



Innovative Cell culture and purification approaches applied to cost-effective manufacturing of viral vaccines

**DCVMN Training Workshop** 

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## Vaccines are the most efficient tools to prevent infectious diseases



Immunization currently averts an estimated 2 to 3 million deaths every year (of DTP and Measles).

An additional 1.5 million deaths could be avoided, however, if global vaccination coverage improves.

An estimated 19.4 million infants worldwide are still missing out on basic vaccines.

In addition :

Insufficient supply and late availability (i.e.) Prevnar in 2011, USA BCG in 2015, France Meningitis C in 2015, Africa DPTP in 2015, India

Crisis examples

Zika Virus spread Ebola epidemic Increased capacity of production and cheaper vaccines are urgently needed

The global vaccine market will reach 48Bn\$ in 2021, and 90% in the developed countries.

Emerging countries must become able to manufacture their own vaccines more efficiently





The majority of vaccine manufacturing techniques are still based on lab-scale principles "outscaled" to manufacturing scales

• T-Flasks



Roller Bottles







Calls Calls

• Eggs...



Life Science Talks – June 7th 2017









## Viral production can also be done in Bioreactors

Cells will only grow on a solid substrate : example of polymer beads coated with collagen





#### Virus production phase







## Vaccine Manufacturing Today... Limited Innovation



- > Over 80% of viral vaccines are still manufactured by the scaling out of labscale systems
- > Barrier: Very high CAPEX
- > Risk: High number of asceptic manual operations
- > Production capacity $\downarrow\downarrow\downarrow$ , cost  $\uparrow$

- > Some vaccines are manufactured in bioreactors – scaling up
- > Barrier: Extremely high CAPEX
- > Reduced risk: Limited asceptic manual operations
- > Production capacity↑↑, cost↑↑







## Problems with the current technologies... Barriers to entry

Current manufacturing methods require large factories and high CAPEX (>100M\$)
 Manufacturing are complex processes, which needs large, well-trained workforce
 Production is still based on \*Batches\* processes (separated steps of manufacturing)
 The production uses low-density manufacturing technology, leading to high COGS.
 Regulatory and quality-control processes are costly and complicated.

=> Those barriers are preventing small players and emerging countries to enter the market



#### **INNOVATION in MANUFACTURING**

Densification and Chaining of operations Disruptive innovation in the manufacturing technology could reduce the footprint of factories, simplify and automate the Process, which will simplify the QC and be run in a continuous fashion.





### Increase efficiency of cell culture : Single-use fixed-bed Bioreactor Example : the iCellis Bioreactor (Pall Lifescience)





- Increase of density thanks to a fixed bed (3D matric of unwoven polyethylene fibers)
- Allows low seeding density and biomass multiplication by up to 500x
- > Offers 500m<sup>2</sup> of surface in 65L Bioreactor
- Biomass immobilized no perfusion tool needed (perfusion tool by design)
- Cell density reach 40M cells/ml (to be compared with a 1M cells/ml Cytodex)





## Look at history of industrial chemistry – Apply chemical engineering rules that transformed chemical industry during 19th century

Chemical industry transformation







# This is achieved by bringing out technology innovations allowing a rapid deployment of low CAPEX/OPEX production facilities

How Univercells intends to break the barriers to biologics manufacturing







## OmniVax

Development of an Integrated Platform for the Low Cost Manufacture of Vaccines for Global Health

BILL& MELINDA GATES foundation



## New Interventions for Global Health: Vaccine Manufacturing



#### Vaccines

Vaccines, providing tremendous economic and societal value in averted costs, productivity gains and poverty reduction IPV, first target – platform to be universal for virus production



#### Access

Yet a number of factors interact to limit complete global immunization coverage. Among those is the **cost of procuring** and distributing vaccines in lower income countries



#### Innovation

Needed to develop manufacturing platforms that can transform production economics

## Challenge

Identifying viral vaccine manufacturing platforms that are capable of delivering vaccines at a final finished goods cost of <\$ 0.15 per dose. A significant (log) reduction in cost of goods (COGs)



## The Platform goals



## Target \$0.15 per dose vaccine drug product cost

- > Increased process productivity, yield and robustness
- > Reduced process-related operating costs (materials, labour, utilities etc)
- > Simplified, smaller facility with much reduced capital costs



Expansion of market supply - 40M doses / year with 'micro-facilities"

> High productivity ensures global supply from multiple small facilities



### Low hurdle for implementation

- > Low CAPEX
- > Suitable for new facility or retrofit of existing facility
- > Single-use templated platform reduces overall risk
- > High safety and containment



# Representatives of the chosen consortium (out of 155 candidates)



> Consortium integrator, coordinator and responsible party
> Integrated continuous manufacturing technologies
> High cell density bioreactor

## 😼 Natrix

- > High capacity / high flow purification membranes
- > High efficiency affinity ligands

> Viral vaccine process development & manufacturing> Cell line development



### Addressing the Challenge



Optimized cell line and production medium Target: >2-fold increase in virus productivity



