Al collegio docenti del Dottorato in Medicina Molecolare

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Ciclo__XXXIII__ Tutor__Prof.ssa__Elisabetta Cerbai_____

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I started the second year of my PhD in molecular medicine in Amsterdam, working in the laboratories of Carol Ann Remme and Connie Bezzina, on a project titled "Effects of mexiletine on the sodium channel overlap syndrome mutation SCN5A-1795insD". Then, I returned back to Florence working on the electrophysiological characterization of the maturation of cardiomyocytes derived from hiPSC.

Background:

Cardiomyocytes derived from human induced pluripotent stem cells (hiPSC-CMs) are the most promising human model of cardiomyocytes. Here, we are trying to establish a systematic procedure to investigate the functional and molecular development of hiPSC-CMs and therefore, use this information to predict the outcome of genetic cardiomyopathies and identify molecular targets for therapy.

Methods:

- hiPSC-CMs, derived from monocytes of healthy donors or DMD patients (Duchenne muscular dystrophy), grew up on hydrogel-based micropatterned substrates with different stiffness to better mimic the extracellular matrix.
- At different timepoints (d60, d75, d90) after differentiation, cells were incubated, for 30min at 37°C, with a mix of Calcium probe (CAL630), voltage probe (FluoVolt) and PowerLoad.
- Using a custom-made apparatus, we carried out simultaneous optical measurements of action potential (AP) and calcium transient (CT) in single hiPSC-CMs

Results:

- Systematic comparison of control hiPSC-CMs, at different post-differentiation time points, shows that late CMs have a prolonged AP duration and increased calcium transient amplitude but with shorter duration, compared to early CMs.
- Greater substrate stiffness is associated with an increase in calcium transient amplitude
- DMD hiPSC-CMs have shorter AP duration and smaller calcium transient amplitude compared to control hiPSC-CMs.

Summary and Conclusions:

We developed a simple biomimetic culture approach and applied an optical technique for simultaneous comparison of functional output (AP and CT) of hiPSC-CMs at different maturation time points. Data obtained from DMD hiPSC-CM shows shorter AP duration and smaller calcium transient amplitude than control hiPSC-CM starting from early stages. This suggests an impaired development of SR and ionic currents responsible of AP features. Mechanistic insights are still under investigation for a deeper understanding of pathological implications and putative therapeutic targets against cardiac complications of DMD.

Abstracts:

Effects of mexiletine on the sodium channel overlap syndrome mutation *SCN5A*-1795insD

Chiara Palandri, Giovanna Nasilli, Raffaele Coppini, Laura Sartiani, Vincent Portero, Elisabetta Cerbai, Carol Ann Remme and Simona Casini
Congress: HERA - Lisbon 2019

Electrophysiological characterization of induced pluripotent stem cell-derived cardiomyocytes from Duchenne Muscular Dystrophy

Josè Manuel Pioner, Raffaele Coppini, Lorenzo Santini, Chiara Palandri, Elena Bennati, Patrizia Benzoni, Sara Landi, Andrea Barbuti, David L. Mack, Michael Regnier, Leonardo Sacconi, Elisabetta Cerbai, Corrado Poggesi, Cecilia Ferrantini

Congress: FCVB- Vienna 2018

Peer-reviewed Publications *in extenso*:

Br J Pharmacol. 2018 Jul;175(13):2635-2652. doi: 10.1111/bph.14223. Epub 2018 May 3.
"Late sodium current inhibitors to treat exercise-induced obstruction in hypertrophic cardiomyopathy: an in vitro study in human myocardium."

Ferrantini C Pioner JM, Mazzoni L, Gentile F, Tosi B, Rossi A, Belardinelli L, Tesi C, Palandri C, Matucci R, Cerbai E, Olivotto I, Poggesi C, Mugelli A, Coppini R.

Int J Mol Sci. 2019 Aug 3;20(15). pii: E3799. doi: 10.3390/ijms20153799
Optical Investigation of Action Potential and Calcium Handling Maturation of hiPSC-Cardiomyocytes on Biomimetic Substrates.

Pioner JM, Santini L, Palandri C, Martella D, Lupi F, Langione M, Querceto S, Grandinetti B, Balducci V, Benzoni P, Landi S, Barbuti A, Ferrarese Lupi F, Boarino L, Sartiani L, Tesi C, Mack DL, Regnier M, Cerbai E, Parmeggiani C, Poggesi C, Ferrantini C, Coppini R.

Soggiorno di sei mesi nei laboratori della prof.ssa Carol Ann Remme all'Academic Medical Centre (AMC) di Amsterdam.