

Development of A Simultaneous Multimodal Recording Method of Extracellular Field Potentials and Images to Comprehensively Understand Cellular Responses

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Introduction

■ In vitro drug safety evaluation

Current situation : Various data of cellular responses are recorded separately.

Difficulty : Control of cellular conditions homogeneously for a comprehensive understanding of cellular responses

■ Solutions : Simultaneous Multimodal Recordings

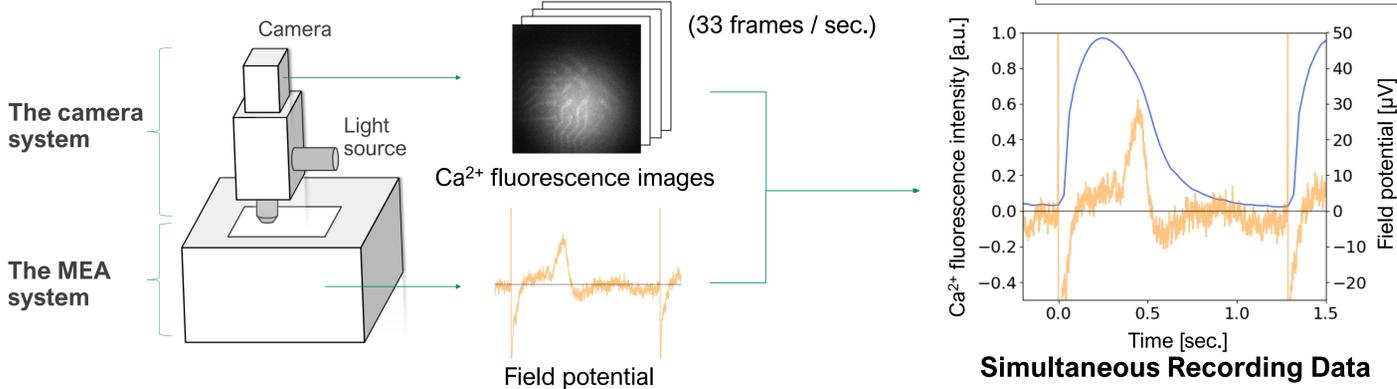
We have developed the simultaneous multimodal recording technique.

- the MEA (microelectrode array) system : **field potential** or impedance
 - the camera system : **fluorescence (e.g., Ca²⁺)** or phase-contrast images
- We examined the potential of the technique to comprehensively understand responses of human induced pluripotent stem cell derived cardiomyocytes, commonly used in drug safety evaluation.

Methods

iCell Cardiomyocytes2 (FUJIFILM Cellular Dynamics, Inc.) were cultured on MEA plates for 8-9 days. Following the loading of Cal-520, AM (AAT Bioquest, Inc.), the cells were exposed to 13 compounds, with cumulative additions to increase their concentrations.

We simultaneously recorded Ca²⁺ fluorescence images and field potential.



