Magnetic nanoparticles as a tool to create, investigate and stimulate multicellular aggregates.

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Multicellular aggregates are currently used as a model for biological tissues: for biophysics, for drug screening, as tumor model systems or as building blocks for 3D bio-printing and tissue engineering. Magnetic nanoparticles are increasingly used in the biomedical field for diagnostic and therapeutic strategies, including imaging, hyperthermia and drug delivery. Recently, they have been proposed to develop new approaches to tissue engineering and manipulation, in which magnetic forces are used to manipulate single cells within a 3D construct.

We have developed a set of methods based on cell tagging with magnetic nanoparticles, to mold multicellular aggregates of chosen shapes (e.g. cylinders) and unprecedented sizes – up to a few mm in diameter – while preserving tissue integrity[1] (A).

The magnetism thus provided to the aggregate can be used as a tool to study and stimulate these model tissues. Subjecting magnetic cellular cylinders to tunable magnetic forces - through the use of an electromagnet - allowed us to investigate the rheological properties as a function of the aggregate maturation time (B).

In parallel, using a fix magnetic attractor, we have been able to assemble a 3D embryoid body from embryonic stem cells (ESCs). Then, by adding a second mobile magnetic attractor (C), we have demonstrated that a cyclic mechanical stretching of the embryoid body drives the ESCs' differentiation towards the mesodermal cardiac pathway[2].

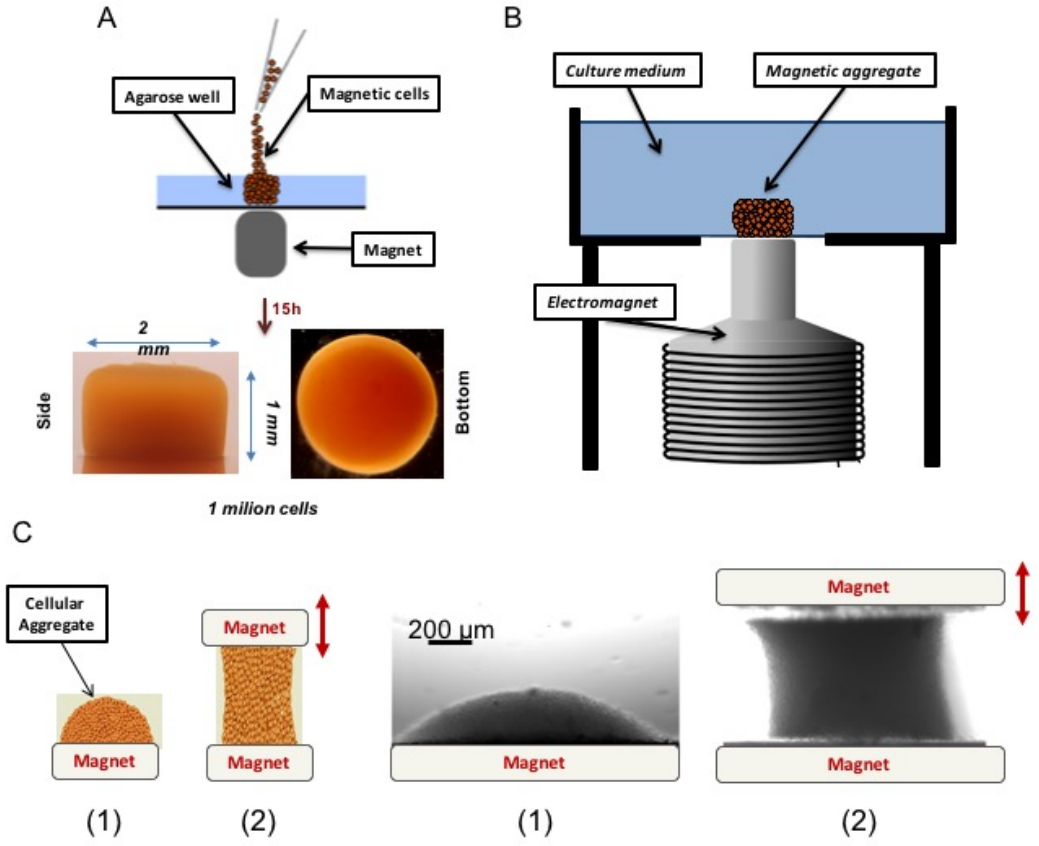

Figure: A) Magnetic molding method of cylindrical-shaped aggregate using magnetic cells. B) Magnetic Rheometer: a magnetic aggregate is stimulated remotely with an electromagnet. C) Magnetic stretcher: formation and cyclic stimulation of a embryoid body.

These new magnetic tools thus provide a promising all-in-one approach to create magnetic tissues, to stimulate them and to investigate their mechanical properties.

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(1) *Mazuel et al. Phys. Rev. Lett.* **114**, 098105 (2015)
(2) *Du et al. Nature Communications* **8**, 400 (2017)