consequence, clearly elevated levels in the circulation is seen only
in individuals with the most active disease. New assays that depict
cleavage neoptetes of ECM-molecules, show a much more
clear distinction between healthy individuals from such affected by
osteoarthritis.

Territorial distribution: Collagen VI and biglycan are particularly
present in the territorial matrix close to the cells. At this time there
are no assays available for these proteins and they may show too
wide a tissue distribution for use as specific indicators of a process
in the cartilage. Temporal specificity is a result of the breakdown of
different proteins at different stages of the OA-process in the carti-
lage, e.g. demonstrated by stimulating cartilage breakdown using
cytokines relevant to the disease process. Available data show that
aggrecan is released in early phases, leaving the hyaluronan
binding part of the molecule in the tissue. COMP and fibromodulin
are release at a later stage and the preferential cleavage of the
major collagen II and its release follows in a final phase.

I-7

THERAPEUTIC APPLICATIONS OF MESENCHYMAL
STROMAL CELLS IN OSTEOARTICULAR DISEASES

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Purpose: Multipotent mesenchymal stromal cells (MSC) are adult
stem cells characterized by their differentiation potential into mul-
tiple lineages and their immunosuppressive properties. This last
property is used here to evaluate the efficacy of primary MSC
to inhibit inflammation-associated symptoms in the murine exper-
imental model of collagen-induced arthritis (CIA). Mesenchymal
stem cells (MSC) are considered suitable sources for cell-based
therapies in cartilage engineering. However, their potential to re-
generate a fully functional and mature tissue relies on the presence
of a differentiation factor. The identification of such a factor spe-
cific for the chondrogenic lineage has still to be performed and
represents the major issue of this study.

Bone marrow-derived human MSC were induced to differenti-
ate towards chondrocytes using the micropellet culture technique
in presence of chondrogenic medium containing hBMP-2 for 21
days. Total RNA were hybridized on DNA microarrays (Aymetrix
U133A). Among the 1354 differentially regulated genes during
chondrogenesis, 705 genes were up-regulated in MSC-derived
chondrocytes. We first focused our attention on transcription fac-
tors and in particular, on Foxo1A which was shown to be increased
by a 13-fold factor using real time PCR, as soon as day 2 of chon-
drogenesis. After the over-expression of the wtFoxo1A or mutated
Foxo1A genes in the C3H10T1/2 cells, we could show the up-
regulation of aggrecan, collagen IIB and the down-regulation of
collagen I, suggesting that Foxo1A is sufficient to induce chondro-
genesis.

To demonstrate the immunosuppressive effect of MSC, we injected
the cells IV in arthritis. MSC were isolated from DBA1 mice and
and wild type (wt), inducible nitric oxide synthase (iNOS)\textsuperscript{-/-} or IL-6\textsuperscript{-/-}
C57Bl6 mice. 10\textsuperscript{6} MSC were intravenously injected at various
times after collagen II immunization of DBA1 mice. Arthritis was
evaluated by the measure of paw swelling. In the CIA model, when
injected on day 18 and 24, syngeneic and allogeneic MSC were
able to significantly decrease the incidence and clinical signs of
arthritis. Compared to wt MSC, iNOS\textsuperscript{-/-} or IL-6\textsuperscript{-/-} exhibited a highly
reduced immunosuppressive effect. When iNOS\textsuperscript{-/-} or IL-6\textsuperscript{-/-} MSC
were injected the clinical scores and incidence were significantly
increased.

Conclusion. Foxo1A is one essential transcription factor involved
in the early steps of chondrogenesis. Moreover, allogeneic MSC
injection have anti-inflammatory effects through iNOS and that could
be relevant for osteoarthritis therapy.

I-8

COPING WITH THE PAIN OF OSTEOARTHRITIS: UPDATE
AND NEW DIRECTIONS

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Purpose: There is growing recognition that the way that persons
cope with the pain of osteoarthritis not only influences their pain,
but also their psychological distress and physical disability. This
presentation provides an update on recent research in this area.
The presentation is divided into three sections. In the first section,
a conceptual background for research on pain coping is presented.
The second section highlights recent research on key topics in the
arthritis pain coping literature include studies of active coping,
pain catastrophizing, biological mechanisms, and the effects of
pain coping skills training protocols. The final section highlights
important new directions for research in this area including stud-
ies of partner-assisted coping interventions and the impact of
maladaptive pain coping behaviors (e.g. overeating, smoking).

