# CellASIC™ ONIX Microfluidic Platform

## Take control.
## Design dynamic experiments the CellASIC™ way.

Merck Millipore is a Division of MERCK

# Think far beyond the limits of static cell culture.

Biology is so much more than DMEM/FBS, 37 °C, 5% $CO_2$. Model your own creative designs and achieve true culture conditions with the new CellASIC™ ONIX Platform. With microfluidic precision, you can push the boundaries of your cell biology experiments in an *in vivo*-like environment. This new perfusion-based system enables you to program automated changes to culture conditions while maintaining optical access to cells through your microscope. You can even track individual cell responses over time by using a time-lapse-enabled microscope for truly dynamic cellular analysis.

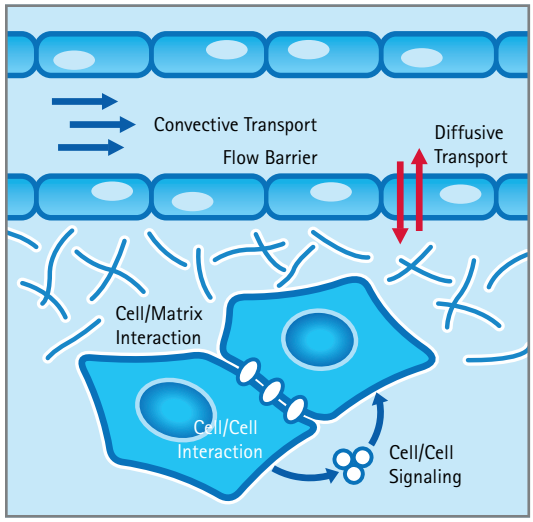
# What's missing from traditional cell culture and analysis?

## Microfluidic perfusion mimics the *in vivo* cell environment

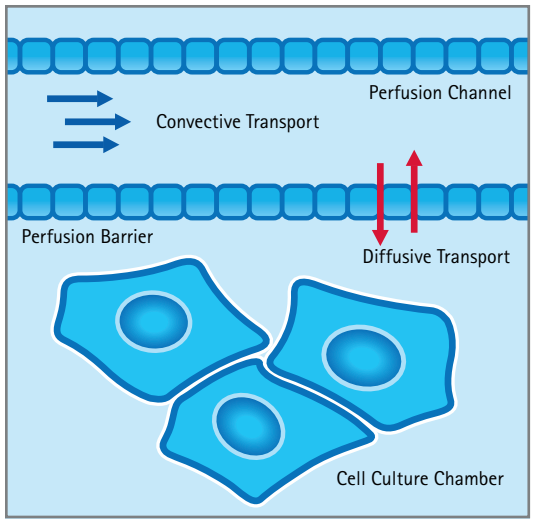
The analysis of living cells *in vitro* is critical to understanding basic biology, signaling pathways, drug effects, and disease models. But despite dramatic advances in detection methods, which have provided excellent means to interrogate living cells, the technology for controlling the environment of living cells during that analysis has not advanced far beyond the culture dish.

Because the cellular microenvironment, or "niche," is as important as genetic factors for determining cell phenotype, a method for providing more accurate, dynamic control of living cells during experimental analysis can add a groundbreaking dimension to the science of cell biology.

The CellASIC™ ONIX Microfluidic Platform was specifically designed to provide the dynamic cellular microenvironment control that has been missing until now.




*In vivo*




Microfluidic

Just as nutrients and gases are transported through blood vessels, culture media components and gases are transported through perfusion channels of the CellASIC™ ONIX Microfluidic System. The perfusion barrier separating the cell culture from the channel (bottom) mimics the endothelial cell layer separating *in vivo* tissues from the blood (top).

# The CellASIC™ ONIX Microfluidic Platform

Delivering advanced control for **live cell imaging** experiments, the system integrates with your existing microscope to enable dynamic time-lapse experiments never before possible. Cutting-edge microfluidic technology provides an improved cell culture microenvironment, exceptional plate imaging quality for high magnification microscopy and superior media switching controls. An integrated Microincubator Controller maintains a temperature and gas environment directly on the microfluidic plate for long-term cell culture on any microscope stage.


