Bioreactor Needs for the Developing world

Vaccine Self Sufficiency and Pandemic outbreaks

XL Lin: VacciXcell-Founder, President & CEO

World Vaccine Congress Washington DC 30 March 16

VACCIXCELL BIOPROCESSING SPECIALISTS
21 Changi South Street 1 • Singapore 486 777
Tel +65 6542 0833 • Fax +65 6542 6920
mail@vaccixcell.com • www.vaccixcell.com

Table of Contents

VACCIXCELL BIOPROCESSING SPECIALISTS

ESCO History

- Founded in 1978
- Pioneer in cleanroom equipment in Asean built the first cleanroom for siemens components in the then burgeoning semiconductor industry in 1980.
- Headquarters in Singapore
- Today:
  - Esco products are in more 100+ countries
  - 300 distributors
  - 20 global offices worldwide
  - 6 Factories (Singapore, USA, UK, Lithuania, China, Taiwan)

VACCICELL BIOPROCESSING SPECIALISTS

ESCO

WORLD CLASS. WORLDWIDE.

ESCO

Group of Companies

Business Units

Life Sciences Lab Equipment

Biosafety Cabinets
Laminar Flow Cabinets
Lab Fume Hoods
Ductless Fume Hoods
CO_2 Incubators
Ultra-low Temp Freezers
Laboratory Incubators
Laboratory Ovens
Lab Freeze Dryers
PCR Products
Lab Animal Workstations
Lab Refrigerators & Freezers

Medical

Time-Lapse Incubator
Benchtop Incubator
IVF Workstation
CO_2 Incubator
Anti-Vibration Table
Gas Analyser

Healthcare

Corporate Venture Arm

Ventures

ESCO VENTURES

VACCIXCELL BIOPROCESSING SPECIALISTS

ESCO® Healthcare

"Discovery to Delivery"

ESCO PHARMA PLATFORM SPECIALIST.

TaPestle R

VACCIXCELL ADHERENT BIOPROCESSING SPECIALIST

VacciXcell:

First Life sciences tools turnkey company dedicated to adherent cell culture US/DS/FF/Cold Chain from R&D to Commercial Production with in house architects, engineering and vertically integrated factories for Vaccine, Cell Therapy and Biosimilar industry.

VACCIXCELL BIOPROCESSING SPECIALISTS

Why the need for self sufficiency?

VACCIXCELL BIOPROCESSING SPECIALISTS

Why the need for self sufficiency?

SO WHAT HAPPENS WHEN SUBSIDIES FOR NEWER VACCINES RUN OUT?

In 2015, sixteen countries – just under one quarter of those currently eligible for GAVI support – are due to graduate. As graduation from GAVI approaches, countries are asked to pay incrementally more each year. The idea is to reduce the financial shock of withdrawn subsidies by gradually weaning countries off GAVI funding. However, whether gradual or not, the final withdrawal of GAVI funding will present many countries with considerable financial challenges – a bill they will find very hard to foot.

TRANSPORTING AND STORING VACCINES IS A CONSIDERABLE ADDITIONAL COST

Many vaccines have to be kept at very low temperatures to remain effective. This means that a 'cold chain' of refrigerators and cold boxes has to be set up and rigorously maintained – a very expensive operation. The cold chain requires considerable logistical resources to keep vaccines cool in places where power supplies are unreliable and daily temperatures can soar to 45°C, particularly in the remote and hard-to-reach areas where many communities live.

Ethiopia found out about the high attendant costs of cold chain when it introduced the pentavalent vaccine, which offers protection against five childhood diseases, into its national immunisation programme in 2007. In order to introduce this one vaccine, the country had to more than double its national capacity to refrigerate products.

WE NEED MORE AFFORDABLE VACCINES

Honduras Will Pay Almost 1,000% More For Just Two Vaccines After Losing GAVI Donor Support In 2015

In 2011
Honduras paid:
$1.43
For PCV and rotavirus vaccines

In 2015
Honduras will pay:
$15.50
For PCV and rotavirus vaccines

Almost 1,000% Increase

In 2015, sixteen countries will lose GAVI donor support because their Gross National Income (GNI) per capita exceeds the GAVI eligibility threshold (currently at $1,520)
GAVI Alliance Graduation Policy [Online]. 2011 [cited 22 March 2012]. Available: http://bit.ly/KI5qFq
PAHO Vaccine Price list: http://bit.ly/IX0QBV
PCV = Pneumococcal Conjugate Vaccine
Prices in US$

Although the average per capita income in Honduras was just $1,800 in 2009, the country will graduate from GAVI support in 2015. When that happens, the price per child for the two newest vaccines, against rotavirus and pneumococcal disease, will rise from the $1.43 Honduras pays today to $15.50. The country will be expected to come up with around $3 million each year to cover the cost of just these two vaccines.

- Costs of Vaccine will increase when countries graduate from Gavi

(MSF & Gavi DATA)

VACCIXCELL BIOPROCESSING SPECIALISTS

Why the need for self sufficiency?

- R&D on diseases which are endemic within the region for both human and animal (prevent zoonotic diseases) which might be considered orphan drugs and not of interest to private industry (Native virus harvested locally might not be safe to export out to CDMO) before outbreaks occur….

- Global Security…Mers from Middle East to South Korea
- Vaccination at source before pandemics occur.

VACCIXCELL BIOPROCESSING SPECIALISTS

Why the need for self sufficiency?

- Better control by using single use technology costs are variable and better planning of volume versus birth rate.

VACCIXCELL BIOPROCESSING SPECIALISTS

Why the need for self sufficiency?

- Allows tech transfer and Product Development Partnerships (Meningitis) with localized distributed manufacturing within different country (assuming same bioprocess method)

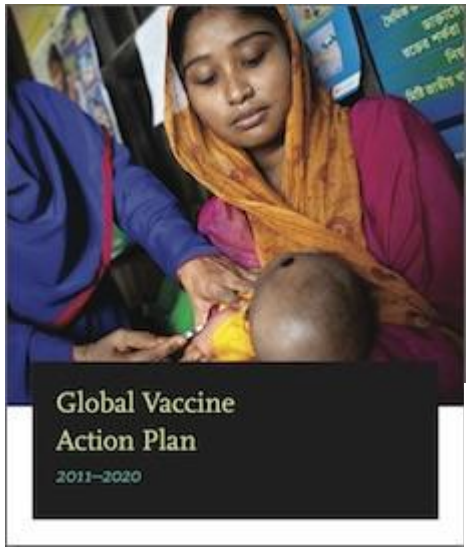
- Suggested new decade of vaccines 2020-2032 is shift towards increased self reliance in addition to financial sponsorship (PPP)

DECADE of VACCINES COLLABORATION

- Bottom up approach versus top down (countries take ownership) as vaccines are national security.

VACCIXCELL BIOPROCESSING SPECIALISTS

Current Methods in the world rely on PPP and Financial Sponsorship



Gavi
The Vaccine Alliance

unicef
70 YEARS FOR EVERY CHILD

PATH

BILL & MELINDA GATES foundation

- However building organic Capabilities is aligned with other NGOs.
- VacciXcell is a 1 stop solution from Upstream to Downstream to Formulation & Filling and Cold Chain for the Vaccine Industry.

VACCIXCELL
BIOPROCESSING SPECIALISTS

Millennium Developmental Goals (2000-2015)

VACCIXCELL
BIOPROCESSING SPECIALISTS

Millennium Developmental Goals (2000-2015)

• UNICEF purchases vaccines, negotiates favourable prices and forecasts vaccine requirements to ensure sustainable supplies.

When delivering vaccines, UNICEF adds micronutrient supplements to offset malnutrition, another critical factor in child survival.

Considerable progress was made in routine immunization against measles worldwide, particularly in Africa, protecting millions of children against this often fatal disease.

In 2008,coverage reached 81 per cent in the developing regions, up from 70 per cent in 2000.

However, projections show that without sustained funding for immunization activities in priority countries, mortality from measles could rebound quickly, resulting in approximately 1.7 million measles related deaths between 2010 and 2013.

VACCIXCELL
BIOPROCESSING SPECIALISTS

Gavi 2000 (now phase 4 2016-2020)

GAVI ALLIANCE

Saving children's lives
and protecting people's health
by increasing access to immunisation
in poor countries

Developing the plan brought together more than 1100 individuals in 140 countries, representing 290 distinct organizations

Gavi funds immunisation programmes in developing countries where the vast majority of the world's unvaccinated children live.

We also support the strengthening of health systems to help ensure vaccines reach people everywhere.

As of December 2014, a total of over US$ 9.6 billion has been committed for programmes in countries between 2001 and 2020.

VACCIXCELL BIOPROCESSING SPECIALISTS

Gavi 2000 (now phase 4 2016-2020)

1- THE VACCINE GOAL

Accelerate equitable uptake and coverage of vaccines

- Support countries to introduce and scale up new vaccines

4- THE MARKET SHAPING GOAL

Shape markets for vaccines and other immunisation products

Gavi will also work to ensure that governments have access to appropriate vaccine prices after Gavi support ends.

Objectives:

- Ensure adequate and secure supply of quality vaccines
- Reduce prices of vaccines and other immunisation products to an appropriate and sustainable level
- **Continue to build a healthy vaccine market, including by working to increase the number of suppliers**
- **Incentivise development of suitable and quality vaccines and other immunisation products**

VACCIXCELL BIOPROCESSING SPECIALISTS

WHO Vaccine Action Plan 2020

New opportunities and challenges for the Decade of Vaccines (2011–2020)

- Good-quality assurance relies crucially on effective standardization, which ensures that each vaccine product can be manufactured consistently and also enables multiple manufacturers to make similar products of the same quality.

- Research is needed to accelerate development, licensing and uptake of vaccines that are currently in early development, including development of technologies for more efficacious and less expensive manufacturing of vaccines.

