Product Guide 2016-2017

VACCIXCELL
ADHERENT BIOPROCESSING SPECIALIST

TideCell®

High-Density Cell Culture System

Introduction

The TideCell® Bioreactor System is the world's largest linearly scalable single-use bioreactor, from seed preparation to 5000 liters with closed automated cell harvesting. It is the pilot/production scale system of VacciXcell's Tide Motion Bioreactors.

One of the main advantages of VacciXcell's Tide Motion Bioreactor system is that it features the same bioprocess method from seed preparation to production scale. This is essential as certain cell lines do not grow well when seed preparation is done in 2D culture then cultured in 3D.

Esco VacciXcell's Tide Motion System is the highest yield and lowest cost fixed packed bed bioreactor and the only packed bed bioreactor that can be placed in an isolator in a Grade C-D background, ideal for wild-type virus production, which reduces costs of cleanrooms by decreasing the need for Personnel Protective Equipment (PPE), Utilities, and Viable/Non-Viable monitoring, as larger Grade A and B cleanrooms with associated gowning airlocks in Grade C and D do not have to be built.

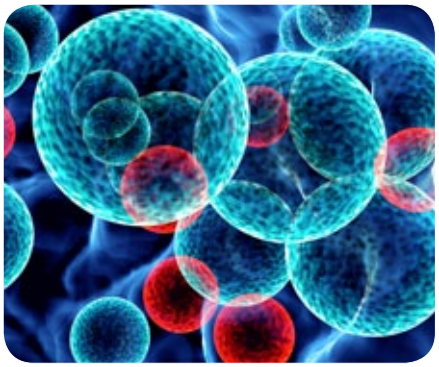
VacciXcell is the first and only life sciences tools company that is able to provide a single source turnkey design & build platform for adherent cell culture from Upstream to Downstream, Formulation & Filling, Cold Chain (Ultra low temperature freezers, Refrigerators), Secondary containment, Dispensing and Sampling Booths, Isolators, Biological safety cabinets, CO_2 Incubators, Autoclaves & Glassware washers. VacciXcell understands adherent and vaccine bioprocessing and is a global leader in adherent cell culture.

Esco VacciXcell understands adherent and vaccine bioprocessing and is a global leader in adherent cell culture. In addition to Vaccine bioprocessing and Biosafety, Esco is one of the world's top 3 Companies in Biological safety cabinets. Esco was the first in Asia and manufactures the world's most certified BSC. Esco is the only life science tools that has mastered the entire range of Biosafety Containment from BSL 1-4 and is able to provide custom applications specific to customer's biosafety needs, integrating packages with the life science tools (Incubators, centrifuges, cold chain, filling lines), which are produced in vertically integrated factories with Esco's own stainless steel and sensors manufacturing and powder coating lines.

VacciXcell Vision

Costs of research and development and bioprocessing time in academic institutions, NGOs and within the industry is the largest contributing factor to the final costs of vaccines, as final vaccine costs needs to recoup costs spent during research and development.

One of VacciXcell's core visions is a world where vaccines are accessible to all mankind, hence by lowering vaccine production costs, all countries can become self-sufficient.



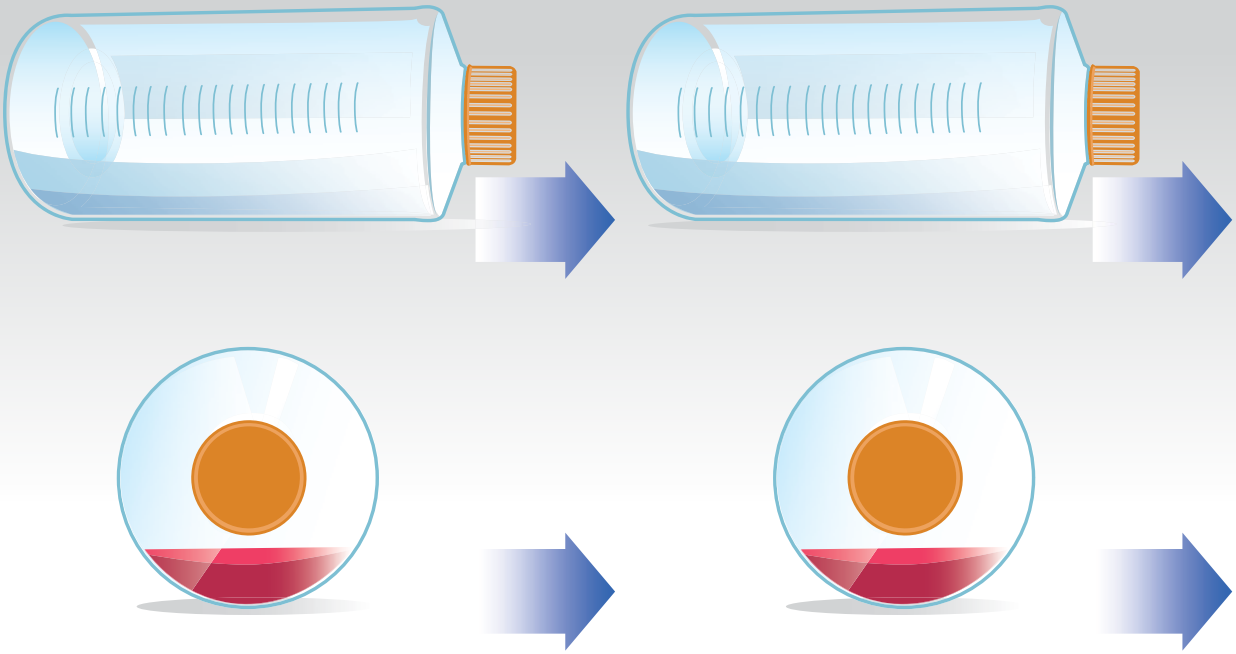
VacciXcell advocates selecting a linearly scalable method beginning with R&D setting, as this canreduce the overall bioprocessing time up to 80%, hence lowering vaccine costs. In addition, VacciXcell advocates that developing countries take ownership of research and build a scientific community within each country to carry out research and development for diseases endemic to their country. By introducing a method that allows rapid transfer across different production sites, production of vaccines during pandemic outbreaks becomes much simpler and faster.

What is the Esco TideCell(R)?

TideCell is the only bioreactor that has truly broken the adherent scale up barrier, enabling adherent scale up to 5000L!

VacciXcell has various 100 liter packed bed bioreactors that are currently being used for commercial production for both human and animal vaccines.

Disruptive Evolutionary pathway!

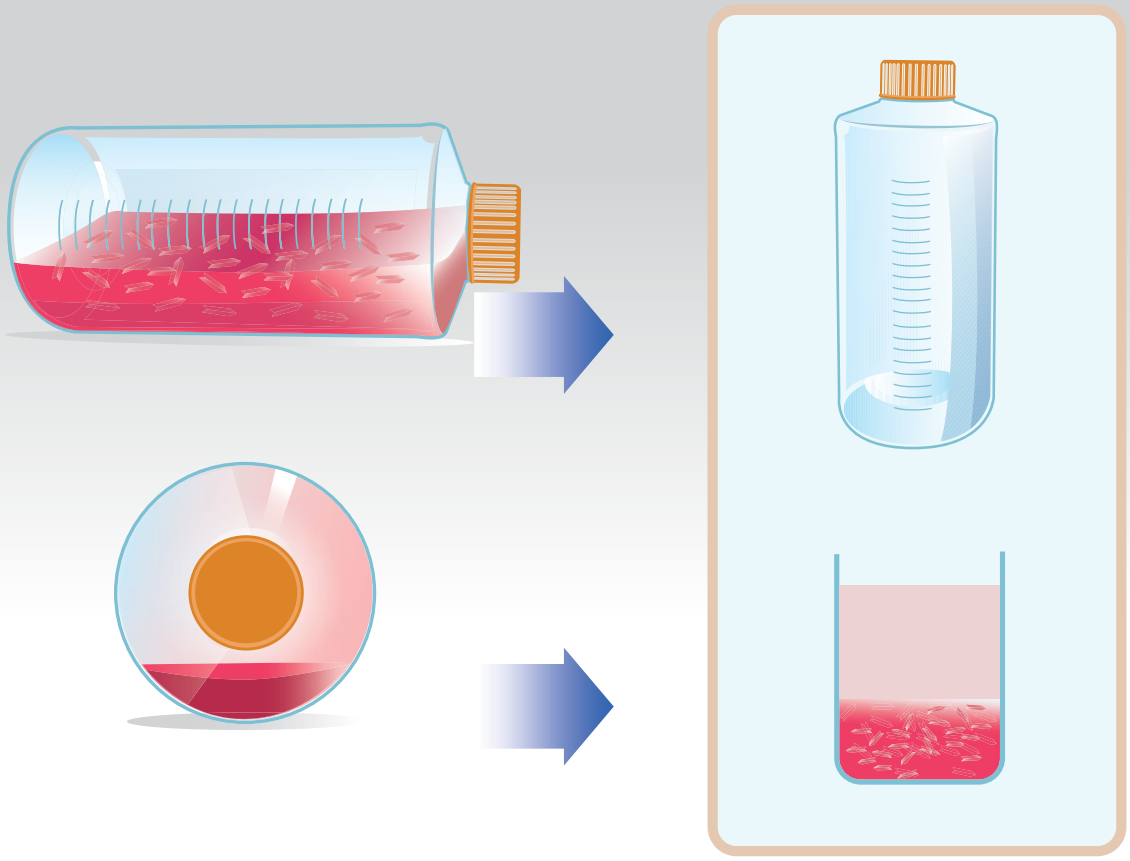


Traditional Roller Bottles

Surface area: Low
Oxygen / Nutrient: High
Labour: Highest
Space: Highest
Media Usage: Highest
Cross-Contamination / Contamination Risk: Highest
Closed Cell Harvesting: No
Cost: Medium (if country has low labor costs)
High (if county has high labor costs)
Continuous processing: No

