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Abaloparatide as a novel therapy for posttraumatic osteoarthritis

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OBJECTIVES/GOALS: Osteoarthritis (OA) is a cartilage destroying disease. We are investigating abaloparatide (ABL) activation of parathyroid hormone receptor type 1 (PTH1R), which is expressed by articular chondrocytes in OA. We propose ABL treatment is chondroprotective in murine PTOA via stimulation of matrix production and inhibition of chondrocyte maturation. METHODS/STUDY POPULATION: 16-week-old C57BL/6 male mice received destabilization of the medial meniscus (DMM) surgery to induce knee PTOA. Beginning 2 weeks post-DMM, 40 Î¼g/kg of ABL (or saline) was administered daily via subcutaneous injection and tissues were harvested after 6 weeks of daily injections and 8 weeks after DMM surgery. Harvested joint tissues were used for histological and molecular assessment of OA using three 5 Î¼m thick sagittal sections from each joint, 50 Î¼m apart, cut from the medial compartment of injured knees. Safranin O/Fast Green tissue staining and immunohistochemistry-based detection of type 10 collagen (Col10) and lubricin (Prg4) was performed using standard methods. Histomorphometric quantification of tibial cartilage area and larger hypertrophic-like cells was performed using the Osteomeasure system. RESULTS/ANTICIPATED RESULTS: Safranin O/Fast Green stained sections showed a decreased cartilage loss in DMM joints from ABL-treated versus saline-treated mice. Histomorphometric analysis of total tibial cartilage area revealed preservation of cartilage tissue on the tibial surface. Immunohistochemical analyses showed that upregulation of Col10 in DMM joints was mitigated in the cartilage of ABL-treated mice, and chondrocyte expression of Prg4 was increased in uncalcified cartilage areas in ABL-treated group. The Prg4 finding suggests a matrix anabolic effect that may counter OA cartilage loss. Quantification of chondrocytes in uncalcified and calcified tibial cartilage areas revealed a reduction in the number of larger hypertrophic-like cells in ABL treated mice, suggesting deceleration of hypertrophic differentiation. DISCUSSION/SIGNIFICANCE: Cartilage preservation/regeneration therapies would fill a critical unmet need. We demonstrate that an osteoporosis drug targeting PTH1R decelerates PTOA in mice. ABL treatment was associated with preservation of cartilage, decreased Col10, increased Prg4, and decreased number of large hypertrophic-like chondrocytes in the tibial cartilage.

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Providers Assessment of Nutritional Practices for the Duchenne and Becker Muscular Dystrophy Population

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OBJECTIVES/GOALS: Nutrition plays an imperative role in the management of Duchenne and Becker Muscular Dystrophy, but guidelines for nutrition counseling are absent. This study was designed to gain insight into provider experiences with nutritional services to find solutions for future counseling. METHODS/STUDY POPULATION: In this prospective, observational exploratory study, semi structured interviews were conducted at Certified Duchenne Care Centers (CDCCs) to gain insight on providers experiences with nutritional services and to identify barriers and solutions to nutrition education/care/counseling at CDCCs. Interviews were video recorded and then transcribed for themes. Overarching themes gave insight for a quantitative survey to be sent out, assessing all members on the multidisciplinary team perceptions, confidence, barriers, and solutions to providing nutritional care to Duchenne and Becker patients. RESULTS/ANTICIPATED RESULTS: We anticipate this study will provide novel data and key information from providers regarding nutrition education /care/counseling efforts in the multidisciplinary care of neuromuscular diseases. DISCUSSION/SIGNIFICANCE: Results will demonstrate the need for higher standards and more specific recommendations in nutritional services at CDCCs, while providing a framework for referrals, continuing education opportunities, and increasing providers' confidence and abilities to provide sound nutritional advice.

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Patients expectations of benefits from large-panel genomic tumor testing in rural community oncology practices

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OBJECTIVES/GOALS: Large-panel genomic tumor testing (GTT) is a new technology that promises to make cancer treatment more precise. However, patients may have unrealistic expectations of its benefits. The goal of this project is to assess expectations for GTT among cancer patients in community oncology practices. METHODS/STUDY POPULATION: A survey assessing expectations of the benefits of GTT was administered to cancer patients participating in a statewide study of GTT implementation, prior to receiving test results. Descriptive and regression analyses were conducted to assess expectations and the factors associated with these expectations. The study sample (N = 1,139) consisted of patients with a range of cancer types (22% gynecologic, 14% lung, 10% colon, 10% breast,and 46% other malignancies). Mean age was 64 years (standard deviation = 11); 668 (59%) were women; 71% had no college degree; 57% came from households with less than $50,000 US dollars household income; and 73% lived in a rural area. RESULTS/ANTICIPATED

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RESULTS: Generally, patients had high expectations that they would benefit from GTT (M = 2.81 on 0-4 scale) and positive attitudes toward it (M = 2.98 on 0-4 scale). Patients also had relatively poor knowledge about GTT (48% correct answers on an objective test of GTT knowledge). Greater expectations for GTT were associated with lower knowledge (b = –0.46; p < .001), more positive attitudes (b = 0.40; < .001), and lower education (b = –0.53; < .001). DISCUSSION/SIGNIFICANCE: This research suggests patients have high expectations that they will benefit from GTT, which is associated with low knowledge, positive attitudes, and low education. Interventions may be needed to boost understanding and moderate expectations, particularly for disadvantaged patients.

