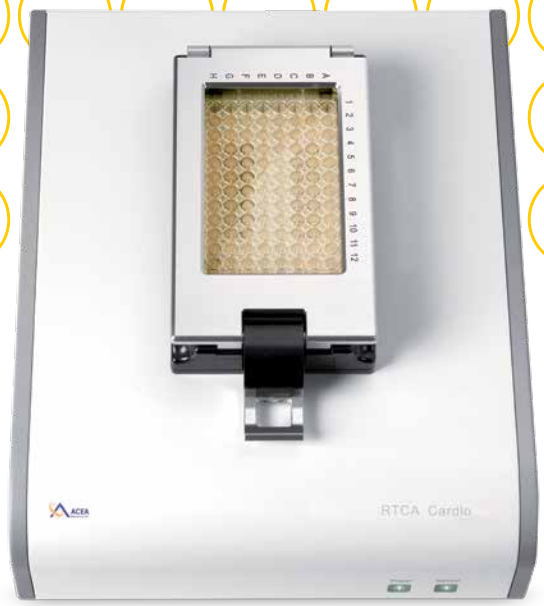
ACEA Biosciences, Inc.

xCELLigence

xCELLigence RTCA Cardio Instrument

Monitor Cardiomyocyte Beating in Real Time for Drug Discovery Research



xCELLigence RTCA Cardio Instrument

A new way to test for compound cardiotoxicity

Cardiac liability is the major cause of safety-based drug attrition, requiring a more complete preclinical safety workflow. Now you can discover more about lead compounds earlier in your pre-clinical drug safety research by using the **xCELLigence RTCA Cardio Instrument** to:

- Detect drug-induced changes and simultaneously assess cardiotoxicity and cell contractility in real time.
- Measure short-term and long-term changes in cell viability and cell contractility in a single experiment.
- Monitor cardiomyocyte beating pattern changes in 96-well format.

- **Accurately identify cardiotoxicity and proarrhythmic risk of drug candidates.**
- **Rule out cardiotoxic compounds earlier in discovery.**
- **Increase the success rate of drug development.**

High-resolution cell monitoring for *in vitro* cardiac safety testing

Part of ACEA's proven xCELLigence System family of impedance-based real-time cell analyzer (RTCA) instruments, the RTCA Cardio Instrument enables continuous, label-free measurement of cardiomyocyte function and cardiotoxicity testing.

Obtain physiologically relevant data:

- Measure cardiomyocyte beating in real time using a high-throughput, 96-well plate format.
- Use stem cell-derived, induced pluripotent stem (iPS) cell-derived, or primary cardiomyocytes.
- Non-invasively monitor short-term (msec) and long-term (days and weeks) cell responses.
- Obtain beat rate and amplitude with rapid data acquisition (12.9 millisecond update rate/plate).
- Achieve optimal cell culture conditions by placing the RTCA Cardio Station and plate into standard CO_2 incubators.
- Ensure temperature stability during experimental procedures.*

RTCA Cardio Temperature Tool

*An accessory for the RTCA Cardio Instrument, the RTCA Cardio Temperature Tool is designed to stabilize the temperature of the E-Plate Cardio 96 during experimental procedures outside the RTCA Cardio Station.

For life science research only.
Not for use in diagnostic procedures.

