2fold reduction in p16 expression consistent with decreased senescence.

Conclusions: This study demonstrated that TNF-α induces NP cell senescence and this involves activation of STAT signaling and IL-6. Senescent cells propagate senescence in healthy cells via a paracrine effect that involves STAT signaling. This paracrine effect may explain why senescent NP cells accumulate in IVD with age. The role of pSTAT3 in regulating NP senescence requires further study.

PRESENTATION NUMBER: 49
THE PATIENT ACCEPTABLE SYMPTOM STATE FOR KNEE PAIN - A SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

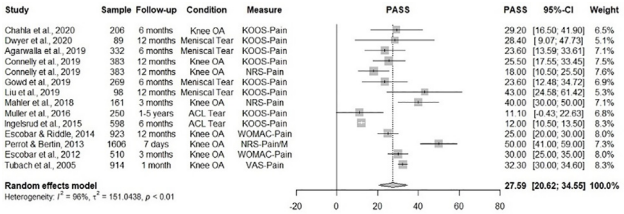
V. Georgopoulos [1], S. Smith [1], D. McWilliams [1], T.L. Vincent [2], F.E. Watt [2], D.A. Walsh [1]. , The STEpUP OA Consortium[1] *Univ. of Nottingham, Nottingham, United Kingdom;* [2] *Univ. of Oxford, Oxford, United Kingdom*

Purpose: Knee pain is highly prevalent, most commonly attributed to osteoarthritis in older people, and in younger people often due to internal derangements. Knee pain can be measured using numerical patient-reported outcome measures (PROMs). Several pain measurement questionnaires have been used for OA pain. These questionnaires each purport to measure the participant's experience of pain, but may address different pain characteristics (recollection over different time periods, pain impact on function, constant or intermittent or other qualitative aspects of pain). Pooling pain data between studies using different PROMs requires demonstration or transformation to ensure that each PROM would give the same value for pain in a single participant. The Patient Acceptable Symptoms State (PASS) indicates a clinical benchmark that permits comparison between PROMs. Current treatments might relieve but often do not eliminate pain, and PASS is the threshold representing pain which a patient would accept for the remainder of their life. We aimed to systematically review PASS thresholds for different pain PROMs used with people with knee pain, and to identify factors that might influence PASS heterogeneity.

Methods: We systematically reviewed literature for PASS scores in knee pain using searches of CENTRAL, MEDLINE, EMBASE, AMED, CINAHL, and SPORTDiscus databases from their inception date up to June 2020. PROMs of interest were pain-specific questionnaires (or their related domains). Title screening, data extraction, and methodological quality assessments were performed independently by 2 reviewers. Outcome scores were standardised and included in meta-analysis models as a 0-100 scale (0: no pain, 100: highest pain severity). Based on a-priori hypotheses (PROMs, diagnoses, interventions, follow-up timepoints and methodological quality) and following review of data from included studies (PASS score derivation methods), potential effects of study and patient characteristics on PASS were explored. Post-hoc meta-regression explored the relationship between baseline pain and PASS scores. The significance of differences observed between subgroups was evaluated via a Cochran's Q-test. Study heterogeneity was evaluated with the I^2 statistic.

Results: Eighteen eligible studies (n=7766 participants) reported PASS from pain PROMs in people with knee pain. All studies were longitudinal and observational, undertaken within the context of a treatment for knee pain. Identified PROMS were the Knee Injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Numerical Rating Scale (NRS) and the Visual Analogue Scale (VAS). Most studies were of low risk of bias (8/18), with 6/18 of moderate and 4/18 of high risk of bias. Thirteen studies (n=6339 participants) reported data that allowed their inclusion in meta-analysis models. The pooled pain PASS score was 27 (95% CI: 21 to 35; n=6339 participants) with significant heterogeneity (I^2 = 96%, p <0.01) (Figure). No significant differences (Q=2.07, p = 0.36) were observed between PASS scores derived for the different knee pain PROMs (KOOS: 23, 95%CI: 16 to 30; WOMAC: 28, 95% CI: 23 to 32; NRS or VAS: 35, 95%CI: 24 to 45). Lower estimates of PASS were associated with lower baseline pain (β=0.60, p=0.02), longer time to follow up at which PASS was estimated (6-months 30, 95%CI: 20 to 40; 12-months: 24, 95%CI: 17 to 30; more than 12-months: 16, 95% CI: 9 to 22), and with surgical (24, 95%CI: 17 to 30) rather than non-surgical interventions (40, 95%CI: 29 to 52). PASS scores were similar between knee osteoarthritis (31, 95%CI: 26 to 36) and meniscal tear (27, 95%CI: 20 to 35) but lower for ligament tears (12, 95%CI: 11 to 13). Observed differences in estimates of PASS due to risk of bias (low: 23, 95%CI: 11 to 35; moderate: 34, 95%CI: 24 to 45; high: 26, 95%CI: 21 to 31) were not significant (Q=1.93, p = 0.38).