**Advanced control for live cell imaging.** The system complements your microscope to provide a total solution for capturing the highest quality data with minimal effort.

"...We've been able to quickly and **easily perform novel and technologically demanding experiments without any prior microfluidic experience.** I've been able to focus on the fundamental biological questions while letting CellASIC™ provide me with the tools I need to answer them."

*Maheshri Lab, MIT*

# Platform capabilities

## Dynamic environmental control over live cells

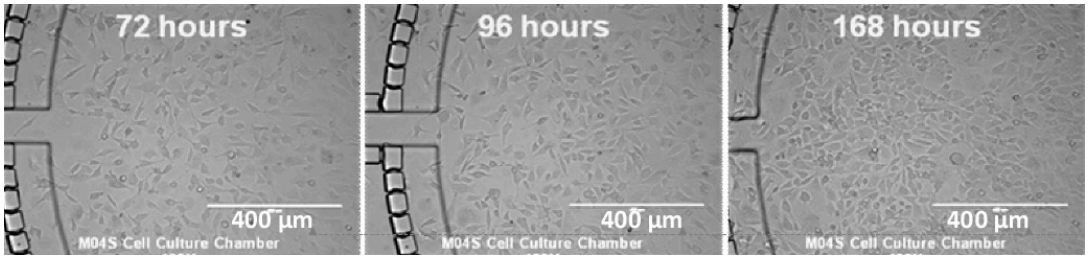
Measure cellular responses to pre-programmed perfusion, temperature, and gas environment changes. The CellASIC™ ONIX Microfluidic Platform automates all the necessary requirements for live cell imaging, while giving you the control to discover new science.

### Microfluidic cell culture plate advantages

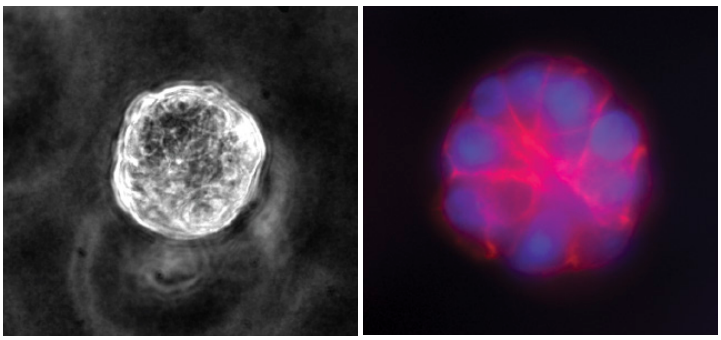
- Perform four independent experiments at once
- Compatible with any standard inverted microscope
- High resolution imaging though thin glass bottom
- Dynamic control over flow, gas and temperature
- Laminar flow for rapid solutions switching and stable gradient formation
- Perfusion barriers allow continuous mass transport without shear stress

## Optimized, bioinspired cell culture

Different cells need different environments. CellASIC™ ONIX Microfluidic Plates are designed to optimize the health of specific cells during dynamic live cell experiments, including analyses requiring long-term culture. Various application-specific plate designs give you the flexibility to probe the questions that interest you most.




**Healthy long-term cultures outside the incubator.** NIH 3T3 cells were cultured in the CellASIC™ ONIX Microfluidic System (M04S plate) with continuous perfusion and monitored using bright field microscopy for 168 hours.



**Robust three-dimensional cell cultures.** MCF10A mammary epithelial cells were suspended in Matrigel® substrate and cultured with continuous perfusion for five days using the CellASIC™ ONIX Microfluidic System (M04L plate). Cells were stained for actin (red) and nuclei (blue). Brightfield and fluorescent images were acquired at 40X magnification.

# Automated integration into virtually any protocol

**You're just minutes away from acquiring data using "load-and-go" CellASIC™ ONIX Microfluidic Plates. Intuitive and easy-to-program CellASIC™ ONIX FG Software automates your entire customizable protocol, so you can spend more time exploring the countless experimental possibilities enabled by this single platform.**

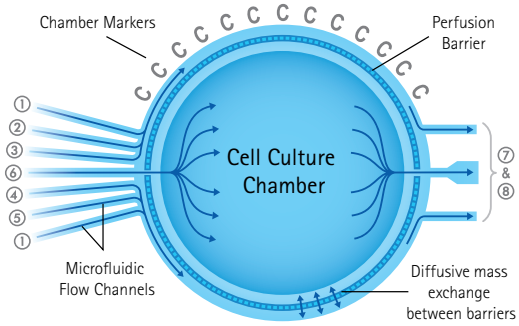
## Follow these simple steps

**1** Prepare the microfluidic plate: Aspirate PBS from cell inlet well 6 and add 10 µL of desired cell suspension into the microfluidic plate. Cells will load automatically through capillary-driven cell loading.