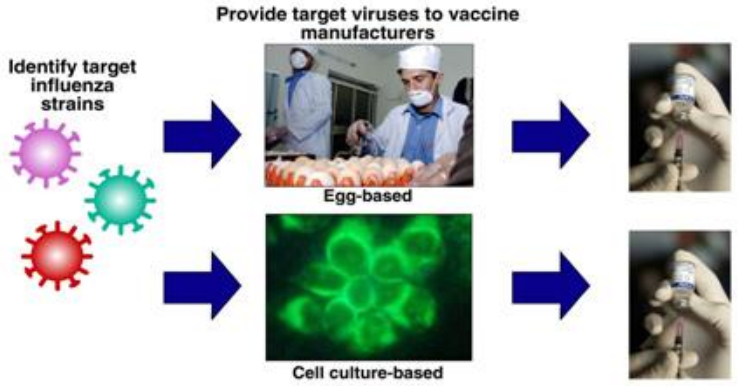
Secure quality supply.

- Develop tools to strengthen global standardization of manufacturing and regulatory processes.

VACCIXCELL BIOPROCESSING SPECIALISTS

Back to Basics-Vaccine Bioprocessing.

Vaccine Bioprocessing what can we do to reduce costs for the developing world.



- Design adherent cell lines to suspension
- Develop new platforms (VLPs)
- Conjugated vaccines
- Utilize more efficient linearly scalable bioprocessing.

VACCIXCELL BIOPROCESSING SPECIALISTS

Challenges in the Developing world

ÅEducation:Healthcare Workers Scientists.

Å10 Times North-South Scientific Gap R&D, Technicians.

ÅShortage of 2.5 Million healthcare workers

VACCIXCELL BIOPROCESSING SPECIALISTS

Challenges in the Developing world

ÅWFI

VACCIXCELL BIOPROCESSING SPECIALISTS

Challenges in the Developing world

ÅEducation

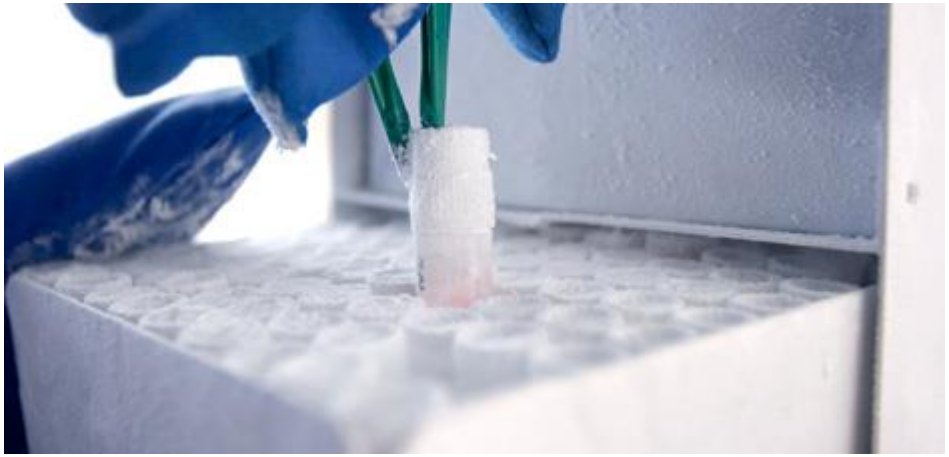
Itri BioMedical Technology Taiwan, 1999

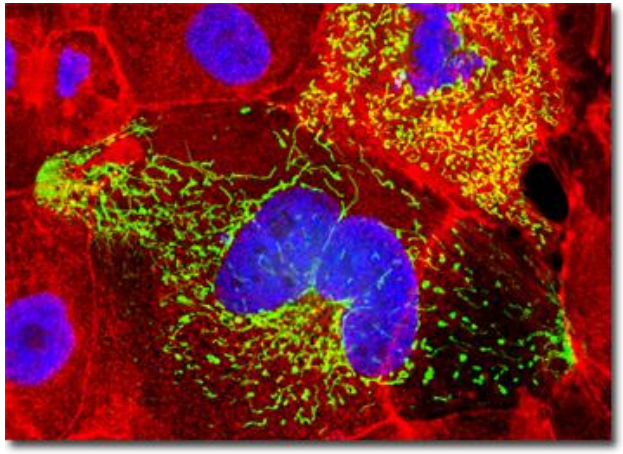
Biopolis Singapore, 2005
Itri BioMedical Technology Taiwan, 1999

VACCIXCELL BIOPROCESSING SPECIALISTS

Challenges in the Developing world

ÅCell Banking





VACCIXCELL BIOPROCESSING SPECIALISTS

Challenges in the Developing world

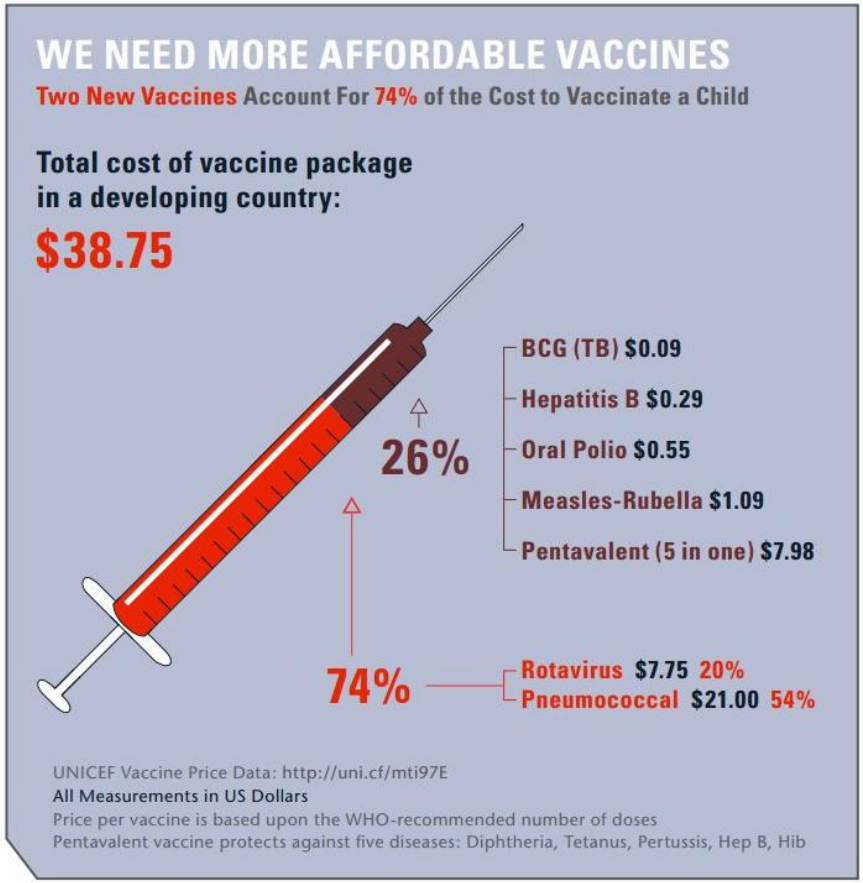
ÅStainless Steel Welding

ÅASME etc….

VACCIXCELL BIOPROCESSING SPECIALISTS

Challenges in the Developing world

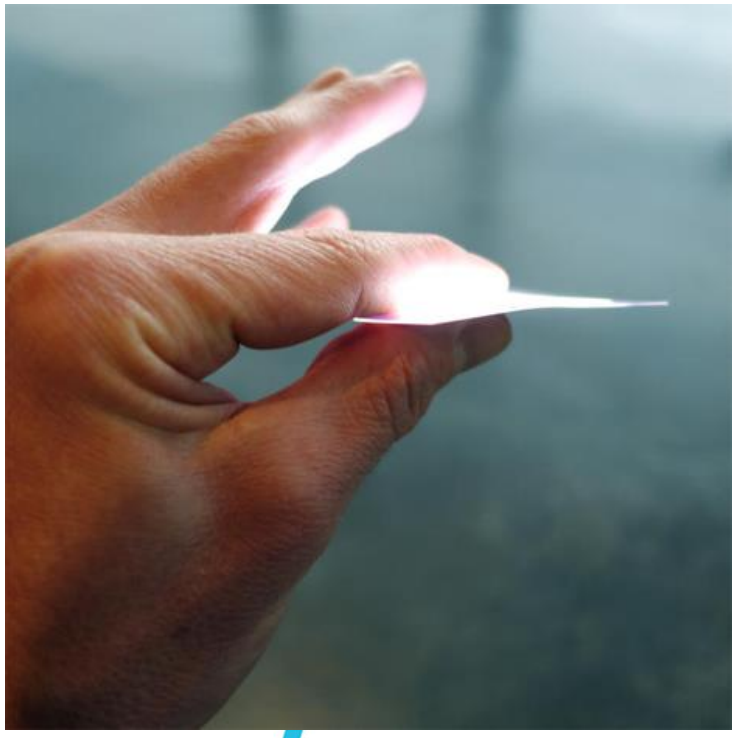
- Salary and ability to afford vaccines.
- Nearly half the world's population, 2.8 billion people, survive on less than $2 a day.
- About 20 percent of the world's population, 1.2 billion people, live on less than $1 a day.

