# Usefulness of collaboration between mathematical models and cell engineering for elucidating complex disease mechanisms and discover effective drugs

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**Funding Acknowledgement:** Type of funding source: Public Institution(s). Main funding source(s): Japan Society for the Promotion of Science, Grant-in-Aid for Young Scientists

**Background:** A missense mutation, CACNA1C-E1115K, located in the cardiac L-type calcium channel (LTCC), was recently reported to be associated with diverse arrhythmias. Several studies reported in-vivo and in-vitro modeling of this mutation, but actual mechanism and target drug of this disease has not been clarified due to its complex ion-mechanisms.
**Objective:** To reveal the mechanism of this diverse arrhythmogenic phenotype using combination of in-vitro and in-silico model.
**Methods and results:** Cell-Engineering Phase: We generated human induced pluripotent stem cell (hiPSC) from a patient carrying heterozygous CACNA1C-E1115K and differentiated into cardiomyocytes. Spontaneous APs were recorded from spontaneously beating single cardiomyocytes by using the perforated patch-clamp technique.
Mathematical-Modeling Phase: We newly developed ICaL-mutation mathematical model, fitted into experimental data, including its impaired ion selectivity. Furthermore, we installed this mathematical model into hiPSC-CM simulation model.
Collaboration Phase: Mutant in-silico model showed APD prolongation and frequent early afterdepolarization (EAD), which are same as in-vitro model. In-silico model revealed this EAD was mostly related to robust late-mode of sodium current occurred by Na+ overload and suggested that mexiletine is capable of reducing arrhythmia. Afterward, we applicated mexiletine onto hiPSC-CMs mutant model and found mexiletine suppress EADs.
**Conclusions:** Precise in-silico disease model can elucidate complicated ion currents and contribute predicting result of drug-testing.