High Cell Density Bioreactor (Target: >20-fold increase in cell density and virus productivity) and

**Natrix** Affinity Purification Membranes (Target: 2-fold increase in recovery, single step purification)



Integrated continuous process Linked process in modular isolators – small footprint, low cost (OPEX and CAPEX), high containment manufacturing environment

## 3 pillars

to establish an integrated manufacturing platform, applicable to multiple vaccines



to 150

per dose

# Path to sIPV at \$0.15/dose – 40M doses/year from a lab-scale micro-facility



#### **Driving down the cost**

- > sIPV process and facility ready for manufacture in 2 yr timeframe
- > Chained process with intensification technologies for fewer, smaller unit ops enables isolators to miniaturize the facility
- > Industrial production at lab scale with isolator-based micro-facility for
  - > Simplified infrastructure and dramatic decrease of CAPEX, the biggest factor driving reduction in cost/dose
  - Simplified operations for a robust platform that can be replicated and/or quickly deployed for in-region manufacturing
- > 40M vaccine doses per year from \$10M investment in the facility that delivers sIPV product at as low as \$0.15/dose



## Pillar 1: Optimized cell line & production medium

## Sub-clone of WHO 10-87 cell line



Increased virus production capabilities

Selected viral sensitizers and (lipid-based) viral yield enhancers



Increased virus yields

## Selected low serum or serum-free growth media



High cell densities and low cost



Conventional reactor + Microcarriers





- > Microcarriers replaced by microfibers
- > High cell density up to 100M cells/ml (20-fold increase compared to microcarriers)
- > Reduced CAPEX & OPEX, small footprint
- > sIPV in 500M<sup>2</sup> (65L) iCellis = 500,000 doses (equivalent to 750L STR)

#### **Univercells Bioreactor**



- > Simpler/lower cost reliable design
- > High cell density up to 200M cells/ml
- > "Integratable" into isolators
- > Reduced CAPEX & OPEX, small footprint
- > sIPV in 500M<sup>2</sup> (25L) = 500,000 doses



#### Univercells Bioreactor – structured fixed bed with multiple embodiments

> Structured bed:

- > Layers of ultrapure, cell-culture treated PET nonwoven
- > Layers of "spacers" for media flow and promote turbulence
- > Multiple options for implementation into a simple, cost effective bioreactor – one example: rotating bioreactor of 500m<sup>2</sup>











MEDIA FLOW



#### Univercells Bioreactor – structured fixed bed with multiple embodiments

- > Benefits of a structured bed:
  - > Homogeneity scale up virtually non limited
  - > Fast cells entrapment/attachment
  - > Easier to fabricate cost effective
  - > Compatible with "roller bottle" principle no costly mixing system is needed





Cell Entrapment Kinetics				
8.00E+08				
7.00E+08				
6.00E+08				
5.00E+08				
4.00E+08				
3.00E+08				
2.00E+08				
1.00E+08				
0.00E+00	Inoculation	Inoc +1h		

#### Univercells Bioreactor – structured fixed bed with multiple embodiments

## > Cell culture and virus production in UNC bioreactors:

- Use of parental cell line
- Target density at infection: 30-40M/ ml
- Reproducible growth in DMEM-Serum
- > 3x 2,5m<sup>2</sup> UNVC bioreactors are installed at BBS
  - Multiple runs show similar cell growth compared to the reference run performed at Univercells and iCellis bioreactor system
- > 25m<sup>2</sup> to be transferred in November





Univercells Bioreactor – structured fixed bed with multiple embodiments

- > Cell culture and virus production in UNC bioreactors:
  - Use of parental cell line first
- > Initial optimization leads to:
  - Doubling of D-antigen output per run
  - Concentrated DU/mL thanks to medium feeding

**Initial results** at small scale show significant volumetric productivity improvements

- > With current small scale yields and parental cell line, OmniVax process would yield:
  - @500m<sup>2</sup> / 37L FB and 2x250L medium in perfusion, ~650DU/mL in 250L
  - ~4.2M doses/run in crude harvest
  - ~9M doses expected with new Vero clone

Production system	D-Ag/mL of culture media	D-Ag/ cm²	D-Ag/cell at infection	D-Ag/mL of fixed- bed
Spin tube @ Batavia	89 ± 31 (n=49)	TBD	TBD	NA
UNC bioreactor (Standard process)	<b>118</b> ± 18 (n=2)	18.8	7.2 x10 <sup>-5</sup>	2664
UNC bioreactor (Optimized process)	646 (n=1)	32.3	1.7 x10 <sup>-4</sup>	4560





## Pillar 2 (2): High capacity purification membranes



- > Affinity membranes drive >3-fold productivity over traditional resins
- > Membranes introduced in 2013, accepted for GMP manufacturing

## Pillar 3: Platform enabled by innovative technologies Streamlined, simplified & miniaturized operations enable cost savings

