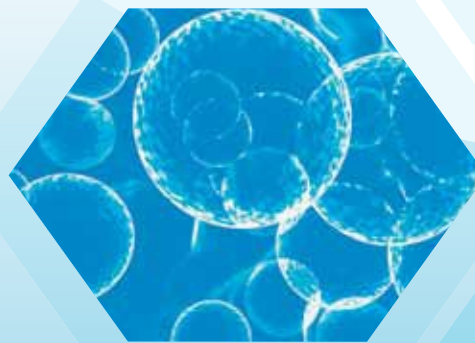




# CelCradle™

Cradle for High Density Cells

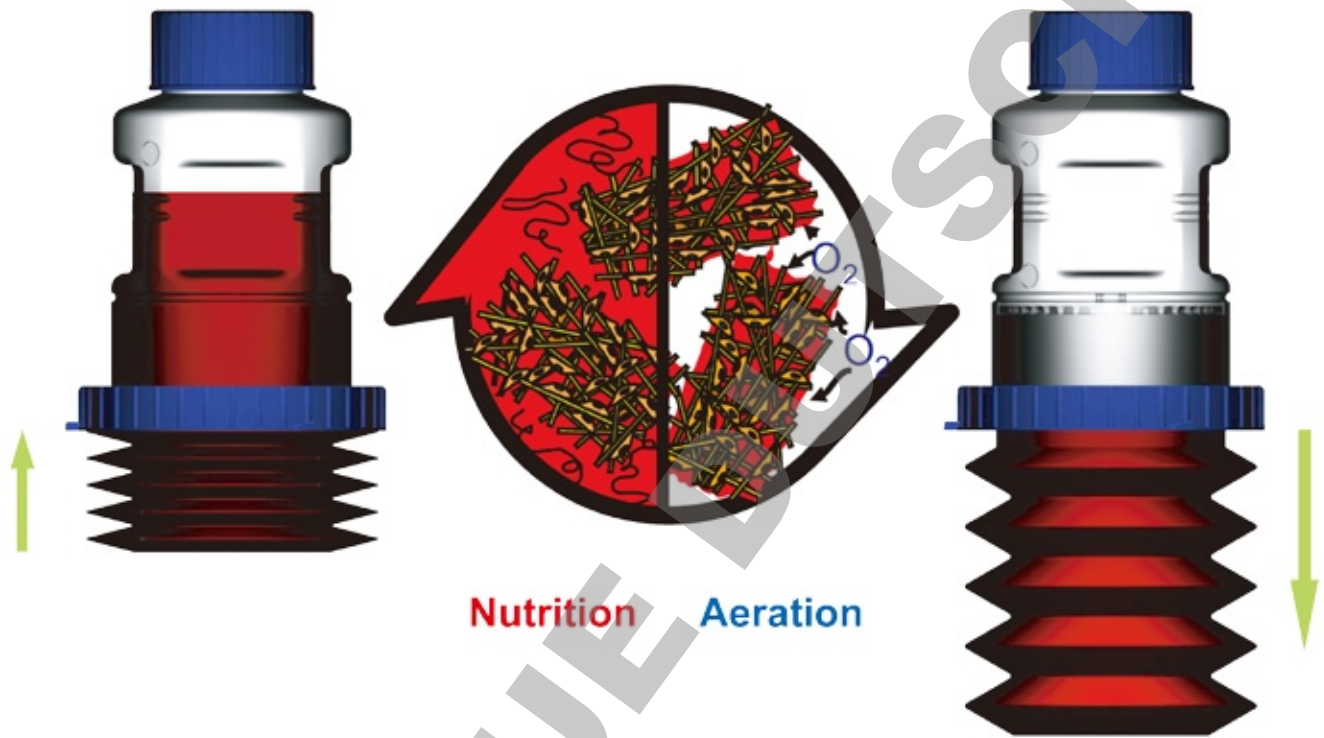


DOMINIQUÉ

## Introduction

The CelCradle™ is a cost-effective, single-use, benchtop bioreactor system capable of supporting high density culture of anchorage-dependent or adherent cells. It is the only single-used packed-bed bioreactor system that has linear scalability from laboratory scale to production scale, complete with automated cell harvesting.

