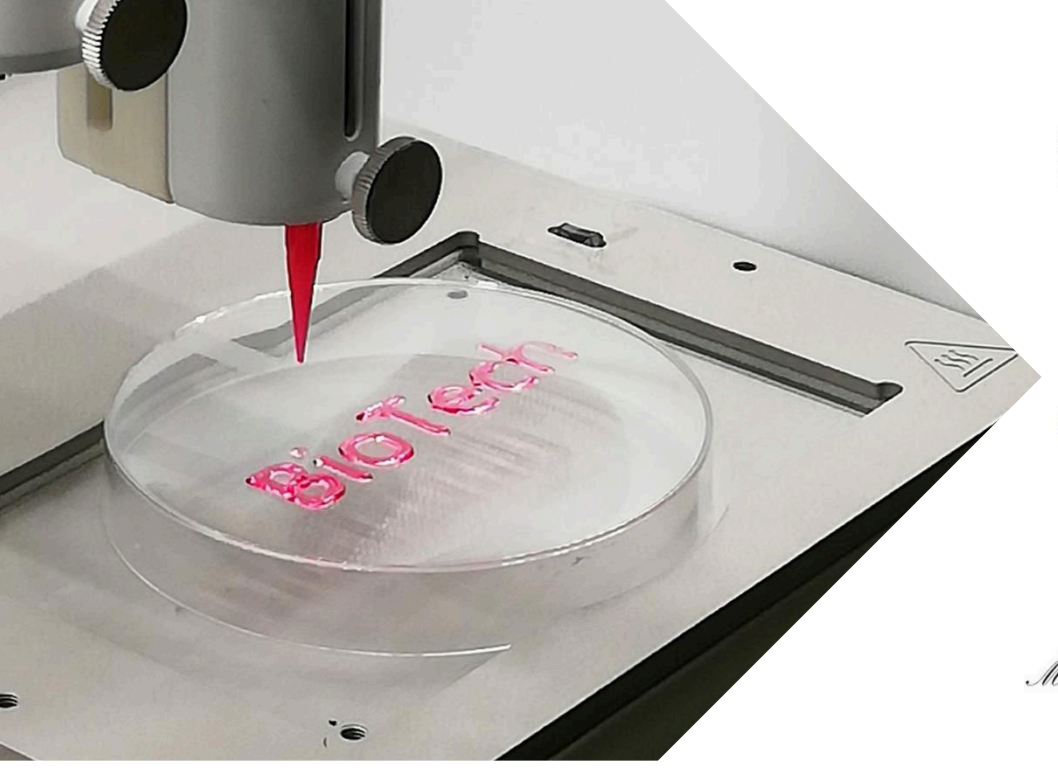

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Biotech Seminars Series

2022-2023

Innovation in biomedical technologies: emerging strategies for human life

Pathological mechanosensing in the failing heart

Speaker:
Prof. **Giancarlo Forte**, St. Anne's University Hospital, Brno, Czech Republic
December 13th, 2022
h. 14.30 pm CEST
Zoom Platform

Abstract

The onset and progression of aging-associated pathologies is paralleled by continuous local extracellular matrix (ECM) remodelling. This process serves as a compensatory strategy for tissues to cope with the altered conditions.
The modifications in the nanostructure and mechanics of cardiac ECM are driven by the activation of cardiac fibroblasts and impair cardiac cell function to progressively lead to organ failure. In turn, cardiomyocytes respond to the ensuing biomechanical stress by re-expressing fetal contractile proteins, by rewiring transcriptional and post-transcriptional processes, such as alternative splicing.
Our group demonstrated that the aberrant activation of mechanosensitive Yes Associated Protein (YAP) alters the assembly of focal adhesions in response to mechanical stress (Nardone G et al, Nat Commun 2017). Additionally, we contributed knowledge on YAP regulation during the acquisition of cardiac phenotype by adult and pluripotent stem cells (Pagliari S et al, Cell Death Diff 2020), and found that its hyperactivation in patient-derived cardiac fibroblasts promotes ECM pathological remodelling, thus favoring the fibrotic process and fueling heart failure (Perestrelo AR et al, Circ Res 2021).
Lately our experimental data highlighted how the pathological remodeling of ECM in the failing heart directly affects the expression and function of RNA binding proteins in cardiomyocytes (Vrbsky J et al, Genomics 20221; Martino F et al, Sci Transl Med 2022).
This discovery demonstrated that mechanical stress can effectively rewire the alternative splicing of numerous genes involved in cardiomyocyte contractility, calcium handling and mechanosensing.
These studies allowed us to describe different layers of intracellular mechanosensing responsible for finely tuning the expression of splicing variants of genes involved in organ function as a response to pathological mechanical turmoil.

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