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바이오헬스

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심근세포의 전기 및 기계생리학적 분석을 위한 기능성 캔틸레버 기반의 약물 독성 스크리닝 플랫폼

Functional Cantilever-based Drug Toxicity Screening Platform for Electro-mechanophysiological Analysis of Cardiomyocytes

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Key words : Cardiomyocytes, Cantilever, Field potential, Contraction force, Strain sensor

During drug development, testing of the adverse effects of the potential drug candidates on the cardiac tissue is carried out at an early stage. This is necessary as drug-induced cardiotoxicity is a major factor of withdrawal of numerous drugs from the market. However, the current method of measuring electrophysiology using patch clamp technique has several limitations, as it can only measure ion channel currents and is an invasive technique. The cardiac cells also possess inotropic characteristics, the responses of which are necessary to assess during drug screening. Therefore, a platform that can measure both electrophysiological and contractile response of the cardiac tissue in a non-invasive manner is the need of the hour. Here, we propose a functional cantilever array-based drug screening platform that serves this purpose. Cardiomyocytes are cultured on the array of eight polymer cantilevers that displace with cardiac contraction force, and the strain sensor patterned on each cantilever can measure the contractility. On the other hand, microelectrodes are patterned on the cantilevers that measure the field potential of the cardiomyocytes. The platform was successfully tested using drugs like blebbistatin and quinidine. The proposed platform has the potential to be used for a complete assessment of cardiotoxicity.

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Functional Cantilever-Based Drug Toxicity Screening Platform For Electro-Mechanophysiological Analysis Of Cardiomyocytes

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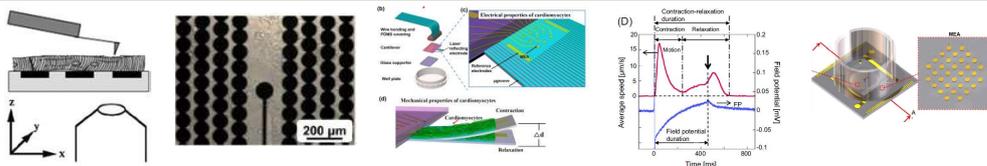
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ABSTRACT

During drug development, testing of the adverse effects of the potential drug candidates on the cardiac tissue is carried out at an early stage. This is necessary as drug-induced cardiotoxicity is a major factor of withdrawal of numerous drugs from the market. However, the current method of measuring electrophysiology using patch clamp technique has several limitations, as it can only measure ion channel currents and is an invasive technique. The cardiac cells also possess inotropic characteristics, the responses of which are necessary to assess during drug screening. Therefore, a platform that can measure both electrophysiological and contractile response of the cardiac tissue in a non-invasive manner is the need of the hour. Here, we propose a functional cantilever array-based drug screening platform that serves this purpose. Cardiomyocytes are cultured on the array of eight polymer cantilevers that displace with cardiac contraction force, and the strain sensor patterned on each cantilever can measure the contractility. On the other hand, microelectrodes are patterned on the cantilevers that measure the field potential of the cardiomyocytes. The platform was successfully tested using drugs like blebbistatin and quinidine. The proposed platform has the potential to be used for a complete assessment of cardiotoxicity.

◆Keywords : Cardiomyocytes, Cantilever, Field potential, Contraction Force, Strain Sensor, Microelectrode Array

INTRODUCTION



Current techniques for simultaneous electrophysiology and contraction force measurement

Motivation and Objective

- Several drugs only show changes in contraction force but not electrophysiology of cardiac cells, and vice versa.
- Objective is to develop a high throughput integrated cardiac sensing drug screening platform for simultaneous measurement of electrophysiological and mechanical properties of cardiomyocytes

DEVICE CONCEPT

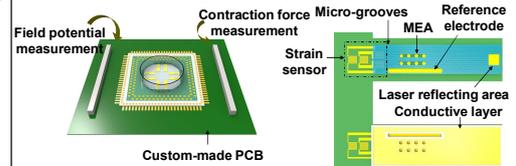


Fig. 1. Schematic of the proposed multi-functional biosensor platform. Total 8 cantilevers with MEA and strain sensors each. Diameter of MEA = 50 μm, pitch = 350 μm. Strain sensor is patterned in the half bridge configuration for the measurement of contractility.

DEVICE FABRICATION

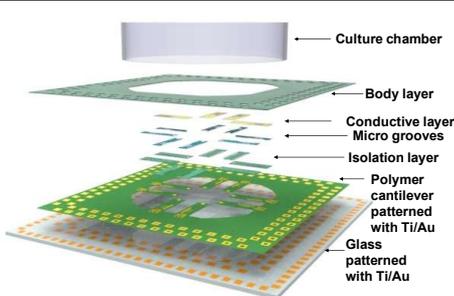


Fig. 2. Layer-wise breakup of the proposed dual-function biosensor. The cantilever-based device is made using SU-8 and bonded to glass using thermal bonding.