The CelCradle™ operates through the tide motion principle wherein cells, which attach to BioNOC™ II carriers, are alternately exposed to aeration and nutrition via the decompression and compression of the bellows holding the culture medium. The gentle vertical oscillation of the culture medium creates a dynamic interface between air and culture medium on the surface of the cells, providing the cells with an environment that is of low shear stress, high aeration and nutrition levels, zero foaming, and no O<sub>2</sub> limitation. This efficient nutrient and oxygen transfer is what allows the CelCradle™ system to produce high density cell yield.



The CelCradle™ system is very simple to use with only 4 parameters to set – bottom holding time, top holding time, up speed, and down speed. Bottom holding time refers to the amount of time cells are exposed to aeration, while the top holding time refers to the amount of time the cells are exposed to nutrition. The up and down speed is the speed of the upward and downward oscillation of the culture medium, respectively. Temperature and aeration levels are controlled by the CO<sub>2</sub> incubator.

The CelCradle™ is an ideal system for the laboratory scale culture of adherent cells used for many different applications including vaccine production, cell therapy, recombinant protein production, and pharmacokinetic studies

### Features

- Compact and small footprint: standard unit fits in a 6 ft<sup>3</sup> CO<sub>2</sub> Incubator
- Compatible with most serum-free medium
- Allows the harvest of whole cells or cell components
- Scale-up by direct multiplication of bottles or the use of TideCell®
- Reduced labor and space requirements
- Large surface area for cell attachment and growth
- Batch, fed-batch, perfusion system
- Single-use, ready-to-use, pre-sterilized

Each CelCradle™ System accommodates up to four single-use bottles, making this an ideal screening device to test varying medium formulations or cell lines.

No steam or water lines, autoclave or utilities required, just a power outlet and CO<sub>2</sub> incubator

Simple to operate - virtually no learning curve

Controller - adjusts nutrient and gas exchange of the bottle

Magnetized controller enables convenient positioning by attaching on the outside surface of the incubator.

Extremely compact system fits in most standard CO<sub>2</sub> incubators.

Bright and large display is easy to read.

Up: 1.5 ml/s  
T.H: 04 M 04 S ^

Useful for batch and semi-batch operation where process components are easily traceable.

0.22 µm ventilation filter is provided in the cap

Cells remain entrapped in the BioNOC™ II matrix bed simplifying media replacement and product harvesting

Sampling Port enables aseptic removal of BioNOC™ II carries for cell counting

Retaining ring locks bottles into place in the CelCradle® Stage console

Collapsible bellows

Useful for continuous operation where process components are easily traceable

Tubing set with peristaltic pump head enable recirculation and continuous feeding of nutrient

CelFeeder enables 4 pumps operation with individual programming setting

Autoclavable pump head support consistent feeding rate with calibration free

## Applications

The CelCradle™ System has been, as exhibited by journal articles (see literature support), and can be used for many different applications. The main applications of the CelCradle™ System include:

- Culture of anchorage-dependent or adherent cells
- Conversion from Roller Bottles to closed system, single-use cell culture
- Overcome limitations of microcarrier-stirred tank bioreactor technology
- Autologous and Allogeneic Cell Therapy
- Human and Animal Vaccines

### Culture of anchorage-dependent cells

The CelCradle™ system is used for the culture of adherent cells, which attach to BioNOC™ carriers. Each CelCradle™ bottle consists 5.5g of BioNOC™ II providing 13200cm<sup>2</sup> of surface area for the attachment and growth of cells. Apart from its high surface area, BioNOC™ II carriers feature enhanced biocompatibility, long hydrophilicity, high porosity, low lint content, and excellent mechanical strength. These BioNOC™ characteristics, combined with the tide motion principle, allow the CelCradle™ system to support the high density culture of adherent cells. Some examples of cell lines that have been cultured with the CelCradle™ System include:

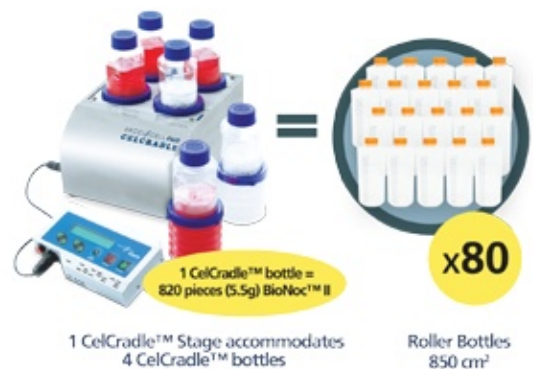
- Vero
- MDCK
- MDBK
- Sf-9
- HEK-293
- BHK-21
- CHO
- XC-18
- ST
- CEF
- GL 37
- Marc145

### Conversion from Roller Bottle to Closed system, single-use cell culture

The roller bottle system plays a major role in cell culture-based vaccine production as it is low cost and easy to operate, has a simple scale-up method, observable cell growth and CPE, and limited contamination ; however, the system has many limitations including intensive labor, large space requirement, high running costs, and low efficiency of culture medium utilization.

