UNIVERCELLS Technologies™
By Donaldson

Advancing Vaccine Production: Leveraging Intensification and Process Integration For Rapid Development and Scale-up

DCVMN

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The next evolution of biomanufacturing

A. Introduction to Univercells Technologies

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The next evolution of biomanufacturing

Univercells Technologies designs and delivers state-of-the-art high-performance, scalable bioproduction technologies for viral products

Univercells Technologies genesis

2013 — Univercells, Biologics for all

Make biologics **affordable and available to all!**

gamma biosciences

KKR

2020 — UNIVERCELLS Technologies

Design and deliver the next evolution of **biomanufacturing**

2023 — UNIVERCELLS Technologies™ By Donaldson

Now a **Donaldson Brand**

Donaldson FILTRATION SOLUTIONS

110+
collaborators

Global Supply & Presence

> Covering all time zones with presence in key regions

Headquarter based in **Belgium**

Services

> **Integrated Services** for Installation, Training & Maintenance
> Helpdesk support **<24h** (b. days)
> On-site support **<72h** or less
> Rated **9.1/10** from 90 responses

B. Vaccine manufacturing challenges

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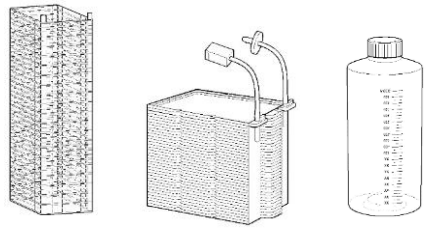
The next evolution of biomanufacturing

Conventional manufacturing technologies are inherently limited in their ability to support **large scale, cost-effective viral production**

Manufacturing scale-up challenges

Scale-out



Cell Factories and Roller Bottles

- (+) > Straightforward process development
- > High specific productivities
- (−) > **Highly manual process** to scale out
- > Risk of failure, **poor reproducibility**
- > Elevated **COGs & CAPEX**

Scale-up

Packed-bed bioreactors

Stirred-tank bioreactor with microcarriers or suspension cells

- (+) > High production capacity; economies of scale
- (−) > Large operating footprint leading to **high CAPEX**
- > **Process variability**
- > Challenges in **scaling up**

Scale-up with scale-X™ bioreactors

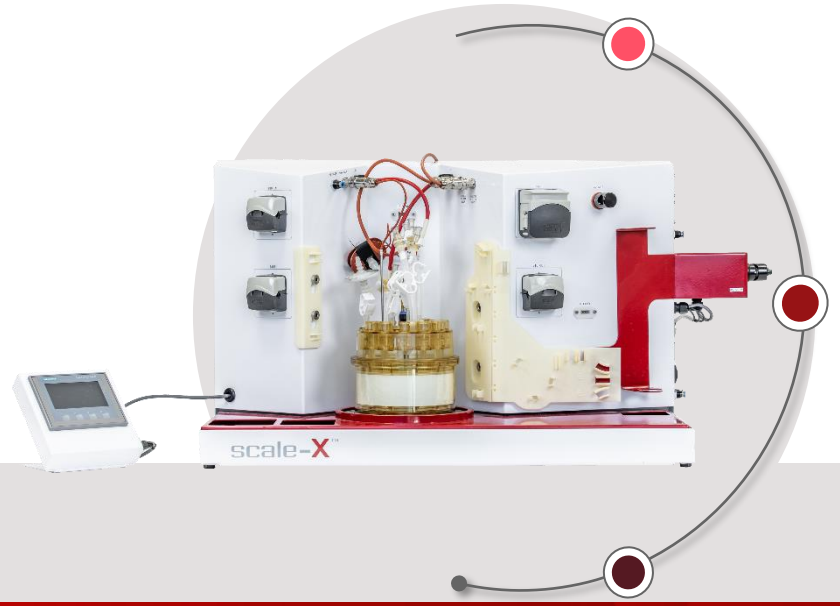
Faster, cost-effective manufacturing for a successful market entry

- Increased and consistent **cell-specific productivity**
- **True scalability** from POC to commercial production
- Enabling **continuous processing** while supporting **diverse applications and configurations**

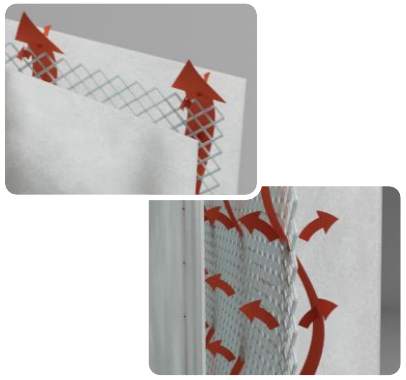
C. scale-X technology innovations addressing market challenges in biomanufacturing

