**Abstract 79** – Knee cartilage morphology in various species and humans

| Species | Number | Cartilage surface area | Cartilage thickness | Cartilage volume |
|---|---|---|---|---|
| Rat | 16 | 6.2±0.9 $mm^2$ | 0.14±0.12 mm | 0.81±0.17 mm3 |
| Rabbit | 6 | 69±4.9 $mm^2$ | 0.37±0.05 mm | 23.5±3.9 mm3 |
| Cat | 3 | 85±9.1 $mm^2$ | 0.67±0.05 mm | 55.8±10.5 mm3 |
| Dog | 18 | 196±18 $mm^2$ | 0.77±0.04 mm | 142±15 mm3 |
| Pig | 1 | 1650 $mm^2$ | 1.4 mm | 2200 $mm^3$ |
| Horse | 1 | 2390 $mm^2$ | 1.4 mm | 3290 $mm^3$ |
| Rhinoceros | 1 | 5460 $mm^2$ | 1.8 mm | 9840 $mm^3$ |
| Human (Women) | 45 | 1050±135 $mm^2$ | 1.9±0.23 mm | 1940±344 mm3 |
| Human (Men) | 72 | 1380±205 $mm^2$ | 2.2±0.26 mm | 2940±622 mm3 |

with those in a data base of young (18 to 35 years) healthy humans (45 women, weight 60 ± 7 kg, and 72 men, weight 77 ± 11 kg) who had been imaged at 1.5T. Sagittal spoiled gradient echo sequences with fat suppression or water excitations were acquired in all knees. The medial tibial cartilage was segmented by tracing the cartilage surface (AC) and subchondral bone area (tAB) throughout the entire medial tibia. The size of the cartilage surface areas (AC), the mean cartilage thickness (ThC) and the cartilage volume (VC) were computed using Chondrometrics software (Ainring, Germany).

**Results:** The size of the cartilage surface areas in the rat (6.2 $mm^2$) was approximately 200x smaller than that in humans (Table 1), whereas that in the rhinoceros was about 4.5 x larger than than in humans. The variability of cartilage thickness between the species, however, was substantially less than for cartilage surface areas. All species (including the rhinoceros: ThC = 1.8 mm) had thinner cartilage than humans (1.9 mm in women and 2.2 mm in men, respectively). The rat displayed the lowest mean cartialge thickness (0.14 mm) amongst the species investigated.

**Conclusions:** To our knowledge these are the first quantitative data on the three-dimensional morphology of tibial cartilage in different species and humans. The data show that the inter-species differences in cartilage surface areas are much more prominent than those in cartilage thickness. This is likely due to the need to keep mechanical stresses (load/area) below a critical threshold at which the cartilage will undergo damage. These data can be used to estimate the appropriate dose of intra-articular medication with potentially beneficial structural or symptomatic effects on articular cartilage in animal models of OA.

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### THERAPEUTIC EFFECTS OF FIBROBLAST GROWTH FACTOR-18 IN A RAT MODEL OF ESTABLISHED OSTEOARTHRITIS

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**Purpose:** FGF18 plays a central role in skeletal growth and development. In contrast to its described role in the growth plate, where it negatively regulates chondrocyte proliferation and differentiation, FGF18 has been shown to have significant anabolic effects on chondrocytes in other cartilaginous tissues. To evaluate whether recombinant human FGF18 (rhFGF18) could facilitate the repair of cartilage damage caused by osteoarthritis (OA), the efficacy of rhFGF18 was tested in a rat meniscal tear model of OA.

**Methods:** In the rat meniscal tear model, a full-thickness cut in the medial meniscus leads to joint instability and progressive development of OA characterized by proteoglycan loss, cartilage fibrillation, chondrocyte death, eventual damage to the subchondral bone, and formation of osteophytes. rhFGF18, formulated in saline, was administered by intra-articular injection beginning 21 days after meniscal tear using three different dose regimens: once per week, twice per week or three times per week with 0, 0.3, 1, 3 or 10 μg/joint overall weekly dose. Evaluation was performed at 3 weeks and, further to an initial evaluation of rhFGF18 in this model, at a 3-week follow-up period after end of therapy to investigate sustained cartilage effects of rhFGF18.

**Results:** Treatment with rhFGF18 induced a dose-dependent increase in cartilage formation and a statistically significant increase in the thickness of the articular surface of the medial tibial plateau. The increase in cartilage formation induced by rhFGF18 was paralleled by significant reductions in multiple degeneration scores. Anabolic effects were seen in most groups and were greatest in the joints treated 3x/week but this dosing paradigm also resulted in excessive inflammation and bone resorption. Weekly dosing with 10 or 3 μg resulted in high therapeutic efficacy. Animals given 3 or 10 μg rhFGF18 had significantly lower cartilage degeneration width (28 and 37% respectively) and moreover animals given 10 μg rhFGF18 demonstrated a 27% increase of viable cartilage matrix. After 3 additional weeks without treatment cartilage degeneration scores of the medial tibia were significantly decreased 38% after treatment with 10 μg rhFGF18 1x/week, which resulted in a significant decrease (31%) of cartilage degeneration in the overall joint. Dose responsive benefit was seen in the significant cartilage degeneration parameter and severe matrix loss, as measured by collagen degeneration, was improved with the once per week dosing regimen, therefore providing the best balance of beneficial effects versus lack of detrimental effects.

**Conclusions:** Overall, these results demonstrate that rhFGF18 can stimulate formation of new cartilage in an animal model of OA, and suggest that rhFGF18 might have clinical utility for treatment of this disease. rhFGF18 is currently tested in clinical trials.

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### MMP-9 MODULATES JOINT INFLAMMATION AND CARTILAGE DEGRADATION AFTER OVERLOAD INJURY

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**Purpose:** MMP-9, or called gelatinase B, is critical for the recruitment of T cells, macrophages, and synovial fibroblasts in synovial membrame, which often initiates a cascade of degradative events through several pro-inflammatory cytokines including interleukin 1 (IL-1) and tissue necrosis factor alpha (TNF-α). MMP-9 is also important for the formation of growth plate carilage and upregulated in OA and injured joint, but its roles in cartilage degradation after injury is not clear. The aim of this study was to establish a murine model to study overload injury in cartilage without alternating joint kinematics and to test our hypotheses that load-injury in cartilage alone induces cartilage degradation in part by chronical joint inflammation and that the