Friedlander, MD,** Neuroapoptosis Laboratory, Department of Neurological Surgery, University of Pittsburgh

G-protein coupled receptors (GPCRs) are classically characterized as cell surface receptors transmitting extracellular signals into cells. Here we show that central components of a GPCR signaling system constituted of the melatonin type 1 receptor (MT1), its associated G protein, and β-arrestins are on and within neuronal mitochondria. We discovered that the ligand, melatonin, is exclusively synthetized in the mitochondrial matrix and activates the mitochondrial MT1 signal transduction pathway inhibiting stress mediated cytochrome c release and caspase activation. These findings coupled to our observation that mitochondrial MT1 overexpression reduces ischemic brain injury in mice delineate a novel mitochondrial GPCR mechanism contributing to the neuroprotective action of melatonin. We propose a new term "automitocrine", analogous to autocrine when a similar phenomenon occurs at the cellular level, to describe this unexpected intracellular organelle ligand-receptor pathway that opens a new research avenue investigating mitochondrial GPCR biology, with particular importance to both the ageing process of well as acute (i.e. cerebral ischemia, TBI) and chronic (i.e. ALS, Huntington's disease) neurodegenerative diseases.

8:05– 8:15

Comparing Costs Of Microsurgical Resection And Stereotactic Radiosurgery For Vestibular Schwannoma Management

Douglas Kondziolka, MD, Zane Schnurman, BA, John G. Golfinos, MD, David R. Friedmann, MD, J. Thomas Roland Jr., MD

Object: Given rising scrutiny of healthcare expenditures, understanding intervention costs is increasingly important. This study aimed to compare and characterize costs for vestibular schwannoma management with microsurgery and radiosurgery to inform practice decisions and appraise cost reduction strategies.

Methods: Hospital accounting data, Medicare rates, and medical records were used to determine index costs (costs from arrival through discharge for initial intervention) and follow-up costs (through 36 months) for 317 patients with unilateral vestibular schwannomas undergoing initial intervention between June 2011 and December 2015. A retrospective matched cohort based on tumor size with 176 patients (88 undergoing each intervention) was created to objectively compare costs between microsurgery and radiosurgery. The full sample of 203 resection patients and 114 radiosurgery patients was used to evaluate a broad range of outcomes and identify contributors to cost within each intervention group.

Results: Within the matched cohort, average index costs were significantly higher for microsurgery ($27,524) than radiosurgery ($10,696), with higher cost volatility. Additionally, microsurgery had higher average follow-up costs ($417 per month of follow-up) compared to radiosurgery ($138 per month of follow-up), largely due to costs incurred in the first months after resection. A major contributor to total cost and cost variability for both resection and radiosurgery was the need for additional interventions in the follow-up period, required due to complications or persistent functional deficits. While tumor size was not associated with increased costs for radiosurgery, linear regression analysis demonstrated that each centimeter increase in tumor maximum diameter resulted in an estimated increase of $12,824 (95% CI $8,899 – $16,745) for microsurgery patients ($p < 0.001$, $R2 = .17$). There were no cost differences associated with the proportion of inpatient days in the ICU or with surgical approach for resection patients.

Conclusions: This study is a comprehensive economic assessment comparing vestibular schwannoma management with microsurgery and radiosurgery. Both index and follow-up costs are significantly higher and with higher cost volatility when managed with resection compared to radiosurgery. Larger tumors were associated with increased resection costs, highlighting the incremental costs associated with observation as initial management.

8:15– 8:25

TUMOR-ASSOCIATED NEUTROPHILS PROMOTE GLIOBLASTOMA GROWTH VIA OSTEOPONTIN IN A TARGETABLE MANNER

Garima Yagnik, PhD, Alan Nguyen, BS, Soeren Mueller, PhD, Beatriz Alvarado, MA, Aaron Diaz, PhD, **Manish K. Aghi, MD PhD**, University of California San Francisco

Introduction: While tumor-associated macrophages have been shown to exert pro-tumoral effects in glioblastoma, there is limited data on the function of tumor-associated neutrophils (TANs), particularly given their role in systemic inflammation.

Methods: To better characterize TANs, our lab isolated CD11b+ CD66b+ CD15+ TANs from patient gliomas (n=16) by FACS and performed single cell sequencing and functional assays examining neutrophil recruitment and downstream effects.

Results: TANs represented 1.4% (range=0.04-9.7%) of glioma cell suspensions. TANs increased as prognosis worsened: in high- vs. low-grade gliomas (2.2% vs. 0.3%, P=0.09), bevacizumab-resistant vs. naive GBMs (9.7% vs. 0.9%), and wildtype IDH1-R132 vs. mutant H132 variants (2.2% vs. 0.6%). Cultured bevacizumab-resistant and IDH1-R132 cells exhibit increased neutrophil chemotactic attraction ($P<0.05$) and increased levels of neutrophil chemoattractant leukotriene B4 ($P<0.01$) compared to bevacizumab-responsive and mutant IDH1-H132. TCGA analysis revealed higher levels of neutrophil marker myeloperoxidase in IDH1 wildtype vs. mutant GBMs ($P<5x10-6$). Principal component analysis of TAN single cell expression data elucidated novel candidate genes defining anti-tumoral N1 vs. pro-tumoral N2 subtypes: CCL20, SPARCL1, AKT2, FGF1, RAP2B, HMOX1, SPP1, FTL, PDGFD, and PDGFA. Reciprocal qPCRs of these genes in tumor cells and neutrophils cultured in conditioned media (CM) revealed osteopontin (SPP1) as a mediator of TAN-tumor crosstalk and a strong N2 protumoral candidate gene. Circulating neutrophils expressed no detectable SPP1, while TANs showed a three-fold increase in response to tumor cell CM. Tumor cells cultured in neutrophil CM demonstrated

increased proliferation, which was eliminated with an osteopontin blocking antibody (P<0.01).

Conclusions: Through reciprocal cross-talk, glioma cells recruit circulating neutrophils into tumors and convert them into a N2 pro-tumoral subtype, which in turn promote glioma cell proliferation and are associated with poor prognosis glioma types. Single cell sequencing identified genes defining potential N1/N2 subtypes, with osteopontin emerging as a potential therapeutic target to inhibit the pro-tumoral effects of TANs.

