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Towards the joint on a chip: A multi-tissue and mechanically active organ-on-chip model to study Osteoarthritis

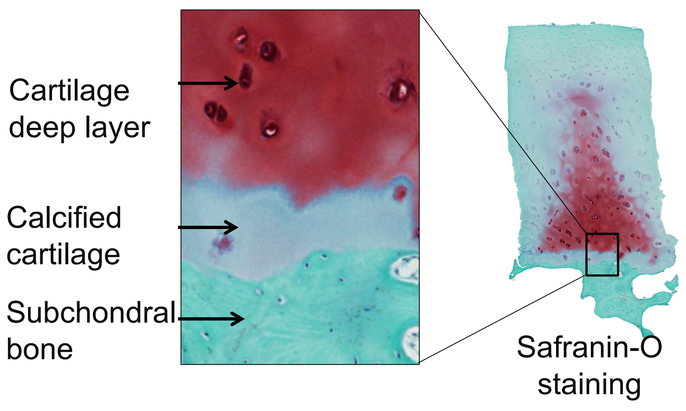
Andrea Mainardi[1,2,3], Paola Occhetta[3], Martin Ehrbar[4], Ivan Martin[1,2], Marco Rasponi[3] and Andrea Barbero[1,2]

1 Department of Biomedical Engineering, University of Basel, Allschwil, Switzerland; 2 Department of Biomedicine, University Hospital Basel, Basel, Switzerland, 3 Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milan, Italy. 4 Department of Obstetrics, University Hospital Zurich, Zurich, Switzerland.

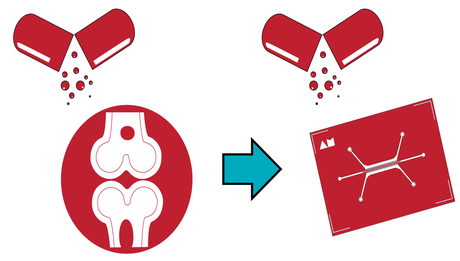
Background

Osteoarthritis (OA) is the musculoskeletal disease with the highest prevalence affecting roughly 20% of women and 10% of men older than 60 [1]. Despite OA's prevalence, however, we still lack Disease modifying anti OA Drugs (DMOADs) and joint replacement remains the only treatment option. This absence is correlated with the lack of representative OA preclinical models able to predicts drugs' responses *in vivo.*

OA's modelling is, however, difficult. OA's correlation with **mechanical risk factors** such as trauma, obesity and joint misalignment has been proven. [2] Moreover, OA is now recognized as a **whole joint disease** affecting cartilage but also, the underlying calcified cartilage layer and subchondral bone.