In principle, the roller bottle system is very similar to CelCradle™ system such that cells are alternately exposed to aeration and nutrition. The CelCradle™, however, can overcome the limitations of the roller bottle system, and as well as improve its output. The advantages of the CelCradle™ system over the roller bottle include:

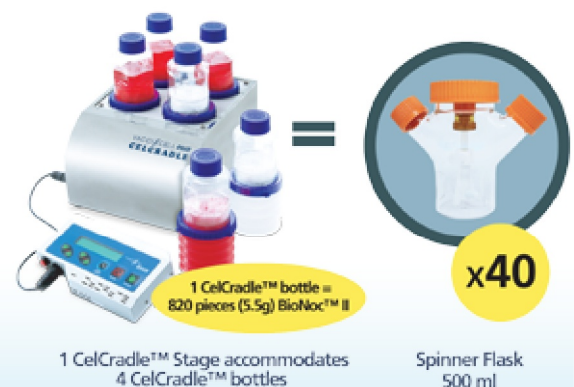
- 1 CelCradle™ system is equivalent to 80 roller bottles:  
reduced labor and space requirements
- More controllable
- Reduced contamination risks
- Cell Harvest in a closed system
- Efficient use of culture medium
- High cell density and virus titer



### Overcome limitations of microcarrier-stirred tank bioreactor technology

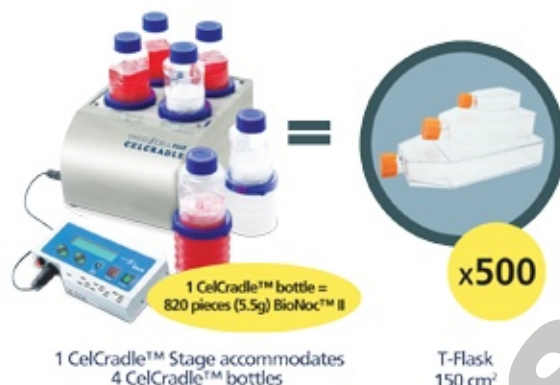
Another technology used for the culture of adherent cells is the use of microcarriers, which are specially-treated microbeads to which cells attach and grow. The microcarriers are then suspended in culture medium in stirred tank bioreactors, where the medium is continuously agitated and parameters automatically monitored and controlled. The microcarrier technology, however, has several disadvantages including reduced cell attachment efficiency, shear stress, foaming, and lack of linear scalability, all of which the CelCradle™ system is able to overcome. The CelCradle™ system also has improve features compared to the microcarrier system in terms of the following:

- Virus titer and cell density
- Cell harvest efficiency
- Culture medium usage efficiency
- Harvest purity



## Autologous and Allogeneic Cell Therapy

Cell Therapy is the use of live whole cells for the treatment of diseases and involves cultivation of cells to a certain density prior to administration. A commonly used cell type used in cell therapy is mesenchymal stem cells, which are both anchorage-dependent. Currently, cultivation of cells for cell therapy is done using T-flasks; however this method is quite laborious and time and space consuming, as T-flasks have limited surface area for growth and thus require handling of several hundred T-flasks and multiple passaging. The CelCradle™ system's large surface area and compact design help solve these problems, with a single CelCradle™ bottle equalling the productivity of a several hundred T-flasks.



## Human and animal vaccine

Cell culture-based vaccine production is the current trend in vaccine production as it offers several advantages over traditional vaccine production technologies including simpler mass production, rapid manufacturing, independent of SPF animal, controllable quality, and hypoallergenic products.

The CelCradle™ is an ideal system for laboratory-scale cell-culture based vaccine production as it is capable of supporting high density cell culture, production of high virus titer, and linear scalability to production level. Vaccixcell's tide motion bioreactor system has been used for the research and development and production of vaccines for several indications including:

- Influenza
- JEV
- Rabies
- Hog Cholera
- Hepatitis A
- EV71
- Rabies
- IBDV

Apart from these, the CelCradle™ has also been used for other applications including recombinant protein production, pharmacokinetic studies, and cellular component production. Details of these applications can be found from literature support.