8:25– 8:35

TUBERCULUM SELLA MENINGIOMAS: GRADING SCALE TO ASSESS SURGICAL OUTCOMES USING THE TRANSCRANIAL VS TRANSSPHENOIDAL APPROACH

Stephen T. Magill MD, PhD[1], Ramin A. Morshed, MD[1], Calixto-Hope Lucas, [BA1], Manish K. Aghi, MD, PhD[1], Philip V. Theodosopoulos, MD[1], Mitchel S. Berger, MD[1], Oreste de Divitis, MD2, Domenico Solari, MD2, Paolo Cappabianca, MD2, Luigi M. Cavallo, MD, PhD2, **Michael W. McDermott, MD[1]**

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Introduction: Tuberculum sella meningiomas (TSM) are surgically challenging tumors. Whether a transcranial (TC) or endoscopic transphenoidal approach (TS) is best for resecting these tumors remains unknown. Furthermore, there are limited pre-operative criteria to assist surgeons in selecting a TC or TS approach.

Methods: A retrospective review was performed at two academic centers comparing TC and TS approaches with respect to vision, extent of resection (EOR), recurrence and complications. We propose a pre-operative tumor grading scale that scores tumor size (1-2), optic canal invasion (0-2) and arterial encasement (0-2), and test its association with outcomes using logistic regression.

Results: One hundred thirty-two patients underwent TSM resection. Median follow-up was 60.5 months. Eighty-seven (67%) cases were approached TC, and 45 (33%) TS. Tumors approached TC had higher tumor score ($p = 0.006$), canal score ($p < 0.0001$) and total score ($p = 0.0024$) compared to TS. EOR was 66% gross-total, 21% near-total (95-99%), and 13% sub-total (<95%). Lower canal ($p = 0.0015$), score was associated with gross total resection. Preoperative visual deficits were present in 67%. Vision improved in 48%, stayed the same in 34%, declined in 9%, and was unknown in 9%. Higher tumor score (p =

0.0129) was associated with worsened vision post-operatively. Complications occurred in 19 (14%) of patients, including CSF leak (5%), infection (5%) and other (6%). There was no difference in total complication rates between TC and TS approaches; however, TS had more CSF leaks (p = 0.0280). Recurrence rate was 9.8%. Multivariate analysis found TS approach (p = 0.0006) and lower canal score (p = 0.001) were associated with increased likelihood of gross total resection, and post-operative visual worsening (p = 0.0022) was associated with tumor recurrence.

Conclusions: TSM can be resected using either a TC or TS approach with low morbidity and good visual outcomes. The proposed grading scale provides a pre-operative method to evaluate TSMs and can guide surgical approach. Higher scores were associated with worsened visual outcomes and sub-total resection, regardless of approach.

8:35– 8:45

5-AMINOLEVULINIC ACID GUIDED SAMPLING OF GLIOBLASTOMA MICROENVIRONMENTS IDENTIFIES PRO-SURVIVAL SIGNALING AT INFILTRATIVE MARGINS

James L. Ross, MD, PhD[1], Lee Cooper, PhD[1], David Gutman, MD[1], PhD, Alexandros Bouras, MD[2], Milota Kaluzova, PhD[1], Daniel J. Brat, MD, PhD[1], **Constantinos G. Hadjipanayis, MD, PhD[2]**

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Introduction: Glioblastoma (GBM) contains diverse microenvironments with uneven distributions of oncogenic alterations and signaling networks. Protein expression levels, including those of potential therapeutic targets, vary across environments and optimal treatments will require understanding differential expression patterns. The diffusely infiltrative properties of GBM result in residual tumor at neurosurgical resection margins, representing the source of relapse in nearly all cases and suggesting that therapeutic efforts should be focused there. To identify signaling networks and potential druggable targets across tumor microenvironments (TMEs), we utilized 5-ALA fluorescence-guided surgery (FGS) and sampling, followed by proteomic analysis of specific TMEs.

Methodology: Reverse phase protein array (RPPA) was performed on 205 proteins isolated from the tumor margin, tumor bulk, and perinecrotic regions of 13 previously untreated, clinically-annotated and genetically-defined high grade gliomas. Differential protein and pathway signatures were established by analysis of variance, hierarchical

clustering, linear discrimination analysis, western blotting, and immunohistochemistry followed by validation using comparable TCGA RPPA datasets.

Results: We identified 37 proteins differentially expressed across high-grade glioma TMEs and established regional expression signatures, demonstrating that tumor margins were characterized by pro-survival and anti-apoptotic proteins, whereas perinecrotic regions were enriched for pro-coagulant and DNA damage response proteins.

Conclusions: In both our patient cohort and TCGA cases, the data suggest that TMEs possess distinct protein expression profiles that are biologically and therapeutically relevant.

8:45– 8:55

MAN'S BEST FRIEND: OVEREXPRESSION OF MAMLD1 IN HUMAN AND DOG CUSHING DISEASE

Andrew Wang, BS[1], Scott Newman, PhD[2], Marianna A. Tryfonidou, PhD[3], Bjorn P. Meiji, PhD[3], Adriana G. Ioachimescu, MD, PhD[4], Stewart G. Neill, MD[4], Michael R. Rossi, PhD[4], **Nelson M. Oyesiku, MD,PhD[4]**

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2. St. Jude Children's Research Hospital
3. University of Utrecht, Netherlands
4. Emory University School of Medicine

Cushing disease is a secondary hypercortisalism caused by adrenocorticotropic (ACTH) secreting pituitary adenomas. Similar to humans, dogs, also suffer from this disorder. In an effort to map common genomic features of Cushing disease between of humans and beagles, we performed whole transcriptome RNA-Seq. Comparing Cushing pituitary adenomas to normal pituitary from humans and dogs, we identified 4 genes (MAMLD1, MNX1, RASEF, TBX19) to be significantly ($P<0.05$) overexpressed in both species. Immunohistochemistry of 31 additional human pituitary adenomas revealed MAMLD1 to be strongly positively expressed in the nucleus of ACTH secreting tumor cells, but absent in healthy pituitary tissues. Although our cohort is relatively small, this data presents new insights into the shared genetic profile of human and beagle Cushing pituitary adenomas and provides a rationale for potential use of a beagle model in development of precision therapeutics. Although other genomic studies have been recently conducted in humans with Cushing disease, our results provide the first insights into the comparative genomic

characterization of human and dog pituitary adenoma with respect to MAMLD1 overexpression.

