We have shown that the non-receptor tyrosine kinase Src phosphorylates syndecan-4 to suppress activation of the small GTPase Arf6. Crucially, syndecan-4-mediated Arf6 activity differentially regulates recycling of the α5β1 and αVβ3 integrin heterodimers to the membrane, to control adhesion complex dynamics. Thus, syndecan-4 phosphorylation functions as a molecular switch to target specific integrin heterodimers to the membrane and modulate FA stability and matrix remodelling. We propose that maintenance of normal tissue architecture and function requires the precise spatial and temporal regulation of syndecan-4 phosphorylation, to coordinate integrin trafficking, dynamically regulate interaction with the matrix, and to control cell migration and the integrity of the extracellular environment.

## I-18
## FEMORAL SHAPE AND IMPINGEMENT

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From a mechanical perspective congruency of the joint is important for appropriate articulation with mechanical loading that is well distributed over the joint surface. Whereas severe abnormal shapes clearly create an articulation problem and can lead to OA, it is currently recognized that subtle shape differences can be a risk factor for OA as well. Bone shapes vary between persons and likely there are good and bad shapes with respect to joint functioning. Variations of bone shape among the population have been investigated ever since the introduction of radiographic imaging. The idea that in hip OA many cases of primary OA is actually secondary to a non-optimal shape of the joint goes many years back. For example Perthes' disease, slipped capital femoral epiphysis and congenital hip dysplasia clearly pose a high risk for developing OA. Therefore mild subclinical forms of these pathological conditions might also form a (smaller) risk factor of OA. Many shape aspects have been identified that are associated with OA such as: a decreased anteversion angle of the femoral neck, retroversion of the acetabulum, a deep acetabular socket or a non-spherical head shape. These are all well (pre)defined geometry aspects. However it is not straightforward to quantify shape variations in general and new methods have recently been introduced that can help to identify and find subtle aspects of shape variation within a given population. The importance of these variations in relation to OA development or OA progression has only started to be uncovered recently.

The most thorough method to determine shape variations from radiographic images is using so-called statistical shape or appearance models, where the latter also provides the density variation. In these models a contour is created along landmark points of the bone that together annotate the shape. For a given population all contours can now be compared through scaling and rotation to obtain a best fit. Subsequently the contour coordinates are recombined with principal component analysis to derive independent components (modes) that represent the variation in shape within that population. Using this methodology specific shape modes can be found that are strongly associated with OA and even certain geometries of the hip were identified that correlate with OA characteristics dependent on the carrier status of the DIO2 gene SNP.

A more direct approach is to use predefined shape parameters that are suspect of contributing to OA. One of the most well studied parameters in this respect is sphericity of the femoral head. A non-spherical head might create a diminished range of motion of the hip joint as a consequence of femoral acetabular impingement. This problem has been well described lately by Ganz and coworkers and often concerns the formation of extra bone at the antero-lateral head neck junction; a so-called Cam-type deformity. There is now general consensus that this deformity is initiated during puberty, likely induced by mechanical loading such as high impact sport activities and not evolves with time in adults. However many clinical studies do show that severe clinical problems related to Cam impingement become evident at adult (but relatively young) age and there is a current trend to operatively remove the Cam deformity in order to prevent OA later in life.

The current work on shape analyses can provide imaging related (bio) markers that might predict OA initiation and/or progression. These shape related reasons of OA puts the definition of 'idiopathic' or primary OA in a new context. Furthermore new tools to quantify joint shape can help to elucidate more subtle risk factors and find cause effect relationships related to genes that contribute to OA.

## I-19
## HEDGEHOG SIGNALING IN OSTEOARTHRITIS

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**Purpose:** Hedgehog signaling plays a critical role in chondrocytes during development and as such could also play a role in articular chondrocyte degeneration. This study will determine the role of hedgehog signaling and in cartilage degeneration and osteoarthritis.
**Methods:** Human osteoarthritis samples were examined to determine if hedgehog signaling is dysregulated in osteoarthritis. Using array analysis and chromatin immunoprecipitation, hedgehog target genes were identified. Genetically modified mice in which hedgehog transcriptional activation can be modulated and in which target genes can be modified were used to determine how this modulates spontaneous and traumatic onset articular cartilage degeneration.
**Results:** Hedgehog signaling is activated in human and murine osteoarthritis. Inhibiting hedgehog signaling pharmacologically or genetically inhibits the development of osteoarthritis, while activating the pathway worsens the severity of cartilage degeneration. Hedgehog signaling regulated genes that modulate intracellular cholesterol. Mice lacking the ability to degrade cholesterol in chondrocytes developed worse cartilage degeneration and inhibiting cholesterol decreased the severity of osteoarthritis.
**Conclusions:** Hedgehog signaling and its target genes regulate articular cartilage degeneration. Pharmacologic inhibition of hedgehog signaling or intracellular cholesterol could be used as a therapeutic approach to prevent or treat cartilage degeneration in osteoarthritis.

## I-20
## WE SHOULD TREAT PAIN!

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Persons with structural changes of osteoarthritis (OA) become patients when they present to health care providers with symptomatic complaints; most often pain, aching or discomfort, but also stiffness. These symptoms may be accompanied by signs on physical examination consistent with OA with or without local inflammation. This presentation will focus on 1) the impact of symptoms of OA on activity limitation, physical disability and reduced health-related quality of life and 2) the effect of improvement in pain on reduction in activity limitation and physical disability and improvement in health-related quality of life.

## I-21
## MOUSE MODELS OF JOINT DISORDERS

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Over the last decade, mice have become a valuable tool in the study of joint disorders. The primary reasons for this include the high degree of similarities that exist between human and mouse joint structures and the genes/proteins involved in joint development and maintenance, the genetic tractability of the mouse, and the develop of methods for the surgical and chemical induction of joint cartilage degeneration. The use of mice and the development of unique murine models of joint disorders have provided enormous insight into the molecular underpinnings of human cartilage related joint diseases. In particular, the use of the Cre-LoxP technology to generate tissue and temporal specific gene deletions/activations within joint tissues has identified specific genes and pathways implicated in normal articular cartilage development and joint maintenance and pathological joint degeneration. Similarly, the surgical destabilization of murine knee joints has served as an important platform for studying the progression of osteoarthritis (OA) and the genes involved in that process. During the course of this workshop we will discuss several important murine models of joint disorders, with a particular emphasis on 1) the utilization of murine surgical models of knee joint destabilization to test a) the involvement of specific genes in OA progression and b) the effectiveness of potential disease modifying osteoarthritis drugs (DMOADs), 2) the selection and utility of various Cre transgenic mice for temporal and tissue specific gene deletions/activations in joint tissues, and 3) the specific roles that various genetic pathways (Wnt/Beta-catenin, TGFb, Ihh, and Notch) play in regulating anabolic and catabolic factors that are important for normal articular cartilage and joint maintenance.