I-9

ANIMAL HISTOPATHOLOGY - DOG

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Purpose: Osteoarthritis (OA) is a common orthopaedic disease
seen in clinical canine patients and as such the dog is an often-
used model for study of OA. Histologic assessment of OA is
currently considered the “gold standard” for determining presence,
extent, and severity of disease. The vast majority of experimen-
tal and clinical canine OA studies have used the Mankin system
(Mankin et al. J Bone Joint Surg 1971;53A:523-37) or modifi-
cations of this system to histologically evaluate OA. While this
methodology has produced useful data, limitations have been
suggested including: 1) lack of assessment of the joint as a whole,
2) inadequate representation of the relative importance of various
types of pathology, and 3) lack of a standardized methodology.
The purpose of our work was to first develop and validate a histologic
assessment system to address these shortcomings, and then use
the novel system to examine stifle joints in a prospective study
comparing three different canine models of OA.

Methods: The OARSI Histopathology Initiative Assessment Sys-
tem in the Dog was developed with a team of experts and analyzed
for reliability. For use of the system in the prospective study, sixteen
dogs received one of three different arthroscopic insults including
anterior cruciate ligament transection (n=5), full-thickness grooves
created on the medial femoral condyle (n=6), or release of the
caudal horn of the medial meniscus (n=5), to provoke OA in the
right stifle (knee) joints. Dogs that received a sham surgery (n=5)
served as controls. Twelve weeks after surgery the dogs were
euthanized and the operated stifle joints and non-operated con-
tralateral stifle joints were histologically evaluated using the OARSI
system and the Mankin system.

Results: The OARSI system was shown to be reliable for pro-
ducing consistent and repeatable scores and grades for cartilage,
osteochondral, and synovial tissue status. The data also suggest
that non-experienced observers using the system for the first time
can effectively assess tissues to acceptable levels of agreement
with experts. In the prospective study, both the OARSI system and
Mankin system were judged acceptable for determining presence,
and severity of OA. Statistically significant differences among OA
severity categories were more often observed using the OARSI
system.

Conclusions: It is important to consider OA as a “whole organ
disease” and keep in mind that a tissue section does not always
represent the true extent and severity of disease. When possible, examination of multiple tissue sections within a joint such as described for the OARSI system will help limit this potential dissociation between histopathologic assessment and clinical, gross and imaging findings of OA.

I-10
ADVANCES IN UNDERSTANDING THE ROLE OF MUSCLE STRENGTH AND PROPRIOCEPTION IN THE DEVELOPMENT AND PROGRESSION OF KNEE OA

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Osteoarthritis (OA) is the leading cause of musculoskeletal disability and the knee is the most common weight-bearing joint affected. Although the causal pathway has not been fully elucidated, local biomechanical changes, such as injuries, are known to play a role. Both strength and proprioception are impaired with increasing age as well as in people with knee OA. Impaired muscle control may lead to fatigue, joint instability, and abnormal loading, a potential risk factor for joint trauma.

Considering that neuromuscular control affects the knee joint environment, impaired muscle strength and proprioception have been hypothesized to be risk factors for development and worsening of knee OA. The rationale for these hypotheses is that proper function of the neuromuscular system, especially activation of knee extensor muscles and sensation of joint position, may protect the knee from potentially adverse impulsive loading. Despite knowledge of cross-sectional associations of impaired strength and proprioception with knee OA, it was not until recently that substantial longitudinal data was available to assess whether impaired strength or joint position sense influenced risk for incident or progressive knee OA.

