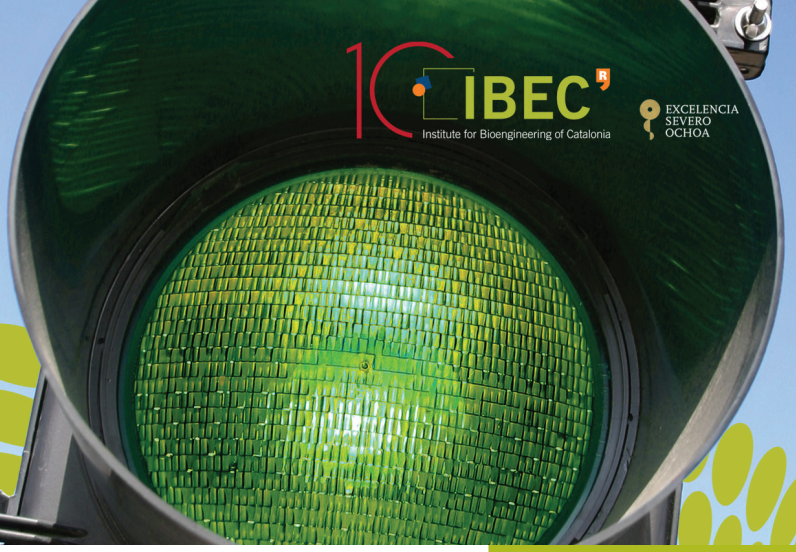
IBEC International PhD Fellowships Programme



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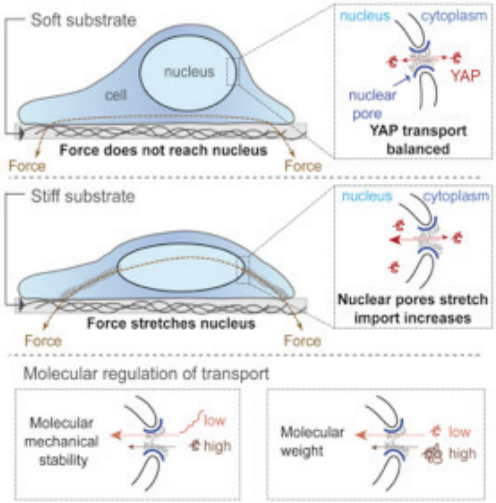
Cellular and molecular mechanobiology group

Group leader: Pere Roca Cusachs

Control of breast cancer by nuclear mechanics

To properly understand tissue and organ function in health and disease, a fundamental aspect is to reproduce in the laboratory the complex microenvironment of cells and tissues, both in terms of their three-dimensional architecture and of the mechanical stimuli that they experience. In this regard, organoids (three-dimensional cell aggregates which reproduce to a good extent the micro-anatomy of an organ) are emerging as useful tools [1]. By taking breast cancer organoids as a model system, this project aims to explore how cells sense their microenvironment to determine function, and its impact in breast cancer progression. Specifically, our lab has recently shown that a fundamental mechanism by which cells sense their environment is by force transmission to the cell nucleus, which changes its shape and leads to the nuclear import of transcriptional regulators [2]. This leads to the exciting hypothesis that nuclear tension and shape control cell function, and that this understanding can be harnessed to both model cancer, and potentially design novel therapeutic strategies. This project will address this hypothesis in organoids, and will primarily involve the design of novel tools to measure and regulate nuclear tension in three dimensions. The expertise acquired will include biomechanical tools, molecular cell biology techniques, and computational modelling, and will also involve collaborations with leading international groups in the Netherlands, the UK, and USA.



Proposed mechanism of regulation of control of cell function by force-dependent nuclear import of the transcriptional regulator YAP (Elosegui-Artola et al., Cell *2017).*

1. *Huch M, Koo BK: Modeling mouse and human development using organoid cultures.* Development *2015, 142:3113-3125.*

2. *Elosegui-Artola E, Andreu I, Beedle AEM, Lezamiz A, Uroz M, Kosmalska AJ, Oria R, Kechagia JZ, Rico-Lastres P, Le Roux AL, et al.: Force triggers YAP nuclear entry by regulating transport across nuclear pores.* Cell *2017:In press.*