F.2

Single cell CRISPR/Cas-9 lineage tracing reveals fitness axis in glioblastoma

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Background: We've adopted a novel approach that combines cellular barcoding with CRISPR/Cas-9 technology and single-cell RNA sequencing known as continuous lineage tracing to track the development, treatment and inevitable recurrence of glioblastoma. Methods: Patient derived glioma initiating cell lines were engineered with expressed DNA barcodes with CRISPR/Cas-9 targets and engrafted into NOD scid-mice. Clonal and relationships are surmised through identification of expressed barcodes, and cells were characterized by their transcriptional profiles. Phylogenetic lineage trees are created using lineage reconstructive algorithms to define cell fitness and expansion. Results: Our work has revealed a significant amount of intra-clonal cell state heterogeneity, suggesting that tumour cells engage in phenotype switching prior to therapeutic intervention. Phylogenetic lineage trees allowed us to define a gene signature of cell fitness. GBMs exist along a transcriptional gradient between undifferentiated but "high-fit" cells and terminally differentiated, "low-fit" cells, lending further evidence that these tumours consist of pools of cells that are capable of recapitulating the tumour microenvironment after treatment. Conclusions: We have successfully engineered a set of glioma initiating tumours with a novel lineage tracing technique, creating a powerful tool for real-time tracing of tumour growth through the analysis of highly detailed singe-cell RNA sequencing data with associated clonal and phylogenetic relationships.

F.3

fMRI-based deep brain stimulation programming: a blinded, crossover clinical trial

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Background: Deep brain stimulation (DBS) in Parkinson's disease (PD) requires extensive trial-and-error programming, often taking over a year to optimize. An objective, rapid biomarker of stimulation success is needed. Our team developed a functional magnetic resonance imaging (fMRI)-based algorithm to identify optimal DBS settings. This study prospectively compared fMRI-guided programming with standard-of-care (SoC) clinical programming in a double-blind, crossover, non-inferiority trial. Methods: Twenty-two PD-DBS patients were prospectively enrolled for fMRI using a 30-sec DBS-ON/OFF cycling paradigm. Optimal settings were identified using our published classification algorithm. Subjects then underwent >1 year of SoC programming. Clinical improvement was assessed under SoC and fMRI-determined stimulation conditions. Results: fMRI optimization significantly reduced the time required to determine optimal settings (1.6 vs. 5.6 months, $p<0.001$). Unified Parkinson's Disease Rating Scale (UPDRSIII) improved comparably with both approaches (23.8 vs. 23.6, $p=0.9$). Non-inferiority was demonstrated within a predefined margin of 5 points ($p=0.0018$). SoC led to greater tremor improvement ($p=0.019$), while fMRI showed greater bradykinesia improvement ($p=0.040$). Conclusions: This is the first prospective evaluation of an algorithm able to suggest stimulation parameters solely from the fMRI response to stimulation. It suggests that fMRI-based programming may achieve equivalent outcomes in less time than SoC, reducing patient burden while potentially enhancing bradykinesia response.

F.4

Risk factors for 30-day postoperative infection in pediatric ventricular shunts for hydrocephalus

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Background: Ventricular shunt infections lead to significant morbidity and mortality. This study aimed to identify risk factors for 30-day postoperative infection outcomes of ventricular shunts for pediatric hydrocephalus. Methods: A retrospective cohort study using the National Surgical Quality Improvement Program (NSQIP) Pediatric database for years 2016-2021 was conducted. Patients under 18 years undergoing ventricular shunt surgery were included. The primary outcome was 30-day postoperative shunt infection. A multivariable logistic regression analysis of fourteen prognostic variables was performed. Results: A total of 10,878 patients (mean age 3.1 years, 44.2% female) were included. The 30-day postoperative shunt infection rate was 3.7%. Infection risk increased with nutritional support, longer operating room duration, and congenital hydrocephalus. Risk decreased with increasing age, intraoperative intraventricular antibiotics, and first-time shunt placement. Variables not significantly affecting infection risk included sex, BMI, ostomy, tracheostomy, neuromuscular disease, structural pulmonary/airway abnormality, steroid use, antibiotic-impregnated shunts, and endoscopic catheter placement. Conclusions: Postoperative shunt infections in pediatric patients are influenced by both modifiable and non-modifiable factors. Identifying and addressing modifiable risks can significantly reduce infection rates, minimize the need for surgical revisions, and enhance therapeutic outcomes and overall quality of life.

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