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Hollow, Degradable poly(N-Isopropylacrylamide) Derived Nanoparticles for the Delivery of Anti-Inflammatory Peptides for the Treatment and Prevention of Post-Traumatic Osteoarthritis

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OBJECTIVES/GOALS: Knocking down the inflammatory response following joint trauma may halt the cytokine cascade and prevent the resulting cyclic degradation of articular cartilage. MK2 inhibiting (MK2i) peptides are an emerging and promising class of pharmaceutical to treat post-traumatic osteoarthritis (PTOA); however, these peptides are susceptible to proteolytic degradation in the extracellular space. Our objective is to encapsulate MK2i in thermoresponsive hollow nanoparticles (hNPs) to knockdown the inflammatory cytokine IL-6 to prevent the cyclic degradation of articular cartilage. METHODS/STUDY POPULATION: *NP Synthesis:* N-isopropyl acrylamide (NIPAm) cores was initiated by potassium persulfate (KPS) in aqueous solution with sodium dodecylsulfate (SDS) at 70°C under a nitrogen for 2 hours. Then exposed to oxygen for 45 min, followed by a nitrogen purge. NIPAm, 2-acrylamindo-2-methyl-1-propanesulfonic acid (AMPS), N,N'-bis(acryoyl)cystamine (BAC), and Acrylic Acid (AAc), in fluorescent batches rhodamine b isothiocyanate (RBITC), were polymerized around the core to form the shell. NPs were purified using tangential flow filtration. The NPs were dialyzed at 4°C for 14 days to remove the core and form hNPs. *Loading & Release:* hNPs and MK2i were incubated at 1 mg/ml at 4°C for 24 h. MK2i released into 1x PBS and analyzed on HPLC. *IL-6 Expression*: Bovine chondrocytes seeded at 10,000 cell/cm^2 were stimulated with 20 ng/ml IL-1b daily and treated once with 100 μg/ml MK2i loaded-NP or 100 μg/ml free MK2i treatment on day 2. Analyzed on bovine IL-6 ELISA. *In Vivo Intra Articular Injections:* 75 μl of 2 mg/ml hNPsRHB or a PBS control was injected into the right knee of 4-month old Fischer 344 (Envigo) rats. Rats were imaged daily for 7 days then euthanized, legs dissected, and imaged. RESULTS/ANTICIPATED RESULTS: Core removal facilitated increased MK2i release from hNPs, Fig 1A, allowing up to 63% after 5 days in PBS. The hNPs generated here offer a continual sustained release of MK2i and hNPs are non-cytotoxic (data not shown) up to 12 mg/ml. MK2i loaded-NPs significantly knocked down IL-6 production after a single treatment after 2 days, Figure 1B, and continued knockdown for up to 4 days. hNPsRBITC was successfully injected into rat joint space and was retained for at least 7-days compared to pre-injection and PBS control, Fig 1 B-C. DISCUSSION/SIGNIFICANCE OF IMPACT: hNPs protect MK2i from ECM degradation and offer continual sustained release into chondrocytes. Core removal allows for MK2i release *in vitro* with further sustained release compared to previous non-degradable model. The single MK2i treatment lead to a significant IL-6 knockdown bovine chondrocytes for up to 4 days in hNPs. We were able to successfully inject and retain fluorescently labeled hNPs within rat knees for 7 days. Our translational therapeutic shows the promise of delivering a degradable, non-cytotoxic hNP into the joint space to knockdown the inflammatory response to halt the cyclic progression of articular cartilage degradation and progression of PTOA. CONFLICT OF INTEREST DESCRIPTION: The authors declare the following competing financial interest(s): Moerae Matrix, Inc. has a worldwide exclusive license to the CPP (MK2 inhibitor peptide). A. Panitch owns greater than 5% of Moerae Matrix, Inc.