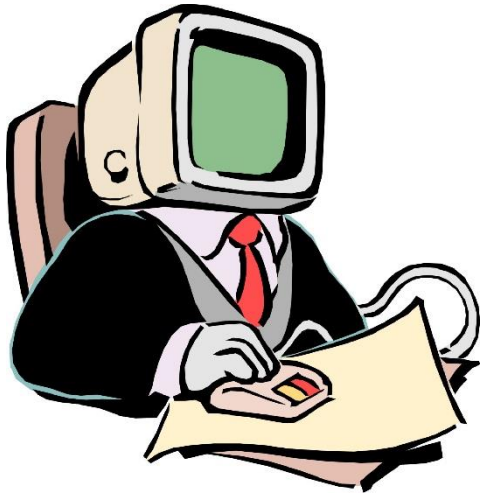


VACCIXCELL BIOPROCESSING SPECIALISTS

Challenges in the Developing world

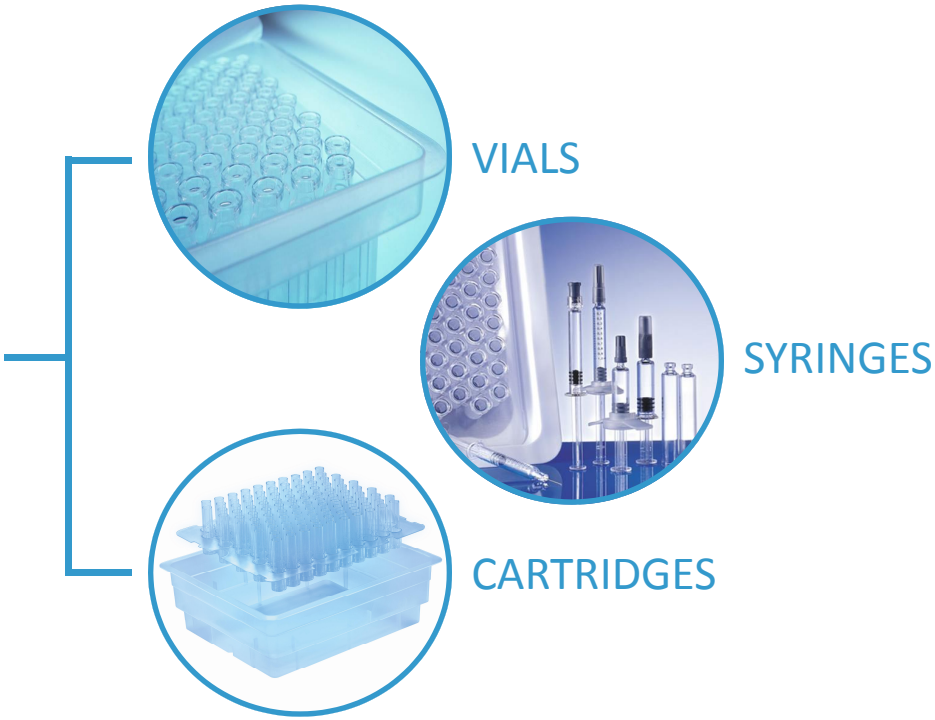
ÅCompliance to cGMP





VACCIXCELL BIOPROCESSING SPECIALISTS

ASEPTiCell™



ASEPTiCell™ is a fully integrated robotic, highly flexible manufacturing system designed to aseptically fill-finish sterile injectable products.

VACCIXCELL
BIOPROCESSING SPECIALISTS

Challenges in the Developing world

ÅCold Chain

VACCIXCELL BIOPROCESSING SPECIALISTS

Vxl Platform

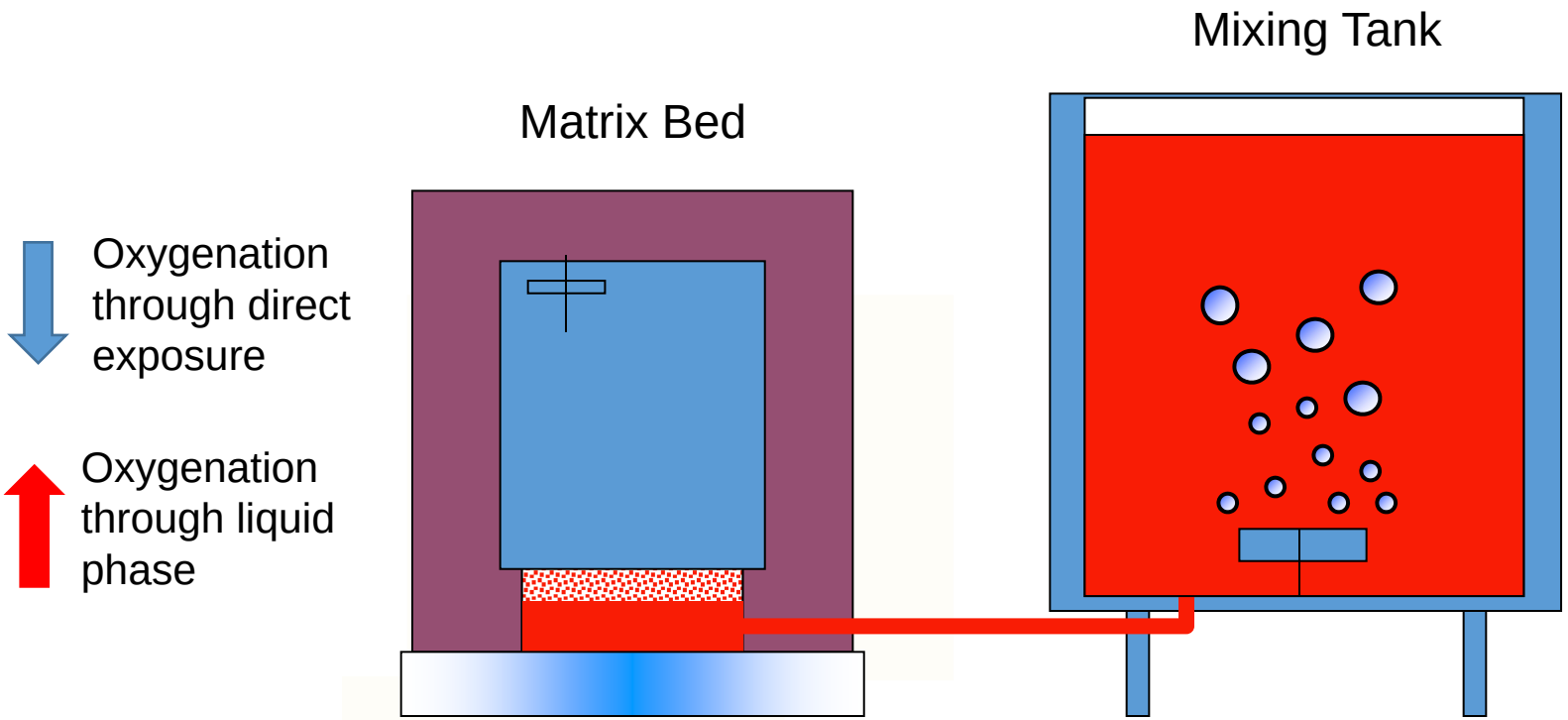
- Single use-Variable Costs
- Closed systems within Isolators means background CNC hence less running costs
- Robotic Aseptic Filling
- Localize production running on Tide Method means less bioprocess costs and faster to scale up as well as faster tech transfer.
- Tide Factories in strategic hubs within developing countries can quickly produce same vaccine if needed
- Easy to operate (basic scientific background)

VACCIXCELL BIOPROCESSING SPECIALISTS

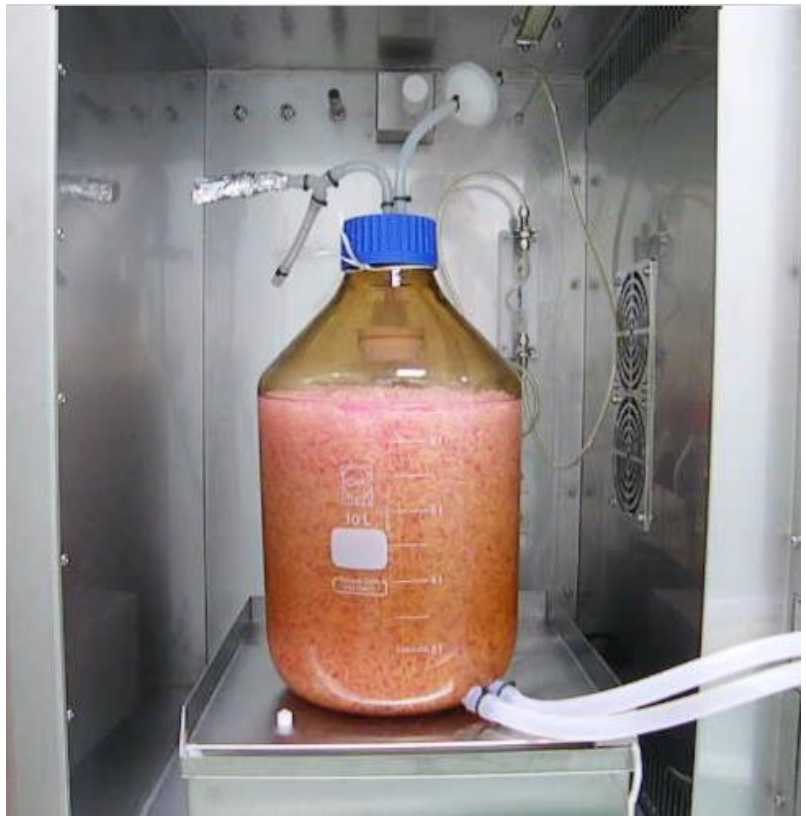
Tide Motion (Video)

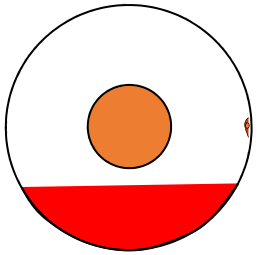
VACCIXCELL BIOPROCESSING SPECIALISTS

Dual Directional Aeration maximizes Oxygenation Effect.

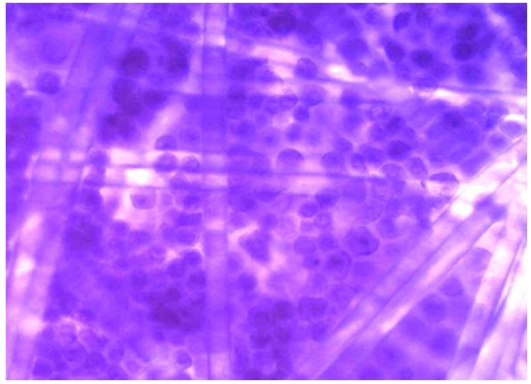


Roller Bottle-like Culture Mechanism





Submerge and emerge cycle ensures a sufficient supply of nutrient and oxygen



Cells are embedded inside matrixes without interferred by the Tide motion

VACCIXCELL BIOPROCESSING SPECIALISTS

TideCell Thermostatic Mixing System

Single-Use. Homogenizes solution within minutes; Warms solution within 1~4 hours at various scales.

