A predictive human 3D cartilage-on-chip model for screening anti-osteoarthritis drugs and medical devices

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BACKGROUND

Osteoarthritis (OA) is a prevalent musculoskeletal disease with no treatments available to restore degraded cartilage or decelerate OA progression. Novel predictive in vitro screening models are needed to advance drug development of disease-modifying OA drugs (DMOADs) and medical devices for effective treatment of OA.

PURPOSE

The purpose of this study was to establish and validate a novel and predictive human 3D cartilage-on-chip model for screening anti-osteoarthritis drugs and medical devices.

The model could later be used for assisting in decision making in early drug development.

METHOD

We describe uKnee, a novel mechanically active 3D human osteoarthritic cartilage-on-chip model. In this unique model, 3D cartilage-like constructs are subjected to a hyper-physiological mechanical microenvironment provided by a proprietary uBeat® technology (Figure 1) that triggers OA-induced changes in primary human articular chondrocytes.

In this study, we demonstrate validation of the uKnee model and show effects of standard-of-care (SOC) therapies in the model.

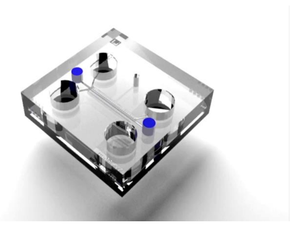

Figure 1: uBeat® Platform that is used for providing mechanical stimulus to 3D organ-on-chip cultures.

SUMMARY OF uKNEE

In uKnee, 3D healthy human cartilage-like constructs are subjected to a hyper-physiological OA resembling mechanical microenvironment provided by a proprietary uBeat® technology.

The uKnee model can be exploited to analyse gene expression profiles and molecular mechanisms corresponding to human OA onset and to study effects of SOC anti-OA therapies.

RESULTS

A summary of the uKnee 3D cartilage-on-chip model is presented in Figure 2. The development of a stable cartilage phenotype was evident after a 2-week culture of human primary chondrocytes as analysed by increased expression of specific genes including *ACAN* and *PRG4* for articular cartilage, *GDF5* and *ATX* for joint interzone, *FRZB and GREM1* as hypertrophy brakes, and by the deposition of a cartilage-like matrix assessed with immunofluorescence staining including Aggrecan and Collagen II (Figure 3). When these OA microtissues were subjected to a hyperphysiological compression (HPC) for 7 days (uBeat, 30% confined compression at 1 Hz), induction of OA-like gene expressions was observed, including enhancement of catabolic and inflammatory responses demonstrated by increased *IL-8* gene expression and *MMP13* gene and protein upregulation, and switching towards hypertrophic cartilage phenotype including *COL10A1* upregulation and *FRZB* and *GREM1* downregulation (Figure 4). When the OA microtissues were treated with SOCs (Rapamycin, Celecoxib, IL-1Ra and dexamethasone) or two hyaluronic acid -based medical devices for 3 days, a reduction in the expression of *MMP13* and *IL-8* was observed (Figure 5).

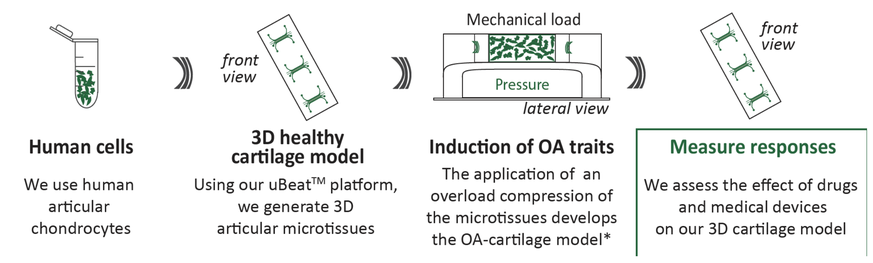

Figure 2: Summary of the uKnee OA cartilage-on-chip model. Human primary chondrocytes are cultured in 3D organ-on-chips. After maturation of the cartilage constructs they are subjected to HPC stimulus using uBeat® platform that stimulates osteoarthritic changes. The uKnee model can be effectively used to test effects of DMOADs and medical devices.