Traditional Roller Bottles+ Automation

Surface area: Low
Oxygen / Nutrient: High
Labour: High
Space: High
Media Usage: Highest
Cross-Contamination / Contamination Risk:
Medium Lower than manual
Closed Cell Harvesting: Possible in some cases but complicated and expensive.
Continuous processing: Possible in some cases but complicated and expensive.
Cost: High (if country has low labor costs)
Medium (if country has high labor costs)

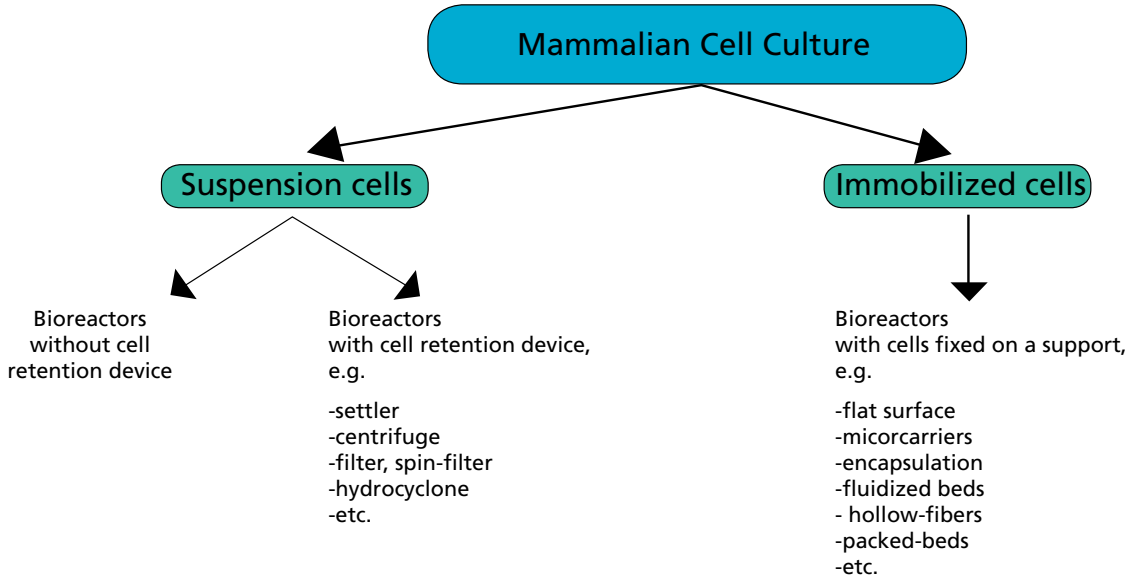


Traditional Roller Bottles+ Automation+ Microcarriers

Surface area: Increased
Oxygen / Nutrient: Low
Space: Medium
Media Usage: Medium
Cross-Contamination / Contamination Risk: Highest
Closed Cell Harvesting: Possible in some cases but complicated and expensive.
Continuous processing: Possible in some cases but complicated and expensive.
Cost: Medium (if country has low labor costs)
Medium (if country has high labor costs)

TideCell + Macrocarriers

Surface area: Highest
Oxygen / Nutrient: Highest
Space: Medium
Media Usage: Lowest
Cross-Contamination / Contamination Risk: Lowest as Closed system
Closed Cell Harvesting: Yes
Continuous processing: Yes
Cost: Lowest regardless of country labor costs.
Allows Continuous
Processing: Yes

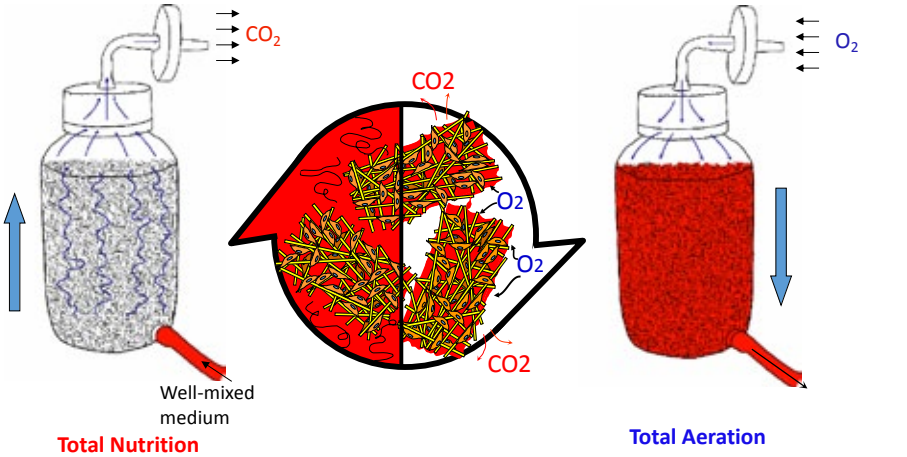


TideCell® Principle

The TideCell® System is comprised of the TideCell® Incubation and control System Unit, which houses the matrix vessel, the TideCell® Mixing System, which holds the mixing bag/tank for the culture medium. Cells attach to and grow in the BioNoc™ II carriers placed in the matrix vessel, while culture medium is pumped in to the matrix vessel from the mixing tank and back.

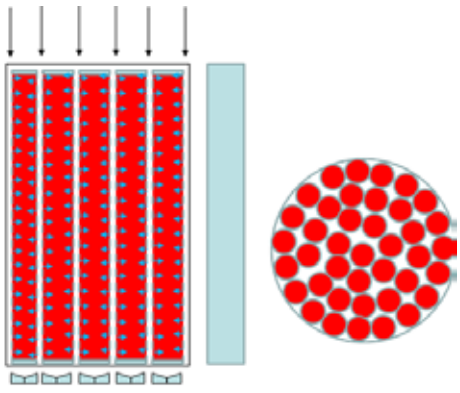
When the matrix vessel is filled with medium, cells are exposed to nutrients. On the other hand, when medium is pumped back to the mixing tank, cells are exposed to aeration and O_2-CO_2 air exchange occurs. In this way, cells are alternately exposed to nutrition and aeration, similar to the roller bottle principle.

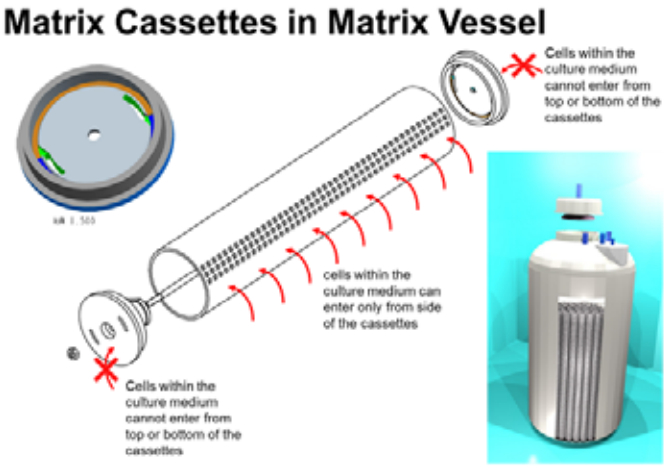
Tide Flush enhances O_2/CO_2 and Nutrient/ Waste Exchange



In addition to the incubation system and mixing system, optional harvest and feed tanks can be connected to the TideCell® System in order to run the system in perfusion/continuous culture.

Homogenous seeding can be achieved across the entire packed bed with our patented single use cassettes. The Esco TideCell Matrix Bed is packed with various porous cassettes, which house our BioNoc II macrocarriers; this results in the packed bed being spliced into numerous small sections and cells are forced to flow inwards in a horizontal radial direction instead of a vertical direction. In this way, the distribution gradient effect during seeding phase, which normally occurs in other packed bed bioreactors, can be minimized.





