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Numerical modeling of cartilage growth under mechanical stresses. Mechanical and biological analysis on *in vitro* «micropellet» model.

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SUMMARY: The project concerns the modeling of the growth of new-cartilage samples generated from mesenchymal stem cells. These samples reproduce the embryonic formation of cartilage. We first propose to set up a device for analysing the mechanical features of neocartilage samples and then to investigate the role of mechanical stresses on the extra-cellular matrix production. This approach aims at evaluating and classifying the influence of mechanical stresses in respect of the growth factors on growth process.

DESCRIPTION: Cartilages are living tissues whose growth is a long process of which the exact role of mechanical stresses is misunderstood. This topic is crucial in the aim to improve current therapies devoted to regenerate new cartilage secondary to diseases such as degenerative osteoarthritis. Indeed, even if biologists know how to use growth factors to generate new cartilage, the resulting samples have mechanical properties that do not reach those of physiological mature cartilage. Moreover, there is no published study concerning the control of the mechanical environment during cartilage growth.

The present project aims at studying and modeling 1) the generation and growth of cartilage after differentiation of bone marrow mesenchymal stem cells (MSC) in micropellet culture that reproduces embryonic cartilage formation and 2) the role of mechanical stresses on their growth by evaluating extracellular matrix production.

A first step of this study concerns the biomechanical characterization of micropellets by using both biological and mechanical analysis techniques. To do so, the IRMB team differentiates MSC toward cartilage using the micropellet culture system and a chondrogenic medium containing TGFβ3 for 3 weeks (Fig. 1). Afterwards, the micropellets are mechanically characterised at the LMGC by harmonic compression tests at 1 Hz associated to video image correlation (Fig. 2). Then, immunohistochemical characterization is performed to reveal the quality of the produced cartilaginous extracellular matrix.