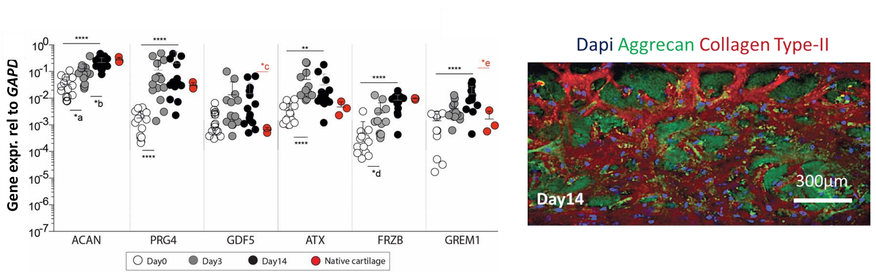

Figure 3: During the culture period, the expression of cartilage-related genes (*ACAN, PRG4, GDF5, ATX, FRZB, GREM1*) resembles their expression in healthy human (native) cartilage (in red). After 14 days, the cultures demonstrate organized matrix as shown by aggrecan and type-II collagen staining.

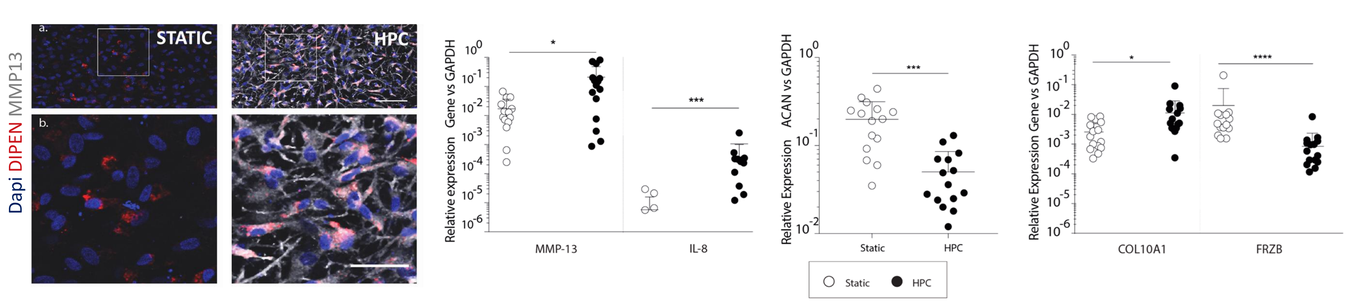

Figure 4: HPC-induced osteoarthritic changes in the cartilage-on-chips, including enhancement of catabolic and inflammatory responses demonstrated by increased deposition of *MMP13*, upregulation of *IL-8* and downregulation of *ACAN* gene expression, and a swift towards hypertrophic cartilage demonstrated by upregulation of *COL10A1* and downregulation of *FRZB* gene expression.

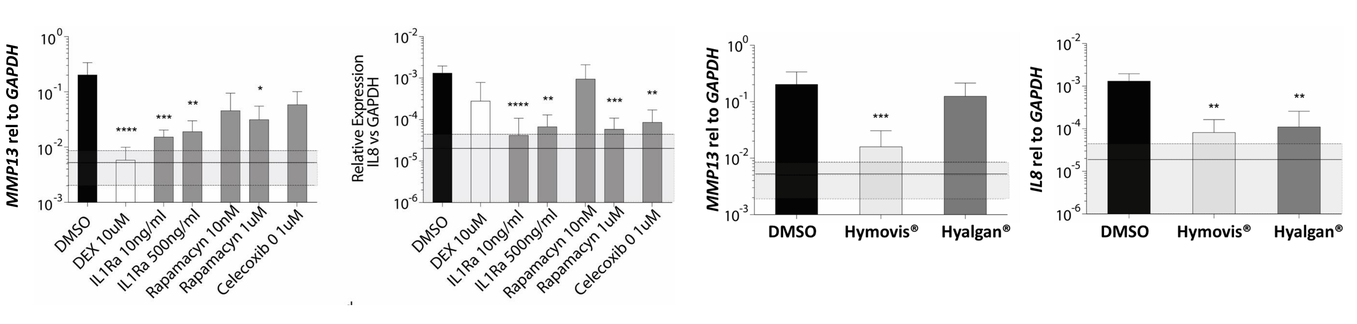

Figure 5: Treatment responses of SOCs and two medical devices examined as changes in *MMP13* and *IL-8* gene expression. The horizontal lines in all figures represent the expression levels in healthy cartilage.

CONCLUSIONS

Hyperphysiological mechanical stimulation is fundamental for eliciting OA pathogenesis in the uKnee cartilage-on-chip model, and uKnee is a validated model for predictive screening of DMOADs and medical devices. uKnee can be used as a drug screening tool for assisting in decision making before moving to animal studies.

REFERENCES

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BiomimX is preclinical CRO that offers uKnee model as a service. OncoBone Ltd is a non-exclusive commercial partner of BiomimX.

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