The scale-X structured fixed-bed bioreactor enables **cell immobilization, streamlined workflows and linear scalability** for both adherent and suspension cells

scale-X technology innovation advantages

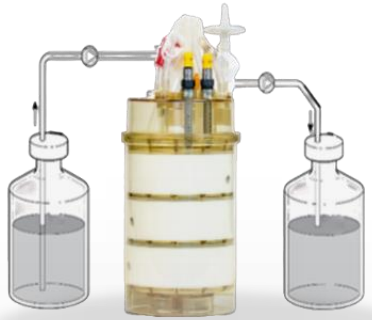


1 Cell immobilization



> **Homogenous** cell and nutrient distribution
> **Low shear** environment
> Intensified **Perfusion**

2 Redesigning workflows



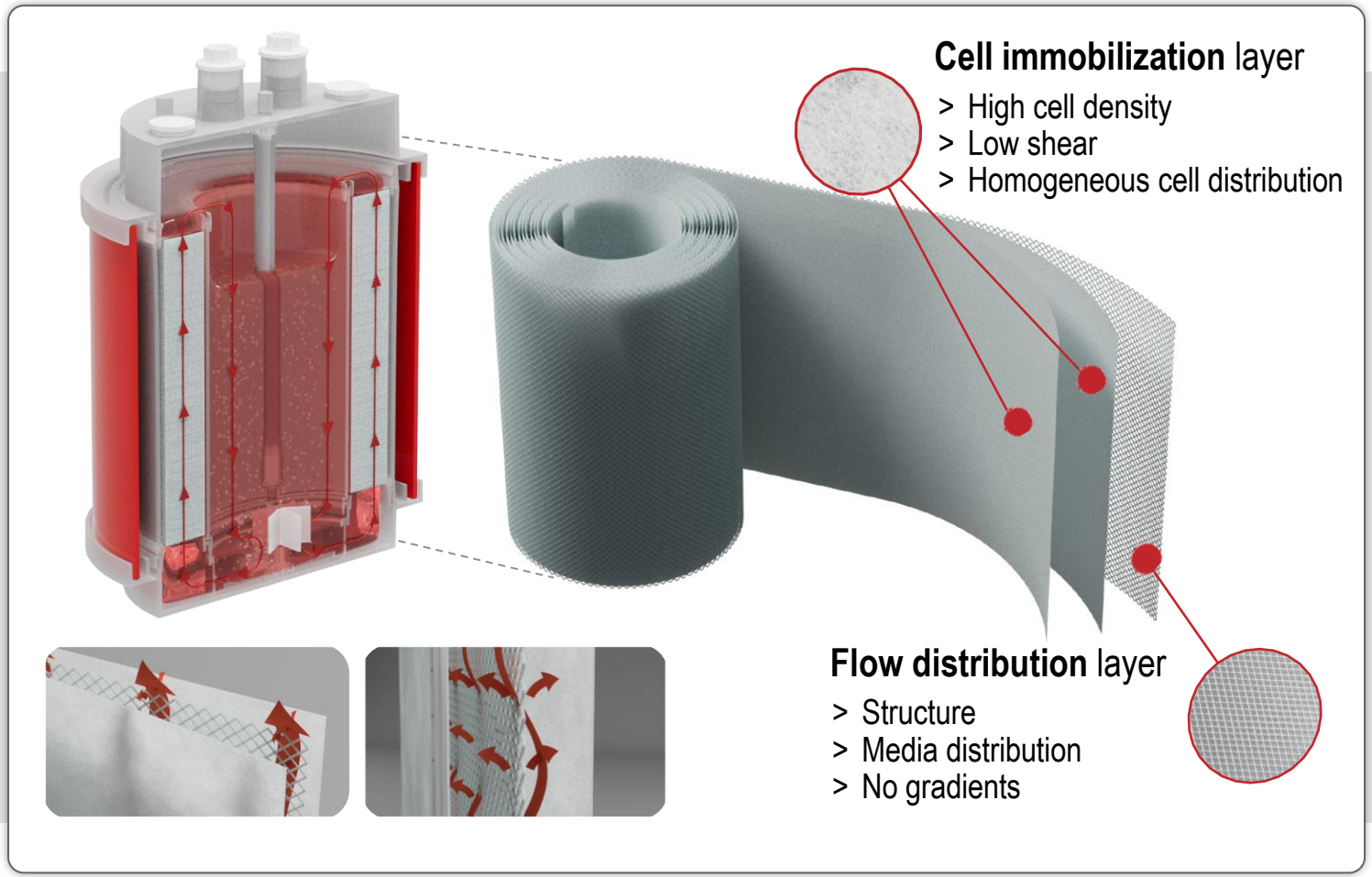
> **Low working volume** 10's of liters harvest
> Reduced **operational footprint**
> **Continuous Processing**