8:55– 9:05

USING FOCAL THERAPIES TO KINDLE A SYSTEMIC ANTITUMOR IMMUNE RESPONSE

Michael Lim MD, Dimitrios Mathios MD, Jennifer Kim MD, Christopher Jackson MD, Tomas Garzon-Muvdi MD, Zineb Belcaid MD, Eileen Kim BS, Betty Tyler BS, Henry Brem MD, Drew Pardoll MD, PhD

With the advent of FDA approval of immunotherapy agents for multiple tumor types, checkpoint inhibitors are being actively studied in GBM. With the disappointing results of a recent anti-PD-1 trial on GBM, combination strategies are currently being explored. We studied the combination of focused radiation or localized chemotherapy with checkpoint inhibitors in a preclinical GBM model. We found that the combination approaches resulted in improved survival and increased the number of infiltrating effector immune cells. Conversely, systemic therapies appear to hinder an anti-tumor immune response and caused lymphopenia. Hence we believe that localized therapies can augment immunotherapy strategies.

9:05– 9:15

INDUCED PLURIPOTENT STEM CELL (IPSC)-DELIVERY OF PRO-APOPTOTIC GENES FOR HIGH GRADE GLIOMAS.

Isabelle M Germano, MD, Mount Sinai Beth Israel

Introduction: The generation of human induced pluripotent stem cells (hiPSC) from somatic cells enables the possibility to provide patient-specific hiPSC for cell-based therapy, drug discovery, and other translational scopes. The risk of genomic modification when iPSC are derived using viral transgenes and risk of teratoma formation if undifferentiated cells are engrafted hinders their use in clinical trials.

Methods: hiPSC were generated from adult human dermal fibroblasts reprogrammed using the mRNA reprogramming technique with microRNA booster. "Footprint free" iPSC were derived using differentiation and cell cultures techniques, as we previously reported. Fluorescent cell sorting analysis was used to purify astrocytic differentiation,

immunocytochemistry to characterize astrocytes, qRT-PCR experiments to quantify Aldolase c (ALDOC) and glutamate transporter 1 (GLT1), glutamate assay for physiological characterization. iPSC engineering prior to differentiation included insertion of the pro-apopoptotic gene mda-7. Migration was assessed in vitro and in vivo after transplant in the mouse brain. U87 cells were used to confirm pro-apoptotic activity.

Results: Our results show the feasibility of differentiating astrocytes from "footprint-free" iPSC, without requiring viral induction. The purification techniques used, allow obtaining a pure astrocytic population. This was confirmed by lack of teratoma formation after engraftment in the brain. iPSC-derived astrocytes had anatomical and physiological features of fully differentiated astrocytes, maintain homing characteristics typical of stem cells in vitro and in vivo. Astrocytes were obtained in sufficient numbers, aliquoted, frozen, thawed, and used when needed. Finally, our data confirm the ability to insert a pro-apoptotic gene prior to differentiation and its pro-apoptotic activity on high grade gliomas.

Conclusions: "Footprint-free" hiPSC-derived astrocytes represent a new potential source for cell-based therapy vectors for treatment of high-grade human gliomas. Since they can be induced from patients' specific cells, and do not require viral vectors for induction, they can be considered for clinical trials. Additionally, they can be used for drug discovery and modeling of neurological diseases. Current efforts to overcome technical challenges, including reducing labor and cost, will expedite their integration to the clinical setting.

9:15– 9:30 | Break

9:30– 9:40

PITUITARY CARCINOMA: OUTCOME OF MULTIMODALITY TREATMENT AND CORRELATION WITH BIOMARKERS

Ian E. McCutcheon, MD, Maxwell Tran, BS, Sherise D. Ferguson, MD,
Gregory N. Fuller, MD, PhD, University of Texas M D Anderson Cancer Center

Introduction: Pituitary carcinoma is a rare neuroendocrine tumor defined when a pituitary adenoma becomes metastatic. Prognosis after metastasis is poor, with reported overall survival of 3 years. Although no standard treatment exists, surgery, radiotherapy, and chemotherapy are generally used. We present the largest series of patients with

pituitary carcinoma from one institution, reflecting multi-modality management of this condition.

Methodology: We analyzed presentation, interventions, outcomes, and clinicopathological correlates predicting survival in patients with pituitary carcinoma (n=18) treated at our institution from 1994-2016. MIB-1 index, tumor hormone status, and metastasis location were analyzed for predicting aggressive tumor behavior and poor survival. Statistical analysis was done using SPSS and included univariate and bivariate analyses.

Results: Median age of onset was 37 years and mean MIB-1 of primary tumor (MIB-1-P) was 16.1% (range, 7-40%) with MIB-1 usually higher in metastasis than primary. Mean time to metastasis was 7.1 years from adenoma discovery. Treatment regimens were varied and complex, but most patients received multimodality therapy with an average of 1.2 treatments/year, consisting of transsphenoidal surgeries, craniotomies, and fractionated and stereotactic radiotherapy early on; and later adding chemotherapy (temozolomide, n=14) and in recent years, targeted therapies. Treatment in all modalities increased after metastasis to 1.8 treatments/year. Mean overall survival was 10.3 years, and 2.9 years after metastasis. Survival at 5 years decreased from 72% overall to 28% after metastasis. Hormone production and location of metastasis were inconclusive in predicting survival and/or tumor aggressiveness; MIB-1-P ≥ 20% had high sensitivity and clinical utility for detecting aggressive tumors.

Conclusion: Although these tumors can show an indolent clinical course, they pose major challenges. MIB-1-P ≥ 20% predicts an aggressive clinical course, and indicates more frequent monitoring. Tumor control (sellar/parasellar and metastatic) lengthens overall survival, and management generally entails a multidisciplinary effort including transsphenoidal surgery (which is never curative), multiple craniotomies, radiotherapy, and temozolomide, yielding improvement over historical results. More effectively targeted therapies, and improvements in biomarkers predicting later metastasis, are keys to improving survival.

9:40– 9:50

THE GEISINGER MYCODE PROJECT: A RESOURCE FOR PRECISION MEDICINE AND NEUROGENOMICS

Atom Sarkar MD, PhD, Neil A Martin MD, David J Carey PhD

Introduction: The realization of Personalized/Precision Medicine will require novel tools and approaches, building on the foundations of molecular biology, genetics, and other fields. To this end, Geisinger Health System initiated the MyCode project in 2007 to create a repository of DNA samples linkable to individual participant's longitudinal electronic health records for broad research use.

Methods: Patient input into MyCode was obtained from participant focus groups. Participation in MyCode is based on opt in informed consent and allows recontact, which facilitates collection of data not in the electronic health record. Through a collaboration with the Regeneron Genetics Center MyCode DNA samples undergo exome sequencing. Linking of exome variant and clinical data enables phenome first, e.g disease-specific, and gene-first approaches.

