High through put assessment system of proarrhythmic potential of drug candidates by multi-spheroid Ca-imaging analysis of human iPS-derived cardiomyocyte

A large percentage of new drugs fail in clinical studies due to cardiac toxicity. Therefore development of highly predictive in vitro assays which use clinically relevant cell-based models and are suitable for high throughput screening (HTS) is extremely important for early lead optimization process. Human induced pluripotent stem cell-derived cardiomyocytes (hiPS-CM) are especially attractive because they express ion channels which are similar to those of adult hearts and demonstrate spontaneous mechanical and electrical activity. Actually, many publications showed that QTc prolonging effect in clinical correlates with prolongation of field potential duration in electrophysiological assessment with a multi-electrode array system. At the last JSOT annual meeting, we presented a method for the assessment of cardiac toxicity of anti-cancer agents by multi-spheroid imaging analysis using hiPS-CM. In the present study, we would like to introduce a new high throughput screening method to assess proarrhythmic potential of a drug candidate as application of multi-spheroid Ca-imaging analysis.

At first, hiPS-CM (iCell® Cardiomyocytes) was pre-cultured 7-10 days in gelatin-coated 6 well plate and then the number of 15,000 cells was seeded into 96-half well plate which has fibronectin-coated spots in each well. The spheroids formation was confirmed in a plate on all fibronectin spots after 7 days culture. Ca sensing fluorescence dye and test compounds solutions, such as E-4031, terfenadine, flecaainide, chromanol293B, moxifloxacin, verapamil, cisapride, isoproterenol, propranolol and aspirin, were added and the dynamic changes in fluorescent intensity (Ca peak) of all spheroids were measured using Cellvoyager CV7000 system. The beat rate, Ca peak duration and sign of arrhythmia were analyzed from 30 seconds captured live-image for each well at 20 minutes after compound addtiton. Detail results will be introduced in JSOT annual meeting.