needing revision surgery. To improve nonunion healing, we develop automated design optimization methods for biodegradable Mg alloy IMNs to control local reloading. METHODS/STUDY POPULATION: Finite element analysis (FEA) is performed on 3D bone-IMN representations to establish this study's baseline strain states for existing inert IMN geometries within QCT-informed femoral models under simulated biomechanical loading. FEA with Mg alloy properties for same IMN designs simulate transient IMN material loss through discrete time-step models with experimental in vivo Mg corrosion rates and strain-based bone density evolution using remodeling algorithms from literature. Transient stability and strength metrics, fracture zone stress profiles under gradual reloading and manufacturing constraints are formulated through gradient-based sensitivity analysis into a topology optimization framework (TOF) incorporating a reaction-diffusion degradation model to generate IMN topologies. RESULTS/ANTICIPATED RESULTS: TOF designs for Mg alloy IMNs with transient allowable strength constraints, using safety factors to prevent IMN failure, demonstrate higher compliance than standard inert IMNs with mechanical properties closer to native cortical bone. The biodegradation model within the TOF, informed by corrosion behavior from bone-IMN FEA study, predicts how potential design evolutions affect transient strain states of the system. Thus, local fracture region stress states are controlled by the algorithm optimizing for desirable transient stiffness profiles based on a minimum variance objective of fracture zone stress compared to a target bone stress profile. Optimized IMNs with porous, high surface area features achieve 50% decrease in IMN stiffness over 6 months recovery time and complete in vivo degradation in 24 months. DISCUSSION/SIGNIFICANCE: Our TOF reduces "stress-shielding" effects via design for controlled IMN biodegradation to gradually increase fracture zone loading, stimulating remodeling and reducing current risk of post-operative fracture and surgical removal in ~15k cases/yr. in the U.S. In vitro mechanical and in vivo clinical testing is required to validate design results.

412

Synergistic Targeting of Lysine-specific demethylase 1 (LSD1) and MAPK Signaling: A Mechanism-Guided Therapeutic Approach for Glioblastoma (GBM)

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OBJECTIVES/GOALS: LSD1 is a histone demethylase important in GBM regulation. Our goal is to design a therapeutic strategy for LSD1 inhibitors to meet clinical needs in GBM. Despite the abundance of LSD1 inhibitors, resistance emerges in GBM mouse models. We aim to understand the relevance of proliferative signaling pathways, such as MAPK, in LSD1 inhibitor resistance. METHODS/STUDY POPULATION: Following LSD1 knockdown in GBM cells, we determined differentially expressed genes using RNA-seq and gene set enrichment analysis (GSEA). Kinase signaling processes enriched for LSD1 expression were identified. Utilizing western blot, we assessed LSD1's impact on MAPK signaling in patient-derived GBM stem cells (GSCs) and pediatric high-grade glioma cell models. Pharmacological evaluation of LSD1 involved five inhibitor candidates. Additionally, we explored LSD1 inhibition in combination with brain penetrant kinase inhibitors, osimertinib and ulixertinib, directed against the epidermal growth factor receptor (EGFR) and MAPK, respectively. The treatment combinations were assessed at multiple concentrations and analyzed using SynergyFinder. RESULTS/ANTICIPATED RESULTS: Pharmacological LSD1 inhibition after 24 hours induced increased phosphorylated ERK1/2 across multiple glioma cell lines. Concurrent LSD1 and EGFR/MAPK inhibition demonstrated improvedin vitro efficacy compared to individual agents. Notably, the combination of Iadademstat (ORY-1001) and osimertinib demonstrated the highest synergy score of 37.2 using the bliss synergy model in the GSC17s. Furthermore, 11 out of the 12 combination treatments tested had a synergistic relationship, with bliss synergy scores greater than 10. DISCUSSION/SIGNIFICANCE: Our study addresses the pressing need for novel therapeutic strategies in GBM. We leveraged pharmacological tools of LSD1 inhibition to determine how they could be used most effectively, revealing kinase inhibition as a promising strategy with demonstrated in vitro efficacy. Future efforts will focus on validating these findingsin vivo.

413

Perceptions and Concerns: Navigating Genetic Research Participation Among At-Risk Individuals for Inherited Conditions

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OBJECTIVES/GOALS: Motivations and hesitations about participating in genetic research among those at risk of inherited conditions are unclear. We aim to understand perceptions, perspectives, and concerns of these individuals regarding genetic research studies, especially for hard-to-diagnose diseases. METHODS/STUDY POPULATION: Mix method study of 150 Hispanics individuals in Puerto Rico (PR) at risk for in heriting a condition. These individuals, with limited diagnostic data, are attending genetics clinics or invited to a genetics study at the University of Puerto Rico Medical Sciences Campus. Structured surveys and interviews will be conducted. Surveys will gauge general perceptions and feelings toward genetic research, while interviews will provide a deeper understanding of participants' personal narratives and experiences. All sessions will be recorded, transcribed, and analyzed using NVivo qualitative analysis software. Thematic analysis will be employed to identify recurring themes and sentiments. RESULTS/

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ANTICIPATED RESULTS: Weanticipatevaried responses: some enthusiastic about genetic research benefits, others having reservations due to privacy, cultural beliefs, or past experiences. A significant portion may express concerns about genetic research's impact on insurance and potential discrimination. We also expect to uncover systemic challenges that hinder participation among Hispanics living in PR, such as a lack of information or misconceptions about genetic research. This study will overview factors, both encouraging and inhibitory, influencing decisions to join genetic research. Quantitative genetic literacy survey data will undergo descriptive analysis and multivariate logistic regression. DISCUSSION/SIGNIFICANCE: Hispanics in PR exhibit a rich tapestry of genetic variations being a focal point for genetic research. Understanding perceptions is vital among those at risk for inherited conditions. Insights can shape outreach and education strategies, ensuring participants are informed, concerns met, and empowered to make decisions alignined their views.

