disappointing results both on the structural evolution and on pain. Similarly anti nitric oxide agents failed in a long term study to slow down the progression of knee OA.
Owing to these repeated negative results with biologics, new strategies should be contemplated such as gene therapy.
On the other hand, new emerging treatments may be more related on the repair side of cartilage. This could be targeted by using growth factor delivery. Intra articular administration of autologous platelets is widely used by the level of proofs still need to be confirmed in large randomized trials. One placebo controlled study using repeated intra articular administration of FGF 18 failed to demonstrate neither any pain relief nor any structural changes. The therapeutically option consisting in the intra articular administration of autologous stem cells is ongoing in a phase 1 study in humans. In the next future, new lubricants agents such recombinant lubricin also offers an appealing approach.
Finally, recent placebo controlled study with ranelate strontium, a decoupling bone agent, showed promising results on the evolution of joint space narrowing in patients with knee OA.
Conclusions: Looking for new treatments options in OA should not only consider new drugs with an appealing mechanism of action but should also consider to whom patient and when those therapies could be at best prescribed.

I-10
A STEM CELL-BASED APPROACH TO CARTILAGE REPAIR

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Osteoarthritis (OA) is a degenerative joint disease that involves destruction of articular cartilage and eventually leads to disability. Molecules that promote the selective differentiation of multi-potent mesenchymal stem cells (MSCs) in to chondrocytes may stimulate the repair of damaged cartilage. Using an image-based, high throughput screen we identified the small molecule kartogenin, which promotes selective chondrocytes differentiation (EC50 = 100 nM), shows chondro-protective effects *in vitro*, and is efficacious in two OA animal models. Kartogenin binds filamin A (FLNA), disrupts its interaction with the transcription factor CBFβ and induces chondrogenesis by regulating the CBFβ-RUNX1 transcriptional program. This work provides new insight into the control of chondrogenesis that may ultimately lead to a stem-cell based therapy for osteoarthritis.

I-11
SURGICAL ASPECTS OF OA (MENISCUS)

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The menisci are internal structures that are of central importance for a healthy knee joint; they have a key role in the structural progression of knee osteoarthritis (OA), and the risk of the disease dramatically increases if they are damaged by injury or degenerative processes. Meniscus damage might be considered a signifying feature of incipient OA in middle-aged and elderly people. As approximately every third knee of people in this group has a damaged meniscus, tears are common incidental findings of knee MRI. However, as most tears do not cause symptoms, careful clinical evaluation is required to determine if a damaged meniscus is likely to directly impact a patient's symptoms. Conservative management of patients with knee pain and a degenerative meniscal tear should be considered as a first-line therapy before surgical treatment is contemplated. Patients with mechanical interference of joint movements, such as painful catching or locking, might need surgical treatment with meniscal repair if possible. In a subset of patients, meniscal resection might relieve pain and other symptoms that potentially originate directly from the torn meniscus. However, the possibility of an increased risk of OA if functional meniscal tissue is removed cannot be overlooked.

I-12
AUTOPHAGY IN THE PATHOGENESIS OF AGING-RELATED OA

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Although aging represents one of the most important risk factor for OA, mechanisms leading to aging-related cartilage degeneration remain to be determined. Consequently, there are no approaches to target aging-related changes in cartilage therapeutically, even in preclinical experimental models. Autophagy plays a fundamental role in cellular homeostasis and organismal health. It is a major physiological mechanism that eliminates altered and dysfunctional cytosolic macromolecules, membranes and organelles by lysosomal degradation. In most experimental models, suppression of relevant autophagy genes leads to cell death, indicating a protective and survival-promoting function. In articular cartilage, which is characterized by a very low rate of cell turnover this mechanism appears to be essential to maintain cellular integrity, function and survival. Furthermore, while aging-related changes in autophagy have been demonstrated in various models and tissues, this is only the beginning of studies focus on articular cartilage. Our recent observations in human knee joints and in experimental models indicate that aging and OA are associated with defective autophagy in articular cartilage. This provides a unique opportunity to study a new dimension of cartilage aging mechanisms and simultaneously explore the therapeutic potential of pharmacological enhancement of autophagy in OA.

I-13
OPTIMAL COMBINATIONS OF SCAFFOLDS AND GROWTH FACTORS FOR TISSUE ENGINEERING OF CARTILAGE

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Purpose: Since cartilage has poor regenerative capacity by itself, its regeneration using a tissue engineering technique may greatly benefit the treatment of various cartilage disorders that cannot be treated by conventional methods. Although autologous chondrocyte transplantation has been already available for clinical use, the size is limited to a filler of focal articular cartilage defect or an injectable material for the nasal cosmetic augmentation. In order to broaden its clinical indication to major disorders such as osteoarthritic joints, microtia or cleft lip/palate, we should make an “implant-type” tissue-engineered cartilage with a greater firmness and a 3D-structure.
Methods: For that, we developed 1) a proliferation medium for chondrocytes to realize a more than 1000-fold increase in number without using fetal bovine serum that has been restricted to clinical application, and 2) a scaffold system that effectively preserves chondrocytes in the engineered tissue and provides the adequate 3D shape to the tissue.
Results: For the proliferation medium, we examined the optimal combination from 12 putative soluble chondrocyte regulators including FGF-2, IGF-I, insulin, BMP-2, PTH and others. Using the statistical method that is termed “analysis of variance by fractional factorial design”, the effects of the individual factors and the synergy of the combinations were evaluated. As a result, the combination of FGF-2 and insulin with 5% human serum showed a 10–12-fold increase in number within one week and provided an approximate 1000-fold increase around 3 weeks. In order to fabricate the scaffold system, we should realize 1) sufficient mechanical strength mimicking native cartilage, 2) preservation of seeded cells and their even distribution, and 3) good biocompatibility/biodegradability. To meet with these requirements, we decided to use the combination of hydrogel and porous scaffolds. Considering biological effects and clinical availability, atelocollagen may be accessible for hydrogel. Next, we investigated the structure and composition of porous scaffolds. We prepared ones of a classical polymer PLLA or PLGA with various kinds of porosity and pore sizes. The porous scaffolds possessed sufficient strength even with high porosity (>95%) and good interconnectivity, which showed favorable cartilage regeneration when transplanted in the subcutaneous space of nude mice with chondrocyte/atelocollagen mixture. In order to examine the biocompatibility, we conducted a canine model for autologous transplantation of the tissue-engineered cartilage, and compared between such scaffolds of PLLA and PLGA. The tissue-engineered constructs using PLLA contained abundant cartilage after transplantation, although the PLGA constructs did not show the cartilage and could not maintain their shapes. The PLLA scaffolds were suitable for cartilage tissue engineering under the immunocompetent conditions, because of the retard at degradation properties and the decrease in the severe tissue reactions during the early stage of transplantation.
Conclusions: With these technologies, we applied the implant-type tissue-engineered cartilage for treatment of a nasal deformity in patients with cleft lip/palate. We would also apply these elemental techniques for the development of tissue-engineered trachea or joints, and the preclinical experiments are underway. We hope these tissue-