Results: MyCode has a consent rate of >85% with >150,000 current participants and an active enrollment of 3,000 patients per month. More than 92,000 MyCode samples have been used to generate exome sequence and other molecular data. Exome sequencing has identified more than 4 million unique genetic variants in the population, 98% of which are found at low frequency. Functional genetic variants have been linked to a range of clinical traits.

Conclusion: MyCode offers a unique resource for Personalized/Precision Medicine initiatives, including NeuroGenetics. By linking genetic data to electronic health records, associations between genetic and clinical states is possible. This is particularly crucial for neurologic/neurosurgical conditions, especially for afflictions that are rare, or complex and multi-modal.

9:50 – 10:00

A Phase I Clinical Trial Of Regulated Interleukin-12 Immunogene Therapy For Recurrent Glioblastoma

E. Antonio Chiocca, MD, PhD, Brigham and Women's Hospital, Francois Lebel, MD, ZIOPHARM Oncology, Inc, Rimas V Lukas, MD, Northwestern University, John S. Yu, MD, Cedars Sinai Medical Center

Recurrent GBM patients have a median overall survival (mOS) of 6-7 months. OS in patients who have failed temozolomide, bevacizumab or equivalent salvage chemotherapy, is ~3-5 months. New therapies are urgently needed. Ad-RTS-hIL-12 is a novel gene therapy expressing IL-12 under the control of an oral activator ligand, veledimex, via the RheoSwitch Therapeutic System® gene switch. Intratumoral administration of Ad-RTS-hIL-12 results in targeted tumor cytotoxicity and induction of systemic T cell memory. Ad-RTS-hIL-12 + veledimex is a treatment strategy to extend the IL-12 therapeutic window.

In a multicenter, Phase I dose escalation trial and expansion cohort of subjects with recurrent or progressive Grade III or IV glioma undergoing resection, Ad-RTS-hIL-12 + veledimex was well tolerated; toxicities were predictable and reversible upon discontinuing veledimex with a correlation between veledimex dose, Blood Brain Barrier penetration and drug related Adverse Events to assigned dose level. The most common adverse reactions were related to cytokine exposure in the form of fever, decrease in peripheral lymphocytes and platelets, and elevation of liver transaminases. Serum interleukin 12 levels and its downstream signal (interferon gamma) correlated with veledimex dose, indicating that the drug turned on the IL12 "switch" in the brain tumor.

Emerging biomarker data appear to show that serum CD8+/FOXP3 ratio might represents a putative predictor of response. Subjects treated with 20mg of veledimex had a median overall survivorship of 12.5 months. Interestingly, when patients were given only ≤10mg of dexamethasone during the first 15 days of treatment, overall survival was improved, possibly suggesting a negative effect of steroids on immunostimulation. Some patients who were thought to have progressed were re-operated on months later. Extensive inflammatory changes with little tumor residual were observed suggestive of inflammatory pseudoprogression, rather than tumor recurrence. The tolerability and encouraging survival observed to date warrant additional clinical studies of this immunogene therapy.

10:00– 10:10

INTRAOPERATIVE ASSESSMENT OF TUMOR AND RESECTION MARGINS DURING GLIOMA RESECTION BY DESORPTION ELECTROSPRAY IONIZATION MASS SPECTROMETRY

Aaron A. Cohen-Gadol, MD, MSc[1], Eyas M. Hattab, MD[2], Valentina Pirro, PhD[3], Clint M. Alfaro[3], R. Graham Cooks, BS, MS, PhD [3].

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Gliomas infiltrate into the surrounding healthy tissue. Microsurgical resection aims for maximal tumor resection while minimizing morbidity. Surgical margins are defined based on surgeons' experience, visual observation, and neuronavigation according to pre-operative MRI. Pathological assessment of surgical margins is rarely undertaken intraoperatively due to time constraints and an unreliability of suboptimal preparations. We developed a molecular-based diagnostic tool using desorption electrospray ionization (DESI) mass spectrometry for intraoperative assessment of surgical margins. DESI-MS allows analysis of unprocessed tissue (i.e. tissue smears and sections). It desorbs and ionizes molecules using a solvent as a projectile that hits the tissue, molecules that are soluble in the solvent are extracted in charged microdroplets and mass analyzed. The rapid examination of a tissue smear is completed in 2 min and can be performed directly inside the operating room by using a modified instrument that is self-assembled. The analysis preserves tissue morphology, allowing subsequent pathological evaluation and direct validation of the results. A mixture of organic solvents is used to detect membrane phospholipids, N-acetylaspartate (NAA) and 2-hydroxyglutarate (2HG). The pattern of lipids and the abundance of NAA are altered dynamically with the composition of the infiltrated tissue (i.e. white or grey matter) and the percentage of tumor cells, and therefore can identify presence of tumor and estimate the degree of tumor infiltration at tissue margins. 2HG is a downstream metabolite accumulating into IDH-mutant gliomas and therefore its detection can be used to assess the IDH mutation status of the tumor intraoperatively. Rapid analysis allows the examination of multiple tissue biopsies as tumor resection is executed, providing diagnostic feedback to guide surgical maneuvers. Direct molecular measurement of tissue pathology at surgical margins can be used in conjunction with neuronavigation to support surgical decision making. The results from the first 10 surgical cases show feasibility of the approach as intraoperative tool and good agreement

with histopathology in diagnosis. Highly-infiltrated tissue was found in the majority of the margins even in cases where postoperative MRI showed gross total tumor resection.

10:10 – 10:20

SINGLE-CELL TRANSCRIPTOME ANALYSIS REVEALS A GLIOMA STEM CELL-SPECIFIC CHROMATIN REMODELING COMPLEX ESSENTIAL FOR TUMOR PROPAGATION

Andrew S Venteicher MD PhD[1], Christine Hebert BS[2], Leah Escalante BS[2], Itay Tirosh PhD[3], Brian V Nahed MD[1], William T Curry MD[1], Daniel P Cahill MD PhD[1], Aviv Regev PhD[3], Mario Suva MD PhD[2]

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Introduction: Tumor evolution arises from the natural selection among individual tumor cells that accrue genetic and epigenetic changes, which govern malignant potential, immune evasion, and the ability to overcome surgery and chemoradiation. Thus, we hypothesized that applying single-cell transcriptome sequencing to human gliomas could reveal heterogeneity among tumor cell states. Identifying genes specifically expressed in essential subpopulations of tumor cells may expose previously unappreciated vulnerabilities in human glioma, which might represent targets for a new class of chemotherapeutic agents.

