Focusing on compounds from the habitual diet that may prevent the onset or slow the progression of OA is a strategy that has been under-investigated to date. An approach that relies on dietary modification is clearly attractive in terms of risk/benefit and more likely to be implementable at the population level. However, detailed molecular studies ahead of a full clinical trial are required in order to establish modes of action (which are different from traditional single target pharmaceuticals) at dietary achievable levels and to optimise the design of trials to gain an evidence-base of efficacy.
Methods: There are currently limited data on the interrelationship between diet and OA. Data come from a variety of studies: in vitro cell and tissue explant models, animal models, population-based studies using habitual intakes and risk factors/disease incidence and intervention trials. There is a large variability between studies, e.g. in animal models, a dietary intake approach would be optimal in order to relate to human exposure, but some studies use intra-articular injection and/or concentrations not achievable through the diet. The small and short-term intervention trials conducted to date have many different designs, number of patients, time length and outcome measures.
Results and Conclusions: There are however, a number of pertinent studies in the literature and this presentation will review these. It will also comment on our own experience developing sulforaphane, a compound derived from the consumption of cruciferous vegetables, particularly broccoli, in OA from laboratory models into proof of principle patient trials, as well as the identification of other bioactive diet-derived compounds.

I-8
PROTEOMIC PROFILING OF THE ECM IN HEALTH AND DISEASE

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Purpose: The ECM is a complex meshwork of proteins providing architectural support to cells and conferring biomechanical properties to tissues. In addition, it provides chemical cues that orchestrate cellular functions such as proliferation and survival, adhesion, and migration. Degradation, hyper-production or alteration of the composition of the ECM cause or accompany numerous pathologies such as musculoskeletal and cardio-vascular diseases, cancers, and fibroses. Thus, a better characterization of ECM composition, metabolism, and biology can lead to the identification of novel prognostic and diagnostic markers and offer novel therapeutic opportunities.
Methods: We have devised a unique mass-spectrometry-based proteomic pipeline coupled to computational tools to profile the ECM composition, or "matrisome", of normal and diseased tissues.
Results: In this presentation, I will first discuss how proteomics has emerged in recent years as the method of choice to characterize the ECM composition of normal and pathological samples. I will then illustrate how proteomic profiling has led to the identification of novel proteins playing causal role in the etiology of diseases. Last, I will discuss the latest release and new features of the second version of MatrisomeDB, a searchable compendium of proteomic data on the ECM produced by cells in culture or in vivo that we have made available to the broad scientific community.
Conclusions: We propose that the ECM is an underexplored reservoir of potential diagnostic and prognostic markers as well as therapeutic targets, and that its exploration using proteomics will pave the way for the development of novel approaches to better care patients.

I-9
MEDIATION ANALYSIS: UNDERSTANDING CAUSAL PATHWAYS TO DISEASE OUTCOMES

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Purpose: To understand causal pathways to disease outcomes and to quantify the potential mechanisms of an intervention-disease relationship.
Methods: This workshop discusses recent advances in mediation analysis that are based on modern causal inference methods. It starts with an introduction to the key concepts in mediation analysis and discusses how to assess the importance of the causal mechanisms by which an intervention/exposure affects an outcome.
Results: The workshop enables the implementation of the state-of-the-art techniques for decomposing an intervention effect into natural direct and indirect/mediated effects as well as quantifying interventional direct and indirect effects.
Conclusions: Mediation analysis provides the framework to test causal hypotheses that could ultimately inform utilizing more optimal interventions.

I-10
FROM OA RISK GENES TO UNDERLYING DISEASE MECHANISMS

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The mapping of risk loci for polygenic traits is now a relatively straightforward procedure; the next major step in complex trait analysis is transitioning from association signal to functional characterisation. This offers a realistic means of generating clinically-relevant mechanistic insight that will assist new treatment development. OA is a highly polygenic disease and so far, just over 100 OA risk-conferring association signals have been mapped in the human genome. An overwhelming majority of the associated DNA variants reside in non-protein-coding regions of the genome and, as such, OA genetic susceptibility is presumed to act principally via changes to gene expression. The availability of excised tissue following arthroplasty of an OA joint offers the opportunity to experimentally test this in disease-relevant cells, including cartilage chondrocytes, the single cell type in this tissue. In this session, I will describe the experiments that are undertaken to move from the association signals toward a functional analysis of the genetic risk and how these studies contribute to our understanding of OA disease mechanisms. The session will encompass in-silico analyses and lab-based experimental studies, and will cover genetics, epigenetics, genomics and functional studies in disease-relevant primary cells, tissues and cell lines.

I-11
IN VIVO LOAD-INDUCED OA IN THE MOUSE

M. van der Meulen [1], F.C. Ko [2], O.O. Adebayo [3], D.T. Holyoak [4], S. Ziemian [1]. [1] *Cornell Univ., Ithaca, NY, USA;* [2] *Rush Univ., Chicago, IL, USA;* [3] *Univ. of Massachusetts, Amherst, MA, USA;* [4] *Exponent, Philadelphia, PA, USA*

Purpose: Musculoskeletal tissues not only bear joint loads, but actively adapt their structure and composition to the mechanical environment. However, our understanding of the mechanisms of this functional adaptation is limited, particularly in complex systems such as synovial joints. For example, adaptive changes in articular cartilage and underlying subchondral bone are both key contributors to osteoarthritis (OA) pathogenesis. Using well-controlled mechanical loading, we have been studying the in vivo response of joint tissues to mechanical stimuli. Non-invasive in vivo compression of the mouse tibia can induce both adverse and beneficial effects in bone, cartilage and synovium depending on the experimental conditions. My laboratory has focused on understanding load-induced joint damage and the role of bone tissue properties in this process.
Methods: Our primary experimental model is in vivo loading of the mouse tibia. Under IACUC approval, we apply cyclic compression to the left tibia of the mouse, 5 d/wk for 5 min (4 Hz, 1200 cycles). This loading results in consistent, repeatable kinematics inducing combined compression and shear motions at the joint surface. The load magnitude and duration depend on the experimental question being studied. High loads are selected to induce 1200 με on the mid-diaphyseal cortex. All joint ligaments and surrounding soft tissues remain intact. Right limbs are not loaded and serve as contralateral controls. This approach can be combined with other treatments and mice of different genetic backgrounds to alter joint tissue properties or signaling pathways. For example, to understand the role of bone and cartilage tissue properties load-induced OA, my laboratory has used pharmacologic treatments (alendronate, PTH) and examined different mouse strains (C57Bl/6, cho/+, pOC-ERa, FVB).Outcome assays to assess cartilage damage, bone changes and other joint responses include histology, immunohistochemistry and microCT. Tibial cartilage damage is quantified in Safranin-O stained tissues using OARSI scoring. Bone morphology is measured by microCT. Synovial inflammation can be scored from H&E-stained sections. If osteophytes are present, width is measured and maturity scored based on the relative calcification of the osteophyte. Other assays depend on the research question, mouse strain and other experimental manipulations.