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NOVEL SOLUTIONS FOR CARDIAC DRUG SAFETY AND TOXICOLOGY RESEARCH

James Costantin[1], Ronald Knox[1], Elena Dragicevic[2], Krisztina Juhasz[2,3], Oliver Reinhardt[4], George Okeyo[1], Sonja Stölzle-Feix[2], Frauke Alves[4,5], Rodolfo Haedo[1], Niels Fertig[2]

[1]Nanion Technologies Inc., 1 Naylon Place, Livingston, NJ, 07039, USA;
[2]Nanion Technologies, Munich, Germany;
[3]Institute for Nanoelectronics, Technische Universität München, Germany;
[4]Translational Molecular Imaging Group, MPI of Experimental Medicine, Göttingen, Germany;
[5]Clinic of Hematology and Medical Oncology, University Medical Center Göttingen, 37075 Göttingen, Germany

Human induced pluripotent stem cells (hiPSCs) have been proven instrumental for cardiac safety and toxicology testing due to their validated predictivity (e.g. CiPA study). We combined impedance and extracellular field potential (EFP) measurements with solid-supported membrane (SSM) based electrophysiology to study drug safety and toxicology in hiPSC-CMs. We have performed dual impedance and EFP-recordings to monitor cell proliferation and contractility, over prolonged time periods, contrary to standard mostly endpoint cytotoxicity assays. As the emerging field of cardio-oncology aims to find a balance between oncologic efficacy and reducing adverse cardiovascular effects, we tested the same treatment used in breast cancer chemotherapy, on hiPSC derived cardiomyocytes (iPSC-CMs). One of the standard clinical regimens for breast cancer is a combination of cyclophosphamide, adriamycin (doxorubicin) and 5-fluorouracil (CAF) administered for 4 months. We investigated putative cardiovascular side effects of CAF mix and paclitaxel and their long-and short-term implications on iPSC-CMs viability. We show a dose dependent negative effect of paclitaxel on iPSC-CMs viability (base impedance reduction). This was also observed for doxorubicin alone, but not the rest of the CAF compound mix. Paclitaxel and CAF also induced negative changes in cell contraction properties. We also investigated the role of the Na^+/Ca^{2+}-exchanger (NCX) in cellular Ca^{2+} homeostasis of iPSC-CMs. NCX is important for Ca^{2+} homeostasis, and it can contribute to cell damage by Ca^{2+} overloading or induce an anti-arrhythmic effect, when inhibited or when direction reversed. By developing a suitable sensor-based method (SSM based electrophysiology) we recorded specific NCX current responses of high amplitude. These currents showed similar Ca^{2+} affinity compared to NCX1 expressed in HEK cells and were sensitive to nickel, KB-R7943 and SEA0400. Using the impedance-based system, we also observed a significant increase in beating rate, as a long-term effect, when inhibiting NCX with SEA0400, in contrast to previous studies using non-human systems and focusing on short-term effects. In summary, we demonstrate the importance of new combination of tools, which help generate new insights into the pharmacology and toxicology of iPSC-CMs.