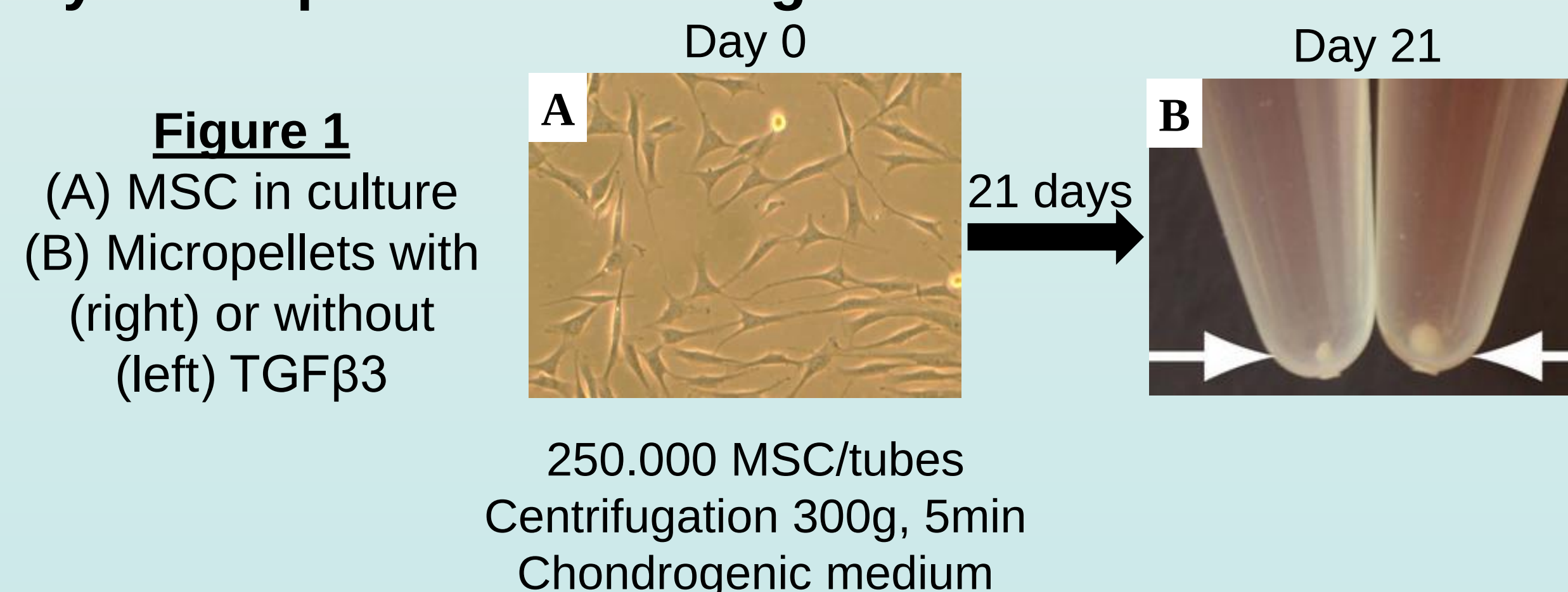
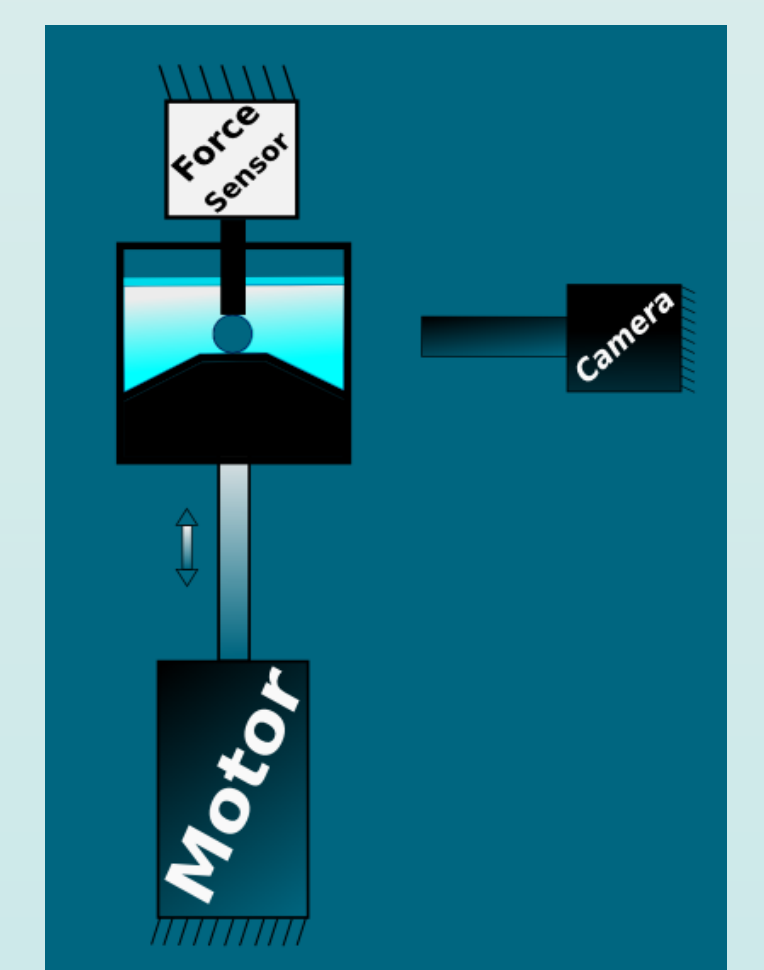


Figure 2:
Compression device



RESULTS:

➤ Molecular characterization of micropellets

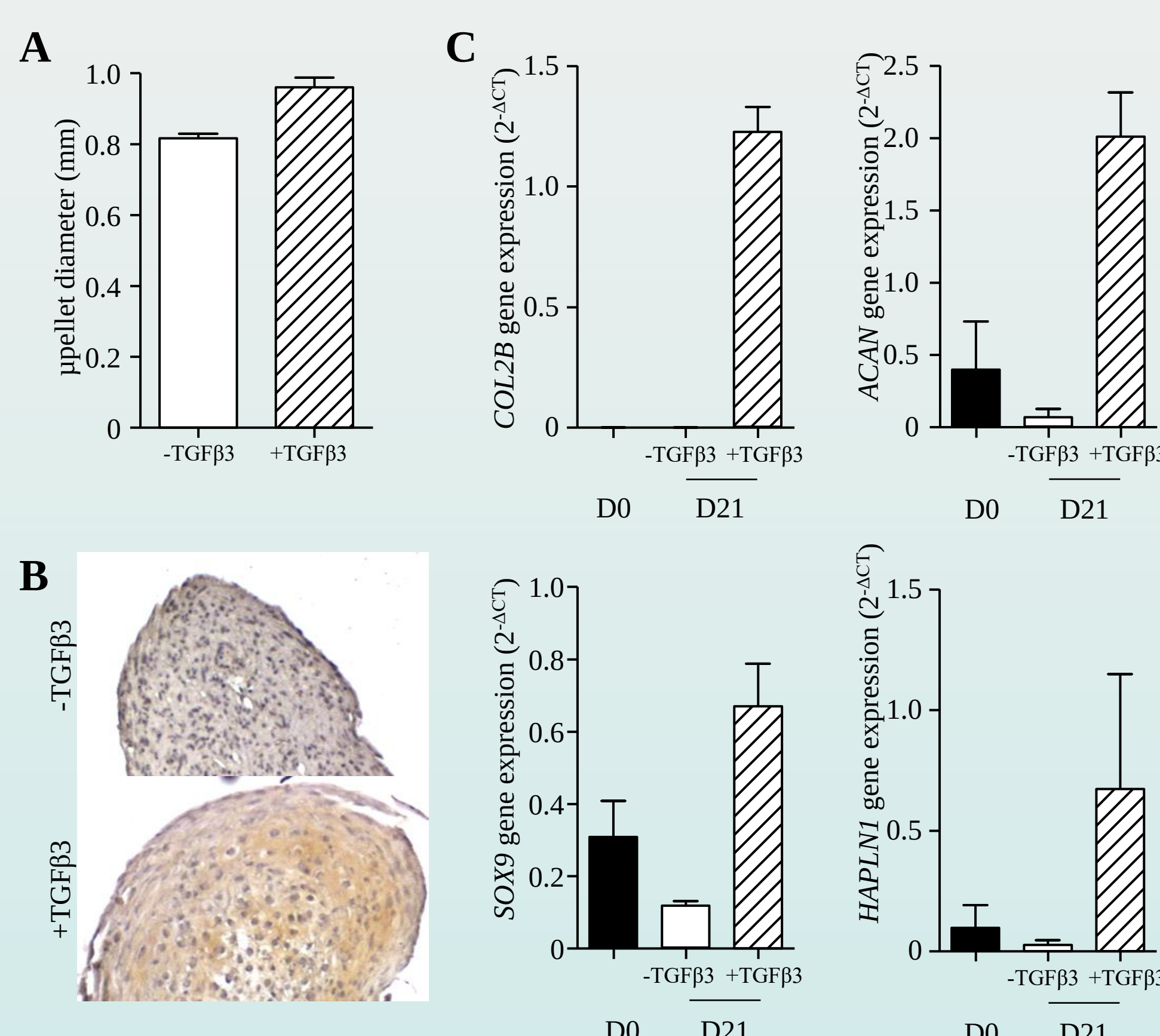


Figure 3: Micropellet diameter (mm) (A), collagen II staining (B) and specific chondrogenic marker gene expression (C) after 21 days of chondrogenic differentiation.