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MYC Inhibition Overcomes IMiD Resistance in Heterogeneous Multiple Myeloma Populations†

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OBJECTIVES/GOALS: Immunomodulatory drugs (IMiDs) are critical to multiple myeloma (MM) disease control. IMiDs act by inducing Cereblon-dependent degradation of IKZF1 and IKZF3, which leads to IRF4 and MYC downregulation (collectively termed the "Ikaros axis"). We therefore hypothesized that IMiD treatment fails to downregulate the Ikaros axis in IMiD resistant MM. METHODS/STUDY POPULATION: To measure IMiD-induced Ikaros axis downregulation, we designed an intracellular flow cytometry assay that measured relative protein levels of IKZF1, IKZF3, IRF4 and MYC in MM cells following ex vivo treatment with the IMiD Pomalidomide (Pom). We established this assay using Pom-sensitive parental and dose-escalated Pom-resistant MM cell lines before assessing Ikaros axis downregulation in CD38+CD138+ MM cells in patient samples (bone marrow aspirates). To assess the Ikaros axis in the context of MM intratumoral heterogeneity, we used a 35-marker mass cytometry panel to simultaneously characterize MM subpopulations in patient samples. Lastly, we determined ex vivo drug sensitivity in patient samples via flow cytometry. RESULTS/ANTICIPATED RESULTS: Our hypothesis was supported in MM cell lines, as resistant lines showed no IMiD-induced decrease in any Ikaros axis proteins. However, when assessed in patient samples, Pom treatment caused a significant decrease in IKZF1, IKZF3 and IRF4 regardless of IMiD sensitivity. Mass cytometry in patient samples revealed that individual Ikaros axis proteins were differentially expressed between subpopulations. When correlating this with ex vivo Pom sensitivity of MM subpopulations, we observed that low IKZF1 and IKZF3 corresponded to Pom resistance. Interestingly, most of these resistant populations still expressed MYC. We therefore assessed whether IMiD resistant MM was MYC dependent by treating with MYCi975. In 88% (7/8) of patient samples tested, IMiD resistant MM cells were sensitive to MYC inhibition. DISCUSSION/SIGNIFICANCE: While our findings did not support our initial hypothesis, our data suggest a mechanism where MYC expression becomes Ikaros axis independent to drive IMiD resistance, and resistant MM is still dependent on MYC. This suggests targeting MYC directly or indirectly via a mechanism to be determined may be an effective strategy to eradicate IMiD resistant MM.

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Transcriptomics for gallbladder cancer prognosis

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OBJECTIVES/GOALS: Recent research has attempted to identify diagnostic, prognostic, and predictive biomarkers, however, currently, no biomarkers can accurately diagnose GBC and predict patients prognosis. Using machine learning, we can utilize high-throughput RNA sequencing with clinicopathologic data to develop a predictive tool for GBC prognosis. METHODS/STUDY POPULATION: Current predictive models for GBC outcomes often utilize clinical data only. We aim to build a superior algorithm to predict overall survival in GBC patients with advanced disease, using machine learning approaches to prioritize biomarkers for GBC prognosis. We have identified over 80 fresh frozen GBC tissue samples from Rochester, Minnesota, Daegu, Korea, Vilnius, Lithuania, and Calgary, Canada. We will perform next-generation RNA sequencing on these tissue samples. The patients clinical, pathologic and survival data will be abstracted from the medical record. Random forests, support vector machines, and gradient boosting machines will be applied to train the data. Standard 5-fold cross validation will be used to assess performance of each ML algorithm. RESULTS/ANTICIPATED RESULTS: Our preliminary analysis of next generation RNA sequencing from 18 GBC tissue samples identified recurrent mutations in genes enriched in pathways in cytoskeletal signaling, cell organization, cell movement, extracellular matrix interaction, growth, and proliferation. The top three most significantly altered pathways, actin cytoskeleton signaling, hepatic fibrosis/hepatic stellate cell activation, and epithelial adherens junction signaling, emphasized a molecular metastatic and invasive fingerprint in our patient cohort. This molecular fingerprint is consistent with the previous knowledge of the highly metastatic nature of gallbladder tumors and is also manifested physiologically in the patient cohort. DISCUSSION/SIGNIFICANCE: Integrative analysis of molecular and clinical characterization of GBC has not been fully established, and minimal improvement has been made to the survival of these patients. If overall survival can be better predicted, we can gain a greater understanding of key biomarkers driving the tumor phenotype.

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Rib Fractures in Geriatric Trauma: A Review of 1,037 Cases at a Single Level I Trauma Center

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OBJECTIVES/GOALS: Rib fractures are common traumatic thoracic injuries and are associated with high rates of morbidity and mortality. In those age â‰¥ 65, the rate of these complications double. This study sought to identify the extent to which injury-related predictors influence

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