3 Linear Scalability

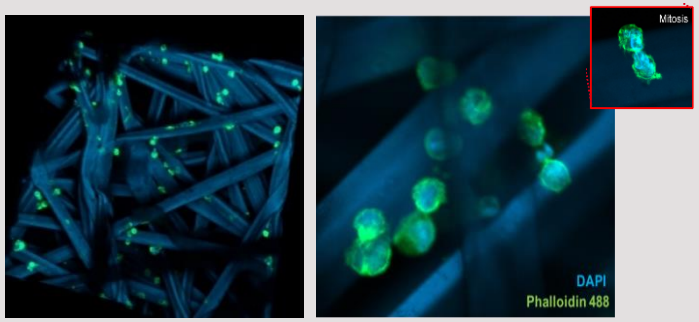
Retaining a geometric coherence for linear scale-up of key process parameters

Cell immobilization within the fixed-bed bioreactor unlocks homogenous cell & nutrients distribution and low shear environment

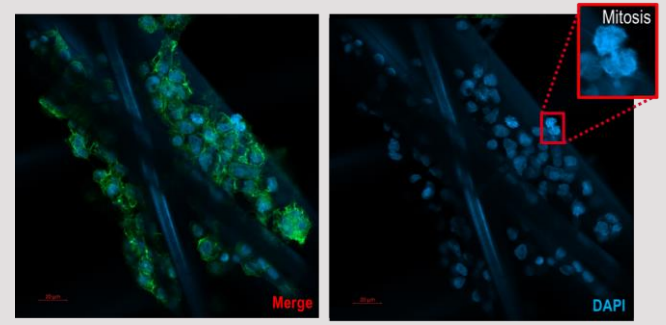
Dual layer structure of the fixed-bed



Suspension adapted cells (HEK293)



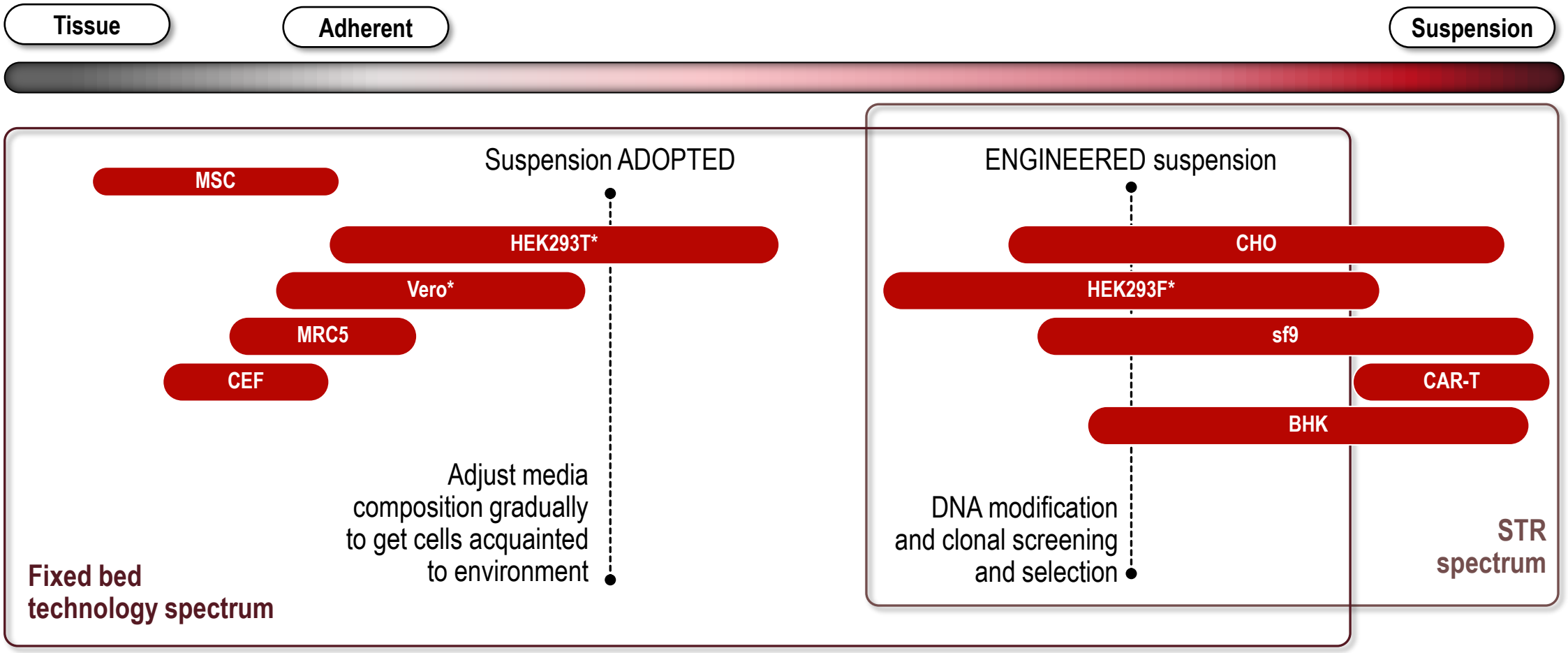
Adherent cells (HEK293)