Methods: We prospectively consented patients with human gliomas for single-cell transcriptome sequencing at time of resection. Using gene expression analysis, we sought to identify different malignant cell subpopulations based on their differential gene expression and epigenetic cellular state. A specialized subset of tumor cells expressed a program highly related to stem/progenitor cells, and we identified a handful of specifically enriched genes in these tumor cells. One of these genes, a chromatin remodeling factor known to be expressed in normal neural stem/progenitor cells, was further characterized using a combination of genetic loss-of-function, biochemical, and proteomic approaches.

Results: Single cell analysis from human gliomas revealed a chromatin remodeling enzyme enriched in a specialized subset of cells that adopt a stem/progenitor-like expression program. Biophysical separations reveal that this factor participates in a large holoenzyme complex, and components of the holoenzyme were identified using mass spectrometry and proteomic analysis. Chromatin immunoprecipitation reveals that the complex regulates epigenetic cellular state by binding at promoter, enhancer and insulator sites. When this

factor is depleted, glioblastoma cells lose the ability to fully propagate in vitro and in intracranial xenograft models.

Conclusions: Our work (1) defines a new model for the architecture in primary brain tumors, (2) suggests a similar cell of origin and requirement for a stem cell-enriched chromatin remodeling complex shared in normal neurodevelopment and in glioma tumorigenesis, and (3) provides a framework for identifying new dependencies in essential subpopulations of glioma stem/progenitor-like cells that can be used to develop new classes of chemotherapeutic agents.

10:20 – 10:25

INITIATING CHEMORADIATION WITHIN 4 WEEKS OF INDEX CRANIOTOMY IS ASSOCIATED WITH SHORTER SURVIVAL IN HIGH-GRADE GLIOMA

Jay K. Nathan, MD, University of Michigan and Shawn L. Hervey-Jumper, MD, University of California, San Francisco

The Stupp protocol of post-resection external beam radiation therapy and concomitant temozolomide published in 2005 remains the standard of care for patients with newly-diagnosed glioblastoma, with expanded use in anaplastic astrocytoma. Particularly for patients with aggressive disease or significant functional impairment, conventional wisdom advocates earliest possible delivery of post-operative chemoradiation. However, the optimal interval between surgery and these adjuvant therapies, and its impact on survival, is unknown. To investigate this, de-identified claims from a large, private health insurance database of patients throughout the United States were queried to identify adults who underwent craniotomy for resection of a supratentorial neoplasm during the period 2005-2014 and began radiation and temozolomide within 13 weeks following their index operation. A total of 2,535 patients were assigned to groups based on interval from surgery to first radiation treatment of up to 4 weeks (1,098 patients), 4-6 weeks (1,019 patients), or 6-13 weeks (418 patients). There was significant regional variation in treatment schedule, though an overall trend during the study period toward the 4-6 week timeframe. Survival was calculated based on time from index craniotomy to death. Kaplan-Meier plot and multivariate Cox proportional hazard regression demonstrated a statistically significant association between earliest postoperative radiation and decreased survival (hazard ratio 1.31), along with increased age and male sex. These data challenge the premise that earlier delivery of post-operative chemoradiation maximizes its efficacy. Rather, beginning radiation treatment within 4 weeks of index craniotomy was associated with significantly

worse survival compared to initiation of treatment after 4-13 weeks. This is the largest population-based study to date regarding timing of Stupp protocol initiation.

	Hazard Ratio	**Confidence Interval**	***P*-value**
Age at craniotomy	1.031	1.026 – 1.036	< 0.0001
Female sex	0.837	0.742 – 0.944	0.0038
Postoperative radiation initiation			
0-4 weeks	1.310	1.152 – 1.491	< 0.0001
6-13 weeks	1.024	0.853 – 1.231	0.80
Race			
Black	1.027	0.783 – 1.346	0.84
Hispanic	0.854	0.653 – 1.116	0.25
Asian	1.002	0.810 – 1.239	0.99

ABSTRACT SESSION: GENERAL, PERIPHERAL NERVE & TRAUMA

10:25– 10:35

DIRECT EMPLOYER-PURCHASED DESTINATION CENTER OF EXCELLENCE SPINAL CARE: EXPERIENCE WITH WALMART, LOWE'S, MCKESSON, AND JETBLUE

Jonathan Slotkin MD, Sanjay Konakondla MD and Neil Martin MD

Introduction: Direct purchasing of bundled healthcare services by large employer-purchasers has become an important form of payment innovation. Traditional fee-for-service models have left payers facing significant unwarranted variation in care delivery and costs. Since 2015, we have partnered with Walmart, Lowe's, McKesson, and JetBlue to provide destination center of excellence (COE) spinal care for their employee associates from a large portion of the United States.

Methods: The Employers Center of Excellence Network (ECEN) selects participating centers through a rigorous review of internal system and individual surgeon specific data. Prospective, episodic bundled rates are negotiated between purchasers and delivery systems, and generally are 10-15% below standard fee-for-service rates. Employee associates of these companies receive one hundred percent coverage for all travel, medical, and associated fees across the episode of care. All patients are evaluated by spinal surgery, psychology, physiatry, and internal medicine in an interdisciplinary, integrated practice model.

Results: 62% of patients (279) recommended for surgery by home providers were found to not be appropriate surgical candidates by COE sites. 37.3% (111) of patients referred to our institution were suitable candidates and underwent surgery. Analysis of 12 month's claims data for Lowe's associates demonstrated that 5.9% of patients having spine surgery under traditional insurance needed skilled nursing facility placement vs 0% for those receiving care at COE sites. Patients who were treated under traditional insurance had a 6.6% incidence of 30-day readmission as compared to 0.4% of those patients treated by COEs. Per unit individual employee cost-share reductions of $3,300 were observed for those associates receiving care at COEs.

Conclusion: Direct employer purchasing of healthcare services by large employers has gained significant national attention and will continue to grow. We have observed that the care delivery reengineering efforts required for participation in programs like these have notable additional positive impacts on care across our healthcare system. Efforts of this type are labor intensive, but are a worthwhile proposition for institutions prepared to participate.

10:35– 10:45

BREATHING ABOVE THE BRAINSTEM: VOLITIONAL CONTROL AND ATTENTIONAL MODULATION IN HUMANS

Jose Herrero, PhD, Feinstein Institute for Medical Research, **Ashesh D Mehta, MD, PhD,** Hofstra Northwell School of Medicine

Background: Most research on the neurophysiology of respiration has focused on automatic breathing and its control by the brain stem. This has left higher brain mechanisms underlying the cognitive aspects of breathing relatively unexplored. For millennia, therapeutic techniques have used conscious control and awareness of breathing as techniques for promoting wellbeing with little understanding of the mechanisms underlying their efficacy.

