Algorithmic Auto-Recreation System of hiPSC-CMs Simulation and Prediction of Drug Testing

Hirohiko Kohijitani  
Shigeya Kouda  
Takeru Makiyama  
Tomohiko Imamura  
Takanori Aizawa  
Asami Kashiwa  
JingShan Gao  
Hai Huang  
Yimin Wuriyanghai  
Yuta Yamamoto  
Satoshi Sizuta  
Takeshi Kimura  
Akinori Noma

**Introduction :** Mathematical optimization is core technology which makes fundamental of "AI". We use this for analysis of action potentials (APs) from human induced pluripotent stem cell derived cardiomiocytes (hiPSC-CMs) , in order to understand its heterogeneity and its complicated system of many ion-channels. HiPSC-CMs show different action potential (AP) morphology among cells and cell lines, and electrophysiological reaction for drug is also different among cells. In order to understand those phenomena, mathematical models for AP analyzation is needed. So, we aimed to construct precise model that is compatible for drug testing and molecular disease prediction using mathematical optimization method.

**Methods :** For analysis of APs from hiPSC-CMs, we developed comprehensive hiPSC-CMs mathematical models, and applied mathematical optimization for this model, and explored a method for simulational re-creation of APs. We recorded APs from 50 hiPSC-CMs and emulated all AP morphologies simulationally by changing conductance of each ion current, using autonomic mathematical fitting method. After that, we compared AP morphological change between in-silico and in- vitro IKr-blocking test.

**Result :** All 50 AP morphologies were successfully recapitulated in ±1mV error range of each points. Morphological change of AP after E4031 application was well recapitulated. APD90 was 269ms (in-vitro AP) vs. 274ms (in-silico AP). After application of IKr-blocking, APD90 was prolonged to 463ms vs. 440ms, respectively.

**Conclusion :** In-silico approach that includes algorithmic emulating simulation system enables prediction of in-vitro drug testing using hiPSC-CMs.