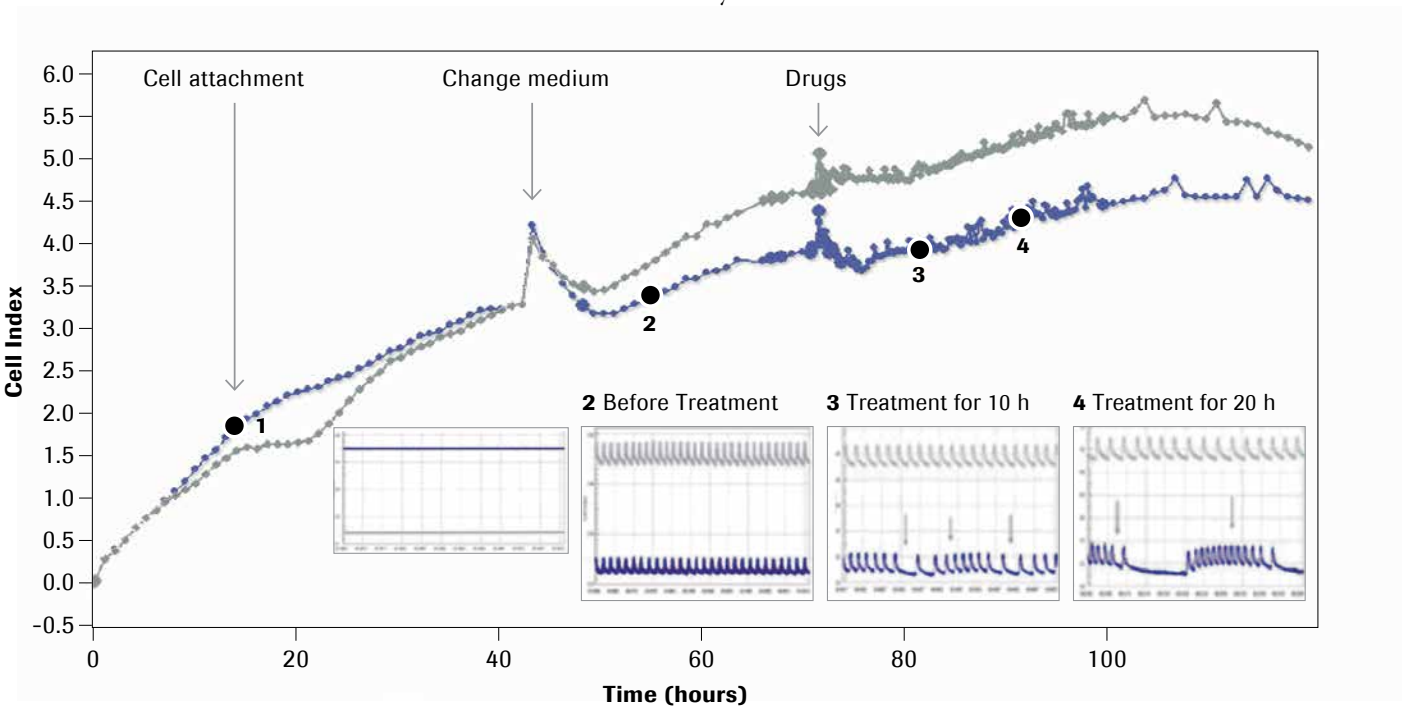
Simultaneously Assess Cell Viability and Contractility

The xCELLigence RTCA Cardio Instrument provides predictive information about cardiac safety during drug development by measuring cardiomyocyte beating under physiological conditions in cell culture.

This data can be used to identify evidence of cardiotoxicity earlier in drug development.

Use the xCELLigence RTCA Cardio Instrument to answer the key question:
Is your candidate compound cardiotoxic?

- Test structural cardiotoxicity and functional arrhythmogenesis in one experiment.
- Assess compound effects through monitoring hERG channel disruption.
- Evaluate compound effects continuously – over days.



Cell viability and cell contractility were monitored for up to 100 hours, capturing changes in cardiomyocyte contractility.

Control

400 nM E4031 (known hERG channel blocker)

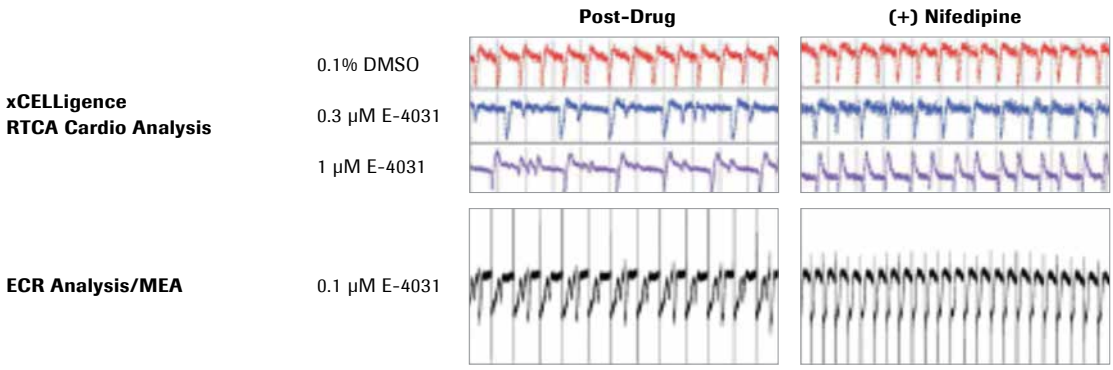
The xCELLigence RTCA Cardio Instrument simultaneously provides two vital pieces of information within one experiment.