Methods: Using direct intracranial recordings in humans, we correlated cortical and limbic neuronal activity as measured by the intracranial electroencephalogram (iEEG) with the breathing cycle in six subjects undergoing invasive electrode monitoring using grid, strip and depth electrodes, including steroelectroencephalographic monitoring. The coherence of the iEEG to the breath cycle was computed with respect to intracranial sites as defined by mapping electrode location to Freesurfer parcellation. The dynamics of this coherence was examined by having subjects perform breathing exercises related to interoceptive and tasks related to exteroceptive attention.

Results: We demonstrate that the iEEG signal tracks the breathing cycle across a widespread network of cortical and limbic structures. We show that this reflects neuronal activity as opposed to pulsation artifact by demonstrating specificity of findings to the cortical grey matter and phase locking of the gamma band (40-150 Hz) envelope in these structures. We further demonstrate a sensitivity of this tracking to cognitive factors using tasks adapted from cognitive behavioral therapy and meditative practice. Particularly, volitional control and awareness of breathing engage distinct but overlapping brain

circuits. During volitionally-paced breathing, iEEG-breath coherence increases in a fronto-temporal-insular network, and during attention to breathing, we demonstrate increased coherence particularly in the anterior cingulate as well as in the premotor, insular and hippocampal cortices.

Conclusions: Our findings suggest that breathing can act as an organizing hierarchical principle for neuronal oscillations throughout the brain and describe how interoceptive cognitive factors can impact otherwise-automatic neuronal processes. Accordingly, the anterior cingulate cortex sits at a critical position to link the control of perception of the breath cycle to interoceptive phenomena, which, in turn, may relate to clinically relevant factors including pain, anxiety and consciousness.

10:45– 10:55

TESTING THE EFFECTIVENESS AND THE CONTRIBUTION OF EXPERIMENTAL SUPERCHARGE (REVERSED) END TO SIDE NERVE TRANSFER

Mustafa Nadi MD, Sudheesh Ramachandran MCh, Joanne Forden and **Rajiv Midha MD**, Department of Clinical Neurosciences and Hotchkiss Brain Institute; University of Calgary

Objective: Supercharge or reversed end to side transfer (RETS) distal to severe nerve compression neuropathy or in-continuity nerve injury is gaining clinical popularity despite questions about its effectiveness. Here, we examined RETS distal to experimental neuroma in continuity (NIC) injuries for efficacy in enhancing neuronal regeneration, functional outcome and for the 1st time definitively evaluated the degree of contribution of the native and donor motorneuron pools.

Methods: The study was conducted in 2 phases. In phase I, rats (n=35) were assigned to one of five groups (G) for unilateral sciatic nerve surgeries: G1=tibial NIC with distal peroneal-tibial RETS), G2=tibial NIC without RETS, G3= intact tibial and severed peroneal, G4=tibial transection with RETS, G5=severed tibial and peroneal nerves. Recovery was evaluated biweekly using electrophysiology and locomotion tasks. At phase I endpoint, following retrograde labeling, spinal cords were analysed to assess the degree of neuronal regeneration. In phase II, 20 new animals underwent primary retrograde labelling of the tibial nerve, following which they were assigned to one of the 3 groups: G1, G2 and G4. Then secondary retrograde labeling from the tibial nerve was performed at study endpoint to quantify the native versus donor regenerated neuronal pool.

Results: In phase I studies, a significantly increased neuronal regeneration in G1 (RETS) compared to all other groups was observed, but with modest (non-significant) improvement in electrophysiological and behavioral outcomes. In phase II experiments, we discovered that secondary labelling in G1 was predominantly contributed from the donor (peroneal) pool. Double labelling counts were dramatically higher in G2 vs G1, suggestive of hampered regeneration from the native tibial motorneuron pool across NIC in the presence of SETS.

Conclusions: RETS is indeed an effective strategy to enhance axonal regeneration, which is mainly contributed by the donor neuronal pool. Moreover, the presence of a distal RETS coaptation appears to negatively influence neuronal regeneration across the NIC segment. The clinical significance is that RETS should only employ synergetic donors, as the use of antagonistic donors can downgrade recovery.

10:55– 11:05

TRENDS IN PATIENT CARE FOR TRAUMATIC SPINAL INJURIES IN THE UNITED STATES: A NATIONAL INPATIENT SAMPLE STUDY OF THE CORRELATIONS WITH PATIENT OUTCOMES FROM 2001 TO 2012

Andrew T. Dailey, MD, Marcus D. Mazur, MD, Erica F. Bisson, MD, Christopher M. Holland, MD, University of Utah

Study Design: A retrospective database review.

Objective: The aim of this study was to examine whether patient characteristics, distribution of care, and patient outcomes for spinal cord injury (SCI) in the United States have changed between 2001 and 2012.

Summary of Background Data. Although patient outcomes after cranial injury are better at high-volume centers with specialized, multidisciplinary teams, similar assessments have not been done for spinal injuries.

Methods: We retrospectively reviewed the National and Nationwide Inpatient Samples for the years 2001, 2002, 2011, and 2012 to identify patients with spinal fracture with or without SCI. The demographic characteristics of the patient cohort, clinical course, hospital characteristics, interhospital transfer, and disposition were statistically analyzed relative to patient mortality, total hospital costs, and length of stay. How these data changed over this 11-year period was also evaluated.

Results: A total of 159,875 cases were identified, with 141,737 fractures without SCI and 18,138 SCIs with or without fracture. There was a statistically significant decrease in the percentage of patients transferred with spine injury from 4.2% to 3.4% (P<0.001) from the early years to the later years and in patient transfers for SCIs (8.1% vs. 6.5%, P<0.001). Interestingly, the overall mortality rate (3.5% vs. 3.6%) remained unchanged (P .0.679), but mortality from SCI increased (6.6–7.4%, P.0.021).

Conclusion: From 2002 to 2012, the rate of interhospital transfer of spinal injury patients declined, while the mortality rate for patients with SCI increased. Interestingly, there was an increase in transfers after spinal surgery at the index hospital. The decentralization of spine care may be responsible for the increase in mortality.