Parameter Control

Culturing cells in bioreactors require constant monitoring and control of several critical parameters including pH, dissolved oxygen (DO), and temperature. With the TideCell® System, pH and dissolved oxygen levels are monitored and regulated at the mixing system, while temperature can be measured and controlled at two points – the mixing system and the incubation system.

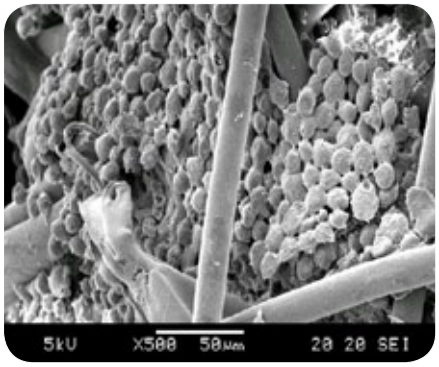
Key Benefits

The TideCell® System has three main features - highest yield, lowest cost, true linear scalability.

Highest Yield

The heart of the TideCell® system is the BioNOC™ II, which is a 100% PET fibrous culture matrix with stability of up to 5 years. These macrocarriers provide cells with a large surface area for attachment and growth and 3D matrix that closely mimics a cell's in vivo environment. Furthermore, the efficient oxygenation and nutrition exchange in the matrix vessel allows cells to proliferate well and produce high yields of bioproducts.

BioNOC™ II Macrocarriers



Cells attached on BioNOC™ II Macrocarriers

Lowest Cost

The TideCell® system reduces production costs in different ways. First, space, utilities and labour requirements are lowered due to the TideCell®'s compact and automated design, in spite of having the same productivity as that of 20,000 850cm2 roller bottles. Second, consumption of culture medium, which is one of the largest cost drivers in biologics production, can be reduced because of the high nutrition and oxygenation exchange levels of the tide motion principle. Third, the risk of contamination and cross-contamination (for instance from breaches in aseptic processing, non-cGMP facility design and practices, gowning or open handling roller bottles), which when happen leads to grave losses, is greatly decreased by the TideCell® being fully enclosed and ULPA-filtered design and using single use disposables. Finally, downstream costs can be reduced for several reasons due to the nature of the BioNOC™ II macrocarriers and gentle oscillation of medium.

The BioNOC™ II macrocarriers have very low fibre content thereby reducing downstream processing steps, while with the gentle tide motion, cells do not experience shear stress, thereby resulting to minimal to zero cell debris.

Bioprocessing utilizing the microcarrier – stirred tank bioreactor technology have several folds higher impurities with host cell protein and DNA/RNA. During agitation in the stirred tank bioreactors, cells post infection, might detach and get milled by microcarrier beads, as the environment experiences high shear forces; this may release large amounts of host cell proteins and nucleic acids, which need to be purified during downstream processing. This amount is compounded significantly if the cells lines are tumorigenic cells.

In VacciXcell's fixed packed bed bioreactor, cells even if they are lysed after viral infection will remain trapped within the matrixes, hence they will not be flushed into the harvest media during our gentle tide motion. This reduces host cell protein, DNA/RNA nucleic acid residues by several folds.

Moreover, cell harvesting costs is lower in tide method, as compared to other systems. In the microcarrier – stirred tank bioreactor system, ells are cultivated in large bioreactors, which can be time consuming and expensive to maintain, particularly with regards to validating SIPs. Moreover, most contamination can occur from microbial contaminants trapped within gaskets. Stirred tank bioreactors require large floor space for scale up and high labor cell harvesting. Cells are mixed together with the microcarriers, and thereby requires additional centrifugation or filtration to isolate the cells; this results lower cell yields and more downstream washing, at larger volumes. In turn, larger working volume results in more complex downstream processing, higher recovery cost, and lower cell recovery.

In the roller bottle system, cell harvesting from individual bottles is required, which not only incurs high labour but also introduces potential contamination and cross-contamination during aseptic processing. Microcarriers used in roller bottles face similar issues in cell debris during recovery, while automated roller bottle factories whilst removing the human component are still costly in terms of media consumption. In other packed bed bioreactors, it is extremely difficult or impossible to harvest cells from the system due to the weight and dimension of the packed bed. These packed beds tend to be too large and heaving, making it almost impossible to agitate; freeze and thawing is also not an option as the packed beds do not fit in conventional freezers.

Esco TideCell concentrates cells within the matrix vessel, reducing total working volume to 1/5~1/25, which also lowers media consumption. This simplifies cell harvesting and downstream recovery processes, thereby reducing overall downstream processing costs via the reduction of space, labor and recurring costs from utilizing columns. Columns are the most expensive component of any downsteam process whilst concurrently maintaining high cell recovery. Esco's fixed packed bed matrix vessel, with its concentric cylindrical design even in 100 liter, can be separated from our mixing vessel in a closed manner and placed in a freezer for direct freezing and thawing, making cell harvesting simpler and more efficient.

Linear Scalability

VacciXcell's Tide Motion System is the only truly linearly scalable system from laboratory scale to production scale. It employs the same culture principle from seed preparation using the CelCradle™ System to succeeding larger scale TideCell® Systems, all the way to TideCell® 100L. It also features the TideCell® Cell Harvesting System, which facilitates in the automated and closed system cell harvesting and seed transfer from one TideCell® System to another. True linear scalability allows faster and easier technology transfer from R&D to production scale with minimal bioprocessing time.

TideCell is a gentle giant! Despite being the largest packed bed bioreactor (5000 liters), it is truly linearly scalable and has the lowest downstream costs and bioprocess development time, as compared to other bioprocessing methods

Component Description and Specification

TideCell Incubation Control System 2 - 20L / 50 – 100L

System Material	Stainless Steel 304 BA Stainless Steel 304 4b
Control Hardware	(-20L) Flexible pc-base/DAQ industrial control interface (-100L) Compact Rio PAC/DAQ industrial controller
Control Software	NI Labview; OS : Windows XP Preinstalled "Tide-Commander" graphic HMI
Incubator	0 – 20% CO_2 PID Control RT +3°C – 60°C temperature PID Control
Control paramete	Temperature CO_2 concentration Up/Down rate Top/Bottom hold time

TideCell Mixing System

Control Parameter: pH, DO, Temperature

1. Magnetic Stirrer Mixing System

System Material	Stainless Steel 304
Control Hardware	100 – 1500 rpm
Control Software	RT – 45°C

2. Recirculation Thermostatic Mixing System

System Material	Stainless Steel 304
Pump Rate	0 – 21 LPM
Temperature Control	RT – 50°C

3. Stir-Tank Mixing System (with SIP system)

System Material	Stainless Steel 316 Stainless Steel 304
Stir Rate	80 –1000 rpm
Temperature Control	RT – 60°C

TideCell Matrix Vessel

Volume	Disposable	Autoclavable
2L	V	V Glass Vessel
10L	V	V Glass Vessel
20L	V	V Plastic Vessel
50L	V	V Plastic Vessel
100L	V	V Plastic Vessel

TideCell Mixing Container

1. Magnetic Stirrer Mixing System

Volume	10L 20L
Material	Glass

2. Recirculation Thermostatic Mixing Disposable Bag

Volume	50L, 100L, 200L, 500L, 1000L
Material	Plastic

3. Stir-Tank Mixing Tank

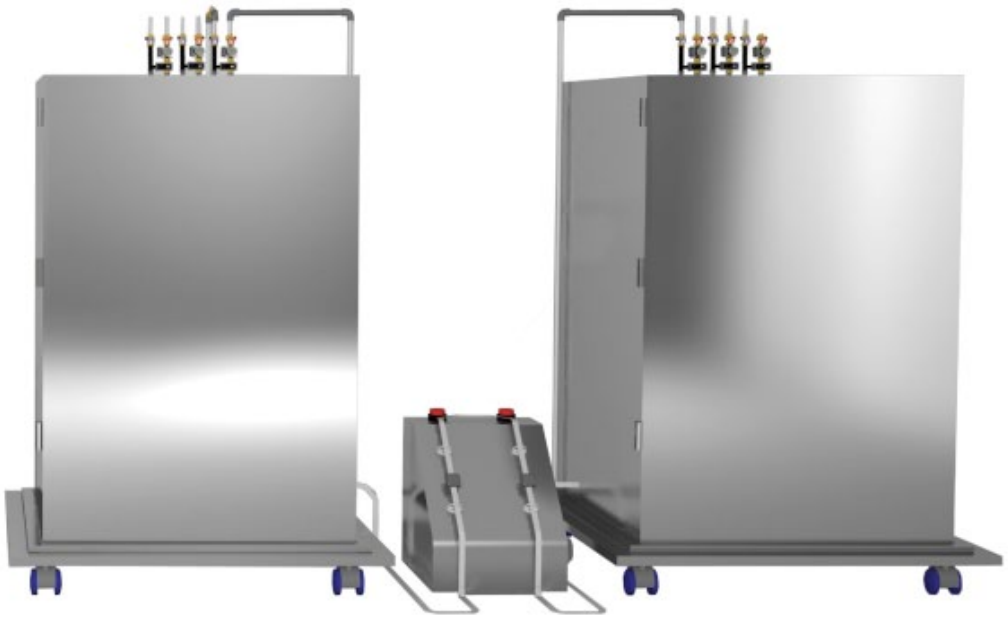
Volume	30L, 50L, 100L, 200L, 500L, 1000L
Material	Stainless Steel 316

