Dynamic Patch Clamp in Cardiac Safety – Insights from Dr. András Horváth

Dr. András Horváth in an interview with Dr. Sonja Stoelzle-Feix

Dr. András Horváth, electrophysiologist with more than five years' experience with iPSC-derived cardiomyocytes (iPSC-CMs), is now part of the assay development team at Nanion and is focusing on automated patch clamp recordings of stem cell-derived cells. He is convinced: applying innovative technology within the wide range of iPSC-CM assays is pushing the field forward. Nanion's CiPA expert, Dr. Sonja Stoelzle-Feix, talked to András about his views on this topic.

Munich 24. April 2019: Dr. András Horváth (Application Scientist at Nanion) in an Interview with Dr. Sonja Stoelzle-Feix (Director of Scientific Affairs at Nanion).

SSF: What is your experience with hiPSC-CMs?

AH: During my PhD studies at UKE-Hamburg I worked with hiPSC-CMs cultured in Engineered Heart Tissues (EHT). The overall goal was to investigate the cellular electrophysiological effects of the EHT-format on hiPSC-CMs and test the effects of cardiovascular drugs. I got to understand the challenges that will have to be surmounted before successful establishment of hiPSC-CMs as a predictive model for drug safety assays. Electrophysiological properties of hiPSC-CMs are different compared to human adult cells due to the different expression levels of certain cardiac ion channels, indicating immaturity of the cells. This can be a limiting factor in testing responses to drugs that can be pro-arrhythmic in humans.

SSF: Which factors do you think need to be evaluated next?

AH: Here at Nanion, in collaboration with Prof. Dr. Teun de Boer from the University of Utrecht, we have developed an automated dynamic clamp system which is integrated into a multichannel automated patch clamp system, the Patchliner. The aim is to increase throughput and develop new predictive assays using hiPSC-CMs that are in line with the aims of the CiPA initiative. Crucial endpoints include giga-Ohm seal patch clamp recordings with acceptable success rates on commercially available hiPSC-CMs and stable action potential recordings. Additionally, APD prolongations and shortenings in the presence of reference compounds must be possible.

Patchliner Paradise: András Horvárth, an application scientist who joined us in 2018, installing new Patchliners at a long-term customer site.

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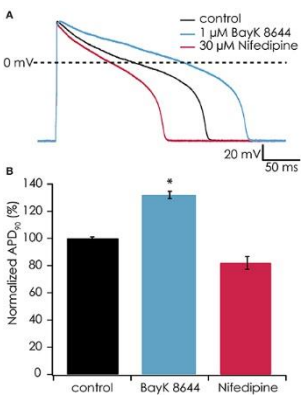
SSF: What did you achieve so far and what's next?

AH: We fully integrated the dynamic clamp functionality in an 8-channel Patchliner system. With iCell Cardiomyoctes^2, for example, we routinely achieve a success rate of around 70% for >20 min stable giga-Ohm seal recordings. This enables us to obtain reliable IC_{50} curves from action potentials. A typical workflow on a Patchliner with control and 3 compound applications takes approximately twenty minutes. Action potentials more representitive of adult cardiac cells are recorded. This success rate is a good prerequisite in order to continue and focus on evaluating a larger set of reference drugs, which we are currently doing.

SSF: Which cardiac ion channel modulators or blockers did you already investigate?



Action potential of stem-cell-derived cardiomyocytes using Dynamic Patch Clamp. Ref: Front. Physiol. DOI: org/10.3389/fphys.2017.01094

AH: After establishing a routine workflow with high success rate I looked at nifedipine, BayK 8644, and found expected APD modifications or IC_{50}s. We are planning to launch the fully automated 8-channel dynamic clamp Patchliner in Q4 this year and until then I'm planning to continue testing more of the reference drugs from the CiPA compound list, including hERG inhibitors like E-4031. A solid amount of evaluation data is key for the cardiac safety community to be able to judge the capabilities of this assay and then to adopt such an assay for their future projects.

About the Authors

Dr. András Horváth finished his PhD in April 2019. He worked in Prof. Thomas Eschenhagen's group at UKE-Hamburg and in Prof. András Varró's group at Unversity of Szeged. His focus was on the properties of cardiac ion currents in human and mammalian atrium and ventricle, and in human induced pluripotent stem cell-derived cardiomyocytes. As an expert in his field, Nanion was delighted when he joined the electrophysiology team. András is part of the team developing new safety pharmacology in vitro assays.

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Dr. Sonja Stoelzle-Feix is an active member of the CiPA HTS ion channel working group as well as the myocyte group. Hereby facing and understanding the current challenges within safety pharmacology electrophysiology approaches she is translating and driving innovation projects as Director of Scientific Affairs at Nanion Technologies.

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Dr. András Horváth and Dr. Sonja Stoelzle-Feix, photographed by Mary Kasoha, Product Marketing Assistant at Nanion.