interventions (pharmacologic and non-pharmacologic), 6) types of outcome measures (self-reported, performance-based, examination, imaging), and 7) considerations in the statistical analysis of data. Participants will complete an exercise that designs a clinical trial for symptom and structure modification in patients with knee osteoarthritis.

10 ROLE OF MATRIX METALLOPROTEINASES IN CARTILAGE AND BONE DURING SKELETAL REMODELING
Stephen M Krane

Matrix metalloproteinases (MMPs) are expressed in cartilage during embryonic development and later during remodeling. Mmp9, although not a collagenase is expressed early in embryogenesis during endochondral ossification and Mmp9 deficiency in mice results in abnormalities that affects growth plates. Mmp13 (collagenase-3), a highly expressed collagenolytic MMP in cartilage and in developing and remodeling bone, also has a role in the joint tissue destruction that is a major feature of various forms of human arthritis. We have targeted a null mutation in mouse Mmp13 that resulted in a profound embryonic and adult skeletal phenotype characterized by abnormal growth plates and delayed ossification. During embryonic development at the earliest stage examined, Mmp13-/- mice had growth plates in long bones almost double in length, accounted for by increases in the zone of hypertrophy. Mmp13, produced by chondrocytes but not by osteoclasts/chondroclasts, is particularly effective in proteolysis of type II collagen. In vivo evidence for Mmp13 cleavage of type II collagen in vivo in wt mice, but not in Mmp13-/- mice. It is thus unlikely that other Mmps compensate for the loss of Mmp13 function in cartilage. The delay in ossification, so prominent in 15.5 dpc Mmp13-/- embryos, is largely transient and older Mmp13-/- mice have increased bone deposition. Mmp8 is also expressed in newborn Mmp13-/- and wt skeletons but Mmp8-/- mice have normal skeletons. Type X collagen deposition was significantly increased in growth plates but not in Mmp8-/- mice.

11 INTEGRIN-SYNDECAN CO-OPERATION GOVERNS THE ASSEMBLY OF SIGNALLING COMPLEXES DURING CELL MIGRATION
Martin J Humphries

Cell adhesion receptors play a fundamental role in integrating the extracellular matrix with cell signalling complexes, and thereby control diverse, distal events in metabolism such as cell fate and tissue structure. Within cells, adhesion signalling occurs at focal sites and involves the formation and maturation of discrete adhesion complexes. The sequential modulation of Fho family GT-Pase activity is a critical control point determining the efficacy of adhesion signalling. Adhesive responses to the extracellular matrix protein, fibronectin (FN), which are mediated by members of the integrin and syndecan adhesion receptor families, have served as a prototype for many of these studies, and the outcomes are generally applicable to a large majority of adhesive responses. Interestingly, cells plated onto a FN fragment that binds the integrin β5α1 are able to spread but fail to form adhesion complexes or fully organise actin into bundled stress fibres unless co-stimulated with a distinct FN fragment that binds syndecan-4. Engagement of syndecan-4 in such pre-spread cells recapitulates the Fho family activation profiles observed during spreading on whole FN. We have found that adhesion to a ligand of β5α1 alone does not activate one member of the Fho family, Rac1, indicating that engagement of syndecan-4 is an absolute requirement for this key signalling event. In related work, we have examined differences in the mechanism of adhesion complex formation mediated by different FN-binding integrins, δ4α1 and β5α1. Two signalling differences were found. First, while β5α1 required a proteoglycan co-receptor (syndecan-4), δ4α1 did not. Second, adhesion contact formation via δ5α1 required PKCα activation, but only basal PKCα2 activity was observed following adhesion via δ4α1. These findings demonstrate that different integrins can signal to induce focal adhesion formation and migration by different mechanisms, and provide insights into the ways that the extracellular environment controls cell morphology and movement.

12 NOVEL GENETIC MARKERS OF OSTEOARTHRITIS
John Loughlin

Early cross-sectional and longitudinal studies demonstrated familial clustering of primary osteoarthritis, implying a genetic component to the disease. However, such clustering could also be the result of shared environmental factors within a family. Twin studies have since been performed that demonstrate a clear heritability to OA at a number of skeletal sites, including hands, hips, knees and the spine [1]. Other epidemiological studies have also been performed investigating the nature of OA transmittance from parents to offspring and the prevalence of disease between relative-pairs, particularly siblings. These studies have confirmed a major genetic component to OA, which is transmitted in a non-Mendelian, complex manner. It has gradually become apparent that the nature of the genetic risk is likely to vary somewhat between different skeletal sites and may also vary between the sexes, although this latter observation is based on a small number of studies and needs further investigation to confirm its veracity.

With a genetic component established the next step was a hunt for the risk alleles. Investigators initially focussed on genes encoding the major structural components of the cartilage extracellular matrix, such as aggrecan and type II collagen. These studies did not provide the expected breakthroughs and prompted a re-think on the nature of OA susceptibility: instead of the cartilage matrix being poorly constructed could the susceptibility be...