Install/remove mixing bags from side

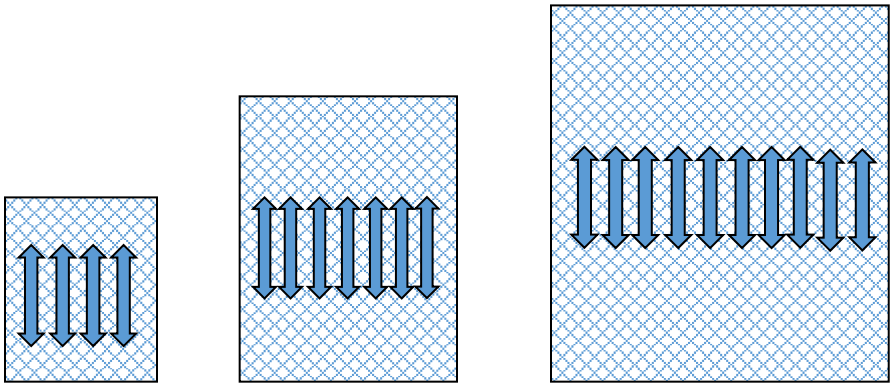
Single-use wearing-less, bearing free pump head.

Re-usable probe assembly

VACCIXCELL BIOPROCESSING SPECIALISTS

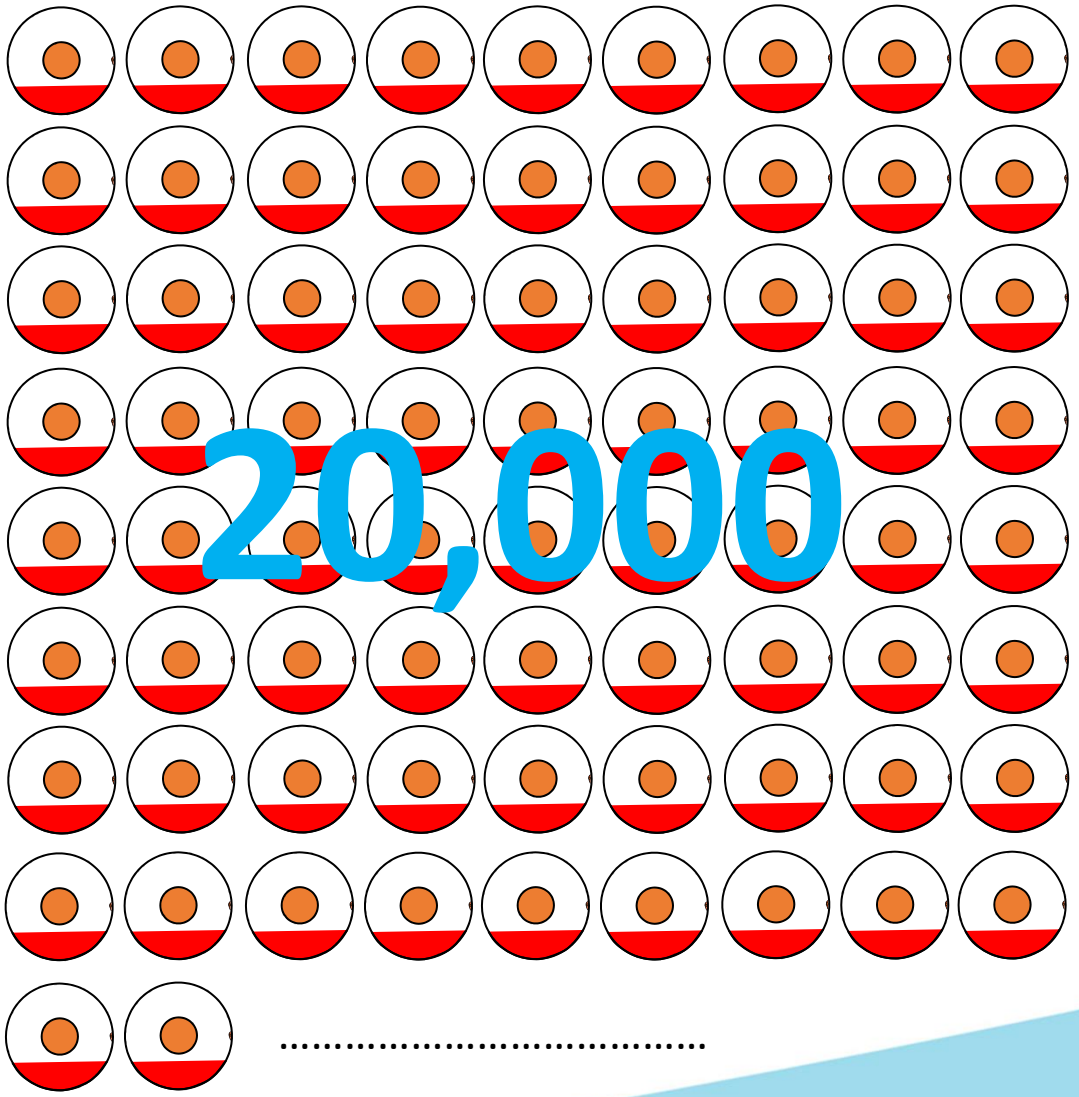
TideCell System

- The matrix surface area (area for oxygen transfer) linearly increases with volume
- Direct exposure of matrices to air. Oxygen can penetrate the Matrix Bed.
- Dual direction oxygenation capability maximize oxygenation capability
- Alternative Emerge and Submerge motion eliminates the channeling effect



VACCIXCELL BIOPROCESSING SPECIALISTS

20,000x Roller Bottles in One 100 L Matrix Vessel



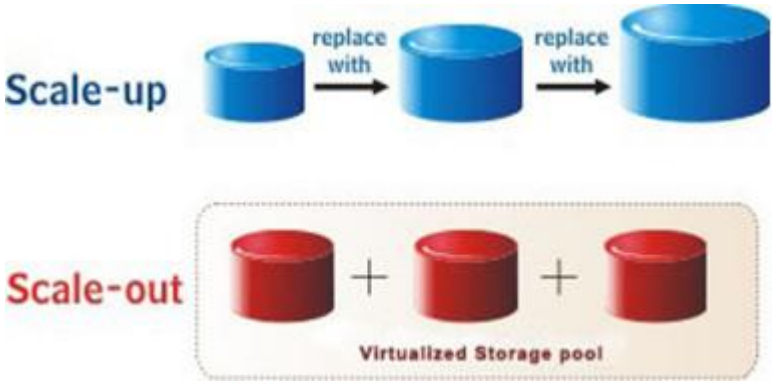
VACCIXCELL BIOPROCESSING SPECIALISTS

Linearly Scalable

VACCIXCELL BIOPROCESSING SPECIALISTS

Between Scale-up and Scale-out

- Scale up : increase the volume of single container
- Scale out: multiply the containers in smaller volume to reach the final larger volume



e.g. STR, packed-bed bioreactor, Wave bioreactor, TideCell bioreactor,… etc.

e.g. roller bottle, cell factory, cell stack, hyperstack, cell cube

VACCIXCELL BIOPROCESSING SPECIALISTS

What does linear scale up mean

- All culture environment kept the same from small to large scale this includes:
  - Shear stress
  - pH
  - DO
  - Temperature
  - Nutrient

VACCIXCELL BIOPROCESSING SPECIALISTS

Is there real linear scale up bioreactors?

	Temp	pH	Aeration	Shear	Nutrient	Conclusion
STR	O	O	**O**	**X**	O	Non-linear 4/5
Packed-Bed	O	Δ, plug flow	**X**	**X**	Δ, plug flow	Non-linear 3/5
Wave	O	O	**X**	**X**	O	Non-linear 3/5
Fountain fixed-bed	O	Δ, plug flow	**X**	**O**	Δ, plug flow	Non-linear 4/5
TideCell	O	Δ, plug flow	**O**	**O**	Δ, plug flow	Linear 5/5

Major challenge for scaling up is the balance between oxygen transfer and shear force generated by impeller in most submerge type bioreactors, except TideCell.

Δ, plug flow means there are gradient distribution along the flow path which is not homogeneous.

STR and Wave is supposed to be homogeneous but only ideally especially Wave has lower agitation rate.

VACCICELL BIOPROCESSING SPECIALISTS

Aeration Capability in all bioreactors

- Aeration capability = S/V (S = surface area contact between oxygen and liquid; V = total volume of the liquid)

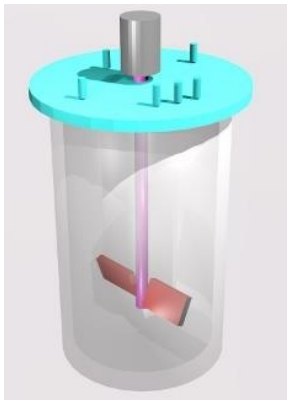
VACCIXCELL BIOPROCESSING SPECIALISTS

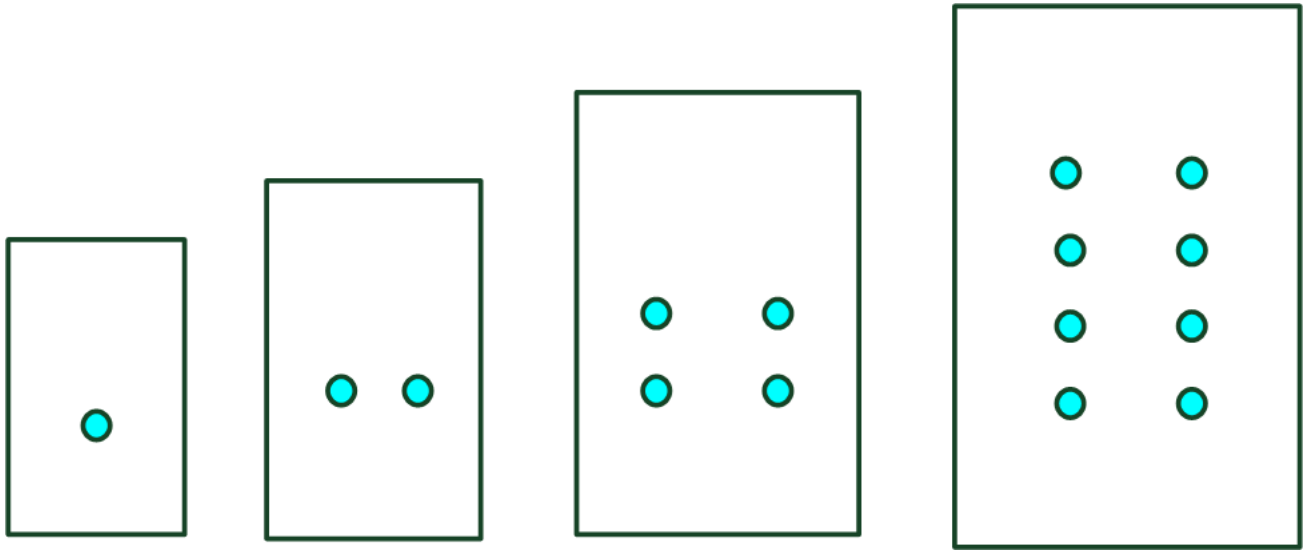
Linearity in Aeration Capability (S/V)

