Results: Both adverse and beneficial effects of loading on joint health are present. High magnitude loading results in OA-like pathology including cartilage damage, osteophytes and bone sclerosis. At the metaphysis, high magnitude loading induces anabolic bone formation, which stiffens the bone structure and also may contribute to the changes present at the joint surface. On the other hand, the same approach with low magnitude loading can be beneficial to joint tissues and attenuate cartilage damage and osteophyte formation following joint injury by destabilization of the medial meniscus. These findings demonstrate the importance of the loading environment to joint health and the differential tissue responses.
Conclusions: The development and progression of cartilage damage and OA is complex and multifactorial. Load-induced damage is one contributing mechanism. Loading models are valuable tools to identify the relationship between sub-failure mechanical forces and progressive tissue changes in OA, without the confounding effects of surgery. In addition, thisapproach allows the interaction of joint loading with other tissues including subchondral bone to be studied, to address key questions in developing preventative strategies and disease modifying therapies for OA.

I-12
METABOLIC DISORDERS AND TRANSCRIPTIONAL REPROGRAMMING IN OA PATHOGENESIS

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Although osteoarthritis (OA) is currently considered to be associated with metabolic disorders and metabolic syndrome (MetS), direct evidence for this is lacking. Because MetS is associated with abnormal cholesterol levels and production of oxysterol metabolites, we aim to characterize the role of abnormal cholesterol metabolism in OA pathogenesis. We present evidences that the CH25H-CYP7B1-RORα axis of cholesterol metabolism in chondrocytes is a crucial catabolic regulator of the pathogenesis of OA. OA chondrocytes had increased levels of cholesterol because of enhanced uptake, upregulation of cholesterol hydroxylases (CH25H and CYP7B1) and increased production of oxysterol metabolites. Adenoviral overexpression of CH25H or CYP7B1 in mouse joint tissues caused experimental osteoarthritis, whereas knockout or knockdown of these hydroxylases abrogated the pathogenesis of osteoarthritis. Moreover, retinoic acid-related orphan receptor alpha (RORα) was found to mediate the induction of osteoarthritis by alterations in cholesterol metabolism. These results indicate that OA is a disease associated with metabolic disorders and suggest that targeting the CH25H-CYP7B1-RORα axis of cholesterol metabolism may provide a therapeutic avenue for treating osteoarthritis. We will also present evidences that various metabolic disorders and transcriptional reprogramming regulates OA pathogenesis in mouse models of OA.

I-13
PREVENTION OF OA, UNDER THE LIGHT OF PHENOTYPES

F. Berenbaum. *Sorbonne Université Saint-Antoine Hosp., Paris, France*

Given our inability to cure osteoarthritis (OA) today, the only way to act effectively is the primary/secondary prevention of the illness. However, it is a real challenge to disseminate prevention messages early in life when the disease itself often only appears late in life. Current research to try to phenotype the disease is an opportunity to improve prevention by delivering specific messages to specific populations. The purpose of this lecture is to discuss the optimization of OA prevention based on the recent attempts to delineate OA phenotypes.

I-14
CARTILAGE/BONE CROSSTALK IN JOINT HEALTH AND DISEASE

T. Alliston. *Univ. of California San Francisco, San Francisco, CA, USA*

Purpose: Understanding the mechanisms that maintain cartilage homeostasis and disease requires consideration of how spatial and physical features of the joint, across multiple length scales, shift the activity of biological signaling pathways. With a focus on well-known participants in cartilage health and disease, TGF-beta and MMP13, this talk will explore these concepts in joint crosstalk between cartilage and bone.
Methods: This study examines bone and cartilage outcomes in several models, including human surgical specimens, mouse models, and in vitro systems, with a range of biological and mechanobiologic approaches.
Results: Our results shed light on the mechanisms by which TGF-beta both supports joint homeostasis, and by which disruption of TGF-beta signaling can exacerbate joint disease, through its cell intrinsic effects in bone and in cartilage.
Conclusions: Understanding the compartment and cell type specific effects of TGF-beta, and how this signaling pathway is regulated by physical cues, is essential for understanding the important and multifaceted role of this signaling pathway in joint crosstalk.

