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Letter to Editor

Comprehensive *In Vitro* Proarrhythmia Assay (CiPA): An Update

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The Comprehensive *in vitro* Proarrhythmia Assay (CiPA) is a proposal by the U.S. FDA, HESI (ILSI Health and Environmental Science Institute, US), CSRC (Cardiac Safety Research Consortium, US), SPS (Safety Pharmacology Society, US/Europe), EMA (European Medicines Agency), PMDA (Pharmaceuticals and Medical Device Agency, Japan), and Health Canada ultimately aimed at revising the non-clinical ICH S7B [1] and elimination of the clinical ICH E14 [2] guidances. The objective of the CiPA initiative is to facilitate the adoption of a new paradigm for assessment of clinical potential of TdP (Torsades de pointes) that is not measured exclusively by the potency of hERG block and not at all by QT prolongation. The CiPA paradigm is driven by a group of mechanistically based *in vitro* assays coupled to *in silico* reconstructions of cellular cardiac electrophysiologic activity, with verification of completeness through comparison of predicted and observed responses in human-derived cardiac myocytes [3].

The CiPA is based on a mechanistic understanding of proarrhythmic risk and is built around a three-component process:

(i) Candidate drugs are tested in multiple and standardized ion channels assays using overexpressing cell lines. This includes Nav1.5 (peak and late currents), Kv4.3 (Ito), hERG (IKr), KvLTQ1/mink (IKs) and Kir2.1 (IK1);

(ii) The data from the ion channel assays are used in a computational model of a CM (cardiomyocyte) action potential model to see if the compound yields proarrhythmic markers. This model is calibrated using data from well characterized reference compounds; and

(iii) The results from the *in silico* simulations are verified using iPSC-CMs (induced pluripotent stem cell derived cardiomyocytes).

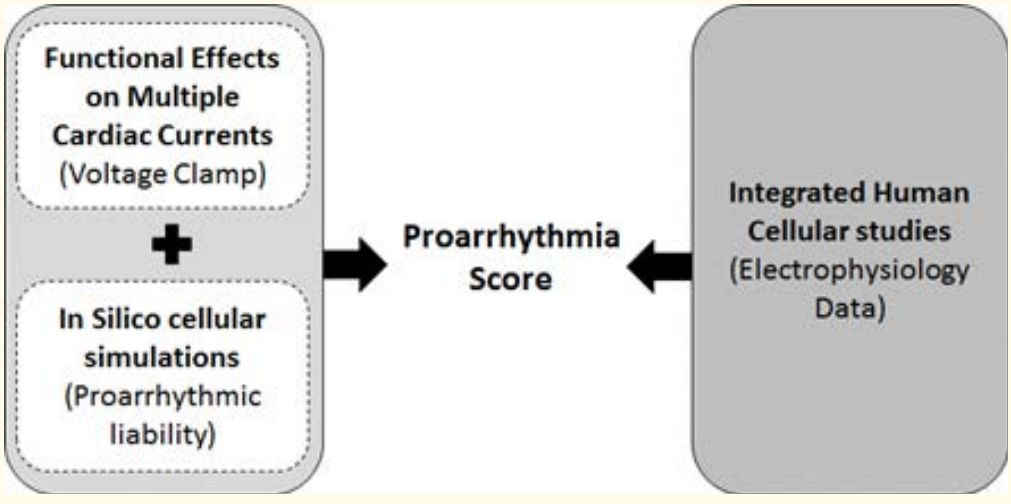

Figure 1: *Elements of CiPA.*

The last core assay of the CiPA platform proposes assessing the integrated electrophysiological effects of drug candidates on the hSC-CM (human stem cell derived cardiomyocytes) electrical activity and, ideally, on the action potential profile. The results of an FDA (Food and Drug administration, USA) pilot study indicate that hSC-CMs can identify drugs prolonging the repolarization phase as a result of either dofetilide-induced blockade of expressed hERG channels or from hERG trafficking inhibition produced by pentamidine [4-6]. Thus, these results appear to confirm the ability of currently available hSC-CMs to identify and grade the proarrhythmic risk of established drugs. However, it remains to be established whether the target sites of action of these agents in hSC-CMs are the same as those in native, healthy, adult human CMs. This critical question requires experimental clarification as the aforementioned study found that the proarrhythmic risk of hERG channel (Human ether-a-go-go-related gene) blockers was substantially greater than that clinically estimated from ECG (electrocardiogram) QTc (QT corrected interval) prolongation for comparable exposures [7]. Nevertheless, there is robust experimental evidence that hSC-CMs can correctly identify numerous, albeit not all, proarrhythmic drugs as indicated by published works [8-10].

hSC-CMs and iPSC-CMs have the potential to enrich the battery of cardiac electrophysiology test assays. At present, iPS (induced pluripotent stem) cell lines are derived from a small set of individual human beings. Thus, only a few individual genomes are reflected in the phenotype of the available iPSC-CMs. While it is a major benefit of iPSC-CMs to be individual-specific, this might also be one of the biggest drawbacks. In the end, all data will be based on genetic material of a few single human beings from which the respective cell lines have been produced. Even though so far it can only be speculated to what extent other individual cell-specific mechanisms are influencing ion channel properties, the limited angle of vision might result in a biased understanding of cardiac mechanisms. To avoid a limited view, a broad genetic variability of the cell lines will have to be assured. To summarize, there is still a lot of validation work ahead of us, but the potential of a highly specific and sensitive assay is worth the effort [11].

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