➤ Mechanical characterization of micropellets

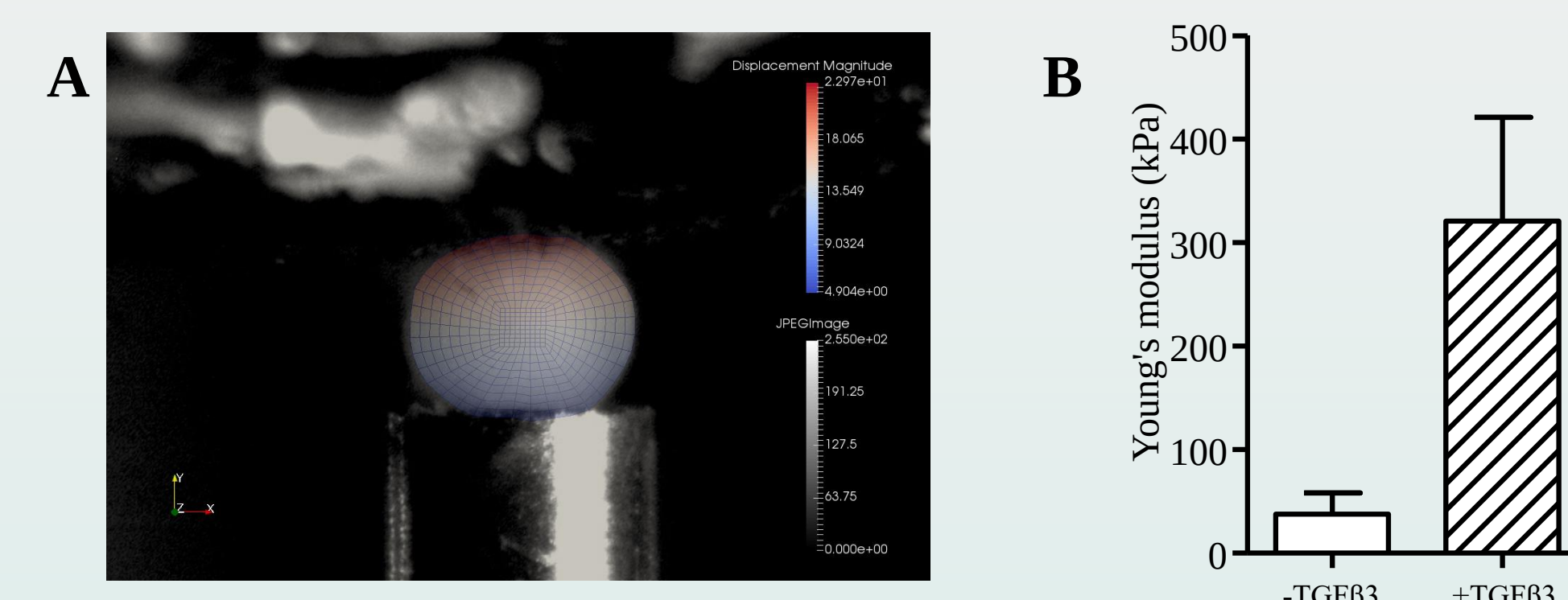


Figure 4: Micropellet under compression test and displacement field (A), and corresponding mean Young's modulus for 8 micropellets by culture condition (with or without TGFβ3) (B)

CONCLUSION:

- MSC cultured with TGFβ3 differentiate into cartilage as shown by the larger size of the micropellets, the expression of molecular markers specific for articular cartilage and their higher rigidity. These results validate the usefulness of the device we developed for measuring the mechanical characteristics of these very small size neotissue samples.
- Moreover, the mean value of Young's modulus of TGFβ3-micropellets is 320 kPa, in between that of immature fibrocartilage (~ 110 kPa) and of mature cartilage (~ 1-4 MPa). This underlines the limitations of the micropellet culture system and suggests that the device could be of high interest for evaluating different combinations of cells and factors to enhance cartilage formation with proper mechanical features.