AutoFeeder

Control Unit	Industrial PLC
Communication	Modbus ASC II
Protection	Maximum & minimum net weight stop protection
Control Parameter	pH Control DO Control Feed and Harvest control • -10 – 900 L / day • 1 – 96 cycles / day

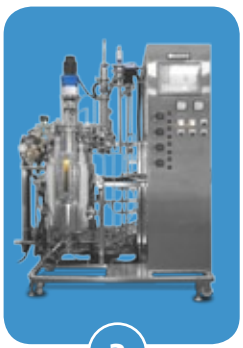
Optional AutoSwitch System

Control Unit	PLS-28 connectors
Communication	AutoFeeder-1200
Protection	Individual warning lights for indicating depletion of feed tanks
Control Paramete	In-line and non-invasive bubble detector




1


2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Feed / Harvest Tank

Tontrolled by	Autofeeder
Culture System	Fed-Batch Culture Perfusion Culture
Control Software	

1. Single Use System

Volume	50L, 100L, 200L, 500L, 1000L
Tank Material	Stainless Steel
Bag Material	Disposable Plastic Bag

2. SIP System

Volume	30L, 50L, 100L, 200L, 500L, 1000L
Tank Material	Stainless Steel
Sterilization	SIP System

TideCell® Incubation & Control System

The TideCell® Incubation System consists of the Esco's top of the line CO_2 incubator, with additional features. It has an integrated weighing scale at the base, which allows the measurement of the amount of culture medium pumped in and out of the matrix vessel.

The TideCell® Incubation System features 2 ULPA filters. The first ULPA filter is used to ensure air quality inside the incubator, while the second ULPA filter is used to filter exhaust air, allowing the culture of BSL 3-4 virus strains. The incubation system further provides operator, environment, and sample protection with its magnetic door interlock and UV light.

Additional features of the TideCell® Incubation system include a glass window on the front door, which enables end users to observe the matrix vessel without the need to opening the incubator, reducing fluctuations in parameter values.

VacciXcell offers 2 different models of TideCell® Incubation and Control System: for 2 – 20L scale incubation & control system and 50 – 100 L scale incubation & control system. Esco's TideCell® Incubation & Control System has user friendly design and interface and its controls are CFR 21 Part 11 compliant.

The Esco CO_2 incubator provides optional sprinkling of media on the top of the packed bed, which ensures that the top of the packed bed receives nutrients while waiting for the nutrition phase; this further increases the bioreactor yield. Moreover, The Esco CO_2 incubator features UV-C germicidal lighting for surface sterilization and an optional Esco BioVap system can be added, which guarantees 6-log bio-decontamination of the internal surface, hence operators do not need to rely on surface sterilization.

TideCell® Matrix Vessel

VacciXcell provides a wide range of matrix vessels, depending on user's production density requirements..

TideCell System	TideCell System 2 - 20L					TideCell System 100L	
Matrix Vessel	2-4L		10L	20L		100L	
	Multiple use	Single use	Multiple use	Multiple use	Single use	Multiple use	Single use
Working Volume	1-2L		5-10L			50-100L	
Closed Sampling Port No.	0	1	0	0	1-4	0	1-5
Pre-Packed Carrier (g)	0	55 110	0	0	275 550 1100	0	2750 5500
Material	Glass	PP	Glass	PP	PP	PP	PP
AutoFeeder	Integrated / AF-1200					AF-1200	

Different matrix vessels can be used in the same TideCell® Incubation System. Furthermore, the working volume of the matrix vessel depends on the quantity of BioNOC™ macrocarriers used. These two features provides users with more choices and more flexible production.

VacciXcell also offers a choice between multiple use and single use matrix vessels. Multiple use vessels are autoclavable and must be refilled with fresh and autoclaved BioNOC™ II macrocarriers. Qualitative tests for cells must be done through the direct sampling of carriers performed in a BioSafety Cabinet. Quantitative tests, on the other hand, can be performed by directly by carrier sampling or indirectly by measurement of glucose uptake rate.

Reusable Matrix Vessel

Single-use Matrix Vessel

Single-use matrix vessels are gamma-irradiated, ready-to-use, and are pre-packed with BioNOC™ II macrocarrier, the amount of which depends on the client's inquiry. Single-use matrix vessels feature patent pending closed sampling ports, which consists of a basket immersed within the matrix vessel and connected to the sampling port tube on the lid of the matrix vessel. During sampling, a cord in the sampling port is pulled, bringing along with it the small basket of carriers. Once the basket is out of the matrix vessel, the sampling port tube is sealed to prevent contamination. This allows in-process QC without the risk of contamination and allows cytopathic effect to be monitored. Sampling ports can be placed in different parts of the packed bed to allow determination of CPE and better bioprocessing in-process quality control.

TideCell Mixing System

Component Description and Specification

The TideCell® Mixing System holds the culture medium throughout the culture process; it is where the culture medium is continuously mixed and parameters such as pH, dissolved oxygen (DO), and temperature are monitored and regulated. This is in contrast to other bioreactor systems, where control and mixing of the culture medium takes place in the same vessel where the cells are grown. Separating culture medium vessel and culture vessel greatly decreases the problems caused foaming and bubbling, which typically occur during mixing. Foaming oxygen in the air from dissolving in to the culture medium, thereby decreasing DO levels; in order to counter this problem, anti-foam reagents are added, which may affect cell growth and development. On the other hand, bubbling is caused by agitation, which is needed to increase dissolved oxygen and homogenize the culture medium; however, bubbles can entrap cells or can cause cell death upon popping, thereby decreasing cell density. The TideCell® System overcomes these problems by having a separate mixing system for the culture medium and matrix vessel for cell growth.

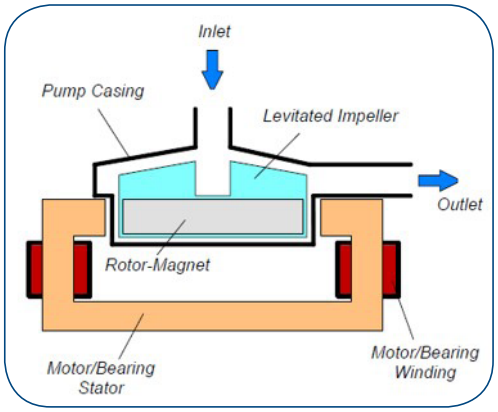
To offer more options, VacciXcell has adopted 3 different types of mixing system: magnetic stirrer mixing system, recirculation thermostatic mixing system and stir tank mixing system.

Magnetic Stirring System

Magnetic stirrer mixing system, as name the name implies, uses a magnetic stirrer. This system is used for relatively small scale mixing system. Glass mixing vessel (up to 20L) is placed on the magnetic stirrer; stir speed can be set from100 to 1500 rpm. With this system, temperature is controlled by a heating jacket; which has a maximum temperature of 45°C. For use in a production setting, Esco has designed a stainless steel magnetic stirrer for easier sterilization, with optional capability for hydrogen peroxide (H_2O_2) bio-decontamination in the room.

Recirculation Thermostatic Mixing System

Recirculation thermostatic mixing system is designed for relatively larger scale production. Recirculation mixing system consists of a rectangular stainless steel vessel, which holds a disposable mixing bag. Each side wall of vessel has thermostatic panel, which regulates temperature faster. Internal experiment proves that heating up 100 to 500L of media from 20°C to 37°C will take only less than 4 hours. The recirculation thermostatic mixing system uses a magnet-driven impeller, allowing mixing without housing contact and bearing, which may be a source of contamination. The magnetic pump head is single-use and is directly mounted to the motor. pH, DO and temperature probes are located in the probe holders on the side wall and can be autoclaved and reused. Installation and removal of the mixing bag from the vessel, can be done using the side door.



