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.

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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.

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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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