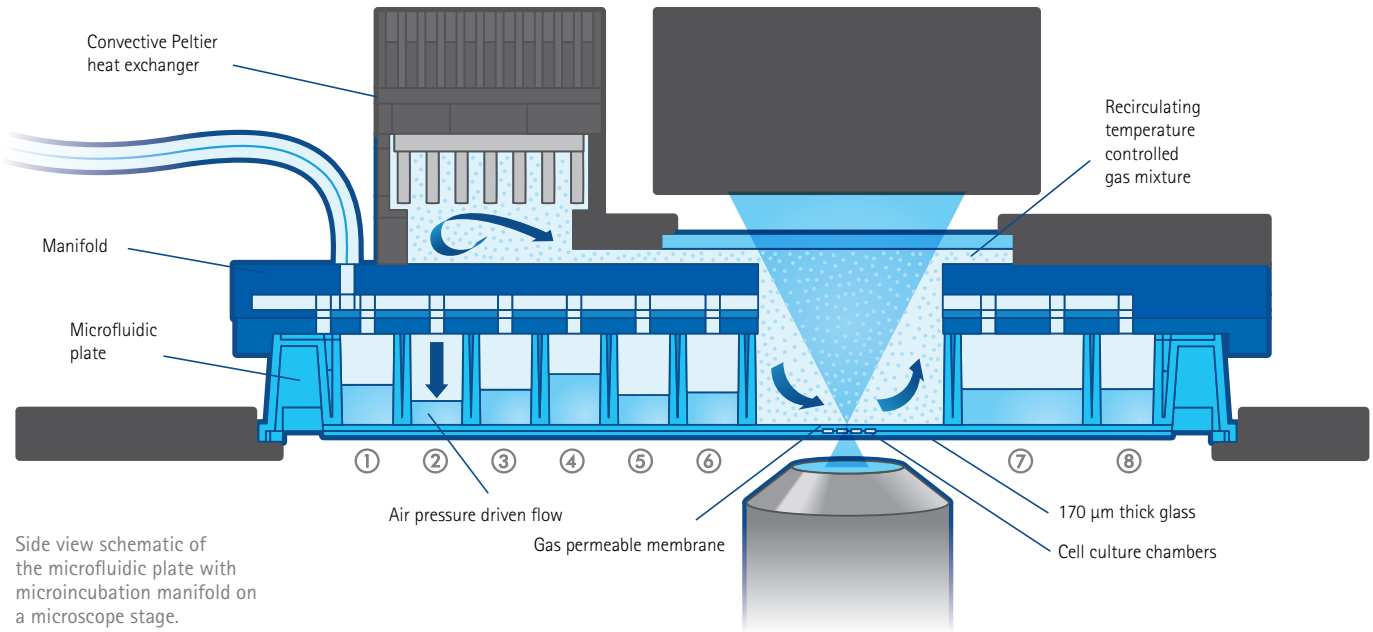
**2** Pipette reagents and media that will be used during your perfusion protocol into the four solution inlets (wells 2-5).

**3** Seal plate to manifold by aligning the plate onto the manifold and turning on the vacuum switch on the CellASIC™ ONIX Microfluidic Platform. The plate is sealed when the green "sealed" light is lit.

