

Biowire™ II Matured Human Engineered 3D Cardiac Tissues for Drug Discovery and Cardiotoxicity Applications

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Introduction

Cardiomyocytes derived from human induced pluripotent stem cells (hiPSC-CMs) have immense potential in drug discovery and cardiotoxicity assessment, but their fetal-like phenotype hinders their predictive value as models of the adult human myocardium. Biowire™ II 3D cardiac tissues were generated from iCell Cardiomyocytes² (Cellular Dynamics International) and matured through mechanical and electrical stimulation in a polydimethylsiloxane-free device, designed to provide non-destructive direct measurements of contractile force and Ca²⁺ transients, as well as action potential readouts. The resulting tissues express many of the physiological hallmarks of the adult human myocardium including a high degree of cellular alignment, a positive force-frequency relationship, post rest potentiation, little or no spontaneous beating, and an action potential profile characteristic of human adult myocytes (rapid upstroke velocity, resting membrane potential more negative than -75mV).

Maturation

Figure 1. Biowire™ II tissues have improved structural alignment. The Biowire™ II platform facilitates both tissue maturation and the ability to directly measure force. A representative image of Biowire™ II tissue and platform is shown on the left. Inset shows a representative section of mature Biowire™ II tissue stained with cTroponin (green) showing highly organized myofibril structure.

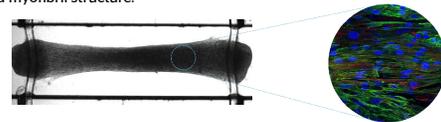


Figure 2. Positive force-frequency relationship. Increasing the frequency of external field stimulation results in increased force of contraction from 1 Hz to 4 Hz, a hallmark of adult human myocardium.

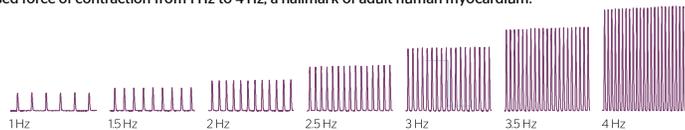


Figure 3. Positive inotropic response to β-adrenergic agonists. Addition of isoproterenol increases the amplitude of calcium transients and the force of contraction at 1 Hz external field stimulation.

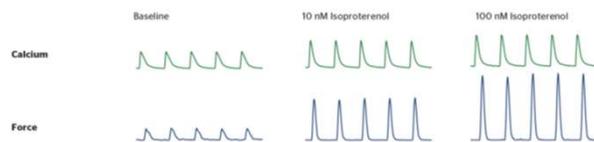
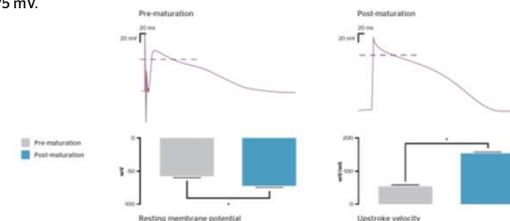


Figure 4. Adult-like action potential profile. The action potential of mature Biowire™ II tissue show characteristics of adult human myocardium including a fast upstroke velocity and a resting membrane potential more negative than -75 mV.



Drug Response

Figure 5. Predictive electrophysiological response to ion channel modulators. Representative action potential recordings from Biowire™ II tissue treated acutely with HERG channel blockers ibutilide or dofetilide or calcium channel blockers nifedipine or verapamil recorded at 1 Hz stimulation is shown on the left. A summary of the action potential response of Biowire™ II tissue to various ion channel modulators is presented in the table.

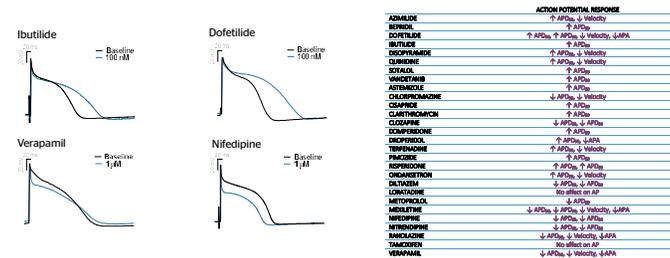


Figure 6. Predictive contractility response. Representative force traces from Biowire™ II tissue treated with omecantiv, FPL 64176, digoxin, or nifedipine recorded at 1 Hz stimulation is shown on the left. A summary of the contractility response of Biowire™ II tissue to a variety of compounds is presented in the table.

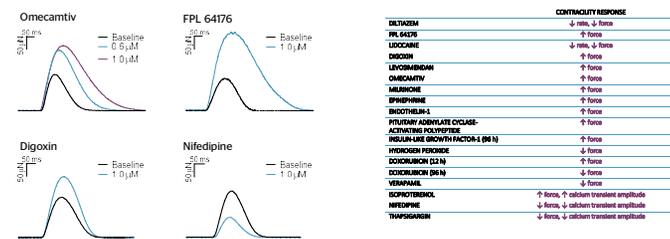
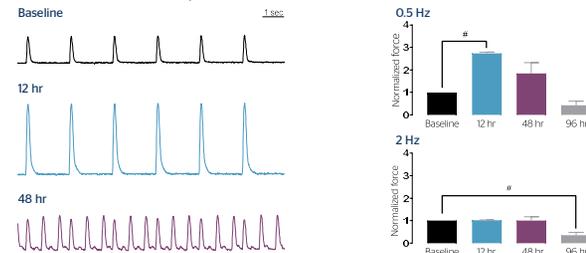


Figure 7. Chronic contractility response with doxorubicin treatment. Representative force recordings from Biowire™ II tissue treated with 2 μM doxorubicin is shown on the left. Recordings were done at 0.5 Hz external field stimulation. Summary of chronic doxorubicin effects on contractility are shown on the right. Recordings were done at 0.5 Hz and 2 Hz external field stimulation up to 96 hr.



Summary

The Biowire™ II matured human 3D cardiac tissue and associated platform enables an integrated physiological readout of contractility, calcium handling, and electrophysiology providing more predictive drug discovery and cardiotoxicity assessments.