	Lab Scale	Bench Scale	Pilot scale	Production Scale	Conclusion
STR	Surface area for aeration/volume keep a constant				Could be Linear if conquer shear stress issue
Packed-Bed	Volume for aeration to the volume for cell growth (packed bed) keeps decreasing				Non-linear
Wave	Surface area for aeration increased 2D, volume for cell culture is increased 3D.				Non-linear
Fountain fixed-bed	Surface area for aeration increased 2D, volume for cell culture is increased 3D.				Non-linear
TideCell	Surface area for aeration / surface area for cell culture is kept constant				Linear

VACCIXCELL BIOPROCESSING SPECIALISTS

Stir Tank Reactor (STR)

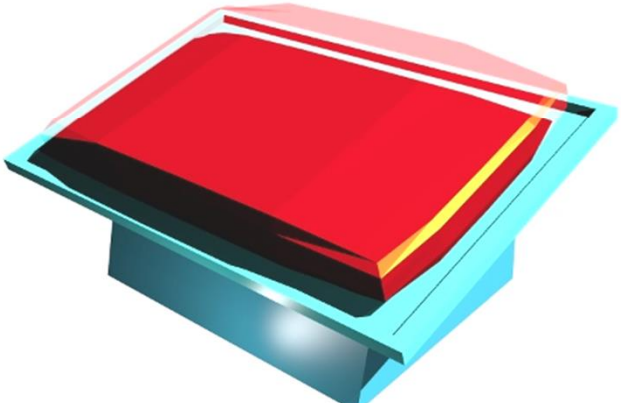


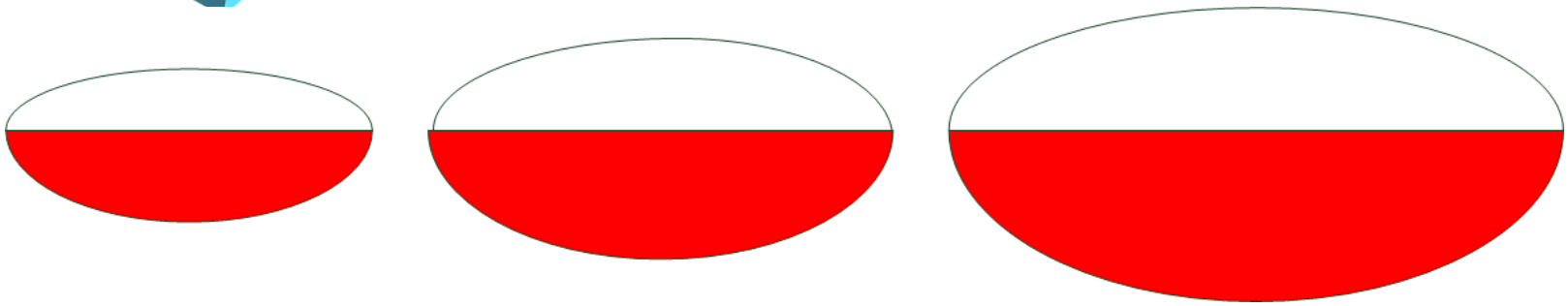


Aeration linearity can be achieved in STR by maintaining the same oxygen transfer coefficient (kLa).
However, shear stress might exceed the critical value and result in cell damage.

VACCIXCELL BIOPROCESSING SPECIALISTS

Wave Bioreactor

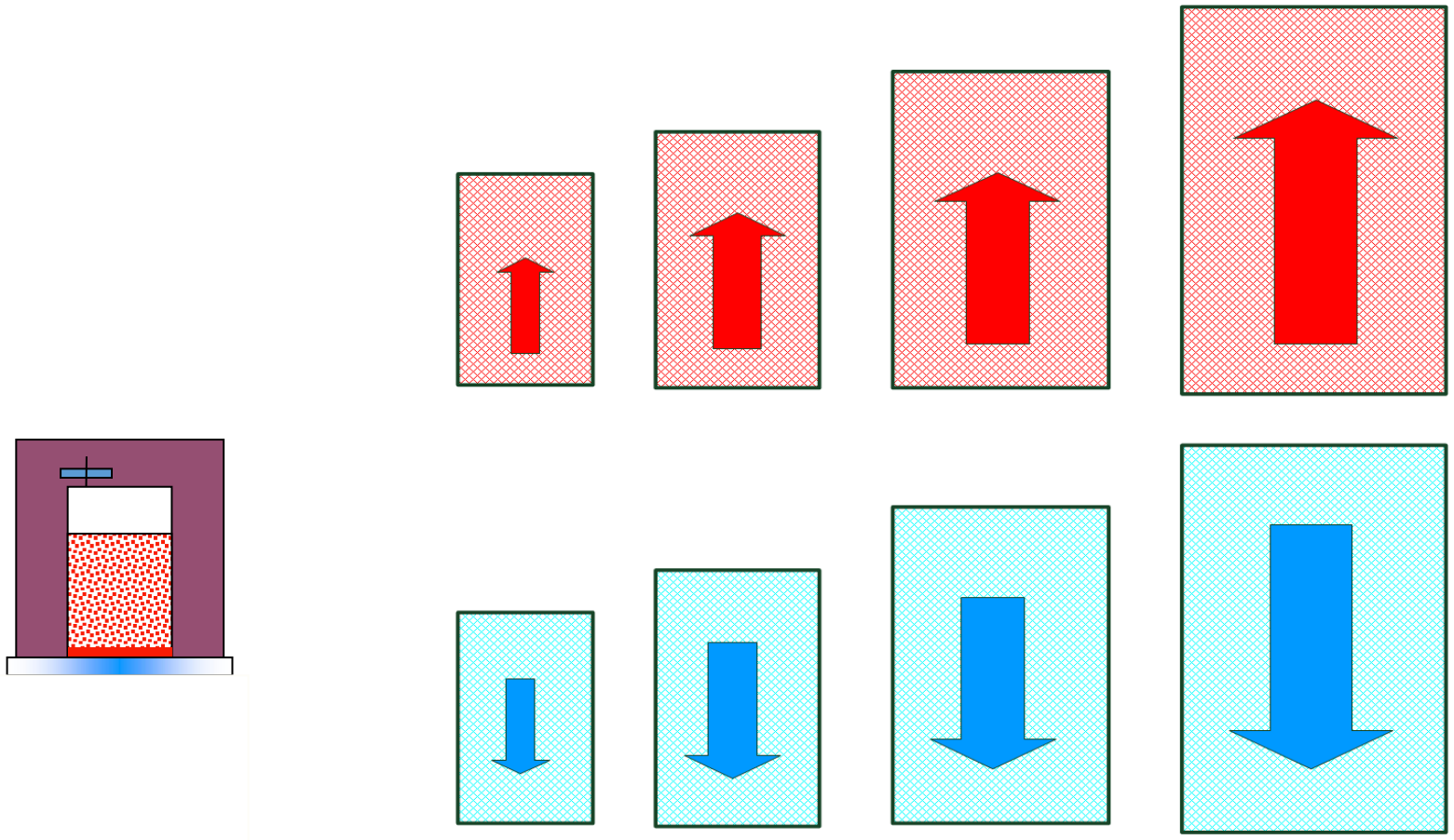




Aeration surface area depends on the top exposure surface which is 2D expand (ab -> AB) but the cell culture volume is 3D expand (abc -> ABC). Only the depth C keeps the same, or the areation to volume is not linear.

VACCICELL BIOPROCESSING SPECIALISTS

TideCell Bioreactor



Aeration surface area is linearly increased as cell culture volume increases.
All scales from 500ml to 5000 liters maintain the same S/V ratio.
Therefore, it is linear scale up in teams of aeration.

VACCICELL BIOPROCESSING SPECIALISTS

Is Tide method really Linearly scalable?