## Literature Support

The following are some of the available literature support online for the various applications of the CelCradle™ system.

- [1] Asaoka, Y., Tanaka, T., Tsumoto, K., Tomita, M., & Ide, T. (n.d.). Efficient expression of recombinant soluble human FcγRI in mammalian cells and its characterization. *Protein Expression and Purification*, 155-161.
- [2] Brown, A., Singer, D., Mcsharry, J., Barnard, R., Hazuda, D., & Drusano, G. (n.d.). In Vitro Dose Ranging Studies for Serine Protease Inhibitor, MK-4519, Against a Hepatitis C Virus (HCV) Replicon using the BelloCell System. *Antiviral Research*.
- [3] Chen, Y., Wu, J., Wang, K., Chiang, Y., Lai, C., Chung, Y., & Hu, Y. (n.d.). Baculovirus-mediated production of HDV-like particles in BHK cells using a novel oscillating bioreactor. *Journal of Biotechnology*, 135-147.
- [4] Drugmand, J., J.-F., J., Agathos, S., & Schneider, Y. (n.d.). Growth of Mammalian and Lepidopteran Cells on BioNOC® II Disks, a Novel Macroporous Microcarrier. *Cell Technology for Cell Products*, 781-784.
- [5] Hammonds, J., Chen, X., Zhang, X., Lee, F., & Spearman, P. (n.d.). Advances in methods for the production, purification, and characterization of HIV-1 Gag-Env pseudovirion vaccines. *Vaccine*, 8036-8048.
- [6] Ho, L., Greene, C., Schmidt, A., & Huang, L. (n.d.). Cultivation of HEK 293 cell line and production of a member of the superfamily of G-protein coupled receptors for drug discovery applications using a highly efficient novel bioreactor. *Cytotechnology*, 117-123.
- [7] Hu, Y., Lu, J., & Chung, Y. (n.d.). High-density cultivation of insect cells and production of recombinant baculovirus using a novel oscillating bioreactor. *Cytotechnology*, 145-153.
- [8] Huang, K., Lo, W., Chung, Y., Lai, Y., Chen, C., Chou, S., & Hu, Y. (n.d.). Combination of Baculovirus-Mediated Gene Delivery and Packed-Bed Reactor for Scalable Production of Adeno-Associated Virus. *Human Gene Therapy*, 1161-1170.
- [9] Lu, J., Chung, Y., Chan, Z., & Hu, Y. (n.d.). A Novel Oscillating Bioreactor BelloCell: Implications for Insect Cell Culture and Recombinant Protein Production. *Biotechnology Letters Biotechnol Lett*, 1059-1065.
- [10] Mcsharry, J., Singer, D., Kulawy, R., Brown, A., & Drusano, G. (n.d.). Use of the BelloCell System to Determine the Optimal Dose of Ribavirin to Inhibit the Expression of an HCV Replicon in 2209-23 Cells. *Antiviral Research*.
- [11] Toriniwa, H., & Komiya, T. (n.d.). Japanese encephalitis virus production in Vero cells with serum-free medium using a novel oscillating bioreactor. *Biologicals*, 221-226.

## Disposable CelCradle™ Bottles

The CelCradle™ product line meets your specific needs. Different CelCradle™ bottles cover 90% of applications in cell culture.

- Batch, semi-batch or continuous culture
- Disposable
- BioNoc™ II carriers or preferred microcarriers
- Cell harvest with or without trypsin
- Pre-sterilized bottles are time and labor saving

Application/ Bottle	Item Code	Secreted Protein, Viruses	Cell Harvest (for non-secreted proteins, viruses or cells)	Carrier Harvest (for protein extraction or reuse of carriers)
CelCradle™ 500	1400001	Best Application	Applicable, but not optimal	Applicable, but not optimal
CelCradle™ 500A	1400003	Applicable, but not optimal	Best Application	Best Application
CelCradle™ 500P	1400002	Best Application	Applicable, but not optimal	Applicable, but not optimal
CelCradle™ 500AP	1400004	Applicable, but not optimal	Best Application	Best Application

## CelCradle™ System Complete

The CelCradle™ System Complete contains all the necessary elements for users to begin a batch type cell culture.