**4** Place on inverted microscope stage and focus on the center of the imaging area.




1 Inlet for gravity driven continuous perfusion
2–5 Independent flow inlets for pressure driven flow
6 Inlet for cell loading
7–8 Outlets to waste wells

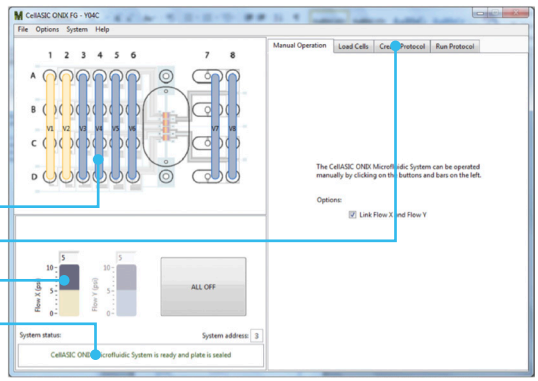



Side view schematic of the microfluidic plate with microincubation manifold on a microscope stage.

**5** Use the CellASIC™ ONIX FG Software's intuitive interface to program and monitor your experiment from one single view screen.

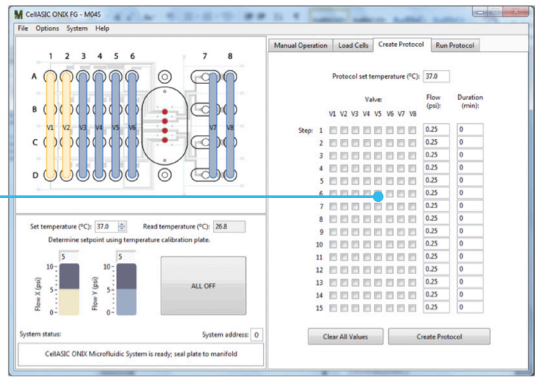
## Three tabs, three easy programming options

**Manual Operation**
Click with your mouse to control inputs, outputs, gas and temperature in real time.

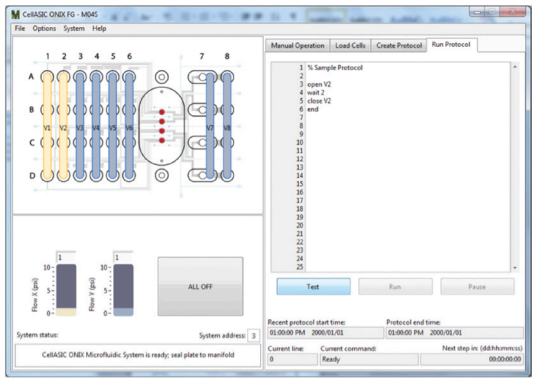



**Create Protocol**
An easy Wizard helps you set up an automated protocol for pre-programmed, walk-away perfusion changes over minutes, hours or days.

**Protocol Wizard:**
Click the valve and enter the time and flow rate for each step. Design 5 steps or 15–it's all under your control.



**Run Protocol**
On this tab, you can save, change or add steps to the protocol you created using the "Create Protocol" Wizard.



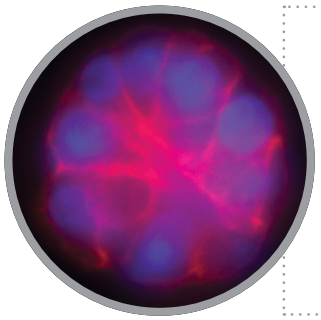
**6** Click "Run" to begin the program. Automate and perform live cell imaging using your microscope's standard methods.

"Since I aim to quantify mitochondrial morphology, I require **constant, stable imaging conditions that maintain the health of the cells, which the CellASIC™ ONIX System does very well."**

*Marshall Lab, UCSF*

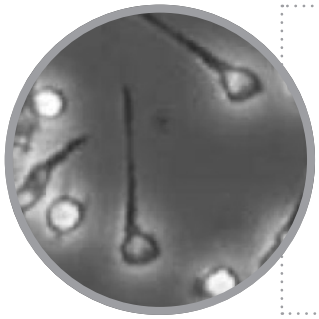
# Popular applications of the CellASIC™ ONIX Platform

**What you've always imagined can now be reality, using the CellASIC™ ONIX Platform to design dynamic cell biology experiments. It's been demonstrated by our own scientists and loyal customers. The applications listed below are just a few of the exciting experiments you can perform with unprecedented precision.**



## Microscopy of 3D cell culture

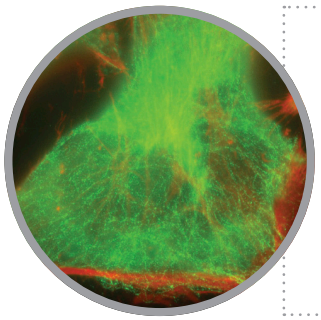
**Observation of multi-day morphology changes of 3D cancer spheroids cultured in extracellular matrix.** MCF-10A breast cancer cells were suspended in Matrigel® substrate and grown in the CellASIC™ ONIX Microfluidic System. Cells were stained for actin (red) and nuclei (blue). Image was acquired at 40X magnification.