The **intensification** technologies, **chained** into a continuous process, allow their integration into highly flexible, low footprint, isolated micro-facilities



#### Key take-aways

- > Low cost sIPV vaccine (as low as 15 cents per dose) seems achievable
- > Platform delivers commercial manufacturing at lab scale new paradigm in vaccine manufacturing

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> Platform applicability and flexible for broad range of vaccines

#### **Core innovations**

- > Chained process (continuous operations) enabled by right-sized tools, fewer steps to pure product
- > Unique bioreactors operating in perfusion mode enable optimized productivity in the smallest footprint
- Inline, single-pass high capacity HD-Membranes- mixed-mode for sIPV, affinity for other vaccines – enable single-step capture and purification of targets and maximum productivity



### Pillar 3: Platform enabled by innovative technologies Streamlined, simplified & miniaturized operations enable cost savings

Isolator & Bioreactor Device Development: full-scale mockup & schematics









## Pillar 3: Platform enabled by innovative technologies

Isolator Device Development: Full Scale Mockup



## Impact of the microfacility of the fully-loaded cost of manufacturing

#### Case study on the manufacturing of a trivalent Sabin Inactivated polio vaccine (sIPV)





Platform parameters (indicative) – based on Biosolve<sup>™</sup> simulations



**Building Footprint** (m<sup>2</sup>): <1000

**CAPEX**: ~€10M

**Doses/Batch** (doses): 2,000,000

Batch/year: 20

**Doses/year** : 40 Million Trivalent sIPV



FTE's (Management-Logistic-QA): 15

FTE's (Technicians-QC): 25

OmniVax vaccine manufacturing platform should deliver trivalent sIPV at a CoG of ~\$ 0.15 per dose



## Vaccine Manufacturing at Laboratory Scale



- > Facility design ongoing with engineering company
- > Challenge Biosolve estimations:
  - > ~ 1,000 m<sup>2</sup> flexible facility with 2 "Micro-facility" skids
  - > CAPEX < EUR 10M capable of ...
  - > ... delivering 40M doses trivalent IPV vaccine / year



## Summary of platform and concept

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concep

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> Highly intensified process allows miniaturization of commercial manufacturing

#### **Delivers Low COGs**

> Step change in manufacturing scale and yields significantly reduces COGs

#### Broadly applicable to viral vaccines

High Containment and safety

#### Rapid response to global threats

- > Factory operational in few months
- > Can be implemented in new or existing facilities
- > Plug & Play system: can be rapidly deployed in-country-for country manufacture



## **Consortium seeking interested Vaccine Manufacturers**



Consortium is **seeking experienced and committed vaccine manufacturers** interested to be recipient of vaccine manufacturing platform developed for sIPV > Consortium available to develop or transfer platform to manufacturer for other vaccines



Manufacturer receives **low cost vaccine manufacturing platform** for **sIPV** (non-exclusive), with option to leverage to **other viral vaccines** 



Manufacturer agrees with **Global Access** and to sell part of manufactured **sIPV vaccine** for fixed price to GAVI countries & agencies (eg: UNICEF)



BMGF will provide **financial support to** Manufacturers **for development and registration of IPV vaccine** 

## Vaccine Manufacturers



## Global Access Commitments for sIPV – What the manufacturer gets

Royalty-free license for uses that benefit developing countries

#### Fully functioning "micro-facility" equipped for sIPV,

- > Up and running in few months, with High Containment and safety
- Each 'microfacility' capable of producing 20M doses/year of trivalent sIPV vaccine (Equipment installed at manufacturer)

#### All documents required to manufacture sIPV using the platform

- Process and containment documents for sIPV
- Equipment documents
- Facility design documents



# Global Access Commitments for sIPV – Vaccine Manufacturer responsibilities

Agreed amount of yearly supply of sIPV vaccine to developing countries Support tech transfer activities

Perform clinical manufacturing and CMC package

Execute clinical trials and product registration

Dedicate part of manufacturing capacity to supply of vaccine to GAVI countries, UNICEF at fixed price



## Vaccine manufacturing platform



**Innovative vaccine manufacturing platform** capable of delivering affordable vaccines for global health

**First vaccine target** (sIPV) in 2-year timeframe including tech transfer to vaccine manufacturer

Technology Transfer planned to start in Q2 2018



## Vaccine manufacturing platform

What's

more

#### Platform provides an affordable path to capacity expansion:

- Industrial production at lab scale
- Plug & Play
- Factory up and running in few months
- High Containment and safety

#### Platform is very versatile and is a first step to:

- Other viral vaccines on adherent cells (Rabies, Rotavirus, MMR,...)
- Other vaccines, VLP based

#### A similar platform has been developed for recombinant proteins (CHO)

- Biosimilars such as Adalimumab, Rituximab, Bevacizumab,...
- > Orphan drugs, such as drugs to fight Pompe, Gaucher, Fabry diseases



Acknowledgements



*"Humanity's greatest advances are not in its discoveries, but in how those discoveries are applied to reduce inequity."* Bill Gates

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