### Features

- Includes a CelCradle™ Stage and necessary accessories for startup of the cell culture upon receipt
- Extremely compact design system fits in most standard CO<sub>2</sub> incubator
- Suitable for batch and semi-batch operation
- Suitable for most protein and monoclonal antibody production applications.

## Ordering Information

CelCradle™ System Complete		
Product Name	Item Code	Package
CelCradle™ System Complete	2230006	1 x CelCradle™ Stage 1 x GlucCell® Glucose Monitoring System

## CelCradle™ Continuous System Complete

The CelCradle™ Continuous System Complete features the same equipment as the CelCradle™ Complete, with the addition of the CelFeeder pump and tubing sets to provide medium exchange in the CelCradle-500P bottles.

Each CelCradle™ 500P bottle is equipped with additional inlet and outlet lines for medium recirculation. Each bottle is linked to an extra medium vessel, thus providing continuous exchange of nutrient, eliminating labor for medium exchange and avoiding possible shock to cells during culture.

### Features

- Each package contains a CelCradle™ Stage, a CelFeeder pump module, two tubing complete sets, and accessories for the easy startup of the cell culture.
- Each bottle connects with independent medium reservoir to eliminate cross-contamination
- Programmable and On/Off pumping control simplifies the setting of recirculation rate for each bottle
- One CelFeeder pump module enables the operation of up to 4 pump heads with individual micro-processor control
- Suitable for cell mass production, cell component production, virus production and protein expression

## Ordering Information

CelCradle™ Continuous System Complete		
Product Name	Item Code	Package
CelCradle™ Continuous System Complete	2230007	1 x CelCradle™ Stage 1 x CelFeeder Pump 2 x Tubing Complete Set

## CelCradle™ Stage

The CelCradle™ Stage is capable of operating 4 CelCradle™ bottles simultaneously. It is compact and compatible in a CO<sub>2</sub> incubator.

## CelFeeder Pump Module

The CelFeeder pump module is an auxiliary peristaltic pump to achieve the recirculation and perfusion processes for CelCradle™ 500 high density continuous cell culture system.

## Tubing Complete Set

The Tubing Complete Set includes pre-assembled tubes, reusable pump head and head plate with a sampling port to support the continuous culture in CelCradle™-500P system.

## Disposable Tubing Accessory

The Disposable Tubing Accessory provides simple options to replace the tubes in the Tubing Complete Set, thus avoiding wear out of the tubes during operation. It is recommended to replace the tubes after 3x of use.

## GlucCell® Glucose Monitoring System

The GlucCell® Glucose Monitoring System is a portable, light-weight, and palm-sized kit suitable for glucose measurement for both serum and serum-free culture medium in mammalian and insect cell culture, without affecting the accuracy of the results. The GlucCell® glucose monitoring system responses promptly and gives reliable result. It has an accuracy of greater than 90%, precision of 95% and linearity of 0.9997.



## Crystal Violet Dye Nucleus Count Kit

The Crystal Violet Dye Nucleus Count Kit contains crystal violet dye, citric acid and detergent used to disrupt the cells and release cell nuclei for cell count. The CVD kit is an efficient reagent for cell count in a porous matrix.



## Ordering Information

Product Name	Item Code	Package
CelCradle™ Stage	2230005	1x Main Console 1x Control Box 1x 100-240 V power adapter 1x Signal Cable 1x Manual CD 2x Forceps 1x Crystal Violet Dye Nucleus Count Kit
CelFeeder Pump	1400067	1 x CelFeeder Pump
Tubing Complete Set	1400011	1x Disposable Tubing Accessory 1x Pump Head
Disposable Tubing Set & Pump Head	1400012	1x Tubing Set 1x Pump Head
Disposable Tubing Accessory	1400013	5x Disposable Tubing Accessory
GlucCell® Glucose Monitoring System	1400009	1 x GlucCell® Glucose meter 2 x Glucose Test Strip/bt
GlucCell® Glucose Test Strip	1400010	2 x Glucose Test Strip bts (2 x 25pcs)
Crystal Violet Dye Nucleus Count Kit	1400014	1 x CVD Bottle (100ml/bt)
Filtered Cap	1400015	Cap for CelCradle™ Bottle
Non-Vented Cap	1400016	Cap for CelCradle™ Bottle
Forceps	1400017	Used for sampling of BioNOC carriers