PROSPECT:

Next step is to follow and analyse the temporal evolution of both the gene expression and the rigidity of micropellets. After that, we want to submit the cultivated micropellets to mechanical loading during the 21 days of chondrogenic differentiation in the aim to determine the role of mechanical stresses regardless the growth factors used and to improve MSC differentiation into cartilage using the micropellet technique. To do so, a specific microfluidic-based device is under design process (Fig. 5).

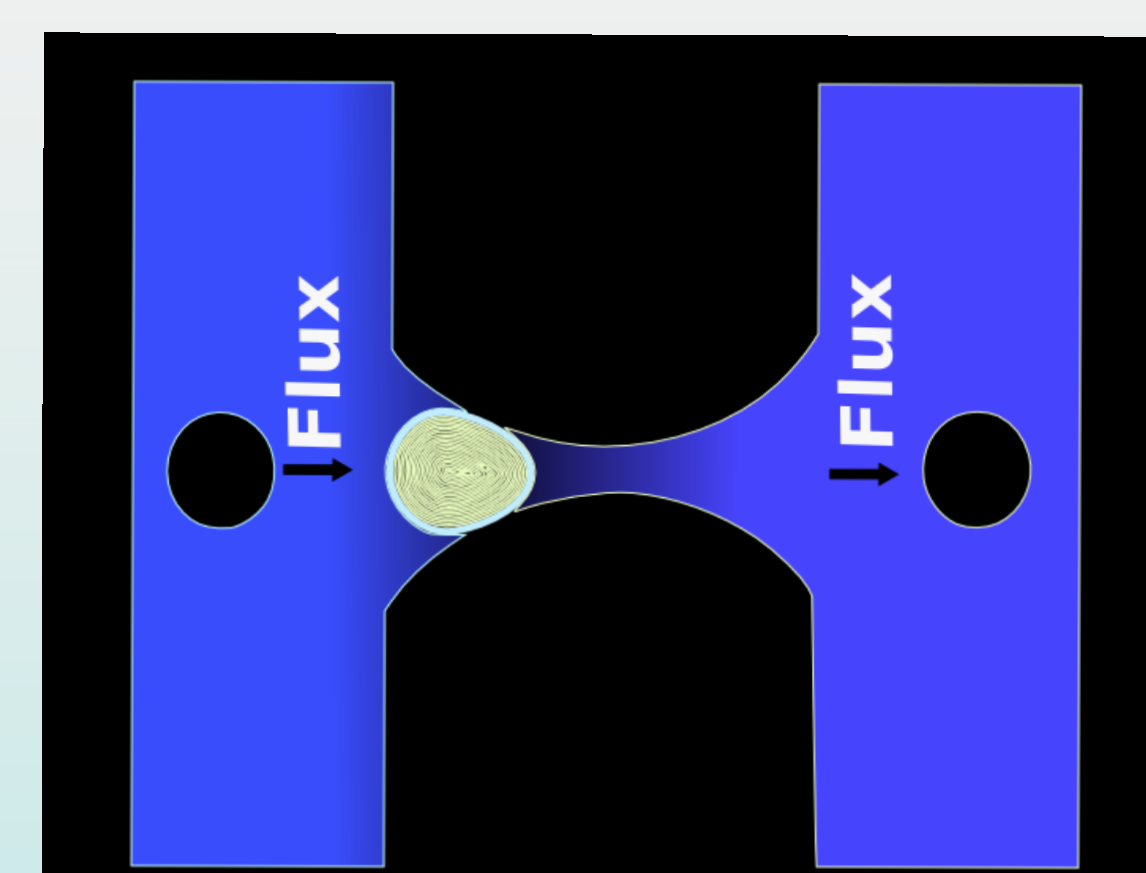


Figure 5: Scheme of principle of the microfluidic-based device that will be used to submit micropellets to mechanical loading while being cultivated.