I-15
SHARING BIOMECHANICAL DATA: CHALLENGES AND OPPORTUNITIES

M.A. Hunt. *Univ. of British Columbia, Vancouver, BC, Canada*

Purpose: The purpose of this workshop is to provide the participant with an understanding of the need for developing large, multi-centre datasets that include movement-based biomechanical outcomes from people living with osteoarthritis.
Methods: Collection of biomechanics data - loosely defined herein as any kinematic, kinetic, or muscle activity data during human movement resulting in direct analysis of global movement characteristics, or used to drive musculoskeletal modeling to estimate in vivo values - can provide important insights into the normal and abnormal functioning of muscles, bones, and joints during movement. However, this is an onerous task that is heavy on time, cost, expertise, and personal resources. As a result, there is much difficulty in obtaining datasets with very large sample sizes, thereby severely limiting the ability to answer many types of research questions that rely on hundreds or even thousands of data points. This known limitation presents a clear need to work collaboratively to conduct multi-centre biomechanics studies to grow the field and increase knowledge. Material presented during this workshop will focus on some of the unique aspects of biomechanics data collection that pose threats to building these large datasets. Data from ongoing attempts to conduct multi-centre biomechanics studies will be reported, and creative solutions and helpful hints to overcome known barriers will be provided. Finally, a collaborative discussion of common goals and opportunities for data sharing will provide a framework for the first steps towards an OARSI-based biomechanics initiative.
Results: Following this workshop, the participant should be able to identify the research opportunities available, and questions that can be best answered, through the use of larger, multi-centre biomechanics datasets. Further, the participant should be better aware of some of the barriers and facilitators associated with establishing a large, multi-centre biomechanics dataset.
Conclusions: There is a growing interest in, and need for, large datasets to answer a multitude of basic and clinical research questions including: exploratory associations and mechanisms, long-term changes, and effectiveness of treatments. These datasets exist in the osteoarthritis field, but are limited to mainly imaging, biomarkers, symptoms, and simple measures of physical function. While joint- and whole body-biomechanics are known to play an important role in osteoarthritis pathogenesis, yet no large cohort study to-date includes these important outcomes. An appreciation of the mechanisms and opportunities available to develop and maintain these large biomechanical cohorts is therefore important.

I-16
GUIDELINES AND RECOMMENDATIONS IN TREATING HAND OA

T. Stamm. *Med. Univ. of Vienna, Vienna, Austria*

Purpose: Hand osteoarthritis has an enormous impact on functioning in daily life. The participants of this workshop will critically appaise the relevant guidelines, recommendations and points to consider and explore their overlaps and differences.
Methods: The participants will discuss potential barriers and facilitators for the implementation of these on the micro, meso and macro levels in small groups. We will consider and include the perspective of patients and different disciplines and professions.

Results and conclusions: We will also explore how these guidelines, recommendations and points to consider can lead the way to value based healthcare in the future.

