group. Similar results were observed for miR-193b. By contrast, ADAMTS5 expression was downregulated in the miR-320c mimic group and upregulated in the inhibitor group. Cell proliferative activity was upregulated significantly in the miR-193b inhibitor group compared with the control group. We believe that miR-199a-3p and miR-193b are involved in the senescence of chondrocytes and that miR-320c is involved in the juvenile properties of chondrocytes.

I-3
OA PHENOTYPE AND THERAPY

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Purpose: There is a massive unmet need for effective osteoarthritis (OA) therapies, both symptom and structure modifying. The application of modern imaging modalities such as magnetic resonance imaging (MRI) and ultrasound has led to ground-breaking advances in understanding of the OA phenotype. As yet the revolution in disease knowledge has not been mirrored by improved therapeutics, but increasingly the OA literature demonstrates a shift toward personalised, pathology-targeted interventions. In typical symptomatic OA, modern imaging has demonstrated abundant pathology; inflammation (visualised as synovitis) and subchondral bone pathology are much more common than previously considered. Synovitis has been reported extremely commonly, with detection reflecting the sensitivity of the imaging tool employed. Although generally less in volume and vascularity than in rheumatoid arthritis (RA), the inflammatory cells and mediators present are very similar. This imaging-detected synovitis has been associated with the pain of OA, and also identified as an independent predictor of progression to joint replacement. Of our current symptomatic pharmacological agents, the 2 with consistently modest analgesic effect sizes are NSAIDs and intra-articular corticosteroids - both of which have significant anti-inflammatory actions. Oral corticosteroid at low dose failed to benefit hand OA in a recent RCT; however a larger dose did have analgesic effects in a knee OA study. Disease modifying anti-rheumatic drugs are used in rheumatoid arthritis (RA) for their effect on the primary disease inflammatory process, resulting in reduction in symptoms and consequent retardation of structural joint damage. Such DMARDs were historically not considered for OA as it was not primarily an inflammatory arthritis. However a small, open label study of methotrexate demonstrated analgesic efficacy equivalent to that of an NSAID. Trials targeting IL-1 with a number of monoclonal antibody inhibitors have been disappointing in terms of symptom control. Several recent studies have investigated the effects of anti-TNF therapies in OA, with variable results. Studies of erosive hand OA have resulted in reduced swollen joint counts and reduced structural deterioration in joints with baseline clinical synovitis, but generally there have been no sustained analgesic benefits, though often anti-TNF therapy was given for short duration. Fewer studies have been conducted in knee OA, although a small number open-label study suggested good analgesic response. MRI-identified bone marrow lesions (BMLs) have provided insights into subchondral bone architectural failure and are related to both pain and ipsilateral compartment progression of knee OA. A number of pharmacological therapies with potential to positively affect trabecular structure (as well as direct potential benefits for cartilage) have recently demonstrated benefits in large OA trials, including calcitonin, strontium and zoledronic acid; the latter 2 therapies have in particular demonstrated reductions in BMLs and associated reductions in knee pain. These exciting though relatively early attempts at phenotype-targeted therapies provide the basis for strong growth in this field, and improved molecular tissue phenotyping should further enhance the range of targets and potential therapeutics.

I-4
NOVEL APPROACHES TO JOINT REPAIR

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Purpose: The repair of articular cartilage following joint injury or degeneration remains an important challenge for the field of tissue engineering. While a number of techniques have been developed over the years for the treatment of small cartilage defects, there have been few attempts at tissue-engineered therapies for end-stage osteoarthritis. Some of the major considerations for this approach include the identification and characterization of an abundant and accessible cell source as well as the design of biologically and mechanically functional scaffolds that can withstand joint loading.

Methods: Here we describe the engineering of large, anatomically-shaped cartilage constructs using different stem cell sources (adipose stem cells, mesenchymal stem cells, or induced pluripotent stem cells), combined with mechanically functional cell-instructive scaffolds. Under appropriate culture conditions, these stem cells exhibit a chondrogenic phenotype and can synthesize cartilage-specific matrix proteins that are assembled in a functional extracellular matrix. An important consideration in the long-term success of such tissue replacements is a more thorough investigation of the influence of biomechanical factors, such as the design and characterization of the mechanical properties of biomaterial scaffolds and the use of biophysical stimuli to control cell differentiation and metabolism.
Results: Using principles of "functional tissue engineering", we have developed novel biomimetic scaffolds, based on techniques for three-dimensional weaving of biocompatible fibers, which can conform to contoured surfaces. Such moldable composite scaffolds can be engineered with initial properties that reproduce the anisotropy, viscoelasticity, and tension-compression nonlinearity of native articular cartilage, providing the potential for complete resurfacing of the entire joint surface. The ability to control stem cell fate in vivo may provide more direct approaches for translation of these tissue-engineering techniques by minimizing ex vivo manipulation of cells and repair tissues. In this regard, these textile processing techniques allow site-specific delivery of proteins or genes to facilitate the formation of complex inhomogenous tissues from a single cell source. Furthermore, this method can be adapted to confer tunable and inducible immunomodulatory properties to stem cells for controlled drug delivery to the joint.
Conclusions: Recapitulating the biomechanical properties of the tissue, in addition to providing developmental, biophysical, and immunomodulatory cues to the stem cells, may provide new advances in the engineering of functional tissue replacements as a therapy for end-stage osteoarthritis.

I-5
STUDIES OF POST-TRAUMATIC OSTEOARTHRITIS-IMPLICATIONS FOR UNDERSTANDING OF THE ROLE OF MECHANICAL FORCES IN THE ONSET AND PROGRESSION OF OSTEOARTHRITIS

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Purpose: Excessive joint loadings, either single (acute contact stress) or repetitive (cumulative contact stress), cause progressive joint degeneration and subsequent development of the clinical syndrome of osteoarthritis (OA). Joint injuries causing acute excessive contact stress are common and often affect young adults: each year one in 12 people between the ages of 18-44 seeks medical attention for treatment of joint injury, and more than 12% of all lower limb OA is caused by joint trauma. Despite advances in surgical treatment and rehabilitation of injured joints, the risk of OA following joint fractures has not decreased in the last 50 years. For these reasons there is a critical need to advance understanding of how mechanical forces cause progressive loss of articular cartilage and the syndrome of osteoarthritis.
Methods: We have conducted a series of in vitro, in vivo and clinical studies with the intent of discovering how acute and cumulative contact stress cause osteoarthritis.
Results: Cumulative excessive articular surface contact stress that leads to OA results from joint dysplasia, incongruity and instability, but also may cause OA in patients without known joint abnormalities. Advances in understanding of the thresholds for mechanical damage to articular cartilage, and of the biologic mediators that cause progressive loss of articular cartilage due to excessive mechanical stress, will lead to better treatments of joint injuries and improved strategies for restoring damaged joint surfaces. Recent *in vitro* investigations show that reactive oxygen species (ROS) released from mitochondria following excessive articular cartilage loading can cause chondrocyte death and matrix degradation and reduce the ability of chondrocytes to respond normally to physiologic loading. Alarmins released from damaged chondrocytes trigger an inflammatory response that can cause loss of cartilage. Preventing the release of ROS or inhibiting their effects preserves chondrocytes and their matrix. Blocking the effects of Alarmins decreases the inflammatory response. Fibronectin fragments released from articular cartilage subjected to excessive loads also stimulate matrix degradation; inhibition of the molecular pathways initiated by these fragments prevents this effect. Distraction and motion of osteoarthritic articular surfaces in humans can promote joint remodeling, decrease