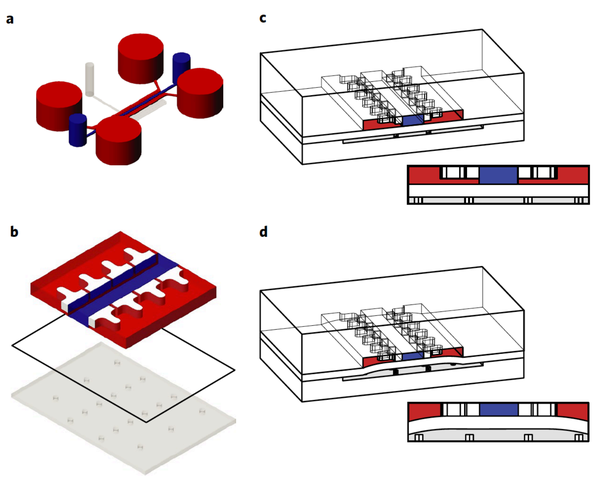
Aim



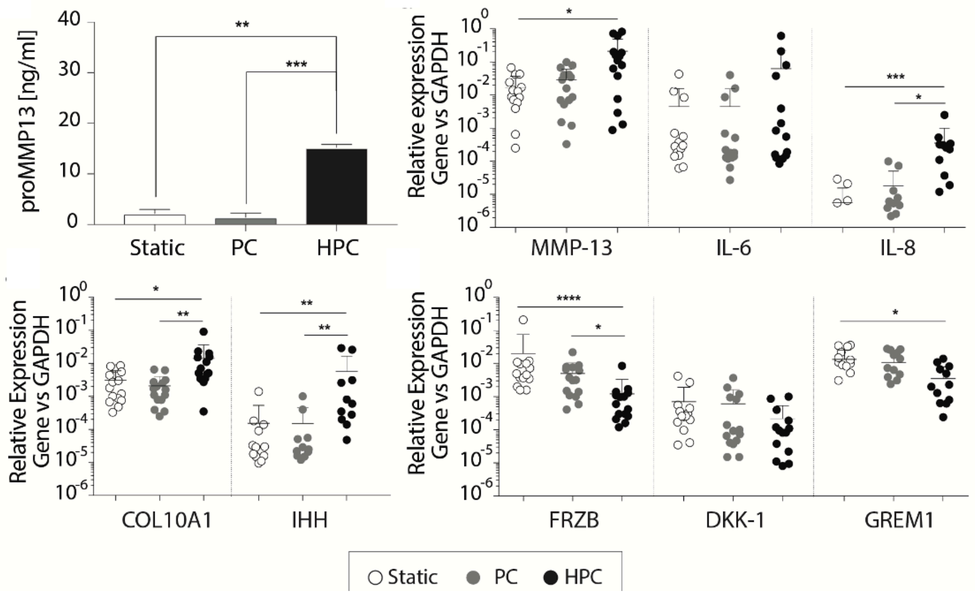
Organ-on-chips (OoCs) are microfluidic based devices recapitulating organ level functions *in vitro* [3]. In this framework we aim at developing an **OoC of OA** that will be used to study the disease progression and to screen promising anti-OA drug candidates