11:05– 11:15

DETECTION OF TRAUMATIC BRAIN INJURY WITH A POINT OF CARE DEVICE: RESULTS OF TBI COHORT FROM THE STABILISER STUDY

Justin F. Fraser, MD, Melissa Bradley-Whitman, PhD, Andrew Bernard, MD, Nessa Timoney, MD, Bryan Eckerle, MD, Jessica Lee, MD, Roger Humphries, MD, Gregory J. Bix, MD, PhD, and Mark A. Lovell, PhD, University of Kentucky College of Medicine

Early diagnosis of Traumatic Brain Injury (TBI) is vital. We developed a point-of-care lateral flow device to rapidly detect an ubiquitinated form of neuron-specific biomarker, visinin-like-protein-1 (ub-VILIP-1). The STABILISER study is a first-in-human evaluation of feasibility and efficacy in rapid diagnosis of patients with acute brain injury. We present the results of feasibility and biomarker detection after mild to moderate TBI.

Methods: Subjects diagnosed with TBI presenting within 8 hours of injury to the emergency department were enrolled in the IRB-approved protocol. 10 mL of whole blood was applied to the device, which was read by clinical assessors. Similarly 10 mL of serum was applied to a device for automated detection. In addition, a group of volunteer control subjects with no recent history of brain injury underwent testing as controls.

Results: 12 Controls (Median age 38, 58.3% male) and 13 Mild/Moderate TBI subjects (Median age 35, 53.8% male) were enrolled. Average time to enrollment was 6.0+/-1.8 hours. Devices were constructed individually in a university of laboratory with internal quality analysis; during the course of the study, 10 devices in a single batch were discovered to have inadequate quality of components and were discarded. All other devices were

usable, and there were no device failures once applied. Laboratory quantification of the biomarker readout on the device from serum demonstrated median concentration of 0.0 pg/mL for controls versus 196.7 pg/mL for any TBI ($p<0.001$). While a similar trend for whole blood was evident (median 84.6 pg/mL for controls vs 178.2 pg/mL for any TBI), the difference was not significant. Spearman correlations were performed to evaluate relationships between clinical raters of the device and quantitative evaluation. Clinical physician raters' evaluation of device readout significantly correlated to quantitative biomarker concentration despite Bonferroni correction (Correlation coefficient 0.537, $p=0.005$).

Conclusions: The STABILISER study demonstrates feasibility and preliminary utility of a point-of-care device to detect ub-VILIP-1 as a diagnostic tool for TBI. Further studies are needed to optimize the device for whole blood versus serum detection.

11:15– 11:20

SUPPORT VECTOR MACHINES FOR OUTCOME PREDICTION FROM CLINICAL FREE TEXT DATA: A NOVEL MORTALITY PREDICTION TOOL FOR TRAUMA PATIENTS

Jason M. Davies, MD, PhD, State University of New York and R. Adams Dudley, MD, University of California, San Francisco

Research Objective: Existing models for mortality in trauma patients rely on manual abstraction from medical charts or use of imprecise and retrospective reimbursement codes. Developing automated methods for predicting mortality from free text might reduce cost and data collection times and improve outcomes. We developed a support vector machine (SVM) classifier to predict in-hospital mortality for trauma patients solely from clinical notes.

Study Design: We selected notes for 3,502 trauma patients from the MIMIC-II database based at Beth Israel Deaconess Medical Center from 2001 to 2008. Using these notes, we developed an SVM classifier to predict mortality and uncover the clinically relevant features. We compared discrimination and calibration of this classifier to an implementation of the ICISS model, estimated using 305,151 ICU stays for trauma taken from New York state hospital discharge databases for the years 2006 to 2008. We further evaluated time sensitivity of the SVM classifier by comparing performance when trained using data from different time intervals after admission.

Principal Findings: Our classifier outperformed ICISS on area under the receiver-operating characteristic (AUC-ROC) (0.902 vs. 0.632; $p<0.001$), and displayed good calibration. Additionally, we observed that including notes from later time periods following admission markedly improved performance (AUC-ROCs 0.918 at 48 h; 0.937 at 72 h; 0.957 at 168 h; 0.974 if all notes are used). Finally, by applying regularization to our classifier, we found that a set of only roughly 300 clinical terms was required to accurately predict mortality.

Conclusions: Overall, our classifiers displayed excellent performance characteristics and outperforms existing models. Although performance improved with the inclusion of additional data over the course of the hospitalization, good performance at even 24- and 48-hours may permit these models to assist in real-time clinical decision support.

Implications for Policy or Practice: SVM-based classifiers can accurately predict mortality among hospitalized trauma patients. These can be used in real-time to inform patient-physician discussions regarding the course of care.

ABSTRACT SESSION: VASCULAR

11:20– 11:30

IN VIVO STUDIES OF NEURONAL ACTIVITY IN THE PRIMARY MOTOR CORTEX AFTER TRANSIENT ISCHEMIC ATTACK

Hang Zhou[1], **Howard A. Riina[2]**, John Ard[1], Andrew Rosenberg[1], Guang Yang[1]

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A transient ischemic attack (TIA) is a brief, reversible episode of neurological dysfunction caused by focal ischemia without acute infarction. Evidence indicates that a transient interruption in cerebral blood flow may impair sensation, motor function, and cognition. However, the effect of focal cerebral ischemia on brain activity at the cellular and subcellular level remains unclear. In this study, we mimicked TIA by producing a targeted ischemic attack in the primary motor cortex using photo thrombosis. Using in-vivo two-photon microscopy, we monitored the cortical activity before and after focal ischemia induction in real time by recording the Ca^{2+} activity of cortical pyramidal neurons that express genetically encoded Ca^{2+} sensor GCaMP6s. Under normal conditions, pyramidal neurons in the motor cortex show increased somatic and dendritic Ca^{2+} activity when the animals are running on a treadmill. Following targeted focal ischemia in the superficial layer of the motor cortex, we

observed a marked reduction of neuronal activity in both layer 2/3 and layer 5 pyramidal cells. This reduction of neuronal activity persists for at least 24 hours after the focal ischemia has been resolved, and is accompanied by an alteration of gait pattern. These results suggest that a transient interruption of cerebral blood flow may have long-lasting effect on neuron activity in local cortical circuitry and lead to behavioral changes. Currently, we are screening compounds that have the potential to mitigate the deleterious effects of focal ischemia on neuronal activity and motor function.

11:30– 11:40

ASSOCIATION OF INTRACRANIAL ANEURYSM RUPTURE WITH SMOKING DURATION, INTENSITY, AND CESSATION

Anil Can, [MD1], Victor M. Castro, MS[2], Yildirim H. Ozdemir, [BA1], Sarajune Dagen, BS[1], Sheng Yu, PhD[3], Dmitriy Dligach, PhD[4], Sean Finan, BS[4], Vivian Gainer, MS[2], Nancy A. Shadick, MD, MPH[1], Shawn Murphy, MD, PhD[6], Tianxi Cai, PhD[7], Guergana Savova, PhD[5], Ruben Dammers, MD, PhD[8], Scott T. Weiss, MD, MS[1], **Rose Du, MD, PhD[1]**

1. Brigham and Women's Hospital
2. Partners Healthcare
3. Tsinghua University
4. Loyola University
5. Boston Children's Hospital
6. Massachusetts General Hospital
7. Harvard T H Chan School of Public Health
8. Erasmus Medical Center

Introduction: Although smoking is a known risk factor for intracranial aneurysm rupture, the exact relationship between intracranial aneurysm rupture and smoking intensity and duration, as well as duration of smoking cessation remains unknown.