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Horizontal ridge augmentation in maxilla using bone expansion vs bone splitting techniques in adult patients: a prospective cohort

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OBJECTIVES/GOALS: The objective of the study is to compare two horizontal bone augmentation techniques (bone expansion and bone splitting) that are currently used for horizontally deficient maxillary ridges. Bone expanded in millimeters (mm), implant stability, and patient satisfaction will be compared with each technique. METHODS/STUDY POPULATION: This pilot (prospective cohort) study will be divided in two sites, a private practice and the Oral and Maxillofacial Surgery (OMS) Clinic at the University of Puerto Rico, School of Dental Medicine. A total of 20 patients will be selected, 10 patients in each site. In both sites, pre-operative and post-operative Cone Beam CT radiographs will be taken to measure bone width. Implant stability will be measured using an Osstell. 2 weeks post-surgery, a patient satisfaction questionnaire will be given to patients. A two-sample T test will be used to compare techniques statistically. RESULTS/ANTICIPATED RESULTS: We anticipate that bone expansion will be as good as (non-inferiority) bone splitting in terms of bone expanded in millimeters to desire width, and implant diameter will not be compromised. We also expect that implants placed with the bone manipulation technique will have a higher implant stability at baseline and less pain, discomfort and swelling in terms of patient satisfaction. DISCUSSION/SIGNIFICANCE OF IMPACT: Our contributions here are expected to illustrate clinical and radiographic bone expansion techniques that will enhance implant placement treatment for implantologists and patient's experience.

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Impact of Gender on High On-Treatment Platelet Reactivity (HPR) and Major Adverse Cardiovascular Events (MACEs) in Caribbean Hispanic patients using Clopidogrel

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OBJECTIVES/GOALS: The use of P2Y12 receptor inhibitors like Clopidogrel is crucial in the prevention of thrombotic events in patients with coronary artery disease, peripheral arterial disease, and cerebrovascular disease. Variation in the level of platelet inhibition is present in many patients, and it is associated with the occurrence of major adverse cardiovascular events (MACEs). The term High-on treatment platelet reactivity (HTRP) is used to describe impaired antiplatelet inhibition while on Clopidogrel. Multiple

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factors have been associated with the presence of HTPR in patients with CAD and PAD, including CYP2C19 loss of function polymorphism, drug-drug interactions, and medical comorbidities. Gender differences are another factor that might influence the levels of platelet inhibition while on Clopidogrel and hence, HTPR. Differences by Gender exist in platelet biology, count, and activation. The evidence for the influence of Gender in HTPR is limited, but a possible association has been described. In this study, we described the association of Gender with HTPR and Major Adverse Cardiovascular Events (MACEs) occurrence. The data is from a sample of Hispano-Caribbean patients on Clopidogrel therapy alone or in combination with Aspirin that were retrospectively evaluated from an ongoing trial in Puerto Rico. The result of this study provided evidence of the influence that Gender has on antiplatelet therapy function and MACEs occurrence. METHODS/STUDY POPULATION: The population in the study consisted of Hispano-Caribbean patients using Clopidogrel alone or in combination with Aspirin for coronary artery disease, peripheral arterial disease, or cerebrovascular disease. The sample was obtained from multiple hospital institutions with cardiovascular services in Puerto Rico during the years 2016-2019. Patients were part of the ongoing trial, "Adopting a precision medicine paradigm in Puerto Rico: leveraging ancestral diversity to identify predictors of Clopidogrel response in Caribbean Hispanics." The sample size consisted of 150 patients. Participants were recruited during routine medical care, pre-admission evaluation for elective cardiac procedures, or during hospitalization in the participating institutions. Platelet reactivity testing was performed with the system Verify Now® to determine PRU values, and High on-treatment platelet reactivity was defined as PRU ≥208. One year after recruitment, the patients were re-evaluated for the occurrence of MACEs. The association of the variables HTPR, occurrence of MACEs, and Gender were assessed using logistic regression in addition to the role of HTPR and Gender for predicting MACE occurrence. The analysis was done using the statistic software Intellectus ©. RESULTS/ANTICIPATED RESULTS: The sample consisted of 67 females and 83 males with and Mean age of 67.87 years and 61.11 years, respectively. The prevalence of HTPR in the sample was 32.67 % (n = 49) with 36% (n = 24) for females, and 30%(n = 25) for males. The mean PRU values were 179.54 for females and 170.81 for males. The percentage of MACEs one year after recruitment was 29.33 % (n = 44) with 43% on females (n = 19), and 57% on males (n = 25). Logistic regression for Gender predicting HTPR was non-significant with a $\chi 2(2) = 0.55$, $p = .758$, and McFadden $R^2 = 0.00$. Also, logistic regression for the effects of Gender and HTPR on the Odds of MACEs occurrence was not significant based on a model with an alpha of 0.05, $\chi 2(2) = 1.99$, $p = .370$, and McFadden $R^2 = 0.01$. DISCUSSION/SIGNIFICANCE OF IMPACT: The sample consisted of 67 females and 83 males with and Mean age of 67.87 years and 61.11 years, respectively. The prevalence of HTPR in the sample was 32.67 % (n = 49) with 36% (n = 24) for females, and 30%(n = 25) for males. The mean PRU values were 179.54 (±70.42) for females and 170.81(±64.89) for males. The percentage of MACEs one year after recruitment was 29.33 % (n = 44) with 43% on females (n = 19), and 57% on males (n = 25). Logistic regression for Gender predicting HTPR was non-significant with a $\chi 2(2) = 0.55$, $p = .758$, and McFadden $R^2 = 0.00$. Also, logistic regression for the effects of Gender and HTPR on the odds of MACEs occurrence was not significant based on a model with an alpha of 0.05, $\chi 2(2) = 1.99$, $p = .370$, and McFadden $R^2 = 0.01$.