414

Post-stroke Cognitive deficits are associated with reduced cognitive conflict evoked mid-frontal EEG theta oscillations and can be potentially improved with prefrontal transcranial electrical stimulation

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OBJECTIVES/GOALS: Cognitive dysfunction and/or depressionfollowing ischemic stroke results in loss of independence in daily functioning. The objective of this work is to assess neural correlates of post-stroke cognitive deficits and the effect of left frontal transcranial electrical stimulation on cognitive control and associated brain rhythms. METHODS/STUDY POPULATION: We recorded mid-frontal scalp EEG from 15 healthy and 13 participants with stroke while they performed a multi-source interference task (MSIT). The stroke cohort also performed additional MSIT sessions where they received active and sham transcranial direct current stimulation (tDCS) on the left prefrontal cortex (PFC). The EEG was pre-processed to get rid of eye movement and other channel noise artifacts and filtered to retain 0.5-55 Hz components. A Morlet wavelet was used to estimate power in theta (4-8 Hz), alpha (8-15 Hz) and gamma (35-50 Hz) frequency bands over a period of 2 seconds following MSIT image presentation. A generalized linear mixed effects model was used to find effect of group on behavior and EEG oscillations. A GLME was also used to find effects of active tDCS on behavior and EEG. RESULTS/ANTICIPATED RESULTS: We found Group (healthy v stroke) as a significant predictor of both response time (behavior) and conflict evoked theta power in the frontal channels (F1-Fz, F2-Fz). We also found that active tDCS significantly improved MSIT performance as compared to sham, after accounting for cognitive load. Active tDCS also induced low frequency oscillations in frontal EEG channels compared to sham. Preliminary results indicate that mid-frontal theta oscillations are a potential neural correlate of post-stroke cognitive deficit and tDCS of the left PFC might be a promising therapeutic intervention to ameliorate this. DISCUSSION/SIGNIFICANCE: Current therapeutic approaches often do not alleviate post stroke executive dysfunction, hence a better understanding of the brain network changes underlying such deficit can elucidate neural correlates of post stroke cognitive deficit to inform the development of neuromodulation interventions.

415

Intraoperative Molecular Imaging of Gliomas using Indocyanine-Conjugated Choline Kinase Alpha Inhibitor

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OBJECTIVES/GOALS: Distinguishing tumor tissue from normal brain parenchyma remains a major challenge during the resection of gliomas, leading to the persistence of tumor cells. This study aims to assess the choline kinase alpha-targeting fluorophore JAS239 as a novel fluorescent agent to intraoperatively visualize gliomas in an orthotopic murine model. METHODS/STUDY POPULATION: The human glioblastoma-derived U87 MG-Luc2 cell line will be intracranially implanted in nude mice and tumor growth will be assessed using bioluminescence imaging. After 14 days, the mice will be treated with either antiangiogenic therapy (10 mg/kg bevacizumab, twice/week) or saline (control). Tumor growth will be monitored until 21-28 days after initial implantation, at which point JAS239 (4.0 mg/kg, 90 min before sacrifice) and Evans Blue (4 ml/kg, 60 min before sacrifice) will be administered. The mice will be sacrificed, and their brains will be harvested and sectioned for near-infrared imaging. The brain sections will be processed for histopathologic analysis, allowing for the correlation of observed fluorescence with the distribution of tumor and comparison of signal-to-background ratios. RESULTS/ANTICIPATED RESULTS: JAS239 is an indocyanine-based choline mimetic (excitation 745 nm, emission 775 nm) that has been shown to cross the blood-tumor barrier (BTB) in rodent glioblastoma studies. PET imaging with choline-based radiotracers like 18F-choline has also been shown to delineate both contrast-enhancing tumor (CET) and non-contrast-enhancing tumor (NCET) regions, supporting the hypothesis that JAS239 will be able to visualize heterogeneous glioma tissue in our mouse model. Evans Blue is a passive dye in the visible light spectrum (excitation 620 nm, emission 680 nm) expected to only fluoresce in CET regions due to the disruption of the BTB. JAS239 is expected to fluoresce in both CET and NCET regions, which will be assessed by the fluorescence in mice treated with bevacizumab (expected to renormalize the BTB and model NCETs). DISCUSSION/SIGNIFICANCE: JAS239 may allow for real-time visualization of heterogeneous glioma tissue, which is important because there are no current intraoperative imaging agents for NCETs. Future research and clinical translation of this class of agents may allow surgeons to maximize the safe resection of gliomas, improving progression-free and overall survival rates.

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