## Chemotaxis/migration in response to chemogradient

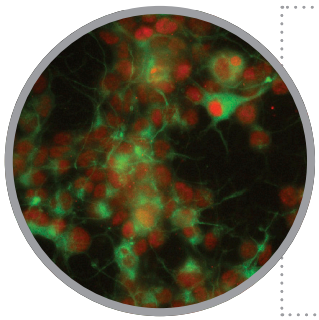
**HL-60 neutrophil migration in response to a chemokine.** This frame from a live cell imaging video shows cells concentrating toward the chemokine.

*Courtesy of Jason Park, Wendell Lim Lab, UCSF.*



## Cell response to changing media conditions

**Long-term live cell microscopy of cellular cytoskeletal changes in HeLa cells with respect to precise micro-environment control.** Tubulin (green) and actin (red) were stained using "on-chip" immunostaining with multi-solution, automated washing and exposure programs. Image was acquired at 100X magnification.

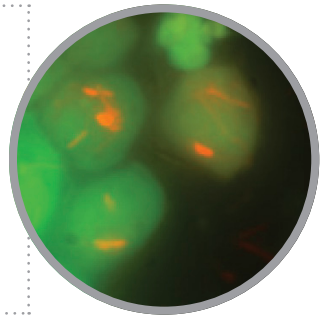


## Neural stem cell imaging

**Rat neural stem cells** (Merck Millipore) cultured for 8 days and immunostained for nestin (green) and Sox2 (red) in the M04S Microfluidic Plate (40X magnification).

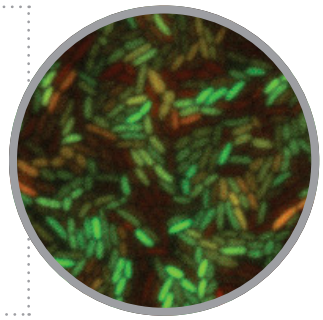
## Host-pathogen interactions

**HT-29 Colorectal Host Cells** were infected by an engineered strain of *E. coli* (red) and monitored over time in the M04S Microfluidic Plate (100X).



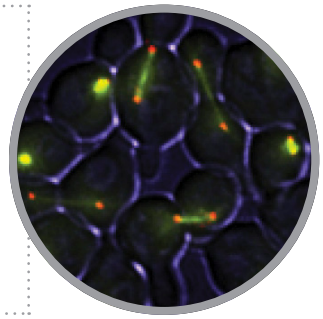
## Bacteria single cell response

**Measurement of multi-generational response of live bacteria cells while maintaining cells in a single focal plane for days.** A gene circuit in *E. coli* was induced and visualized for a time-lapse experiment. Images were acquired at 100X magnification.



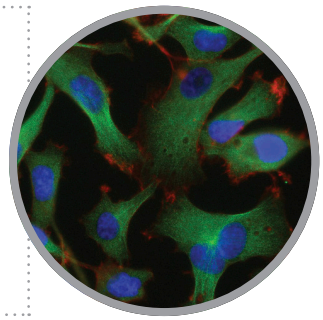
## Yeast single cell response

*S. Cerevisiae* **cells expressing GFP-tubulin and SPC42 mCherry during alpha-factor exposure and arrest.** Images were acquired at 60X magnification. *Courtesy of Soni Lacefield, University of Indiana.*



## Protein localization or translocation

**Localization of actin (green) and microtubules (red) with respect to nuclei (blue)** in the HT1080 human fibrosarcoma cell line immunofluorescently stained in the M04S Microfluidic Plate. Image was acquired at 40X magnification.