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Metabolomic Identifiers Predictive of Adverse Events due to Acetaminophen Administration

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OBJECTIVES/GOALS: Acetaminophen (Tylenol, APAP) toxicity has been well documented and well explored over the last 50 years. However, there has been no investigation into identification of specific metabolites that can *predict* which patients will have adverse reactions to therapeutic doses of APAP. METHODS/STUDY POPULATION: 205 subjects recruited from the Denver, CO community received the highest recommended daily dosing of APAP, 4 grams, for 16 days. Subjects were grouped by 1) alanine aminotransferase (ALT) at any monitored time point above 60units/L (n = 20) vs 2) no increase in ALT at any time point (n = 185). Blood was collected at days 0, 4, 7, 16, and 31. Samples were run on ultra-high performance liquid chromatography mass spectrometry with 27 heavy-labeled standards for metabolites documented to be associated with APAP metabolism. Data will be analyzed to look for significant changes in metabolite and demographic variable expressions using t-tests, chi square and logistic regression, as appropriate. RESULTS/ANTICIPATED RESULTS: It is expected that there will be greater elevations of conjugated non-toxic APAP metabolites (APAP-glucuronide, APAP-sulfate) in subjects whose ALT did not elevate because of successful hepatoprotection. Conjugated APAP metabolites are expected to only be present in samples taken after APAP therapy initiation confirming exposure as compared to being predictive of toxic response. Increases in lactate and cysteine in pre-exposure samples would allow for prediction of APAP toxicity as they are expected to have increased expression in subjects whose ALT became elevated which is indicative of increased hepatic damage due to oxidative damage. DISCUSSION/SIGNIFICANCE OF IMPACT: Identification of metabolites and/or demographic factors associated with toxic response to APAP prior to administration could advise APAP recommendations. Quantification of post-APAP administration metabolites would identify extent of successful hepatoprotective mechanisms.

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Noninvasive hybrid ultrasound and photoacoustic imaging for the assessment of liver fibrosis

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OBJECTIVES/GOALS: The detection of liver fibrotic changes at an early and reversible stage is essential to prevent its progression to end-stage cirrhosis and hepatocellular carcinoma. Liver biopsy, which is the current gold standard for fibrosis assessment, is accompanied by several complications due to its invasive nature in addition to sampling errors and reader variability. In this study, we evaluate the use of quantitative parameters extracted from hybrid ultrasound and photoacoustic imaging to detect and monitor fibrotic changes in

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