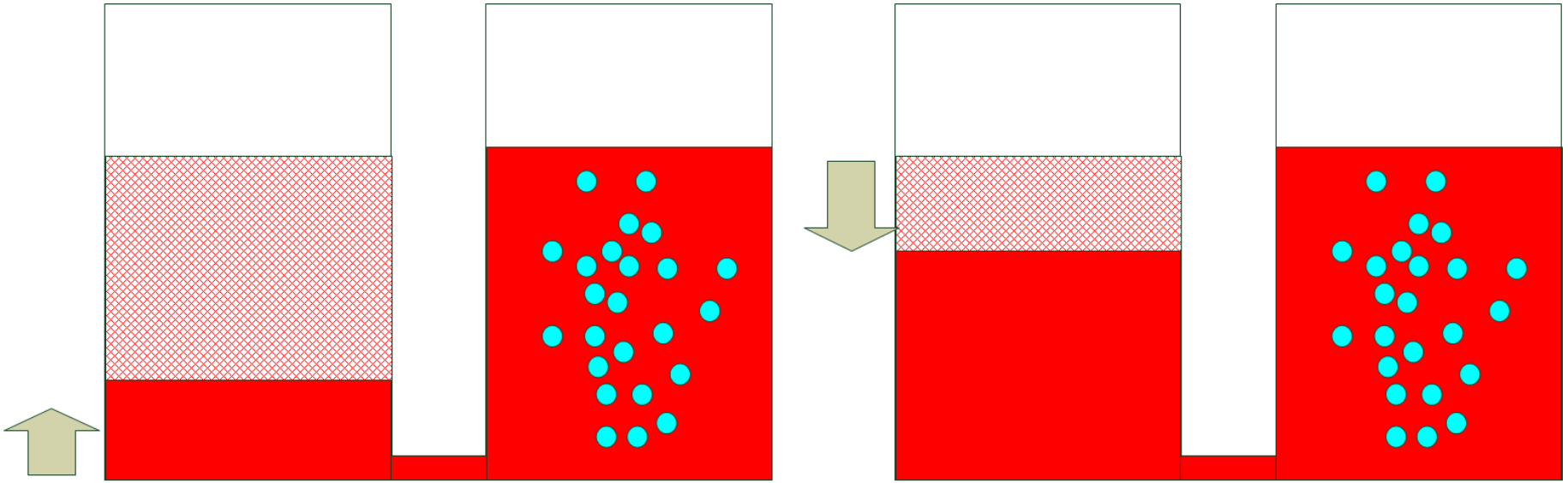
ÅNot quite…but close.

The heterogeneous distribution in packed-bed system of pH, Nutrient, Oxygen along the flow path may affect cell growth.

How was it solved in Tide Method?

VACCIXCELL BIOPROCESSING SPECIALISTS

How TideCell Solve the Aeration Issue?



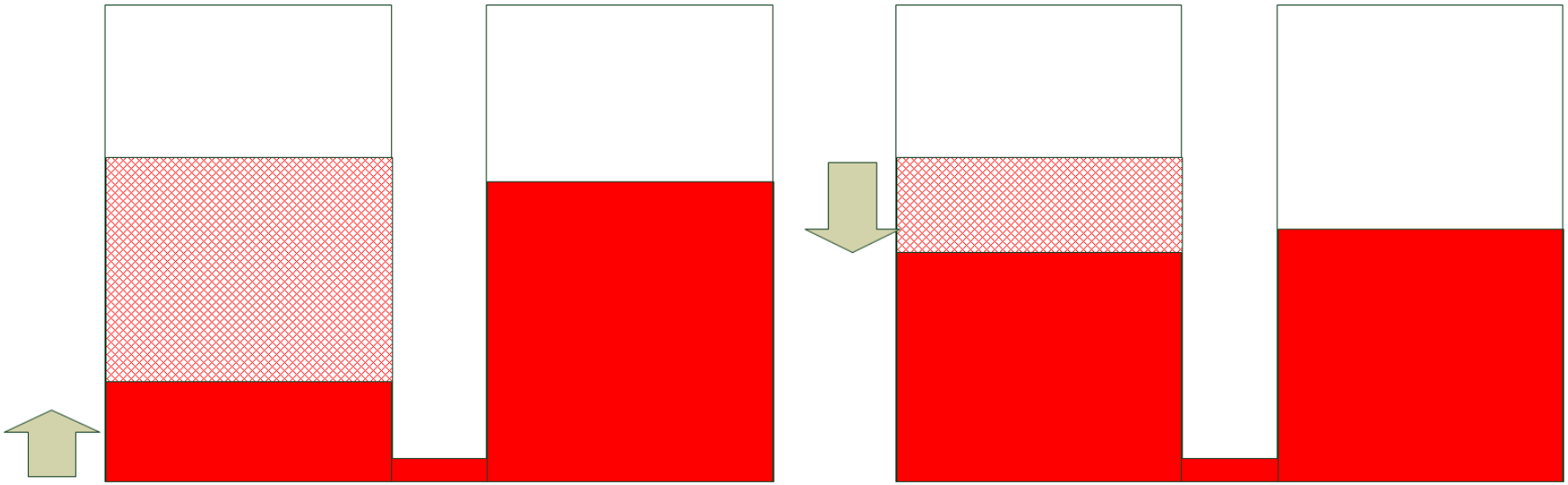
Oxygen-enriched culture medium flow up and submerge the culture matrixes same as other packed bed system.

Air directly enter the matrixes to quickly saturate the oxgen in the matrixes for cell growth.

Dual Direction Aeration provides sufficient oxygen for high density cell growth

VACCIXCELL BIOPROCESSING SPECIALISTS

How TideCell solves Nutrient linearity.



Well nutrient adjusted culture medium flow up and submerge the culture matrixes same as other packed bed system.

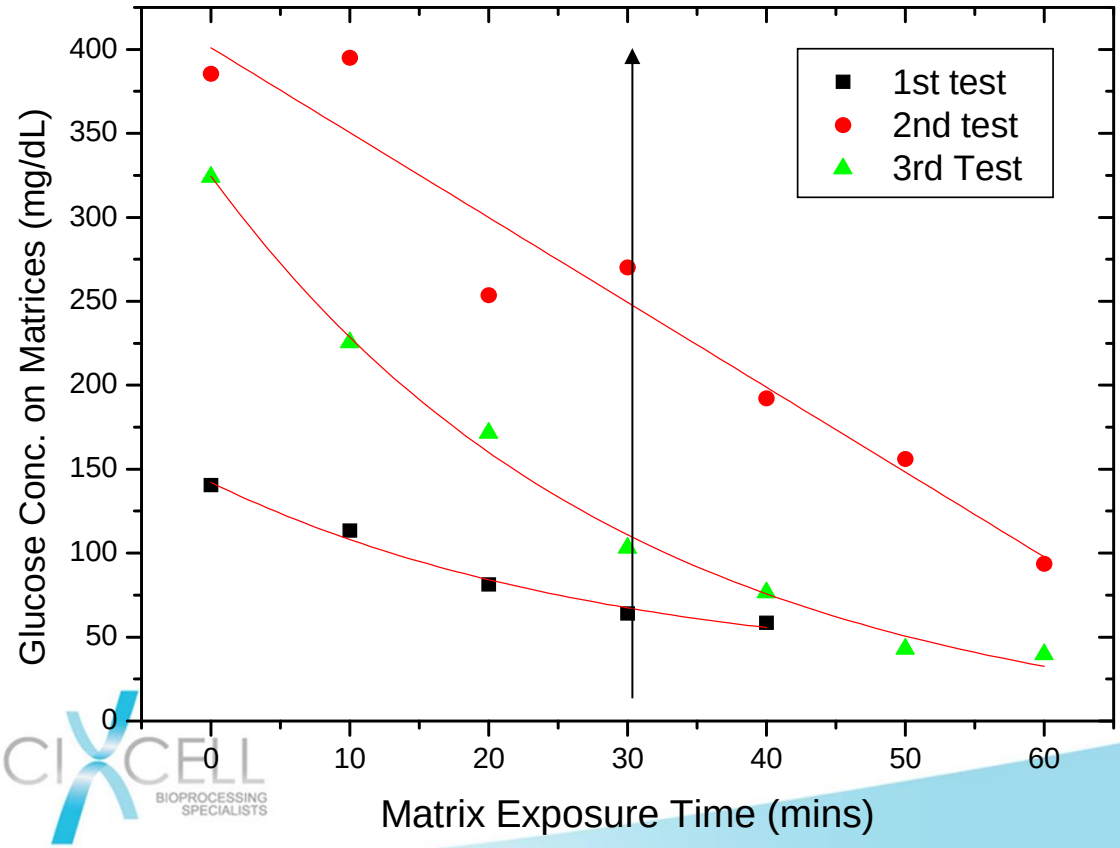
One-fifth culture medium remained on the matrixes to provide enough nutrient before the next cycle. A controlled cycle frequency ensure the nutrient is sufficient for cell growth in high cell density.

High medium absorption rate in the BioNOC II matrixes provide sufficient nutrient for high density cell growth during exposure. (one gram BioNOC II absorbs 4 gram culture medium)

VACCIXCELL BIOPROCESSING SPECIALISTS

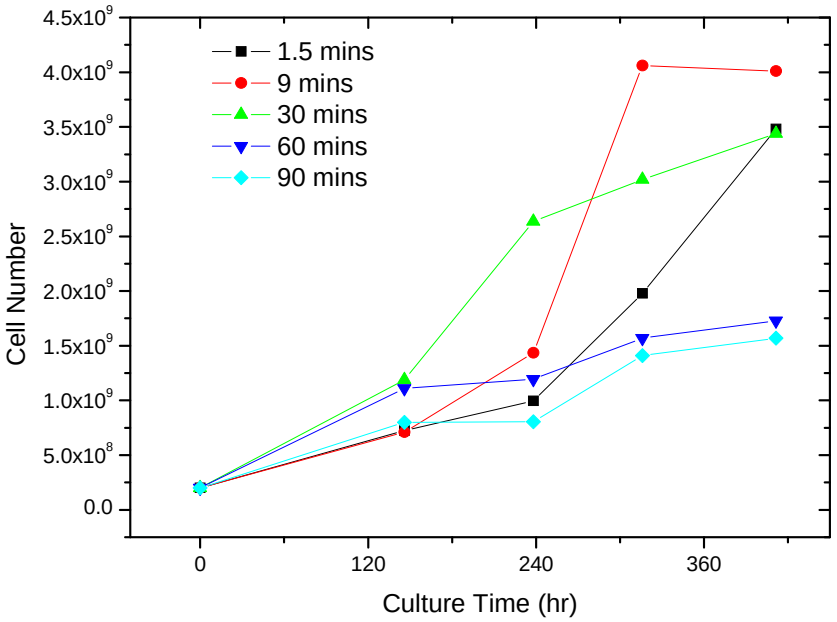
Glucose Profile in the Matrices with Differing Exposure Time

