FLEXCYTE 96 APPLICATION NOTE

From Rigid to Realistic

Improving Inotropic Drug Response in hiPSC-Cardiomyocytes with Physiological Substrate Mechanics

Introduction – Predictive Cardiac Safety Screening Using FLEXcyte 96

High-throughput, scalable assays using predictive cell models are essential to improve the costly and time-intensive drug development process. Cardiac safety remains a key concern, with off-target cardiac effects among the leading causes of late-stage drug failure. Traditional gold-standard methods, such as the *ex vivo* Langendorff setup, are limited by low throughput and non-human biology, making them unsuitable for modern drug screening needs.

Human iPSC-derived cardiomyocytes (hiPSC-CMs) offer a powerful human-based alternative, combining scalability, cost-efficiency, and ethical acceptability. However, culturing these cells on rigid substrates imposes unnatural mechanical stress, impairing physiological maturation and predictive accuracy. Such conditions can lead to transcriptional and metabolic alterations that reduce the model's translational value [1].

To overcome this, the FLEXcyte 96 system enables auxotonic contraction on ultrathin, flexible membranes mimicking native cardiac tissue mechanics [2]. As an integral part of numerous pharma workflows and regulatory initiatives like HESI, the platform supports the broader shift in FDA drug development strategies that aim to phase out animal testing in favour of human-relevant models.

The FLEXcyte 96 reliably detects inotropic effects of benchmark drugs such as isoproterenol, Bay K8644, and omecamtiv mecarbil – compounds that often yield misleading results in static assays [3]. We demonstrate how this technology provides more physiological, predictive drug responses in hiPSC-CMs, helping reduce uncertainty in early cardiac safety screening.

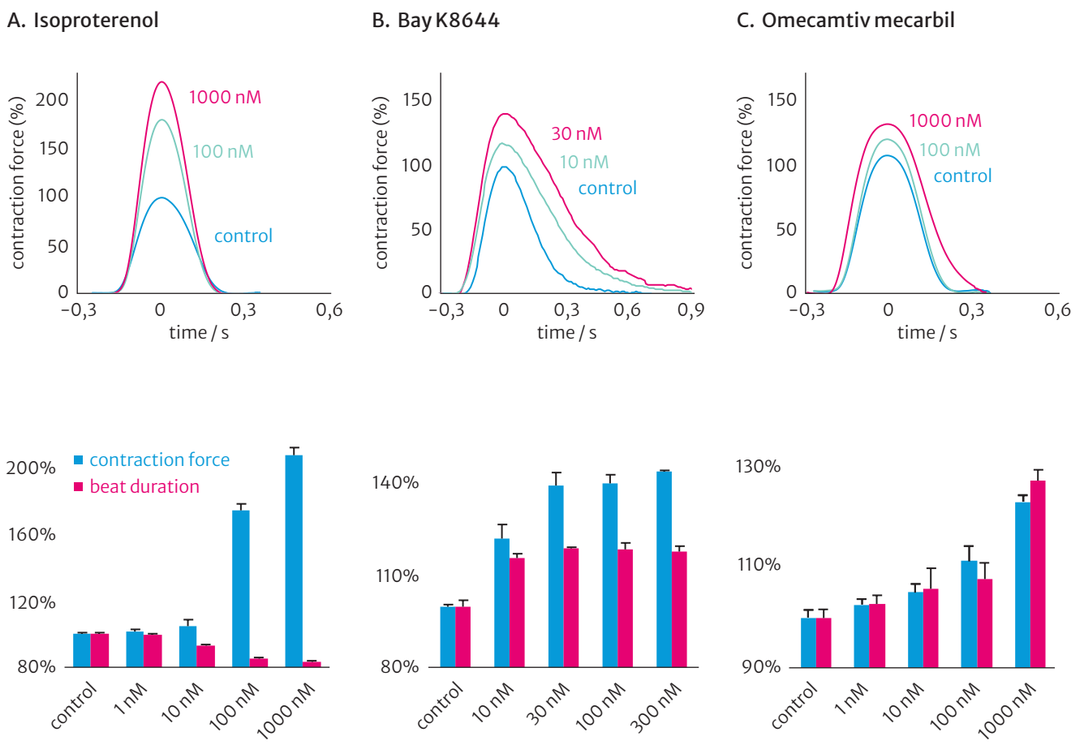

Figure 1. Recorded contraction force and corresponding beat duration analysis of hiPSC-CMs cultured on FLEXcyte 96 plates after treatment with isoproterenol (A), Bay K8644 (B) and omecamtiv mecarbil (C).

Results – Build Around Your Biology

Figure 1 illustrates the dose-dependent effects of isoproterenol, Bay K8644, and omecamtiv mecarbil on hiPSC-CMs cultured in FLEXcyte 96 plates. Isoproterenol showed increased contraction kinetics with a stronger contraction force up to ~210% of control at 1 µM. Bay K8644 prolonged the relaxation phase due to elevated intracellular calcium and increased contraction force to 150% at 30 nM. Omecamtiv mecarbil enhanced contraction force, without altering contraction symmetry, indicating its myosin-driven inotropic effect.

These distinct and physiologically relevant responses to compounds acting through diverse mechanisms underscore the enhanced functional fidelity of hiPSC-CMs cultured in FLEXcyte 96. The platform enables detection of subtle, target-specific effects on contractile behavior that are often missed by conventional assay systems, making it as a valuable tool for translational cardiac safety and efficacy testing [4].

Methods

+ Human iPSC-derived cardiomyocytes were kindly provided by Fujifilm Cellular Dynamics International (Madison, USA) and NEXEL Ltd. (Seoul, South Korea).
+ Cells were cultured on FLEXcyte 96 plates following manufacturers' protocols using 200 µL maintenance medium per well. Seeding was performed ~6 days prior to treatment at 50k (Cardiosight®-S, NEXEL) or 60k (iCell® CM^2, FCDI) cells per well to ensure monolayer and network formation. A final medium change was performed 4–6 hours before compound application.
+ For compound testing, 50 µL of medium was removed and replaced with 50 µL of 4× concentrated compound solution to achieve the desired final concentration.
+ Contractility was recorded using the CardioExcyte Control software. Parameters such as beat rate, contraction force (mN/mm^2), rise/fall time, and beat duration and arrhythmic events were quantified.

REFERENCES

[1] Heras-Bautista CO, Mikhael N, Lam J, et al. Cardiomyocytes facing fibrotic conditions re-express extracellular matrix transcripts. Acta Biomater. 2019;89:180-192. doi:10.1016/j.actbio.2019.03.017

[2] Goßmann M, Frotscher R, Linder P, et al. Mechano-Pharmacological Characterization of Cardiomyocytes Derived from Human Induced Pluripotent Stem Cells. Cell Physiol Biochem. 2016;38(3):1182-1198. doi:10.1159/000443124

[3] Goßmann M, Linder P, Thomas U, et al. Integration of mechanical conditioning into a high throughput contractility assay for cardiac safety assessment. J Pharmacol Toxicol Methods. 2020;105:106892. doi:10.1016/j.vascn.2020.106892

[4] Jiang Y, Park P, Hong SM, Ban K. Maturation of Cardiomyocytes Derived from Human Pluripotent Stem Cells: Current Strategies and Limitations. Mol Cells. 2018;41(7):613-621. doi:10.14348/molcells.2018.0143

Contact us

innoVitro GmbH
Artilleriestraße 2
Jülich, Germany

+49 (0)2461 317 05 61
info@innovitro.de

innovitro.de

FUJIFILM Cellular Dynamics

NEXEL