Results

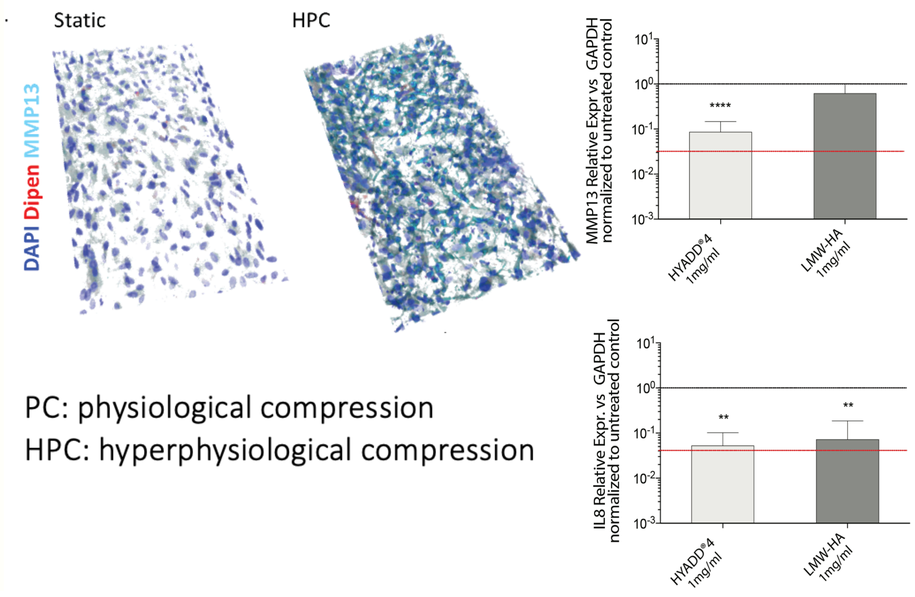
Chip design



OA mechanical induction

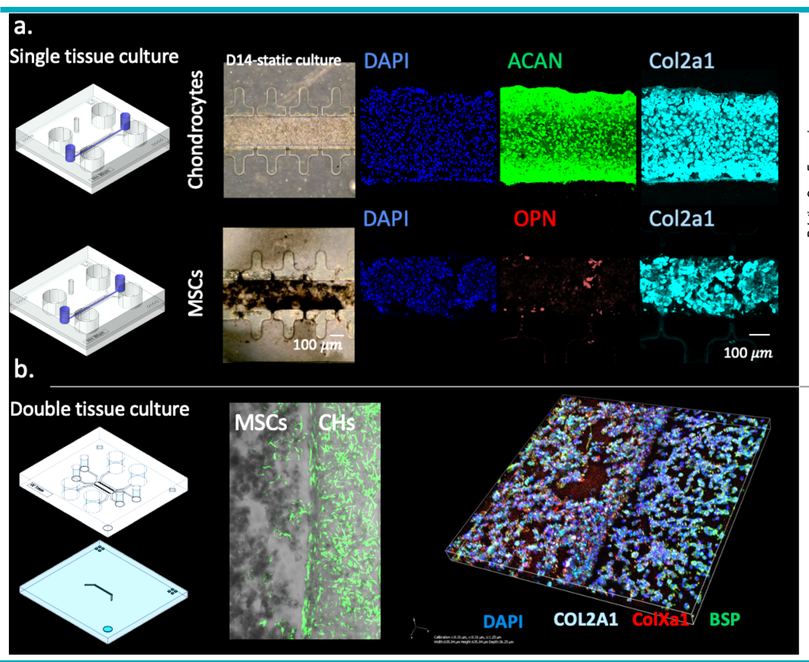


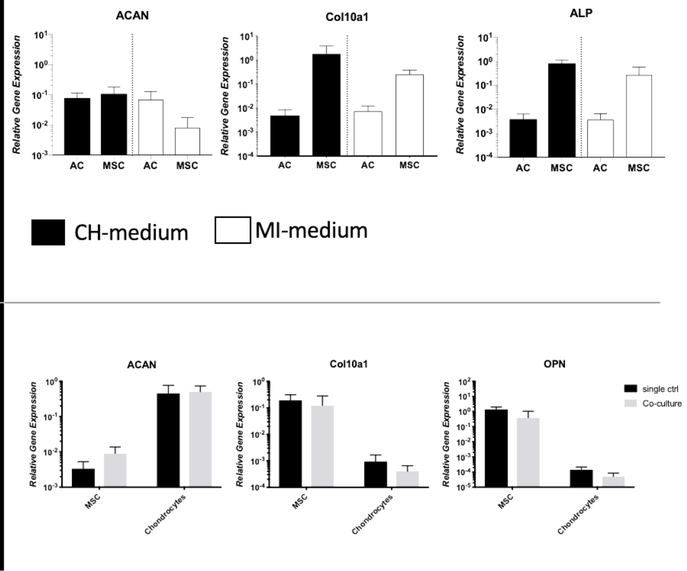
Drug screening



PC: physiological compression
HPC: hyperphysiological compression

A simplified cartilage only based OoC device was designed. The OoC is capable of subjecting cartilaginous micro-construct with either physiological (10%) compression (PC) or hyper-physiological (30%) compression (HPC). Primary chondrocytes were cultured in 3D PEG-based hydrogel within devices for 2 weeks to achieve constructs maturation. Tissues rich in ACAN and Coll2a1 were achieved. HPC (1 Hz, 1 week of stimulation) resulted in OA traits induction i.e. production of degradative enzymes (i.e. MMP13) increased inflammation (i.e. IL6 and IL8) and hypertrophy (i.e. increased expression of COLL10a1 and IHH). The model was adopted in drug screening of known compounds (i.e. Dexamethasone, Rapamycin, Celecoxib, Anakinra, LMW hyaluronic acid and HYADD4) revealing better adhesion to in vivo results with respect to cytokine-based controls [3].





Double layered constructs were achieved inside an OoC model. Microconstructs representative of both a cartilaginous and a calcified cartilage layer were obtained in single culture starting from, respectively, primary chondrocytes (CHs) and bone marrow derived MSCs. A mineralization inducing medium formulation (MI-medium) capable of maintaining CH chondrogenicity while allowing for MSCs deposition of a mineralized tissue was identified.

A direct interface between the two constructs was attained using removable PDMS molds [4].

GFP expressing chondrocytes were adopted to sort cells after the culture period and assess separate gene expression.

Tissue coculture revealed maintenance of distinct tissue phenotypes. Tissue-Tissue interface optimization is ongoing.

To integrate the mechanical actuation with the possibility of interfacing directly two tissues a [redacted] was ideated and introduced in a specifically designed new OoC. The device was functionally validated demonstrating the feasibility of consequently injecting two hydrogels with no leakage. A single actuation system for three devices was incorporated to increase the throughput.

Next steps

OA traits induction in both layers through HPC will be aimed for. Particular focus will be posed on the modification happening at the interface between the two tissues.

Specifically, then, the model could be used to screen putative molecular solution with both cartilage and subchondral layers resident molecular targets.

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Contacts: andrea.mainardi@unibas.ch