Assessment of the drug-induced cardiac functional toxicity by pattern-cultured hiPSC-CMs

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Introduction: Cardiac toxicity is one of the leading causes of attrition during preclinical and clinical drug development. Human iPSC-derived cardiomyocytes (hiPSCMs) have been tested for their use in safety pharmacology and shown to be useful for evaluating pro-arrhythmic potential of the drugs. In contrast, the use of hiPSCMs for evaluating the toxicity against cardiac contraction/relaxation has been still limited, because currently available hiPSCMs are immature and do not reproduce the critical contractile characters of the cardiomyocytes in adult human cardiac tissue.

Methods and Results: In the present study, we developed a novel culture system with pattern-cultured hiPSCMs in a 96 well format. Analysis using motion vector imaging system revealed that in contrast to hiPSCMs cultured in monolayer sheet without patterning, contraction/relaxation velocity and the movement of pattern-cultured hiPSCMs showed positive correlation between the contraction frequency. Moreover, pattern-cultured hiPSCMs fairly responded against various cardioactive compounds based on the compounds' molecular mechanism of action, suggesting the usefulness for assessing the effect of drugs on cardiac contraction/relaxation. We then tested the acute-to-chronic effects of various molecule-targeted anticancer drugs and doxorubicin on pattern-cultured hiPSCMs and identified that each anticancer drug exhibited distinct effects on the contraction, relaxation and total movement of pattern-cultured hiPSCMs.

Conclusions: Our results indicate that pattern-cultured hiPSCMs would be useful for evaluating the cardiac functional toxicity of the drug candidates. Further investigation using animal models would be necessary to correctly interpret the responses of pattern-cultured hiPSCMs.