hERG inhibitory drugs. These data suggest clinical trials for already FDA-approved drugs that also inhibit hERG in high hERG-expressing GBM patients.

**Columbia Softball Charity Award**

140

A High-Throughput In Vitro Drug Screen in a Genetically Engineered Mouse Model of Diffuse Intrinsic Pontine Glioma Identifies BMS-754807 as a Promising Therapeutic Agent

Kyle Gregory Halvorson, MD; Kelly L. Barton, Kristin Schroeder, Katherine Misuraca, Christine Hoeman, Alex Chung, Donna Crabtree, Francisco Cordero, Raj Singh, Ivan Spasojevic, Noah Berlow, Ranadip Pal, Oren Becher

**INTRODUCTION:** Diffuse intrinsic pontine gliomas (DIPGs) represent a particularly lethal type of pediatric brain cancer with no effective therapeutic options. Our laboratory has previously reported the development of genetically engineered DIPG mouse models by using the RCAS/tv-a system, including a model driven by PDGF-B, H3.3K27M, and p53 loss. These models can serve as a platform in which to test novel therapeutics before the initiation of human clinical trials.

**METHODS:** In this study, an in vitro high-throughput drug screen as part of the DIPG preclinical consortium using cell lines derived from our DIPG models identified BMS-754807 as a drug of interest in DIPG. BMS-754807 is a potent and reversible small-molecule multikinase inhibitor with many targets, including IGF-1R, IR, MET, TRKA, TRKB, AURKA, and AURKB.

**RESULTS:** In vitro evaluation showed significant cytotoxic effects with an IC_{50} of 0.13 μM, significant inhibition of proliferation at a concentration of 1.5 μM, as well as inhibition of AKT activation. Interestingly, IGF-1R signaling was absent in serum-free cultures from the PDGF-B, H3.3K27M, p53 deficient model suggesting that the antitumor activity of BMS-754807 in this model is independent of IGF-1R. In vivo, systemic administration of BMS-754807 to DIPG-bearing mice did not prolong survival. Pharmacokinetic analysis demonstrated that tumor tissue drug concentrations of BMS-754807 were well below the identified IC_{50}, suggesting that inadequate drug delivery may limit in vivo efficacy.

**CONCLUSION:** In summary, an unbiased in vitro drug screen identified BMS-754807 as a potential therapeutic agent in DIPG, but BMS-754807 treatment in vivo by systemic delivery did not significantly prolong survival of DIPG-bearing mice.

141

Preoperative Brain Mapping in Neuro-oncology With Graph Theory Analysis of the Functional Connectome

Michael Hart, MBChB; Stephen J. Price, BSc, MBBS, FRCS, PhD; John Suckling

**INTRODUCTION:** Brain mapping has undergone a paradigm shift from functional localization to focusing on complex network connectivity. Central to this has been the search for the connectome or the brain’s wiring diagram. Modeling the effects of focal lesions using graph theory allows consideration of how important a region is to network function and the effects of its removal. Our aim is to determine the feasibility of applying connectomics to neurosurgery and determine the key topological characteristics of patients with real lesion.

**METHODS:** Resting-state functional MRI at 3 T was performed with multi-echo-independent component analysis preoperatively on 5 patients with glioblastoma in the right temporo-parieto-occipital region. Complex networks analysis was performed by parcellating the brain into an anatomically based 116 region template followed by wavelet-based decomposition of time series into correlation matrices that were subsequently thresholded and binarized into individual adjacency matrices.

**RESULTS:** Our data set exhibited the key features of complex networks found in healthy controls including ubiquitous small world features of simultaneous network segregation and integration. An exponentially truncated power law fit to the degree distribution predicted findings of general network robustness and a core of highly connected and integrated hubs with disproportionate vulnerability. Real lesions produced both local and distant effects in terms of reduced connectivity, network fragmentation, as well as alterations to the topological core structure of hubs and robustness.

**CONCLUSION:** Our refined analysis pipeline confirms the feasibility of performing complex network analysis with graph theory in patients with real lesions and is a novel approach to preoperative brain mapping. Potential discrepancies between the effects of real and simulated lesions may allow identification of mechanisms behind network plasticity. Preoperative mapping of network hubs and robustness is a novel approach for understanding the mechanisms of how higher cognitive processes are affected by and recover from real lesions.

142

Stereotactic Radiosurgery for Medically and Surgically Refractory Acromegaly: Long-Term Rates of Remission and Hypopituitarism

Jason P. Sheehan, MD, PhD, FACS; Mary Lee Vance, MD; Zhiyuan Xu, MD; Chun Po Yen, David Schlesinger, Blair Dodson, Cheng-Chia Lee

**INTRODUCTION:** Acromegaly is a challenging clinical entity. Despite improvements in microsurgery and medical therapy, acromegaly persists or recurs in many patients. We evaluate the long-term results of stereotactic radiosurgery (SRS) for acromegalic patients.

**METHODS:** This was a retrospective study of patients treated with SRS at the University of Virginia; the data were collected from 1989 to 2013. A total of 136 patients underwent SRS for acromegaly. Diagnosis of acromegaly was based on the combination of clinical features and biochemical assessment including to serum growth hormone (GH) level, and age- and sex-matched serum insulin-like growth factor 1 (IGF-1) level. All patients underwent a complete endocrine evaluation, neuroimaging study, and ophthalmic examinations before SRS. Patients who had an OGTT GH of <1.0 ng/mL or normal IGF-1 were considered in remission. Postradiosurgical hypopituitarism was defined as a decrease in one or more hormones below normal.

**RESULTS:** With a median follow-up of 61.5 months, 65.4% of the patients achieved remission. The mean time to remission was 27.5 months. The actuarial remission rates at 2, 4, 6, and 8 years postradiosurgery were 31.7%, 64.5%, 73.4%, and 82.6%, respectively. Significant