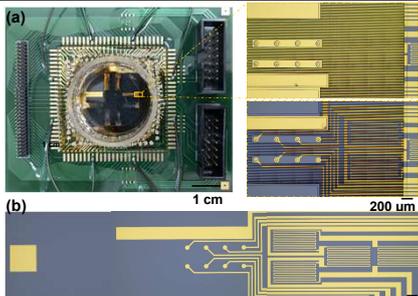


Fig. 3. (a) Photo of the fabricated device connected with PCB. Right side shows photo before and after conductive layer pattern. (b) Photo of cantilever before microgrooves pattern.

DEVICE CHARACTERIZATION

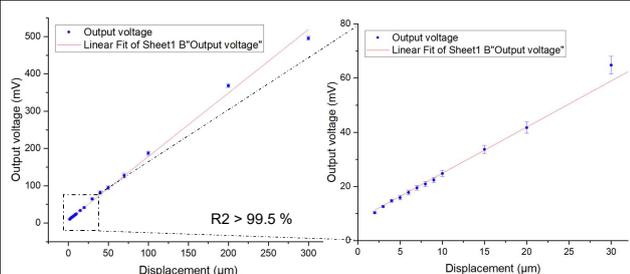


Fig. 4. (a) Characterization of the strain sensor to assess the minimum detectable displacement.

- The sensor output voltage shows high linearity with respect to the cantilever deflection.
- The minimum detectable displacement using strain sensor was 2 μm.

RESULTS

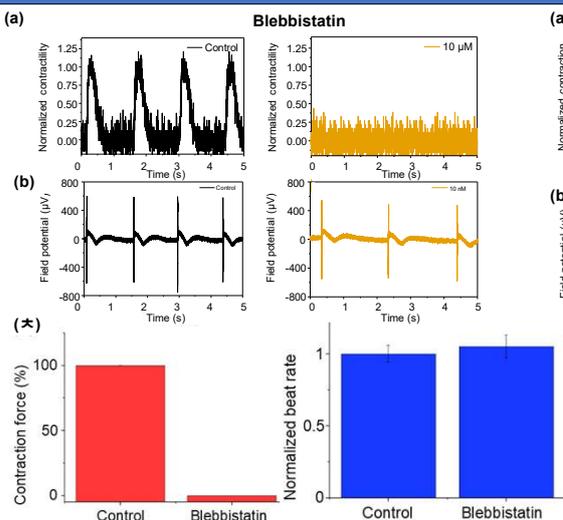


Fig. 5. Drug toxicity screening using Blebbistatin on the fabricated dual function platform. (a) Contraction force and (b) field potential at control and on addition of 10 μM Blebbistatin. (c) Analysis of contraction force and beat rate.

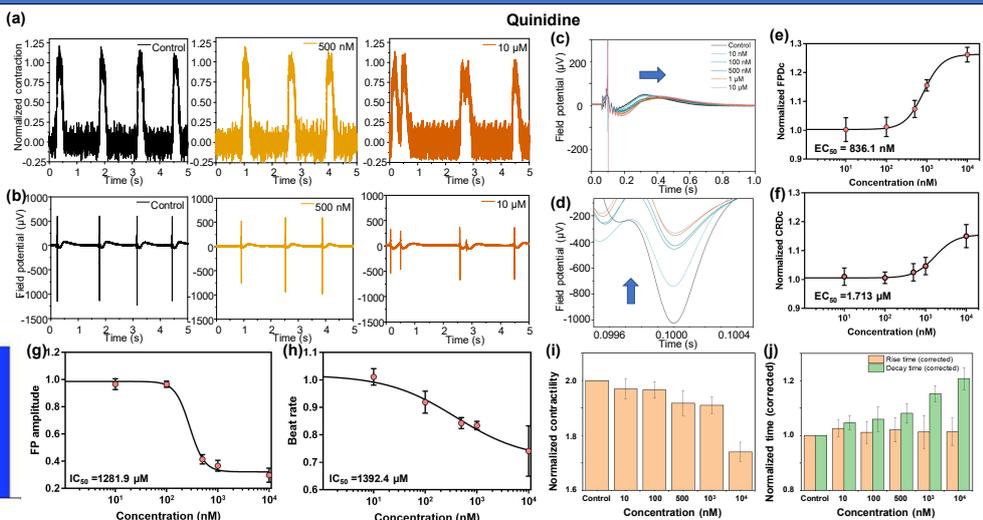


Fig. 6. Drug toxicity screening using Quinidine on the fabricated dual function platform. (a) Contraction force and (b) field potential at control, 500 nM and 10 μM of the drug. (c) Increase in field potential duration (FPD) with the right-shift of the peak, (d) decrease in field potential spike amplitude, (e) change in FPD, (f) contraction-relaxation duration, (g) FP amplitude, (h) beat rate, (i) contractility and (j) rise time/decay time with concentration.

CONCLUSION

This work successfully demonstrated the simultaneous measurements of field potential and contraction force of the cardiac tissue using MEA and strain sensor. The platform could be fabricated using photolithography that can be upscaled for mass manufacturing. The strain sensor was sensitive enough to be able to detect displacement as low as 2 μm. The platform successfully measured field potential and contraction force generated by NRVM and was able to respond to drug toxicity using Blebbistatin and quinidine. Our novel platform has the potential to be used in pharmacological applications for the evaluation of drug induced toxicity.

ACKNOWLEDGMENT

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