Source: Univercells Technologies

Suspension cell lines have been adapted to meet the requirements of conventional large-scale manufacturing platforms; they are no longer the only solution available

Alternative ways to enable cell growth over the time



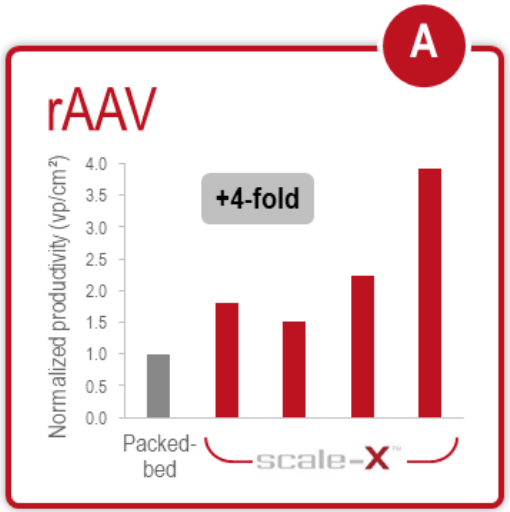
Cells successfully cultivated in scale-X; * in serum free conditions

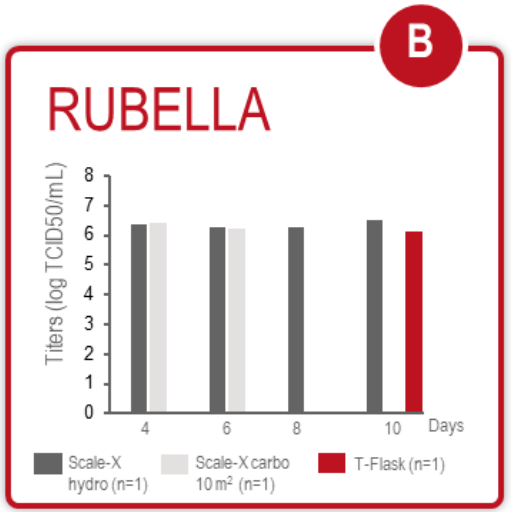
Source: Univercells Technologies

The scale-X bioreactor design supports rapid process transfer with typically higher specific productivities in diverse applications and process configurations

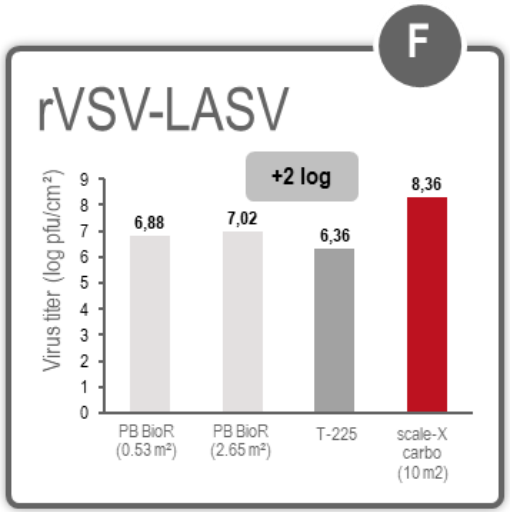
Productivity for adherent and suspension processes