Test 13 compounds

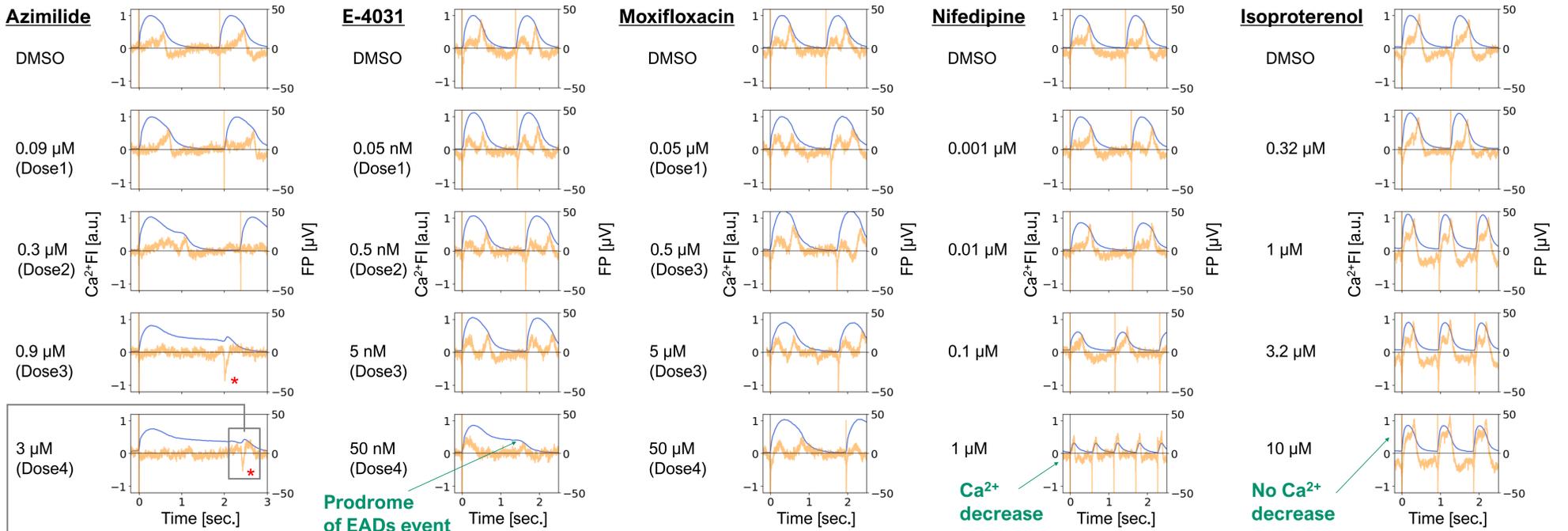
Test Compound	Mechanism of Action (MoA)
DMSO	—
Azimilide*	hERG channel blocker
E-4031*	
Terfenadine	hERG/Cav1.2 channel blocker
Moxifloxacin*	
Clozapine	Ca _v 1.2/hERG channel blocker
Chlopromazine	
Verapamil	Ca _v 1.2 channel blocker
Nifedipine*	
Isoproterenol*	β adrenergic receptor agonist
Ryanodine	Ryanodine channel inhibitor
SEA 0400*	Na ⁺ /Ca ²⁺ exchanger inhibitor
Digoxin*	Na ⁺ /K ⁺ ATPase inhibitor

*The following section discusses representative compounds with various MoAs.

Results and Discussion

■ Simultaneous recording of recognized phenomena was achieved. (Ca²⁺FI : Ca²⁺ fluorescence intensity, FP : Field potential)

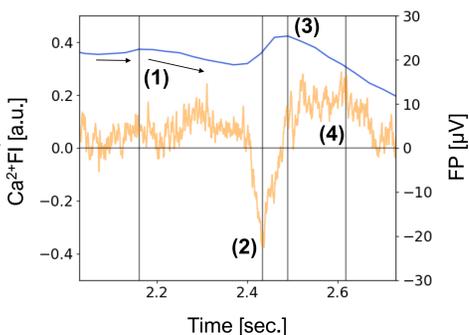
*EAD (early afterdepolarization), **Cardiac Arrest



■ Signal propagation on EADs event

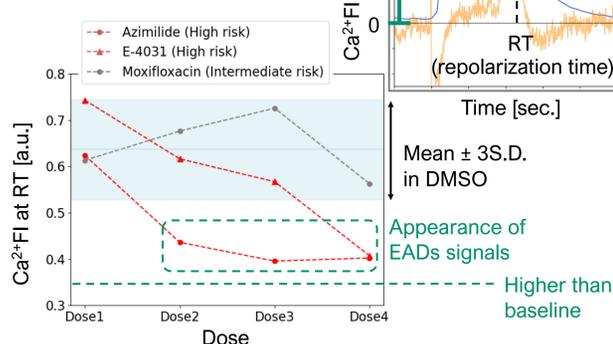
- The Ca²⁺FI increased on EADs event.
- It is suggested that events occur in the following order.

- (1) Reduction of Ca²⁺FI
- (2) Reduction of FP
- (3) Increase of Ca²⁺FI
- (4) Repolarization (the 2nd peak of FP)



■ The dynamics of Ca²⁺ in response to arrhythmia risk

Ca²⁺FI at RT (Ca²⁺ fluorescence intensity at repolarization time)



- There was a difference in Ca²⁺FI at RT between high risk compounds of arrhythmia and the others.
- It is suggested that hERG current is necessary for decay of Ca²⁺FI to baseline.

Conclusion

We confirmed the potential of simultaneous multimodal recordings to understand temporal relationship between signals. This multimodal approach can improve our understanding of cellular dynamics, such as not only cardiomyocytes but also neural cells, by using MEA recording of electrical signals and imaging analysis of various targets (e.g., Ca²⁺, membrane potential or fluorescently labeled receptors).

