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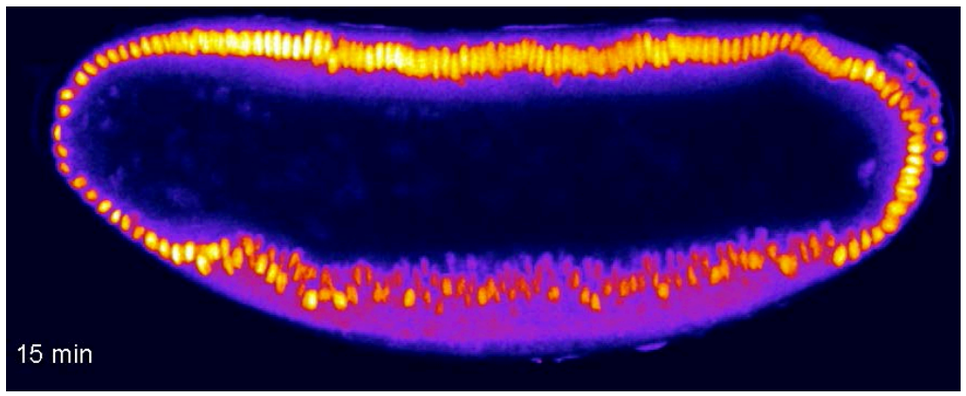
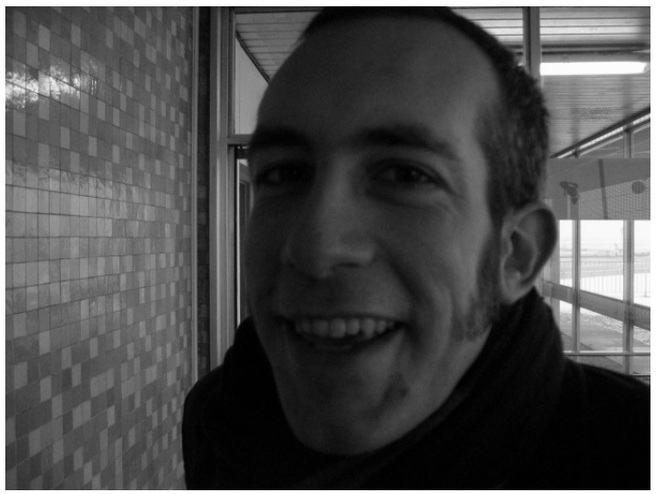
Description of the funded research project

2nd Call for H.F.R.I. Research Projects to Support Post-Doctoral Researchers



Title of the research project:
Role of mechanical forces in development and cancer.

Principal Investigator:
Mitrossilis Démosthène



Reader-friendly title: MechanoCancer

Scientific Area: Life sciences

Institution and Country: BRFAA
(Biomedical Research Foundation, Academy of Athens) - Greece

Host Institution: BRFAA
(Biomedical Research Foundation, Academy of Athens)

Budget: 200.000 Euros

Collaborating Institution(s):

Duration: 36 months

Project webpage (if applicable):

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Research Project Synopsis

Tissues are composed of cells that are connected to one another. In particular, cadherin-mediated adhesions couple the contractile cytoskeleton of cells together to form the mechanical architecture of tissues. Local changes of cell shape and their mechanical properties can drive significant tissue shape change and functionality. While epithelial folding during animal development determines cell fate and tissue topology, leading to the generation of diverse organs, internalization of cells inside tissues in mature organs leads to cancer. My long term goal is to understand how mechanical changes in the cells determine cell behaviour. To achieve this goal, in this proposal, I will first determine a framework for myosin organisation during the ventral invagination in the developing *Drosophila* embryo and then I will study the acinar epithelium formed by human cells, a well established model for cancer. I propose to implement three specific goals, combining biophysical, cellular and genetic approaches :

First, I will quantify the build up tension in the epithelium by utilizing *in vivo* laser ablation and magnetic tweezers in mutants affecting cell shape changes and the ventral invagination. Second, I will determine how the spatio-temporal conditions (density of pulsating cells, amplitude and frequency of cell pulsation) regulates the myo-II apical stabilization and the cadherin adhesion by utilizing suitable FRET-based biosensors, magnetic tweezers and mutants affecting the ventral invagination.

Third, I will study how cells movements occurs in the human acini and quantify the elasticity of the tissue using a calibrated cantilever (force sensor). Collectively, this cutting-edge interdisciplinary research will provide a breakthrough of how cells integrate forces in the living organism and a deeper understanding of how we can combat cancer.

Project originality

This research proposal aims at combining *in vivo* and *in vitro* approaches to understand the interplay between biochemical and mechanical signaling in the self-organization of living matter, in particular during development and cancer. The role of biochemical information in the production of mechanical forces and the formation of new shapes is quite well understood. Conversely, it is less known how mechanical cues developed by the cells and by the morphogenetic movements influence fundamental processes and key features of living matter, such as tissue morphogenesis, cell differentiation, cancer metastasis and tumorigenesis. Deciphering how mechanical cues are transduced into biochemical signal in living system, is essential on understanding the principles of tissue homeostasis and thus on improving modern medicine. Hence, my research project aims at pushing further the understanding of how mechanical forces modulate cellular functions involved in embryo development and cancer initiation by applying an interdisciplinary research approach combining genetics, quantitative imaging and biophysics in the model organism of Drosophila and of the Acinar epithilum.

Expected results & Research Project Impact

The program aims to understand the interplay between biochemical and mechanical signaling in the self-organization of living matter, in particular during development and cancer. Deciphering how mechanical cues are transduct into biochemical signal in living system, is essential on understanding the principles of tissue homeostasis and thus on improving modern medicine. Hence, the research project aims at pushing further the understanding of how mechanical forces modulate cellular functions involved in embryo development and cancer initiation by applying an interdisciplinary research approach combining genetics, quantitative imaging and biophysics in the model organism of Drosophila and of the Acinar epithelium. By fulfilling the research program the necessary technology will be develop to address the scientific questions. Unambiguously, the highly interdisciplinary character of the research program will provide a breakthrough of how cells integrate forces and how tissue change functionality. Definitely, understanding precisely the mechanism of how cells and tissue acquire their shapes will provide not only a better understanding in basic research but a deeper understanding of how we can combat cancer.

The importance of this funding

My long term vision is to develop a research team in the strongly emerging field of mechanobiology. Unambiguously, the ELIDEK proposal for Post-doctoral researcher will definitely enhance my career and give me the opportunity to establish further the field of mechanobiology in Greece. Thus the ELIDEK for Post-Doctoral researchers will directly promote my career development by applying my knowledge and skills in the field of developmental biology and cell biology and supervise successfully Phd students. The proposed project will allow me to develop multidisciplinary research experience and communication skills in a research field at the interface of physics and biology. Taken together, the ELIDEK for Post-Doctoral researcher will provide me an excellent opportunity to strengthen my competitiveness in view of obtaining a permanent position in academia.

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