Stir Tank Mixing System

Stir Tank mixing system is a multiple-use stainless steel mixing tank for pilot/production scale; this mixing system is similar to a stirred tank bioreactor, wherein the culture medium is continuously stirred by an impeller and parameters such as dissolved oxygen, temperature and pH are monitored and regulated. The tank consists of 2 impellers, one on the bottom and another at the center of mixing tank, allowing unified media homogenization. Esco offer more than 10 types of impellers, should the user require a specific impeller type. Agitation rate, in general, ranges from 80 to 1000 rpm and temperature control up to 60°C. The Stir Tank Mixing System has a built-in automated Sterilization-In-Place (SIP) system, allowing individual sterilization of the mixing tank and the culture medium. SIP (sterilize in place) protocol consists of 5 steps: Heating 1, Heating 2, sterilization, Cooling 1, Cooling 2. This protocol can be set and automatically runs according to setting value. Other features of this system include motorized tank lid lifter, which enables viewing of the inside of the tank vessel, optional Wash-In-Place WIP, and glass window and LED light, allows medium observation.

TideCell® Mixing Vessel

In accordance with various mixing systems, Esco offers various option for mixing container. Depends on the system type, Esco offers various option of mixing container.

Mixing System	Magnetic Stirring System	Recirculation Thermostatic Mixing System	Stir Tank Mixing System
Vessel Volume	Multiple use	Single use	Multiple use
Container Volume	10L, 20L	50, 100, 200, 500, 1000L	30, 50, 100, 200, 500, 1000L
Material	Glass vessel	PP bag	Stainless Steel 316 Vessel
Incubation System	2L matrix vessel	2 – 100L matrix vessel	2 – 100L matrix vessel

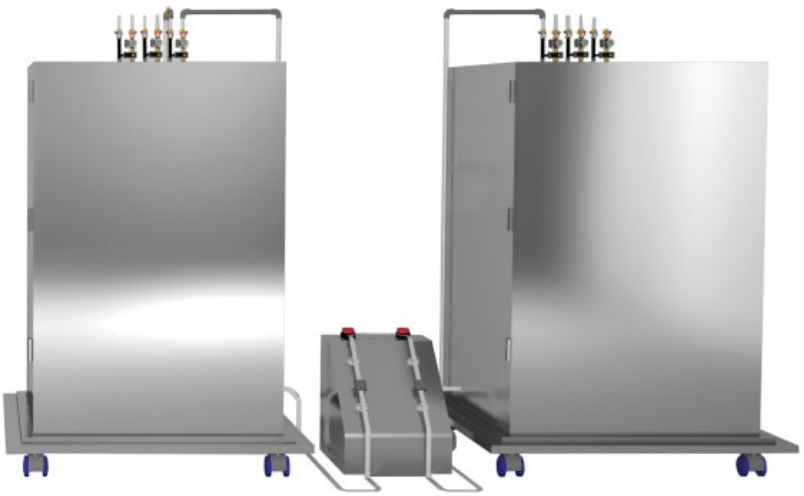
Depending on the cell culture volume and mixing system type, users can choose the type and volume of the mixing vessel. Moreover, the Recirculation Thermostatic Mixing System and Stir Tank Mixing System can be used for culture media preparation. Media preparation is the starting step of entire culture process, hence its preparation and maintaining its sterility is critical to the success of the process. Esco's mixing systems allows faster and better homogenization after addition of reagents; moreover, the media preparation tank can be directly connected to the mixing tank in a closed system, decreasing contamination risk.

All the mixing vessels have ports for pH probe, DO probe, and Temperature probe, and as well as harvest and feed ports, for direct emptying and filling of the vessels. Sampling ports are also available for medium sampling and addition ports can be used to pump in additional reagents.

Feed/Harvest Tank

Feed/Harvest system is an optional system that allows users to run the culture in perfusion/ continuous mode for long periods of time.

This system controls volumetric flow of medium in and out by checking weight of mixing container. In fed-batch mode, volume of the medium to be added is set and pumped into mixing container using autofeeder system. In perfusion mode, the total weight of the mixing container is measured and the system automatically adjusts the volumetric flow of the medium to and from the mixing vessel, allowing same media volume exchange between feed and harvest tank.



AutoFeeder System

AutoFeeder system has 3 major control functions: automatic control of feed and harvest volume by weight calculation, pH control, and dissolved oxygen (DO) level control.

During feeding and harvesting, 2 large peristaltic pump are used to pump medium in and out at a speed of 2000ml/min. This allows up to 900L of culture medium to be transferred each day, which can be divided into 1 – 96 cycles per day. A step program system can be used to set medium exchange volume in a step-wise manner; users can set the medium exchange volume at each step and can create up to 10 steps.

For pH control, a small pump is used for the alkali addition. Users set the sampling and flushing time and lower and upper the limits of the alarm. DO level is controlled by the Autofeeder through levels of air and oxygen.

AutoSwitch System

The AutoSwitch System is recommended if there are two feeding tanks used during fed-batch or perfusion culture and is connected in between two feeding tanks. The pinch valve inside the system will detect and automatically switch from one tank to another once the first tank is empty. An alarm light will turn on once the media in the tank is depleted; there are two individual alarm lights to indicate which feed tank which is empty. In addition, the autoswitch system includes in-line and non-invasive bubble detector.

TideCell® Cell Harvesting System

The TideCell® Cell Harvesting System (TCCHS) allows the automated and closed system harvesting of cells from the matrix vessel. TideCell® Cell Harvesting System utilizes the same conventional cell harvest concept by enzymatic treatment to detach cells from BioNOC™ II carriers.

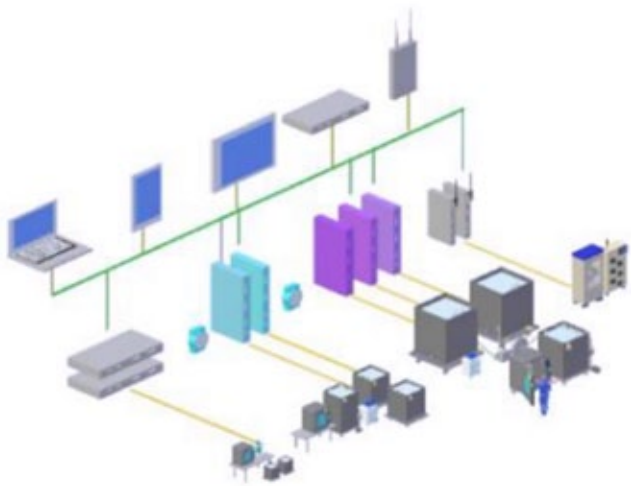
The Tidecell® matrix vessel is transferred to the TCCHS. Harvesting protocol will be similar as user's current harvesting protocol. Buffer is pumped in to clean out media from matrix vessel; followed by enzymes (in general, trypsin) for cell detachment, then an inhibitor (depending on the protocol). The detached cells are then collected with medium.

With this system, buffer is pumped in and out of matrix vessel 1-3 times (VacciXcell recommends to collect cells with media 5 times). This automated harvest system allows harvest cells within 1 to 3 hours, depending on harvest cycles, and shows around 95% viability after harvest. During detaching procedure, harvest equipment shakes matrix vessel at a shaking distance of 10cm and at speeds of up to 300rpm.

SCADA System

The TideCell® SCADA System enables centralized monitoring of multi-systems. The TideCell® incubation & control system, mixing system, autofeeder, and as well as autoswitch system are connected by LAN cable and monitored. With the SCADA system, users are able to access TideCell® System when it is logged in.

The SCADA system collects and records operational data such as temperature, CO_2 level, pump rate; moreover, it can also record manual intervention such as who clicked fill button or who changed settings. All events and alarms that take place during the culture process are recorded and sent to the users via e-mail or other assigned communication systems.