Augment Established Assays for Preclinical Cardiac Safety Testing

Combine the xCELLigence RTCA Cardio Instrument with other cardiac safety testing methods

Gain more information from your preclinical safety assessment workflow by combining RTCA Cardio Instrument data with that from other assays – enabling you to rule out cardiotoxic compounds earlier in drug development.

- Produce data that is complementary to traditional cardiac safety testing assays.
- Identify the need for more complex downstream testing.
- Easily integrate into existing workflows.
- Improve predictive value by combining compound safety testing information from a variety of sources.
- Obtain more physiologically relevant information by using different cell types: stem cell-derived, induced pluripotent stem (iPS) cell-derived, or primary cardiomyocytes.



Evaluation of arrhythmia induction by E-4031 (a known hERG channel blocker) in iPSC-CMs detected with xCELLigence RTCA Cardio analysis and MEA. Arrhythmias were effectively suppressed and the regular beating rhythm restored by Nifedipine.

Guo L. *et al.* "Estimating the risk of drug-induced proarrhythmia using human induced pluripotent stem cell derived cardiomyocytes" *Toxicol. Sci.* 123(**1**), 281–289 (2011).

The xCELLigence RTCA Cardio Instrument detects compound-induced arrhythmic beating which is reflected by the altered field potential pattern observed using Microelectrode Arrays (MEA).

xCELLigence System Technology

Real-time, label-free cell analysis

Cells in contact with E-Plate Cardio 96 electrodes affect the local ionic environment at the electrode/solution interface, leading to an increase in electrode impedance.

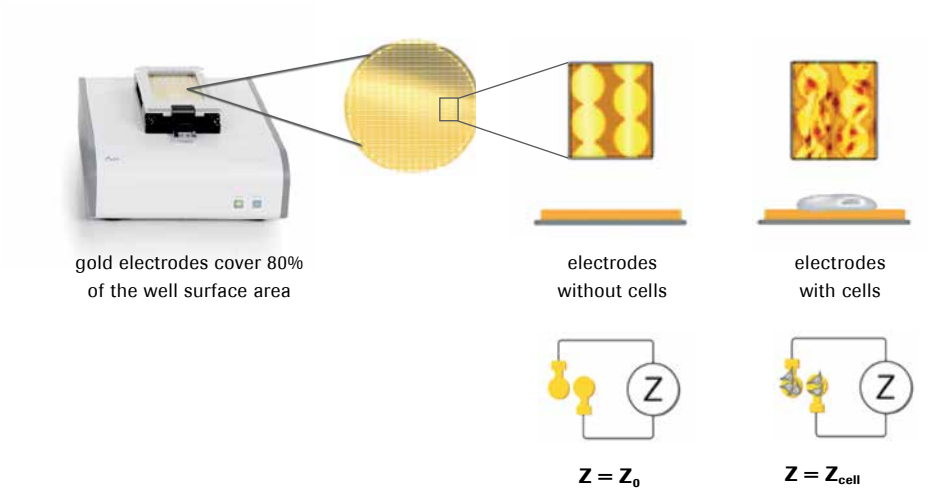
The more cells attached to the electrodes, the larger the increase in electrical impedance. Impedance also changes with respect to the quality of the cell interaction with electrodes; increased cell adhesion or spreading produces a large change in recorded impedance.