Conclusions: Standardised knee pain PROMs scores of approximately 30/100 are considered acceptable by people with knee pain. The level of pain that is acceptable might depend upon the baseline pain severity (higher with worse baseline pain), decrease with time from commencing an intervention and vary according to diagnostic or treatment group. However, different knee pain PROMs when transformed produce similar PASS scores, suggesting that standardised scores derived from multiple instruments might be validly combined in large multicentre studies using historically collected data.



PRESENTATION NUMBER: 50
A PHASE 2, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF SENOLYTIC MOLECULE UBX0101 IN THE TREATMENT OF PAINFUL KNEE OSTEOARTHRITIS

N. Lane [1], B. Hsu [2], J. Visich [2], B. Xie [2], A. Khan [2], J. Dananberg [2]. [1] *Univ. of California Davis, Sacramento, CA, USA;* [2] *Unity Biotechnology, Inc., South San Francisco, CA, USA*

Purpose: To assess the efficacy and safety of single-dose, intra-articular (IA) administration of UBX0101 in patients with painful knee osteoarthritis (OA). UBX0101 is a p53/MDM2 interaction inhibitor that can induce apoptosis of senescent synoviocytes. Results from a recent Phase 1 study (NCT03513016) suggested that IA UBX0101 had dose-dependent, clinically meaningful effects on pain and function in patients with knee OA.

Methods: This was a Phase 2, randomized, double-blind, placebo-controlled, parallel group study in OA patients randomized 1:1:1:1 to IA UBX0101 0.5 mg, 2.0 mg, 4.0 mg or matched placebo. Key eligibility criteria included knee OA by ACR criteria, Kellgren-Lawrence grade (KLG) 1-4, and mean daily pain between 4 and 9 on a Numeric Rating Scale (NRS, 0-10). Study duration was 24 weeks. Clinical outcomes included WOMAC pain (WOMAC-A) and function (WOMAC-C) subscores (each on a 0-4 Likert scale), daily pain NRS, patient global assessment (PGA) and patient global impression of change (PGIC). The primary endpoint was the change from baseline (CFBL) in WOMAC-A at Week 12. Key secondary efficacy endpoints included the CFBL to Week 12 of the WOMAC-C and the weekly mean of the daily pain NRS scores. With 45 patients per group, the study had 90% power and an alpha of 0.10 for a two-sided comparison of UBX0101 versus placebo with an effect size of 0.50 and an assumed standard deviation of 0.75 on the WOMAC-A item score least square (LS) mean change at Week 12.

Results: A total of 183 patients were randomized. The study population was balanced regarding patient characteristics and baseline outcome measure values. Mean age was 62.9 years, 64% of the population was female, and 78% was white. Mean WOMAC-A sub-score at baseline ranged between 2.05 and 2.20. Decreases in WOMAC-A from baseline to Week 12 were similar for all treatment groups. The LS means CFBL in WOMAC-A at Week 12 were -0.924, -1.52, -1.019, and -1.017 for UBX0101 0.5 mg, 2.0 mg, 4.0 mg, and placebo, respectively. Secondary endpoints were not met. An historically high placebo response through Week 12 confounded the ability to discern a UBX0101 treatment effect. Possible reasons for this were the IA dosing route, patient and/or investigator expectedness, and gender dimorphism in pain reporting. Single IA doses of UBX0101 up to 4 mg were associated with an acceptable safety profile and were well-tolerated. Most adverse events (AEs) were mild. Seven, non-related, serious AEs occurred during the study; one was a death due to coronary artery disease.