## Other popular applications

- **Drug dose/response over time**
- **Hypoxic conditions to mimic tumor environments**
- **Cell cycle response to induction events**

# Key publications using the CellASIC™ ONIX Microfluidic Platform


Wei P., Wong W., Park J., Corcoran E., Peisajovich S., Onuffer J., Weiss A., Lim W. *Bacterial virulence proteins as tools to rewire kinase pathways in yeast and immune cells.* Nature, 2012 Aug 16; 488(7411):384-8.

Bermejo C, Haerizadeh F, Takanaga H, Chermak D, Frommer W. *Optical sensors for measuring dynamic changes of cytosolic metabolite levels in yeast.* Nature Protocols. 2011 Oct 27 6;1806-1817.




Doncic A, Falleur-Fettig M, Skotheim J. *Distinct interactions select and maintain a specific cell fate.* Molecular Cell. 2011 Aug 19 4;43:528-539.

Eser U, Falleur-Fettig M, Johnson A, Skotheim J. *Commitment to a cellular transition precedes genome-wide transcriptional change.* Molecular Cell. 2011 Aug 19 4;43:515-527.

Tamura N, Oku M, Sakai Y. *Atg8 regulates vacuolar membrane dynamics in a lipidation-independent manner in Pichia pastoris.* J Cell Sci. 2010 Dec 1;123(Pt 23):4107-16.

Bermejo C, Haerizadeh F, Takanaga H, Chermak D, Frommer WB. *Dynamic analysis of cytosolic glucose and ATP levels in yeast with optical sensors.* Biochem J. 2010 Sep 20.

Dechant R, Binda M, Lee SS, Pelet S, Winderickx J, Peter M. *Cytosolic pH is a second messenger for glucose and regulates the PKA pathway through V-ATPase.* EMBO J. 2010 Aug 4;29(15):2515-26.

Manzoni R, Montani F, Visintin C, Caudron F, Ciliberto A, Visintin R. *Oscillations in Cdc14 release and sequestration reveal a circuit underlying mitotic exit.* J Cell Biol. 2010 Jul 26: 209-22.

Furuya K, Niki H. *The DNA damage checkpoint regulates a transition between yeast and hyphal growth in Schizosaccharomyces japonicus.* Mol Cell Biol. 2010 Jun;30(12):2909-17.

Octavio LM, Gedeon K, Maheshri N. *Epigenetic and conventional regulation is distributed among activators of FLO11 allowing tuning of population-level heterogeneity in its expression.* PLoS Genet. 2009 Oct;5(10):e1000673.

Thorn K. *Spinning-disc confocal microscopy of yeast.* Methods of Enzymology, vol 470, 2010, 581-602.

Lee PJ, Gaige TA, Hung PJ. *Dynamic cell culture: a microfluidic function generator for live cell microscopy.* Lab Chip. 2009 Jan 7;9(1): 164-6.

## Technical Specifications

| CellASIC™ ONIX Microfluidic Platform (EV262 Microfluidic System and MIC230 Microincubator Controller) | |
|---|---|
| Microscope Compatibility | Inverted microscope |
| Microscopy Techniques | Fluorescence, Brightfield, Phase Contrast, Confocal, TIRF, and DIC Microscopy |
| Imaging Substrate | #1.5 glass coverslip |
| Microfluidic Plate Footprint | 96-well plate footprint |
| Number of Chambers | 4 microfluidic cell culture chambers (in parallel) |
| Typical Culture Time with CellASIC™ ONIX Microfluidic Controller | 1-3 days continuous |
| Cell Suspension Volume | 5-10 µL (M04 CellASIC™ ONIX Microfluidic Plates), 50 µl (B04/Y04/C04 CellASIC™ ONIX Microfluidic Plates) |
| Number of Pressure Inputs | 8 inputs |
| Output Pressure Range | 0-10±0.25 psi (0-70±1.7 kPa) |
| Optical Transparency | Optically clear manifold and microfluidic plates |
| Optional Premixed Gas Input | Works with clean, dry, premixed gas containing air, $CO_2$, nitrogen and oxygen up to 25% regulated to between 45-55 psi (310-379 kPa). |
| Temperature Control Range | Room temp. to 40 °C |
| Rise Time (25 °C to 37 °C) | <10 minutes |
| Cooling Time (37 °C to 25 °C) | <15 minutes |
| Gas Consumption | 3 mL/min, ±0.5 mL/min |
| Dimensions | 310 mm Wide x 257 mm Deep x 163 mm High |