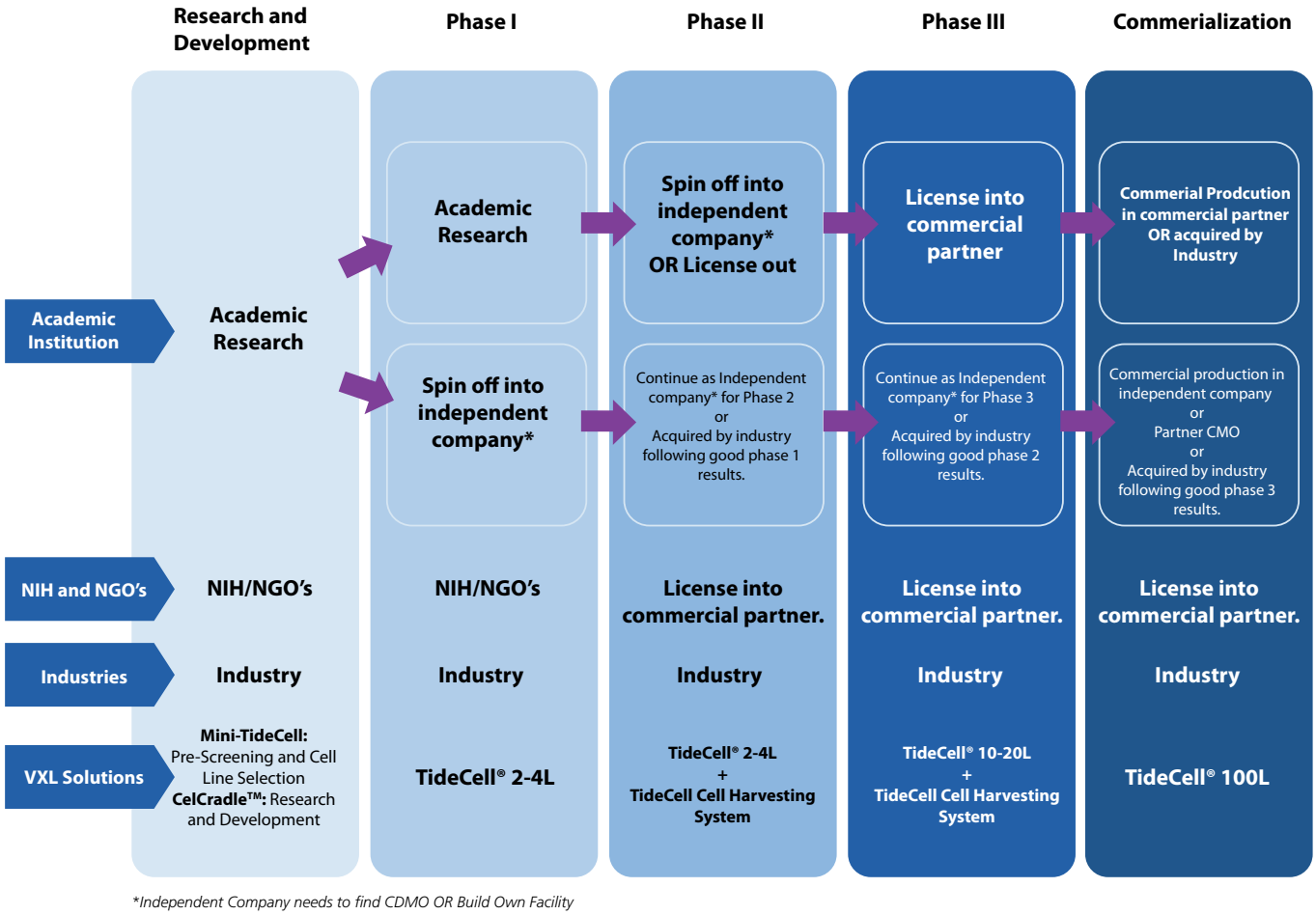
Proven Cell Lines and Indications

Esco TideCell has been used for various human and animal commercial vaccines for PICs, eu cGMP and JIS factories globally. See VacciXcell's cell lines and indications below.

Vero - JEV	Vero - EV71	MDCK - A(H1N1)	ST - Hog Cholera	Marc145 - PRRSV
Vero - Rabies	MDCK - H5N1	PK - Hog Cholera	BHK21 - Rabies	GL37 - HepA

Applications and Target Markets

Providing a complete discovery to delivery translational adherent linear scalability for entire ecosystem



**Independent Company needs to find CDMO OR Build Own Facility*

The TideCell® System and VacciXcell's tide motion system is an ideal platform for different companies such as Academic Institutions, NIH, NGOs, CDMO's, Virtual Companies, Start-Ups and Industries.

VacciXcell's tide motion system can be of great advantage to academic institutions, NIH, and NGO's alike as the system's linear scalability can easily attract industry partners. Academic institutions, NIH, and NGO's can perform research and development as well as phase 1 clinical trials using the laboratory scale CelCradle™ System and can license out the technology to vaccine industry, industrial partners or spin-off companies using the TideCell® System for phase 2 to phase 3 and eventually commercial production. Scaling up from the CelCradle™ System to the TideCell® System virtually has zero bioprocessing time and minimal bioprocess optimization, speeding up vaccine development time, which can often be up to $100 million to develop 1 vaccine, thereby greatly reducing vaccine costs.

CDMO's can benefit from the TideCell® system, as the system provides a low-cost and cutting edge technology with high productivity and yield, which attract future clients. On the other hand, Virtual Companies and Start-Ups looking to setup new research facilities benefit from the system's high production yield at low costs and true linear scalability.

The TideCell® System is an ideal platform for many different applications.

Anchorage-Dependent Cells

VacciXcell's tide motion system is intended for the culture of adherent or anchorage-dependent cells to be used for various applications such as cell banking, cell culture-based vaccine production, biologics production, cell therapy, and biomass production. The system offers advantages over other adherent cell bioreactor systems, such as the microcarrier system and other packed bed bioreactors, as the system features low shear stress and lack of oxygen limitation. Moreover, the system is capable of high cell density yield, with a single TideCell® 100L capable of producing up to a trillion cells (10^{12}) adherent cells.

From Roller Bottles to Closed System.

VacciXcell's tide motion bioreactor system is very similar to the roller bottle system in principle, as it also alternately exposes cells to aeration and nutrition. However, the tide motion system overcomes most of the disadvantages associated with the roller bottle system namely labor and space requirements and contamination risk. As costs of production become more and more expensive, existing facilities that employ the roller bottle system can thereby benefit from switching to the TideCell® System for several reasons. First, the TideCell® 100L can replace up to 20,000 850cm^2 roller bottles, greatly decreasing footprint for the same productivity. Second, the TideCell® System is fully enclosed and automated, which decreases the risk of contamination and labour requirements and increases control of the production. Third, the tide motion principle employed in the TideCell® system allows simple medium exchange and better medium consumption efficiency, thereby reducing medium consumption, which is a large cost in cell culture systems. VacciXcell has successfully conducted the switch from the roller bottle system to the TideCell® system for multiple customers performing vaccine production for both human and animals.

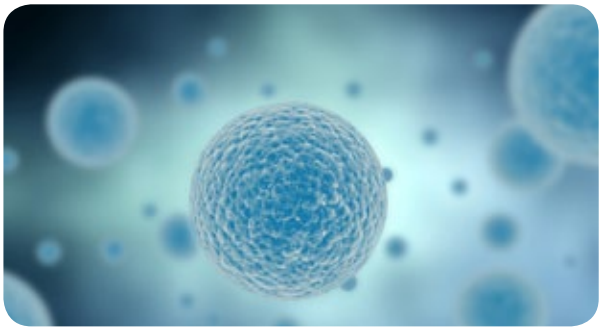
Vaccine Self-Sufficiency for the developing world.

VacciXcell envisions a world of vaccine self-sufficiency for all nations, especially developing lower middle income countries. The Tide Motion System is an ideal platform for vaccine research and production for several reasons. First, the tide motion system is truly linearly scalable from laboratory scale to production scale, thereby greatly reducing bioprocessing time and costs. Second, vaccine production is typically performed in roller bottles and as aforementioned, the TideCell® system can replace thousands of roller bottles with lower risk of contamination and labor and space costs.

Wild Virus Production

Another key advantage of VacciXcell's tide motion system is its capability to produce wild-type viruses in a closed environment. In the laboratory setting, the CelCradle™ system, inside a CO_2 incubator, can easily be integrated in an isolator. This can also be done with other laboratory scale culture systems such as T-flasks, stirred tank bioreactors, and packed bed bioreactors; however, pilot/production scale proves to be much more difficult. Wild-type virus strains cannot be grown in conventional pilot/production scale stirred tank bioreactors, as there are accompanied risks of potential exposure of workers and accidental release to the environment. VacciXcell's TideCell® System overcomes this as it is the only pilot/production scale bioreactor that can be placed in a cGMP isolator, allowing full containment of wild-type viruses during production.

Cell Therapy



VacciXcell envisions a world where more advanced and personalized therapeutics, in the form of autologous and allogeneic cell therapies, are easily accessible to everyone. VacciXcell's tide motion system is an ideal platform for the cultivation of anchorage-dependent cells used for cell therapy such as adipose and bone marrow derived mesenchymal stem cells. The TideCell® system is capable of producing high cell yields in a compact and automated setup and can be placed inside a cGMP isolator, if needed. Because of the TideCell® system's capability to produce high cell density yield, less passaging and trypsinization is required; this is greatly desired for cells used in cell therapy, as frequent passaging can result to cells losing their shape.

BioSimilars/BioBetters

Patents for a large number of biologics have expired and are expiring, which paves the way for the production of biologic generics – biosimilars/biobetters. The TideCell® is also ideal for the production of secreted biosimilars and biobetters, as the cells entrapped within the carriers greatly reduces downstream processing of the product, and as well as its capability of high cell and bioproduct yield. Moreover, bottom holding time or time of exposure to air can be increased, thereby reducing nutrient supply to the cells, leading to nutrient starvation, which freezes the cells in the G0 and G1 phase of replication. This allows cells to produce more of the desired biologic for continuous processing.