Methods: In this case-control study, we analyzed 4,701 patients with 6,411 intracranial aneurysms diagnosed at our institution between 1990 and 2016. We divided individuals into cases with ruptured aneurysms and controls with unruptured aneurysms. We performed univariable and multivariable logistic regression analyses to determine the association between smoking status and ruptured intracranial aneurysms at presentation. In a subgroup analysis among former and current smokers, we assessed the association between ruptured aneurysms and number of packs per day, duration of smoking and duration since smoking cessation.

Results: In multivariable analysis, current (OR 2.21, 95% CI 1.89-2.59) and former smoking status (OR 1.56, 95% CI 1.31-1.86) were associated with rupture status at presentation compared with never smokers. In a subgroup analysis among current and former smokers, years smoked (OR 1.02, 95% CI 1.01-1.03) and packs per day (OR 1.46, 95% CI 1.25-1.70) were significantly associated with ruptured aneurysms at presentation, whereas duration since cessation among former smokers was not significant (OR 1.00, 95% CI 0.99-1.02).

Conclusions: Current cigarette smoking, smoking intensity, and smoking duration are significantly associated with ruptured intracranial aneurysms at presentation. However, the significantly increased risk persists after smoking cessation, and smoking cessation does not confer a reduced risk of aneurysmal subarachnoid hemorrhage beyond that of reducing the cumulative dose.

11:40– 11:50

RESULTS OF MICROSURGERY FOR POOR-GRADE ANEURYSMAL SUBARACHNOID HEMORRHAGE IN THE ENDOVASCULAR ERA

Mustafa K. Baskaya, MD, University of Wisconsin

Objectives: Poor-grade aneurysmal subarachnoid hemorrhage (PGASAH) accounts for approximately 20-30% of all patients with SAH and associated with high mortality and morbidity rates. We aimed to evaluate the safety and efficacy of microsurgical treatment in the management of PGASAH in the endovascular treatment era.

Methods: Health records of 67 patients with PGASAH undergoing microsurgical treatment were retrospectively reviewed.

Results: Forty eight (71.6%) patients were classified as Hunt and Hess grade IV and 19 (28.4%) as grade V at admission. Most patients (76%) underwent surgery within 24 hours of admission (ultraearly treatment). Bypass and trapping of the aneurysm were performed in 13.4%. Vasospasm was noted in 52.2% and shunt-dependent hydrocephalus in 65.7%. Thirty-day mortality rate was significantly higher among grade V patients (26.3% vs 6.3%, p=0.036). Mean followup duration was 5.0±2.7 years. Good outcome (mRS:0-2) at 12 months was achieved in 77.1% of grade IV and 31.6% of grade V patients (overall: 64.2%). In univariate analysis, older age (>65 years), hypertension, hyperlipidemia, HH grade V, modified Fisher grade 4, IVH and/or ICH, larger aneurysms (>7 mm), cerebral infarcts were associated with poor outcome (p<0.1). Multivariate analysis revealed that age>65

years, HH grade V and new ischemic infarcts were independent predictors of poor outcome while smoking was related with favorable outcome ($p<0.05$).

Conclusion: With excellent long-term outcomes, microsurgery is still a viable and important treatment modality in the management of PGASAH in the endovascular era. Appropriate patient selection, early surgery, surgical experience, aggressive intensive care and rehabilitation can improve success of management.

11:50– 12:00

PROXIMAL M1-SEGMENT STENOSIS IS ASSOCIATED WITH RUPTURE STATUS IN MIDDLE CEREBRAL ARTERY BIFURCATION ANEURYSMS

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Introduction: Hemodynamic factors impact cerebral aneurysm development and progression. Parent vessel architectural features, such as caliber, curvature and angle can affect downstream pressure and shear stress. We sought to investigate the association between proximal parent vessel stenosis and aneurysm rupture status at the middle cerebral artery (MCA) bifurcation in a patient population prone to intracranial atherosclerotic disease.

Methodology: Catheter 3D rotational angiographic datasets from 69 Japanese patients with MCA aneurysms (58 unruptured/11 ruptured) were analyzed. The narrowest cross-sectional area (CSA) of the M1 segment leading to the aneurysmal bifiurcation was evaluated through equidistant cross-sectional plane cuts along the M1 length. Sobel edge-detection filtering was performed to insure immunity to thresholding variability.

The CSA ratio of maximal stenosis relative to M1 origin (NarrowToProximalCSARatio) and the distance from maximal stenosis to the aneurysm neck (NarrowToAnDist) at the bifurcation were statistically evaluated. The effects of proximal M1 stenosis severity and distance from stenosis to the aneurysm neck were determined using parametric aneurysm models with/without stenosis using computational fluid dynamic (CFD), finite element analysis (FEA), and combined two-way fluid-structure interaction (FSI) simulations.

Results: MCA bifurcations harboring ruptured aneurysms had significantly tighter stenosis with smaller NarrowToProximalCSARatio (0.69 ± 0.22 vs. 4.66 ± 1.08, $p=0.02$), as well as shorter distance from stenosis to aneurysm neck with NarrowToAnDist (4.26 ± 1.91

vs. 6.94±4.06mm, p=0.02) compared to unruptured aneurysms. Multivariate analysis combining NarrowToProximalCSARatio and NarrowToAnDist resulted in p=0.003, AUC=0.81 (80% sensitivity, 74% specificity). CFD and FSI simulations uncovered a potential mechanism for rupture induction via a synergetic effect of stenosis severity and proximity to aneurysm neck in inducing higher aneurysm inflow velocity and deeper jet penetration, higher dome pressure, and higher tensile stress in the aneurysm wall.

Conclusion: Ruptured status in bifurcation MCA aneurysms was associated with severity of adjacent upstream parent vessel M1 stenosis and its proximity to the aneurysm neck, a novel risk factor, which acts by increasing aneurysm dome wall tension, and should be considered in investigations of rupture risk stratification and taken into account in treatment decision-making.

12:00

Adjourn