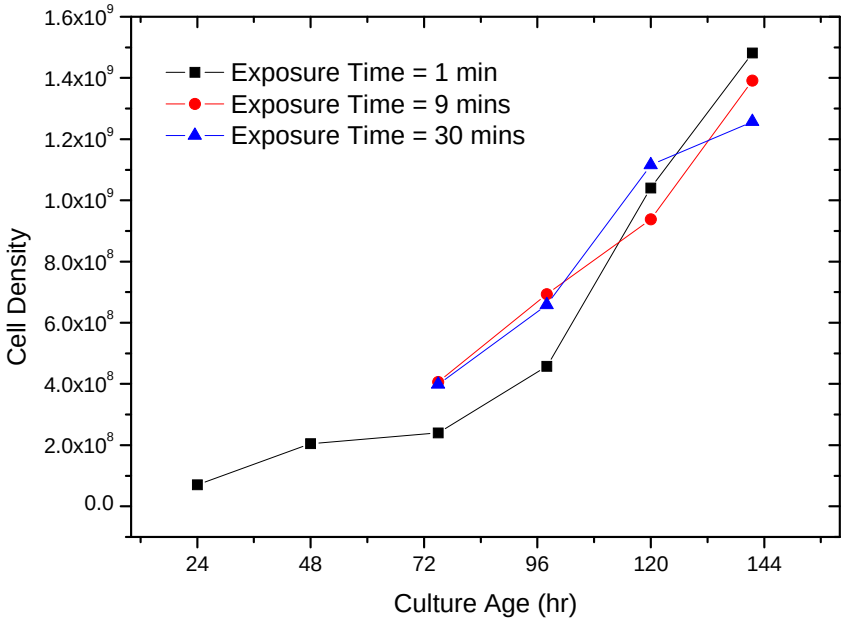
System: CelCradle-500, 5.5 g BioNOC II carriers
Cell line: CHO, Culture Medium: HQ-PF-CHO
Cell Density: 3.48×10^9 cells/bottle = 3.48×10^7 cells/ml matrix = 1.16×10^8 cells/ml
Initial glucose concentration = 400 mg/dL, 325 mg/dL, 150 mg/dL



VACCIXCELL BIOPROCESSING SPECIALISTS

Actual Cell Culture





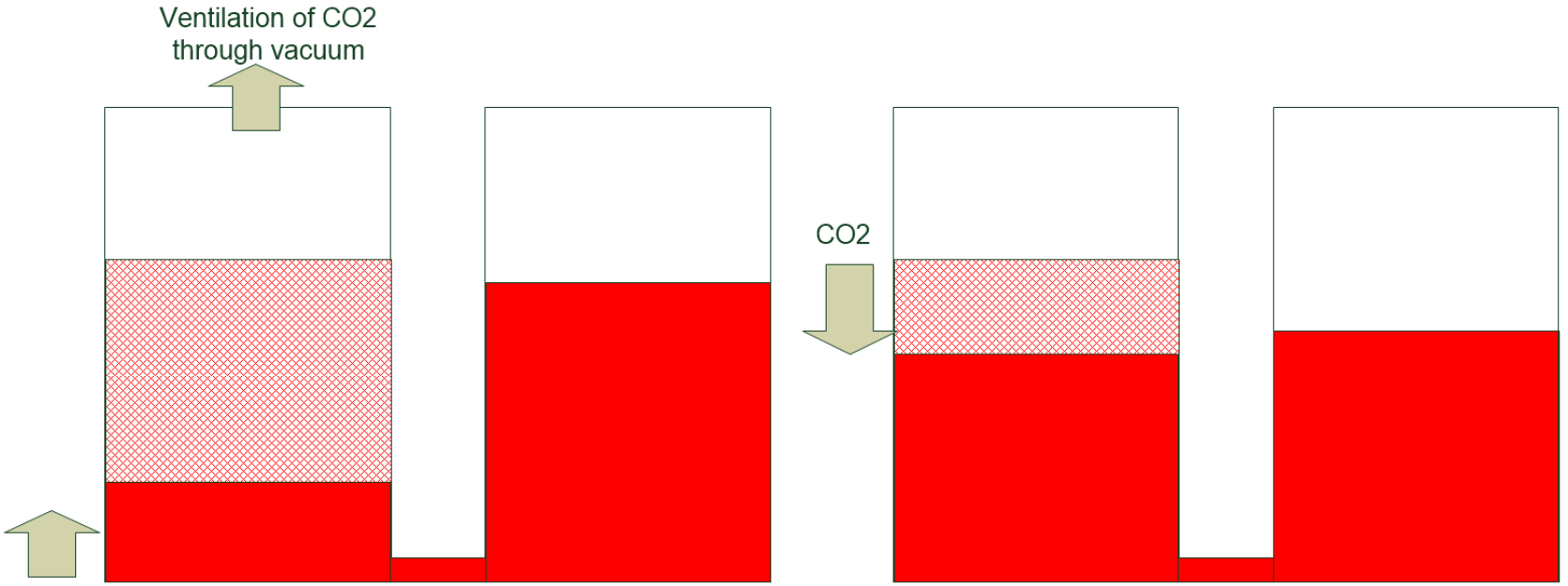
CHO, HQ-PF-CHO

VERO, M199/5%FBS

1~30 mins exposure time obtain similar cell growth profile

VACCIXCELL BIOPROCESSING SPECIALISTS

How TideCell solves pH issue



Well adjusted culture medium in controlled pH flow up and submerge the culture matrixes same as other packed bed system.

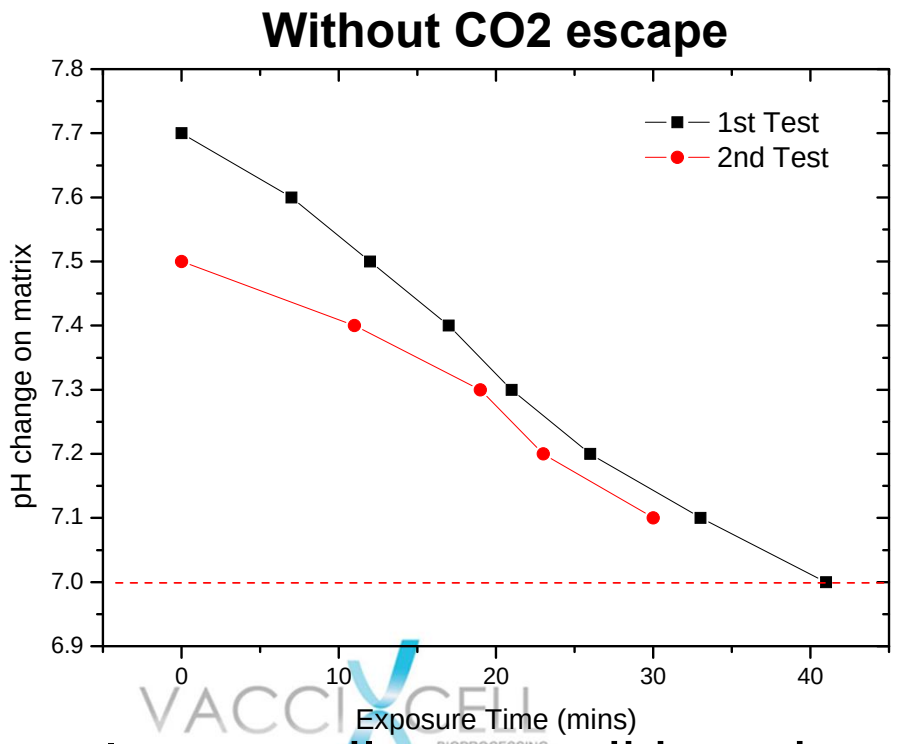
Air directly enter the matrixes with controlled CO2 to stabilize the pH in the matrixes for cell growth. CO2 concentration is adjusted automatically according to cell density.

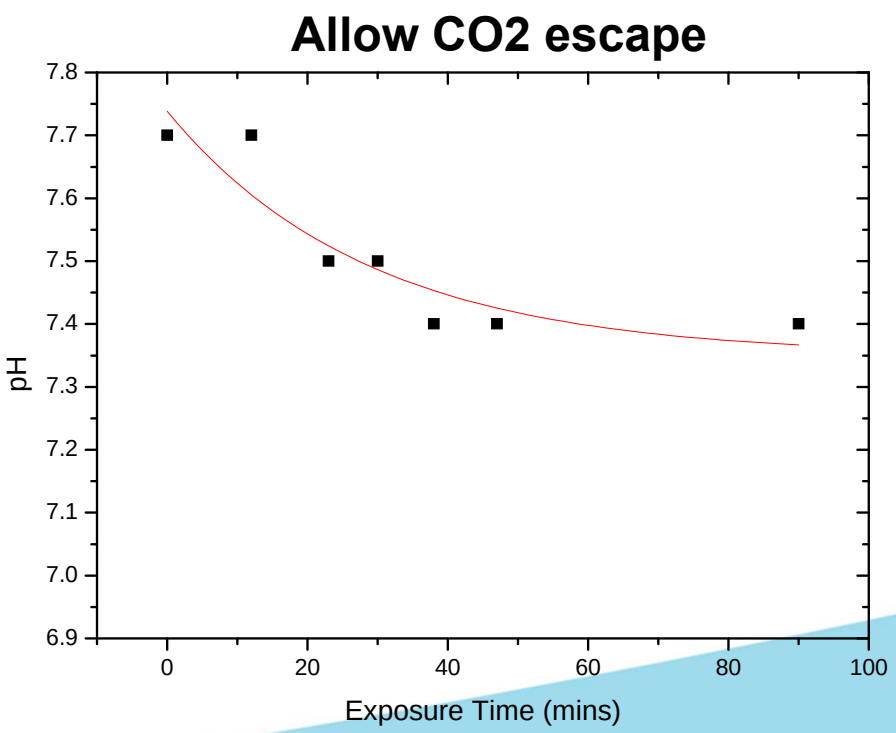
Dual Direction pH and CO2 control provide stabilized pH for high density cell growth.

VACCIXCELL BIOPROCESSING SPECIALISTS

pH Profile in the Matrices with Different Exposure Time

System: CelCradle-500, 6.5 g BioNOC II carriers
Cell line: CHO, Culture Medium: HQ-PF-CHO
Cell Density: 3.48×10^9 cells/bottle = 3.48×10^7 cells/ml matrix =1.16×10^8 cells/ml
Initial glucose concentration = 400 mg/dL





In a ventilate condition, the pH change could be controlled.