| Cell types used with the CellASIC™ ONIX Microfluidic Platform | |
|---|---|
| Adherent Cells | HeLa, CHO Cell, NIH-3T3, MCF-7, MCF-10A, PC-3, HUVEC, PC-12, HL-60, HT-29, Neuron Cells (Hippocampal/Cortical), Cardiomyocytes |
| Non-Adherent Cells | Macrophages, Lymphocytes, T Cell, Bacteria *(E. coli, B. subtillus, Cyanobacteria, M. smegmatis),* Yeast *(S. cerevisiae, S. pombe), Chlamydomonas* |
| ECM Coating Substrates Used | Fibronectin, Collagen, Matrigel® substrate, Poly-D-lysine, Laminin, Hydrogels |

## Ordering Information

| Description | Catalogue No. |
|---|---|
| CellASIC™ ONIX Microfluidic System Package includes CellASIC™ ONIX Microfluidic Perfusion Controller, Manifold, Accessory Box, and CellASIC™ ONIX FG Software | EV262 |
| CellASIC™ ONIX Microincubator Package for Temperature and Gas Control: Includes CellASIC™ ONIX Microincubator Controller, Microincubator Manifold, and Accessory Box | MIC230 |
| CellASIC™ ONIX Tri-gas Mixer: Compressed Air, $CO_2$, and Nitrogen Gas Mixer | GM230 |
| B04A Microfluidic Plate for Bacteria Cells (4 Chambers) | B04A-02-5PK |
| C04A Microfluidic Plate for *Chlamydomonas* Cells (4 Chambers) | C04A-01-5PK |
| M04G Microfluidic Gradient Plate for Mammalian Cells (4 Chambers) | M04G-02-5PK |
| M04L Microfluidic Open-top Plate for Mammalian Cells (4 Chambers) | M04L-03-5PK |
| M04S Microfluidic Switching Plate for Mammalian Cells (4 Chambers) | M04S-03-5PK |
| Y04C Microfluidic Plate for Haploid Yeast (4 Chambers) | Y04C-02-5PK |
| Y04D Microfluidic Plate for Diploid Yeast (4 Chambers) | Y04D-02-5PK |

# Related Products

Get the most from your CellASIC™ ONIX Microfluidic Platform by exploring Merck Millipore's cell culture tools, antibodies, reagents, small molecules and kits for cell-based assays, including reagents specifically optimized for live cell imaging.

## Cell Culture

For the most convenient, reliable, analysis-ready cell cultures, count on Merck Millipore's wide variety of devices and surfaces to provide cell growth, structure, and function that more closely mimic what occurs *in vivo*. Spend less time growing cells and fumbling with clumsy devices and more time on your research.

Learn more at **www.millipore.com/cellculture**.

## Sterile Filtration

Merck Millipore's trusted line of sterile filtration tools have been specifically designed to eliminate contaminants and ensure the reproducibility of your downstream analyses.

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Based on the expertise of Chemicon® and Upstate®, Merck Millipore's highly validated antibodies are guaranteed for quality performance. Many of our antibodies are conjugated to fluorophores and validated for immunocytochemistry.

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## Growth Factors

Merck Millipore offers a comprehensive range of human, mouse and rat cytokines and growth factors for cell culture and cell-based assays. Every lot produced is thoroughly tested for bioactivity, purity, and endotoxin levels.

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## Small Molecule Inhibitors, Activators, Libraries and Pathway Panels

Perturbing cellular pathways using small molecules and then using live cell imaging to analyze impacts on cells in real time can translate into powerful biological discoveries. Merck Millipore's Calbiochem® libraries, pathway panels and individual reagents offer the widest and most cited selection of small molecule inhibitors and activators worldwide.

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## LentiBrite™ Biosensors

New LentiBrite™ Lentiviral Biosensors are pre-packaged lentiviral particles encoding important and foundational proteins of autophagy, apoptosis, and cell structure and enable visualization under different cell/disease states in live cell and *in vitro* analysis.

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