I-17
BIOLOGICAL AGENTS IN OA - HOPES AND DISAPPOINTMENTS

X. Chevalier, Sr., F. Eymard, Sr.. *Hosp. Henri Mondor, Creteil, France*

Purpose: To review the trial in humans using biologics in osteoarthritis (OA) which can be can be categorized according to the main target: pain, structure or both.
Methods: A literature review (Medline, Cochrane, Embase) of the most recent trials in OA using biologics
Results: The analgesic effect of anti-nerve growth factor (NGF) was initially dramatic using high dose and intravenous route of administration, but emerging severe arthropathies (in the targeted knee but not only) have dampened down this enthusiasm. Most recent trials used anti NGF Mab, administered subcutaneously, with lower dose, shorter interval of administration and without concomitant use of NSAIDS. The effect on pain is still superior to placebo but with a much lesser magnitude. Unfortunately, long term follow-up in those trials still shows a concern in terms safety profile. Thus, Patients who will benefit of this anti NGF therapy should be strictly selected and followed up. Biologics agents targeting main cytokines (interleukines 1 and 6, tumor necrosis alpha) have been tested in knee OA and in hand OA. The first randomized controled trial in humans using a single local administration of the antagonist of IL-1, at 2 doses: 50 and 150 mg, failed to show an analgesic effect, except at day 3 with the highest dose. This negative result has been confirmed in trials using systemic administration of monoclonal antibodies directed against only IL1-β or against IL-1 α and Il-1 β in patients with knee OA and in patients with hand OA. However, in the CANTOR trial recruiting patients with cardiovascular disease treated with canakinumab, post hoc analysis indicated that the patients in the verum group, shows a dramatic decrease in the number of total joint replacement (hip and knee) (about 50%). This might open a door for a possible anti IL-1 strategy dedicated to patients with some part of systemic inflammation. Most of trial with anti TNF inhibitors have been performed in patients with erosive digital hand OA and all were negative on pain and on structure (measured by different parameters on magnetic resonance imaging). Finally the last cytokine that has been targeted is IL-6. Results of the RCP trial in hand OA are ongoing. Taking all together, biologics in OA are really disappointing, raising more questions than answers: choice of the targets, choice of selected phenotype of pain, selection of the route of administration, too short time of intra articular residence of the drug etc. News biologics targeting WNT, bradykinin or anti sense micro RNA are under development but so far, the preliminary results needs to be confirmed in large trials in humans. Finally, the last option is to try to stimulate the cartilage repair response which is naturally weak. Fibroblast growth factor 18 (sprifremin), an anabolic and mitogenic factor for the chondrocyte, has been tested against placebo in an ambitious trial over 5 years with 2 years of treatment and 3 years of follow-up. The drug was intra-articularly delivered every 6 months or every 12 months, with 2 different dosages. At the first end point, at year 2, with the highest dose of FGF-18, a statistically significant difference with the placebo was observed on the cartilage volume measured by MRI in the global, medial and lateral compartment on the involved knee. Unfortunately, there was no effect on pain in the ITT population, except in a sub group of patients with a minimum threshold of pain and an initial joint space width between 1.5mm and 3.5 mm (around one third of the population) show a significant effect on pain reduction compared to placebo. If results of this long term trial are confirmed in others trials, FGF-18 may constitute the first real disease modifying drug in OA. Conclusions
Conclusion: The trials in humans using biologics are disappointing. We should keep in mind that blocking a single mediator will not stop the catabolic process in OA. Thus in the next future, we should probably adapt a drug owing to the evolution of the disease, to the profile of patient, to the radiological aspect of the disease and to the phenotype of pain. The story is just starting ……

I-18
THE ROLE OF SYNOVIUM IN THE ONSET AND PROGRESSION OF OA

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Conventionally, the synovial changes in OA are considered to be a secondary event associated with cartilage degeneration. However, recent studies have shown that synovial changes are actively involved in the pathology of OA. This presentation provides an overview of our current understanding of the synovial changes in knee OA. Clinically, the significance of synovial changes in OA is two-fold. First, synovial changes are closely related to the symptoms of knee OA, especially pain. Studies using MRI have revealed that the presence of effusion-synovitis in knee joints is associated with knee pain. Second, synovial changes may be related to the structural progression of knee OA. The results of cohort studies have consistently indicated that knees with effusion-synovitis are at higher risk for disease progression. Thus, synovial changes may play a pivotal role in the pathology of OA by causing pain and cartilage degeneration. The severity of synovial changes in OA joints may change with time. This may explain some of the clinical features of OA. For example, the symptoms of knee OA may fluctuate with time, and the progression of OA is often phasic. These features may be related to the vacillation of synovial changes. Synovial changes may occur irrespective of the severity of structural changes observed on radiographs. Again, this may explain the dissociation between the extent of structural changes and the severity of symptoms which is often encountered with the disease. While most of the above findings were obtained from observations of established OA, recent studies have focused on the knee joints in the very early stage of the disease, or early OA, in an attempt to elucidate the initial change(s) that may trigger the disease. The results of such studies have shown that the synovial changes may occur prior to the development of radiographic changes, and that such changes may cause pain and structural changes in the joints of early OA patients, as occurs in established OA. Thus, synovial changes may be an initial event of OA, which plays a key role in the initiation of the disease. Despite its significance, the mechanism(s) underlying synovial changes in OA has not yet been elucidated. Again, it is not known why synovial changes are related to pain or structural progression. It is therefore necessary to elucidate the mechanism(s) underlying the synovial change in OA since it will be helpful to establish effective treatments for knee OA.