Remote magnetic alignment of spheroids in 3D matrix for muscle-on-chip

Noam Demri[1*], **Simon Dumas**[1], **Manh-Louis Nguyen**[1], **Giacomo Gropplero**[1], **Ali Abou-Hassan**[2], **Stéphanie Descroix**[1], **Claire Wilhelm**[1]

[1]Laboratoire Physico Chimie Curie, CNRS UMR168, Institut Curie, Sorbonne University, PSL University, Paris, France

[2]Nanosystèmes InterfaciauX, PHENIX, CNRS UMR234, Sorbonne University, Paris, France

*noam.demri@curie.fr

Organizing cells anisotropically is essential to recapitulate the skeletal muscle tissue's 3D microenvironment. Most cells alignment methods rely on contact guidance cues [1], but alignment in 3D [2], especially in a gel, remains challenging. Here we propose two innovative magnetic-based approaches for muscle tissue engineering [3]. The first approach generates magnetic spheroids as tissue building blocks, while the second one offers a new way to align magnetic cells or spheroids along a strong uniform magnetic field. Combined, the two-step process enables the on-chip creation of muscle fibers oriented in the magnetic field direction in collagen-based matrix. Cells were labeled with iron nanoparticles, and optimization led to 21pg of iron internalized per cell, with no impact on cell metabolic activity or capacity to differentiate. Microfabricated magnets could then attract the magnetically labelled cells and generate in 3 hours several thousand spheroids of controlled size (10-100 µm range). These spheroids could then be aligned on-chip in a 3D thermoresponsive collagen gel between two strong magnets. Once the gel polymerized, the chains of spheroids were trapped in this configuration. The chains were on average a few hundreds of microns long and could go up to 1 mm under optimal cell density and magnetic labeling. Such structures made with aligned spheroids remarkably maintained their anisotropy overtime. Besides, in a matter of days, the spheroid chains fused into fiber-like structures. These fibers could also be 20% stretched or co-cultivated in the 3D collagen gel with randomly dispersed fibroblasts, and several myofibers formed in the direction of the alignment. Overall, this work demonstrates that combining magnetically assisted 3D strategies with organ-on-chip technology is beneficial for the fabrication of muscle tissue engineered constructs. As many tissues in the human body are anisotropic, these technologies to produce and align magnetic spheroids could open new perspectives for 3D tissue engineering.

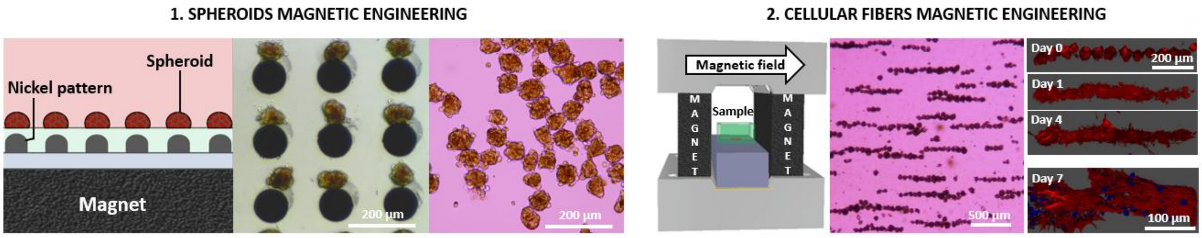

Figure 1: Spheroids' magnetic microfabrication and alignment to form a 3D cellular fiber

References

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