Neglected Tropical Diseases and Orphan Diseases

Neglected Tropical Diseases (NTD's) such as dengue, chagas disease, and rabies affect more than a billion people from developing nations each year. The most affected segment of the population are those who live with scant sanitation and close to disease vectors. On the other hand, orphan diseases are rare diseases that affect a very small percentage of the total worldwide population. For these reasons, costs are the primary concern for the development of drugs and vaccines for both NTD's and Orphan Diseases.

VacciXcell's tide motion system is an ideal platform for the development and production of vaccines for NTD's and Orphan diseases for its two main advantages: high productivity at low cost and true linear scalability from laboratory scale to production scale. The TideCell® system can allow production of vaccines at prices as low as $1 per shot.

Avian Influenza

Vaccine against avian influenza is traditionally produced with eggs. However, the use of closed cell culture systems is much more ideal since during a pandemic outbreak, an entire population of chickens are culled, thereby resulting to loss of eggs and possible subsequent zoonotic outbreaks, for instance the Spanish flu. Esco TideCell is an ideal system that can easily scale up during pandemic outbreaks and is not dependent eggs during production.

Human Influenza and Other Related Respiratory Diseases

Instead of bioengineering adherent cell lines to suspension cells for scalability or using eggs as production vessel, clients can use the Esco TideCell® together with Esco's Vero Plus culture medium. This is an ideal platform for the application and has been successfully used to develop proprietary human influenza vaccine.

Perfusion and Continuous processing to lower costs

Perfusion and continuous processing is an emerging trend in biopharmaceutical productions, as this can greatly lower costs of production. VacciXcell's Tide Motion is the ideal system for this, most especially for secreted bioproducts. The secreted bioproducts can be continuously harvested, while production continues as fresh culture medium is pumped into the bioreactor, where cells remain entrapped within the carriers. Furthermore, the tide motion principle decreases downstream costs, as the harvest medium contains minimal cell debris.

Cell Mass Train

In conjunction with the TideCell® Cell Harvesting System, the TideCell® System can be used to prepare cells to be used for seeding in stirred tank bioreactors and/or other larger scale packed bed bioreactor or as a cell mass production platform. Cells are cultivated in the TideCell® System and then harvested in a closed and automated setting with the TideCell® Cell Harvesting System. This results to a high cell density suspended in culture medium.

VacciXcell's CDMO

VacciXcell takes its bioprocessing services a step further by providing optional process development services at its CDMO facility at Aster Biopharma in Singapore. Apart from potential and existing clients, VacciXcell's CDMO facility may be of great interest as well to virtual companies, still looking to setup their facility.

Aster Biopharma focuses on process development, commercialization of NTDs for both humans and animals, Orphan Drugs, as a CMO for partner TideCell factories looking to gain access into Asean/Anz/Africa. Our vision is to one day operate purely as a Non-Profit Organization.

TideCell® Versus Other Systems

The TideCell® System works under the tide motion principle wherein cells, attached to fibrous macrocarriers, are alternately exposed to nutrition and aeration through the pumping in and out of culture medium into the matrix vessel.

Model	Fixed-Bed Volume (L)	Culture Surface Area (m^2)	Equivalent RB-850 (850 cm^2)	Equivalent CS-40 (25200 cm^2)	Equivalent Cytodex II (0.44 m^2/g)
CelCradle	0.1	1.65	20	0.65	3.75 g
TideCell-002	1~4	66	800	26	150 g
TideCell-010	5~10	165	2,000	65	375 g
TideCell-020	10~20	330	4,000	130	750 g
TideCell-100	50~100	1,650	20,000	650	3,750 g

Static Culture

Culture systems such as petri dishes, t-flasks, and cell factories employ the static principle for culture, wherein cells are continuously submerged in culture medium and exposed to aeration, without any agitation. Apart from the culture principle, the TideCell® System differs from static culture systems in terms of surface area and cell growth. Because of the fibrous macrocarriers of the TideCell® System, there is a larger surface area for cell attachment and growth in a much smaller footprint and labour requirements, as compared to static culture systems. Furthermore, this fibrous system allows cells to grow in a 3D matrix, unlike in static culture systems where cells grow in a 2D monolayer. The 3D matrix mimics cells' in vivo environment, allowing cells to grow and develop as naturally as possible.

Microcarrier Technology

Microcarriers are microbeads, to which cells attach and grow; they are then suspended culture medium in a stirred tank bioreactor, where the medium is continuously agitated for nutrient and oxygen transfer. This agitation causes shear stress on the cells, which typically grow on the surface of the beads, causing cell death. Cell death causes 2 main problems in bioreactor systems: it causes a decrease in product yield and it increases downstream processing steps and costs due to increased cell debris in the harvest medium. The TideCell® System eliminates these problems, as cells experience negligible shear stress, while still maintaining high nutrition and oxygenation levels. In addition, scale up in a microcarrier – stirred tank bioreactor system requires much more complex parameter optimization, as compared to that of the TideCell® System, which only requires optimization of the tide motion parameters. This allows the tide motion system to have a shorter scale up bioprocessing time.

Other Packed Bed Bioreactor

In other packed bed bioreactors, cells are entrapped within a bed of carriers, while culture medium, with nutrients and dissolved oxygen, is recirculated around bed. Although these systems provide high surface area and protection from shear stress, they suffer from a critical drawback, which is oxygen limitation. Oxygen transfer in these packed reactors occur in 2 steps: air to culture medium then culture medium to cells. This two-step transfer can limit the oxygen intake of cells, thereby inhibiting cell growth. The TideCell® System overcomes oxygen limitation via its dual oxygenation scheme. First, the tide motion principle allows the direct exposure of cells to oxygen, allowing direct transfer of oxygen from the air to the cells themselves. Second, even during the nutrition phase of the tide motion, cells are still able to intake oxygen, via the dissolved oxygen in the culture medium. This dual oxygenation allows the linear scalability of the TideCell® up to 5000L.

Where am I made?

Esco TideCell is available for FAT across our Esco Pharma factories in Singapore, USA & UK. Esco is fully ISO certified 9001/14001 factory in addition our Esco TideCell is ISO 13485 certified and is the ideal system to be used for cell culture.

All our components are cUL/CE and from International brands hence spare parts are kept locally by Esco Pharma Factories.

USA-Americas

UK-Europe

Singapore-ROW

St.st. is from Outo Kumpu Finland.

VacciXcell is a division in the Esco Group of companies and we work with Esco Offices globally

Esco Global Offices:
Sydney, Australia | Manama, Bahrain | Beijing, China | Chengdu, China | Guangzhou, China | Shanghai, China | Kowloon, Hong Kong Bangalore, India | Delhi, India Mumbai, India | Jakarta, Indonesia | Rome, Italy | Osaka, Japan | Kuala Lumpur, Malaysia | Melaka, Malaysia | Manila, Philippines Moscow, Russia | Singapore Midrand, South Africa Seoul, South Korea | Bangkok, Thailand | Barnsley, United Kingdom | South Yorkshire, United Kingdom Philadelphia, PA, USA | Hanoi, Vietnam

Enhanced Performance

In addition to our packed bed bioreactors, we have developed proprietary media to increase cell density and support serum-free growth of cells used in the areas of virology, virus production, and biopharmaceutical industry.

Plus MDCK and Plus Vero are serum-free and component-defined media formulated without human- or animal-derived components that support the growth of MDCK and Vero cell lines, respectively.

Super Plus is a cell culture supplement that can replace the expensive animal-derived serum by up to 90% without affecting cell growth performance. Most basal medium available in the market are compatible with Super Plus and supports the growth of many cell lines including MDCK, VERO, BHK, ST, PK-15, HEK-293, and CHO.

The use of serum-free media eliminates the risks of contamination, the culture variance due to inconsistent quality, and the complex downstream purification process associated with serum.

Serum is often dependent on meat supply since it relies on meat consumption as serum is from aborted calves. This results in fluctuations of serum pricing. Our Super+ reduces the amount of serum needed.

VacciXcell's Tide-Centric Turnkey Facility Design Process.

1. Meeting with client and introduction of the tide motion system

2. Client fills up VacciXcell's bioprocessing questionnaire

3. VacciXcell Support Team provides references and recommendation with regards to the client's requirements and process

4. Client performs the Mini-TideCell Experiment in order to check cell adherence on BioNOC™ II macrocarriers. (See Mini-TideCell Protocol from the VacciXcell website)

5.Once good cell adherence is established, VacciXcell Support Team provides protocol for the CelCradle™ System suited for the client's particular requirements.

6. Client can opt to send cell lines to VacciXcell CDMO, Aster Biopharma located in Singapore and USA (end 2016) for testing and optimization.

