Al collegio docenti del Dottorato in Medicina Molecolare

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Ciclo: XXXIV

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Despite major advances in cardiovascular medicine, heart disease remains a leading cause of death worldwide and the end-stages of the disease, which are often refractory to medical therapy, require the implantation of ventricular assist devices or even cardiac transplantation. However, the existing techniques suffer for a number of limitations, thus in this fields new materials are still needed to provide rapid and long-lasting interventions. Liquid Crystalline Elastomers (LCEs) are polymers that can show intermediate phases between solids and liquids, called mesophases. This unique combination of mobility with solid-like order makes these polymers extremely sensitive to external stimuli such as temperature, electric and magnetic field or, in our case, light. LCEs are considered the best candidates for smart artificial materials, in particular for their capability to perform a reversible shape-change in response to light. Thanks to these features, LCEs could be exploited to develop artificial contractile tissues, to be potentially employed as a long-lasting therapy for cardiomyopathies. Specifically, I focused on a severe cardiomyopathy that affects Duchenne Muscular Dystrophy (DMD) patients, as for most of them the progressive cardiac involvement is limiting for survival.

In the field of regenerative therapies, LCEs have received specific attention as biomaterials for the fabrication of medical surgery components and as dynamic cell scaffolds. Thanks to their biological properties (i.e. biodegradability, biocompatibility), these polymers have been considered as possible analogues of muscles, since they are soft, able to mimic the extracellular matrix and opened to 3D surface structuration.

In the second PhD year, the main goal of my study was to characterize the mechanical properties of LCEs in order to better understand their muscle-like features. For this purpose, LCE samples were cut into strips similar in shape and dimension to thin cardiac trabeculae (200-400 um width, 1-4 mm length) and isometrically mounted between a force transducer and a motor. LCE strips were activated by using a wide illumination provided by a green LED lamp (530 nm) as a light source with an illumination beam of about 5 cm. These experiments were performed in order to study how the contraction of our materials could be modulated by the intensity and the duration of the light stimulus. Notably, I found that the activation of LCE samples at increasing light intensities resulted in a progressively higher active tension and the maximal force developed by these polymers depended on light stimulus duration. Then, I did an energetic assessment of LCEs, since this represents a critical parameter in terms of mechanical properties of the materials. In order to study the mechanical efficiency of these polymers, I studied the force development in afterload conditions by applying different weights and monitoring the sample displacement with a camera.

Also, there are currently other experiments still under development that rely on the idea of creating a μLED-array that would provide a more local and non-homogeneous illumination of the samples, with the possibility to create a contractile patch of LCEs with the light source embedded in the material. Interestingly, I observed that the force amplitude and the mechanical efficiency of LCEs were in the same order of magnitude of those obtained with the wide illumination system.
As future perspectives, I will work on changing substrate conditions, modifying the stiffness of these biomaterials in order to mimic the stiffness variation of the extracellular environment during cardiac development and disease. The main idea would be to generate a mechanical stimulus with LCE contractile scaffolds, so to promote stem cell-derived cardiomyocytes differentiation and maturation. In order to create these dynamic cell scaffolds, the 3D printing and photo-polymerization techniques will be used to obtain the desired dimension and shape of the contractile patches to achieve the more convenient contraction pattern.
Furthermore, from February to date, I have been working on a collaborative research project between my group at the University of Florence and Prof. Regnier's lab at the University of Washington to study development and maturation of early stage heart muscle cells derived from human stem cells, their application in studying heart disease and its treatment by cell-based therapies.

• Attendance to 64th Annual Meeting of the Biophysical Society, San Diego (CA), February 15-19, 2020 with the poster *"MicroLED illumination towards Liquid Crystalline Elastomers based cardiac contraction assistance"*

- Attendance to lectures/webinars:
  - *"Modeling altered biomechanics of myosin with disease causing mutations across molecular and cellular scales"*, A. Schroer; 2/03/2020
  - *"A multi-omics approach to cardiovascular disease"*, M. Mayr; 3/04/2020
  - *"Exosomes and Epitranscriptome of the heart"* S. Sahoo; 10/04/2020
  - *"Optimization of hPSC maintenance conditions for true culture versatility"* H. Connor; 15/04/2020
  - *"Atrial myofilament function in genetic cardiomyopathies"* D. Barefield; 19/05/2020
  - *"Cardiac optical mapping, past, present and future"* C. O'Shea; 1/06/2020
  - *"Hypertrophic Cardiomyopathy: sarcomeric mutations and disease modifiers"*, D. Mosqueira; 5/06/2020
  - *"Subcellular discordant calcium release in cardiac myocytes"* L. Gonano; 8/06/2020
  - *"LV unloading and myocardial protection in AMI"* N. Kapur; 11/06/2020
  - *"Single cell sequencing for understanding of human cardiac biology"* N. Tucker; 12/06/2020
  - *"Supraventricular arrhythmias in athletes: basic mechanisms and new direction"* A. D'Souza; 22/06/2020
  - *"Cardiac gene therapy – Joint Session"* M. Giacca, C. Kupatt, S. Yla-Herttuala; 23/06/2020

- *“cAMP binding proteins EPAC in cardiac diseases”* F. Leoualc’h; 25/06/2020
- *“Mechanical control of relaxation: strain rate dependent myosin detachment and its implications on cardiac relaxation”* C.S. Chung; 26/06/2020

- From February 2020 to date, visiting PhD Student at the Department of Bioengineering of the University of Washington in Seattle, under the supervision of Prof. Michael Regnier, Director of the Laboratory.