Electrical impedance is displayed as Cell Index (CI) values. CI values are a reflection of cell viability, cell number, cell morphology, and cell adhesion. This dimensionless unit is the relative change in measured impedance, accurately measuring cell status and changes in cell status.

- When cells are not present or are not adhering to the electrodes, the CI value is zero.
- Under the same physiological conditions, CI values are larger when more cells attach to the electrodes.
- CI values are a quantitative measure of the number of cells in a well.
- Change in cell status, such as cell morphology, cell adhesion, or cell viability produce a measureable, reproducible change in CI values.

Perform real-time, label-free cellular assays to:

- Generate more physiologically relevant data.
- Measure short-term and long-term cellular effects.
- Continuously monitor cell responses without the use of exogenous labels.
- Monitor cells under physiological conditions within standard CO_2 incubators.



gold electrodes cover 80% of the well surface area

electrodes without cells

electrodes with cells

$Z = Z_0$

$Z = Z_{cell}$

Impedance-based measurement provides a holistic way of monitoring changes in cell viability, cell number, cell morphology, and cell adhesion.

Selected Publications

Dynamic monitoring of beating periodicity of stem cell-derived cardiomyocytes as a predictive tool for preclinical safety assessment.
Abassi, Y. a, Xi, B., Li, N., Ouyang, W., Seiler, A., Watzele, M., Kettenhofen, R., et al. (2012).
British journal of pharmacology, 165(5), 1424–41.

Cellular Physiology Biochemistry and Biochemistry In vitro Model for Assessing Arrhythmogenic Properties of Drugs Based on High-resolution Impedance Measurements.
Nguemo, F., Šaric, T., Pfannkuche, K., Reppel, M., & Hescheler, J. (2012).
Cellular Physiology and Biochemistry, 819–832.

Cardiotoxic effects of venom fractions from the Australian box jellyfish Chironex fleckeri on human myocardiocytes.
Saggiomo, S. L. a, & Seymour, J. E. (2012).
Toxicon : official journal of the International Society on Toxinology, 60(3), 391–5.

2011 Annual Meeting of the Safety Pharmacology Society: an overview.
Cavero, I. (2012).
Expert opinion on drug safety, 11(2), 341–53.

Estimating the Risk of Drug-induced Proarrhythmia using Human Induced Pluripotent Stem Cell Derived Cardiomyocytes.
L. Guo, R. Abrams, J.E. Babiarz, J.D. Cohen, S. Kameoka, M.J. Sanders, E. C. and K. L. K. (2011).
Toxicological sciences : an official journal of the Society of Toxicology, 4077(v), 1–36.

Functional cardiotoxicity profiling and screening using the xCELLigence RTCA Cardio System.
Xi, B., Wang, T., Li, N., Ouyang, W., Zhang, W., Wu, J., Xu, X., et al. (2011).
Journal of laboratory automation, 16(6), 415–21.

Impedance-based detection of beating rhythm and proarrhythmic effects of compounds on stem cell-derived cardiomyocytes.
Jonsson, M. K. B., Wang, Q.-D., & Becker, B. (2011).
Assay and drug development technologies, 9(6), 589–99.

Disruption of the cyclic AMP phosphodiesterase-4 (PDE4)-HSP20 complex attenuates the b**-agonist induced hypertrophic response in cardiac myocytes.**
Sin, Y. Y., Edwards, H. V., Li, X., Day, J. P., Christian, F., Dunlop, a J., Adams, D. R., et al (2011).
Journal of molecular and cellular cardiology,. 50(5):872-83.

Ordering Information

Product	Pack Size	Cat. No.
RTCA Cardio System Bundle	**1 Bundle Package**	**00380601060**
RTCA Cardio Analyzer	1 Instrument	06416993001
RTCA Cardio Control Unit	1 Notebook PC	06200184001
RTCA Cardio Station	1 Instrument	06417019001
RTCA Cardio Temperature Tool	1 Tool	06488447001
E-Plate Cardio 96	6 Plates	06417051001
E-Plate Cardio 96	6 x 6 Plates	06417035001

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Not for use in diagnostic procedures.

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