Prior reports as well as the results of several recent epidemiological studies of whether impairments in knee extensor strength or knee joint position sense increase risk for development of incident (new) and progressive (worsening) radiographic and symptomatic knee OA were reviewed. Current evidence does not support an association between impaired knee extensor strength or muscle balance (hamstring:quadriceps ratio) and either incident radiographic tibiofemoral OA, tibiofemoral cartilage loss or development of frequent knee symptoms. Similarly, there does not appear to be a relationship between impaired knee joint position sense and development of incident radiographic knee OA or frequent knee symptoms. In addition, the combination of knee extensor weakness with impaired knee joint position sense as well as their interaction appears to be unrelated to risk for development of incident radiographic and incident symptomatic knee OA. However, knee extensor weakness may predict risk for incident cartilage loss in the lateral patellofemoral compartment as well as development of incident symptomatic whole knee OA (the combination of tibiofemoral or patellofemoral OA with frequent knee symptoms). With regard to progression of knee OA, current evidence does not support increased risk attributable to impaired knee extensor strength, muscle balance or knee joint position sense. However, increased risk for knee OA progression with high knee extensor strength has been reported in the presence of concomitant knee joint laxity or malalignment.

In aggregate, these findings suggest that although adults with knee OA have impaired knee extensor strength and joint position sense, these factors alone or in combination with each other do not increase risk for knee joint structural worsening. Therefore, factors other than sensorimotor dysfunction may be more important in mediating risk for incident and progressive radiographic knee OA. However, there is some evidence that increased knee extensor strength may protect against development of incident symptomatic knee OA or may increase risk for knee OA progression in the presence of malalignment or laxity.

I-11
USE OF ANIMAL MODELS TO DEVELOP SURGICAL METHODS OF STIMULATING RESTORATION OF JOINT SURFACES IN OSTEOARTHRITIC JOINTS

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Although osteoarthritis (OA) might be different from local cartilage defects, unquestionably the larger local defect, specifically those in the weight bearing areas, will quickly lead to OA. In fact it might be disputed whether primary and secondary OA are different entities. Yet, there are many surgical methods studied to repair local cartilage defects; hardly any for OA. Some of these tools entered the clinic with more or less good results. Interestingly, none of them focus on stimulation of intrinsic cartilage repair (see ICRS).

For OA, surgical tools are largely restricted to lavage/debridement, marrow stimulation (subchondral drilling, microfracture), correction osteotomy, and more recently although hardly implemented, joint distraction, and finally joint replacement. Unfortunately, as for surgical treatment of local defects, for none of these approaches well controlled follow-up studies have been performed. Nonetheless, they are considered to have prolonged clinical benefit; whether structure modifying activity is achieved remains disputed.

The lack of well designed studies, largely but not solely relates to the nature of the interventions, making controlled studies difficult. Moreover, evaluation of cartilage in clinical studies remains difficult and restricted to surrogate markers such as imaging and biochemical markers of tissue turnover. Therefore, animal in vivo studies using models of OA might help in defining the actual structure modifying properties of these treatments. Interestingly, only a limited number of studies are reported on. In dogs with natural cranial cruciate ligament disease, tibial plateau leveling osteotomy had no effect on cartilage biomarkers, and was as such concluded not to affect cartilage damage [1]. In guinea-pigs, although the study was designed to demonstrate that loading adds to spontaneous development of OA, diminished loading due to correction osteotomy slowed down the development of cartilage degeneration [2].

Most interestingly, for the clinically less implemented procedure, joint distraction, the most animal studies have been performed. Van Valburg demonstrated improvement of chondrocyte activity in cruciate ligament transacted dogs upon joint distraction, although actual repair could not be demonstrated in this model [3]. Karadam concluded, despite a very limited follow-up, that joint distraction was not effective in papain induced OA in rabbits [4]. Kajiwara demonstrated cartilage repair in local osteochondral femur defects in rabbits [5]. Yanai demonstrated joint surface regeneration upon distraction in full osteochondral tibial defects [6]. More recent data support this benefit of joint distraction in structural repair in rabbits (personal communication). Also Intema demonstrated cartilage repair of joint distraction in the canine Groove model of OA (personal communication).

In general it might be concluded that not only appropriate clinical trials are lacking but also animal models to develop surgical methods of stimulating restoration of joint surfaces in osteoarthritic joints are limited in number.

References