Tide Method Shortest Process Development Time

Process requirements	Length of process development
TideCell Bioreactor	**Medium (Number of bioprocess parameters and formulas to calculate =matrix to medium ration, tidal speed, culture medium, time for infection, temperature, pH, most of them will be fixed during small scale and don't need to modify again.)**
Roller Bottle	Shortest **(Number of bioprocess parameters and formulas to calculate = rpm, culture medium, time for infection, initial pH, directly expand the number of bottles, but the operation time among all bottles will affect the consistency in each bottle)**
Stirred Microcarrier Bioreactor	**Longest (Number of bioprocess parameters and formulas to calculate =rpm for seeding, rpm for cell culture, rpm for virus production, sparging rate, culture medium renewal, anti-foam, time for infection, temperature, pH, DO. rpm, sparging rate, nutrient consumption will be different for different scale.)**
Packed Bed Basket Bioreactor	Longer **(Number of bioprocess parameters and formulas to calculate =rpm during seeding, cell culture, virus production, sparging rate, time for infection, anti-foam, temperature, pH, nutrient renewal. Rpm, sparging rate will be different for different scale)**

VACCIXCELL BIOPROCESSING SPECIALISTS

Tide Method Shortest Bioprocess Development Time

Length of process development and linear scalability

Number of process variables to define & calculate when implementing TideCell:

1.) Matrix to Medium ratio: this is an unique factor that can be done in TideCell to optimize the output.

2.) Tidal Speed: usually not much interferences on cell growth with different Tidal speed. However, fast speed could reduce the cycle time of tide which theoretically could bring in more homogeneous culture condition during operation.

3.) Time of Infection: already determined during small scale T-flask study.

4.) Cycle Time of tide: within 30 minutes does not have any interferences on cell growth.

5.) Temperature for cell culture/virus production: fix already during small T-flask study

6.) pH: fix already during T-flask study

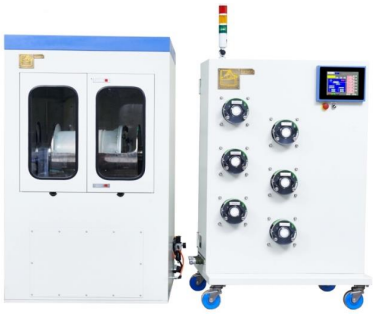
VACCIXCELL BIOPROCESSING SPECIALISTS

Length of process development and scalability

Number of process variables to define & calculate when implementing Microcarrier Stirred tank:

- Type of impeller and CFD
- Type of sparger
- Type of anti-foam
- CFD on shear forces
- Effect of adhesion
- Type of medium exchange
- Additional of baffles
- Type of propeller
- Type of gasket
- Shape / dimension of tank
- Etc……

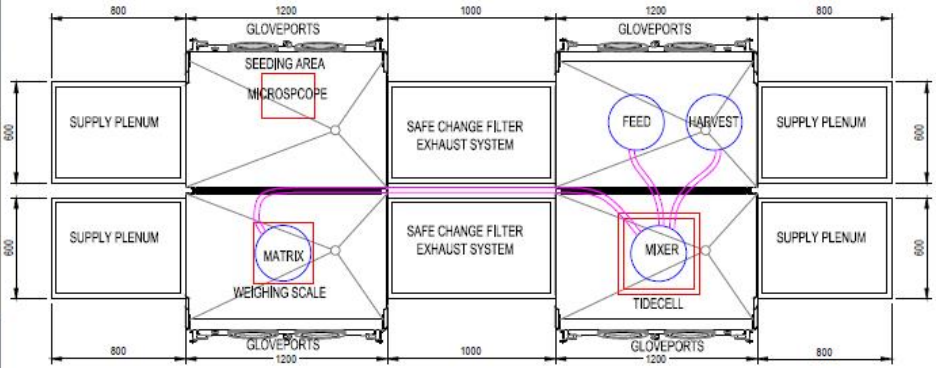
Linearly Scalable R&D to Seed Preparation to Commercial Production same bioprocess method hence scaling up has zero bioprocess time!



VACCIXCELL
BIOPROCESSING SPECIALISTS

Vaccine Facility BSL 3 and BSL 4 Isolator TideCell

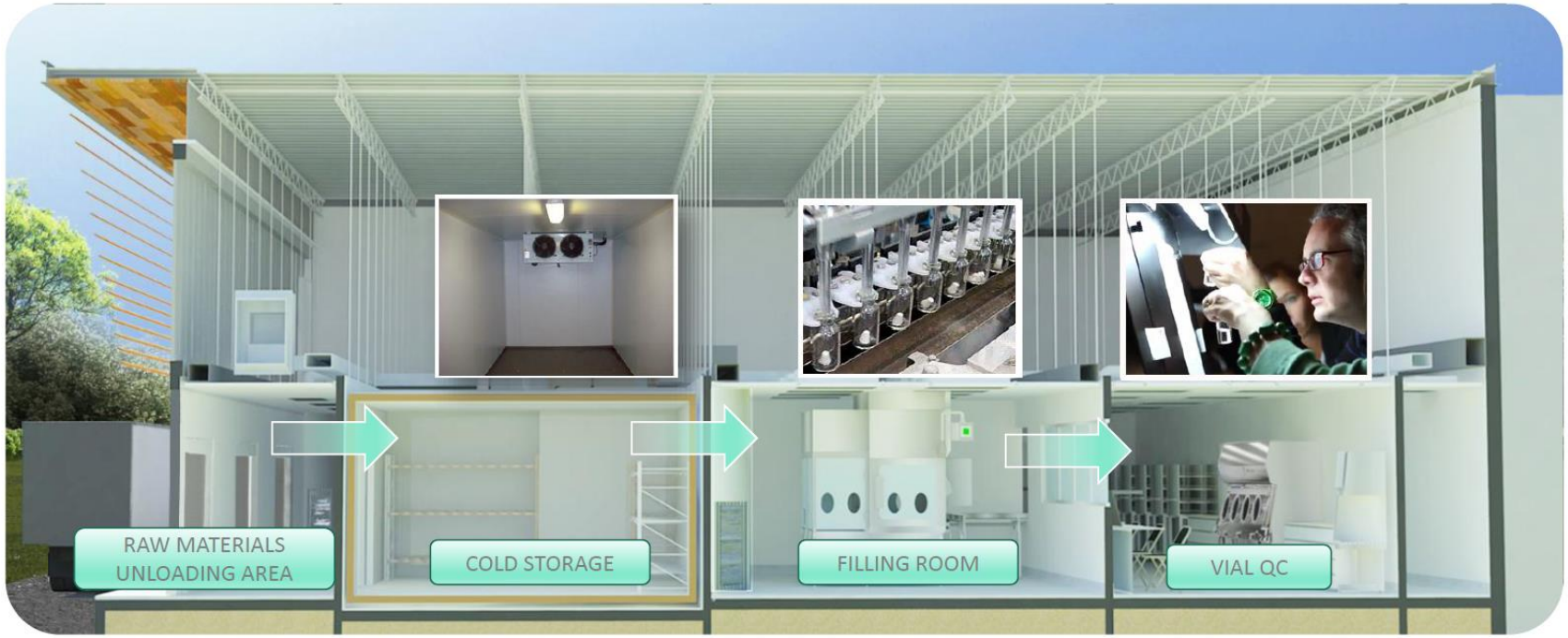
EQUIPMENT 3D VIEW



TIDECELL -2 4 LITER- ISOLATOR
TOP VIEW

VACCIXCELL BIOPROCESSING SPECIALISTS

Vaccine Facility Single Use



400 million doses $10 million to build and commission

- Own US/DS/FF Equipment, Technology, Media Transfer, Validation.
- Cold Chain
- QC
- Containerized Modules with own SCADA and Computer Systems

VACCIXCELL
BIOPROCESSING SPECIALISTS

Why

ESCO® Healthcare | "Discovery to Delivery"

Esco **Vision** is to provide enabling technologies for scientific discoveries to make human lives healthier and safer.

VACCIXCELL BIOPROCESSING SPECIALISTS

- 100% Singapore privately held Company with 2nd Generation in place.
- Proven track-record since 1978 internalizing high end technology, localizing production and making it accessible to Asia and developing nations.
- Brought cleanroom technology, biosafety and isolation technology making it accessible and affordable for developing countries.
- In 2010 we rose up to the challenge to develop technologies for a vaccine self sufficiency project, the developed technologies were spun off into VacciXcell in June 2015

Bioprocessing Challenges in the Developing world solved by Tidecell

Education level (number of trained scientists)	Simple Technology easy to learn with basic science. cGMP training and adherence.
Electrical Supply (unstable) and costs	Single use technology. Lower power consumption as less utilities need to be generated for SIP and Hvac.
Costs of entire system	Within Isolator costs are minimal since cleanroom is CNC, less cGMP issues can operate in shirt sleeve.
St.st. manufacturing locally insufficient skilled welders (not possible to ship large stirred tanks).	Single use technology that doesn't need st.st. vessels. If required for SIP mixer st.st. instead of single use, vessel is small and can be shipped.

VACCIXCELL BIOPROCESSING SPECIALISTS

Concluding Remarks

Selection	Choices for the Developing country
Suspension or Adherent	Adherent
SIP or Single Use	Single Use
Culture Method (2D, Wave, Packed Bed, Stirred Tank, Microcarrier, Fountain, Tide)	Tide Method Linearly Scalable from R&D to Commercial up to 5000 litres with zero bioprocessing scale up time.

- Developing organic capabilities for bioprocessing within developing countries for Gavi Graduates.
- This means R&D on Adherent Vaccines should first start on using our technology to reduce bioprocess scaling up and hence final Vaccine Costs since R&D expenses is 1 component that contributes to final costs of Vaccines.
- We are also looking for novel technologies to further reduce Downstream Processing Costs

VACCIXCELL BIOPROCESSING SPECIALISTS

Contact Details

XL Lin

VacciXcell-Founder, President & CEO

xl.lin@vaccixcell.com

VACCIXCELL BIOPROCESSING SPECIALISTS