7. VacciXcell Support Team sets up the CelCradle™ System and conducts training for the client.

8. Client uses CelCradle™ System for Research and Development.

9. Client optimizes parameters and processes in laboratory scale.

10. VacciXcell Support Team provides the TideCell® protocol suited for the client's process and helps with client's final requirements.

11.VacciXcell's bioprocess engineers optimize and customize the TideCell® System, depending on the client's requirements as per the final URS.

12.Seed train is established based on final scale required.

13.Client chooses among single-use, multiple-use or hybrid TideCell® System.

14.Client decides if TideCell® needs to be placed inside an isolator.

15.TideCell® layouts are given to allow planning to cleanroom contractors (note the TideCell® Closed automated Cell Harvesting system requires special flooring anchorages).

16.VacciXcell can also in conjunction with our design and build sister division TaPestle Rx provide full layout and conceptual design of entire facility.

17.VacciXcell Engineer installs and validates TideCell® System on site.

18.VacciXcell Support Team conducts training for the client

19.Client uses CelCradle™ for seed preparation in the TideCell® 2L System

20.Client uses TideCell® 2L System and TideCell® Closed Automated Cell Harvesting System for seed preparation in the TideCell® System 20L System.

21.Client decides if seed cell isolator for Working Cell Bank and Master Cell Bank is required.

22.Client uses TideCell® 20L System and TideCell® Cell Harvesting System as seed preparation for the TideCell® 100L System

23.Client uses TideCell® 100L for production of bioproduct desired

24.Client enters downstream processing of bioproducts.

25.Downstream Skids can be provided by VacciXcell based on clients' desired columns.

26.Client decides on formulation and filling stage.

27.Client decides on final delivery format (vials, syringe, catridges, inhalation devices, oral BFS, plants, bait or others).

28.Client chooses between RTU pre-nested robotic filling (Asepticell) or traditional filling, in addition to freeze dryers.

29.If the final drug is to be terminally sterilized, an isolator over the formulation & filling line is not required and therefore a larger autoclave size will need to be selected.

30.Client decides if formulation & filling lines will be placed in an oRABs (Open restricted access barrier within a Grade B cleanroom), cRABs (closed restricted access barrier in a Grade C cleanroom) or within an isolator in a Grade D cleanroom).

31.Client chooses between single use and multiple use technologies for formulation & filling line components.

32.Should client choose multiple-use technology, client decides on glassware washers. VacciXcell can design custom glassware washer racks for parts washing prior to sterilization.

33.Autoclave size is decided for formulation & filling parts and clients choose between an isolator to load and unload aseptically into an autoclave. If an isolator is not selected, client decides on size of cuaf (ceiling uni-directional airflow) above the autoclave during loading / unloading.

34.VacciXcell Engineers design formulation & filling lines, according to client's specifications.

35.Autoclaved components will required to be aseptically assembled within the formulation & filling isolators.

36.Client decides between a Sterility Testing Isolator in ISO class 7(Grade D) background and Laminar Flow Cabinet in ISO Class 5 (Grade B) background. Esco Pharma provides both.

37.Client decides on pass-through systems and (ceiling uni-directional airflows) for other parts of facilities (Esco Pharma Cross-Contamination Facility Integrated Barriers)

38.Client decides on additional autoclaves for other facility components which need to be sterilized.

39.Client decides on SCADA connection. VacciXcell software engineers work with SCADA provider to run an entire SCADA network and CSV.

40.Vaccixcell install and validate chosen filling line equipment onsite.

41.Client provides VacciXcell with Dispensing / Sampling Booth requirements.

42.Client provides VacciXcell with Cold Room /Stability Testing Requirements

43.Client provides VacciXcell with secondary containment requirements (BSCs) and their Labs required for Chemical / Biological handling / QC, R&D Chemistry, Wet labs, Lab Furniture is optionally provided by TaPestle Rx.

44.VacciXcell provides design of Cold Room Storage and Walk-in Stability Testing.

45.Client approves of VacciXcell's Cold Room Storage and Walk-in Stability Testing.

46.Building and Installation of approved Cold Room Storage design

47.Equipment packages based on the above equipment URS are then provided VacciXcell designs & builds the equipment.

48.FAT is conducted in VacciXcell multiple factories, equipment is delivered and VacciXcell helps in IOQ and as option guides entire Bioprocess PQ.

TideCell Mixing System

TideCell Incubator & Control System	
Construction	Stainless steel 304 BA inner chamber and stainless steel 304 4b door and system
Electrical requirements	Monophase 3-wires AC 220V ± 10% V 15A max 50/60 Hz
Control Hardware (2-20L)	Flexible pc-base/DAQ industrial control interface; Solenoid valves/PID gauges/Pressure-vacuum motor NDIR CO_2 diffusion-type sensor
Control Hardware (50-100L)	Compact Rio PAC/DAQ industrial controller Solenoid valves/PID gauges/Pressure-vacuum motor NDIR CO_2 diffusion type sensor
Control Software	Development environment : NI labview; OS : Windows XP Preinstalled "Tide-Commander" graphic HMI
Incubator	0 – 20% CO_2 PID Control RT +3°C – 60°C temperature PID Control Front view window; LED inside lighting Emergency power-off button
Connection	CPC nickel-coated brass quick connectors Electric connectors with locking-screw
Communication	9-pin Dsub RS-485 port : Modbus RTU protocol 2 USB Ports for import firmware / software upgrade andexport trend data
Control Features	Simple user's administration Process page & Date viewer page Data logging / Parameters logging / Events logging Individual seed & cultivation conditions setting with default values Automatic switch from seeding stage to cultivation stage (up to 300 min) Gas flow rate : 0.8 – 20LPM depends on system size; PID control; Delay time: up to 99m 59s Individual up/down condition settings; automatic & manual operation Automatic air refreshing mechanism
Protection	Over pressure protection (max. 1 bar) Liquid leaking protection Over suction protection Over time protection

TideCell Mixing System

	Magnetic Stirrer Mixing System	Recirculation Thermostatic Mixing System	Stir-tank mixing system
Construction	Magnetic stirrer 10, 20L glass vessel with stir bar for mixing	Recirculation Mixing with magnetic driven bearing-less impeller	Stir mixing with pre-installed impeller
Electrical Requirements	Monophase 3-threads AC 220V ±10V 5A max 50/60 Hz	Single phase, AC 220V, 9A max , 50/60 Hz	Three phase, 230 VAC, 50/60 Hz
Capacity	10L and 20L	50L, 100L 200L, 500L. 1000L	30L, 50L, 100L 200L, 500L. 1000L
Control	100 – 1500 rpm stir rate RT – 45°C temperature control	Pumping rate 0 – 21 LPM RT – 50°C temperature control	80 – 1000 rpm stir rate RT – 60°C temperature control SIP system (sterilization in plce)

AutoFeeder Specification

Electrical requirements	AC 220V, 50/60 Hz
Control unit	Reliable industrial PLC; Industrial touch screen HMI Electronic balance: 0 – 1500 kg
Control parameters	Transferred volume: 10 – 900L/day Transferred cycle: 1 – 96 cycles/day Up to eight steps for each program : 40 sets memorized in data bank Time span for each step: 2 – 9,999 hr pH: 4 – 10 ± 0.1 DO: 0 – 100 % ± 2.0
Features	Dynamic Feed & harvest weight profiles : feeding & harvesting start/stop recorded Manual & Automatic process : auto-switching for feeding selection Overflow detection for harvest Error message recorded
Communication	Modbus ASCII
Protection	Maximum net weight stop protection : Harvest Minimum net weight stop protection : Feeding Invalid parameters prohibited

Feed Tanks AutoSwitch System

Electrical requirements	Magnetic stirrer 10, 20L glass vessel with stir bar for mixing
Control unit	Monophase 3-threads AC 220V ±10V 5A max 50/60 Hz
Features	Control two feed tanks by switching the feed line from one to another once the one is empty during feeding. Alarm light will on once the liquid in one of the tanks is depleted Alarm buzz will on once two are all empty
Sensors	In-line and non-invasive bubble detector x 2
Protection	Individual warning lights for indicating depletion of feed tanks

TideCell Cell Harvest System

Electrical requirements	220V, 50/60 Hz, 15A
Control unit	Reliable Industrial PLC
Liquid transfer	Six peristaltic pumps, transfer buffer, enzyme, enzyme inhibitor, culture medium, harvest cell solution and waste for cell harvest purpose
Control parameters	Sequential control on each pump On/Off Pump time 0-999 secs Pump rpm : 20 – 250 rpm Shaking speed : 50 – 300 rpm Rotation : continuous, ½ turn Manual and automatic control
Features	Equips with 6 peristaltic pumps for reagent input and output Compatible to 2L and 20L single use matrix vessels
Communication	CF card, RS485 data transfer
Protection	Door open protection Low speed alarm Abnormal alarm

VACCIXCELL

ADHERENT BIOPROCESSING SPECIALIST

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