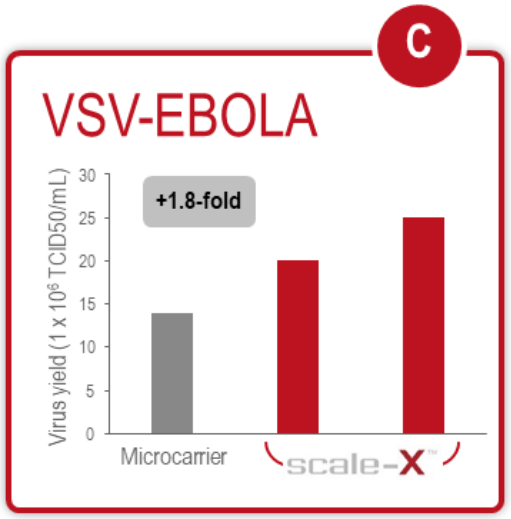
Adherent cells **with Serum**

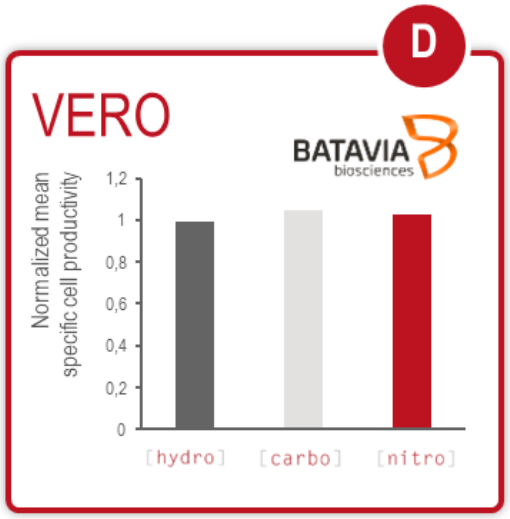


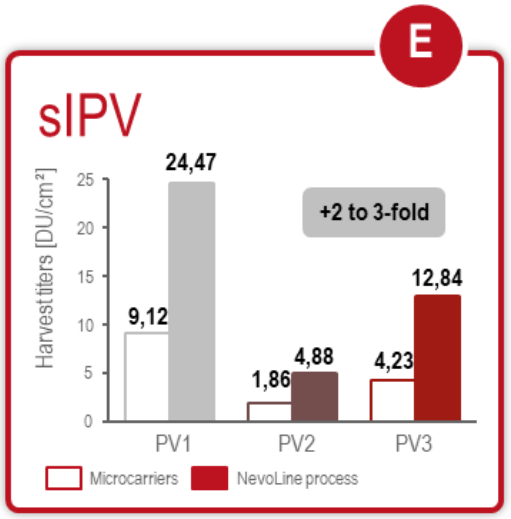


Adherent cells **w/o Serum**

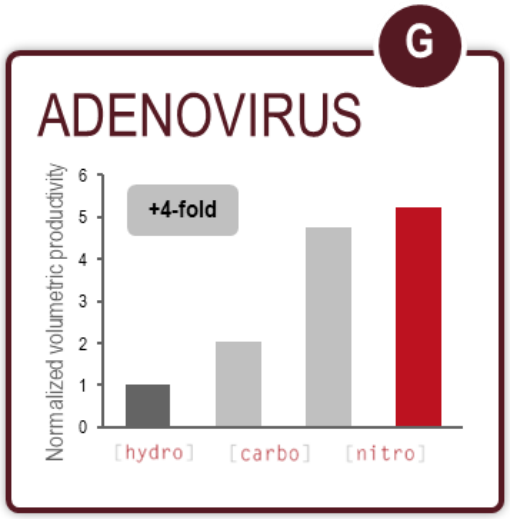








Suspension cells **w/o Serum**



The scale-X bioreactors offer the easiest way to integrate **intensified perfusion** in cell culture processes

Cell immobilization enables easy implementation of perfusion operations

Intensified perfusion

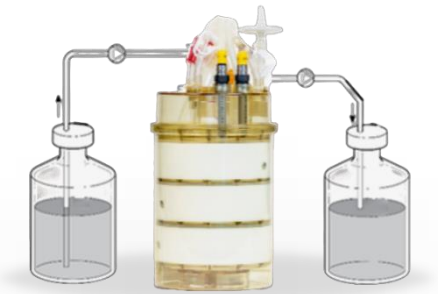
Cells are retained in the bioreactor while product is harvested.

Key BENEFITS

- > **Continuous product harvest**
- > **Improved product quality** and transfer of nutrients
- > **Increased productivity**
- > **Smaller footprint**
- > Enables continuous or semi-continuous DSP

Intensified perfusion

Cell immobilization allows easy implementation of perfusion without the need for cell retention devices



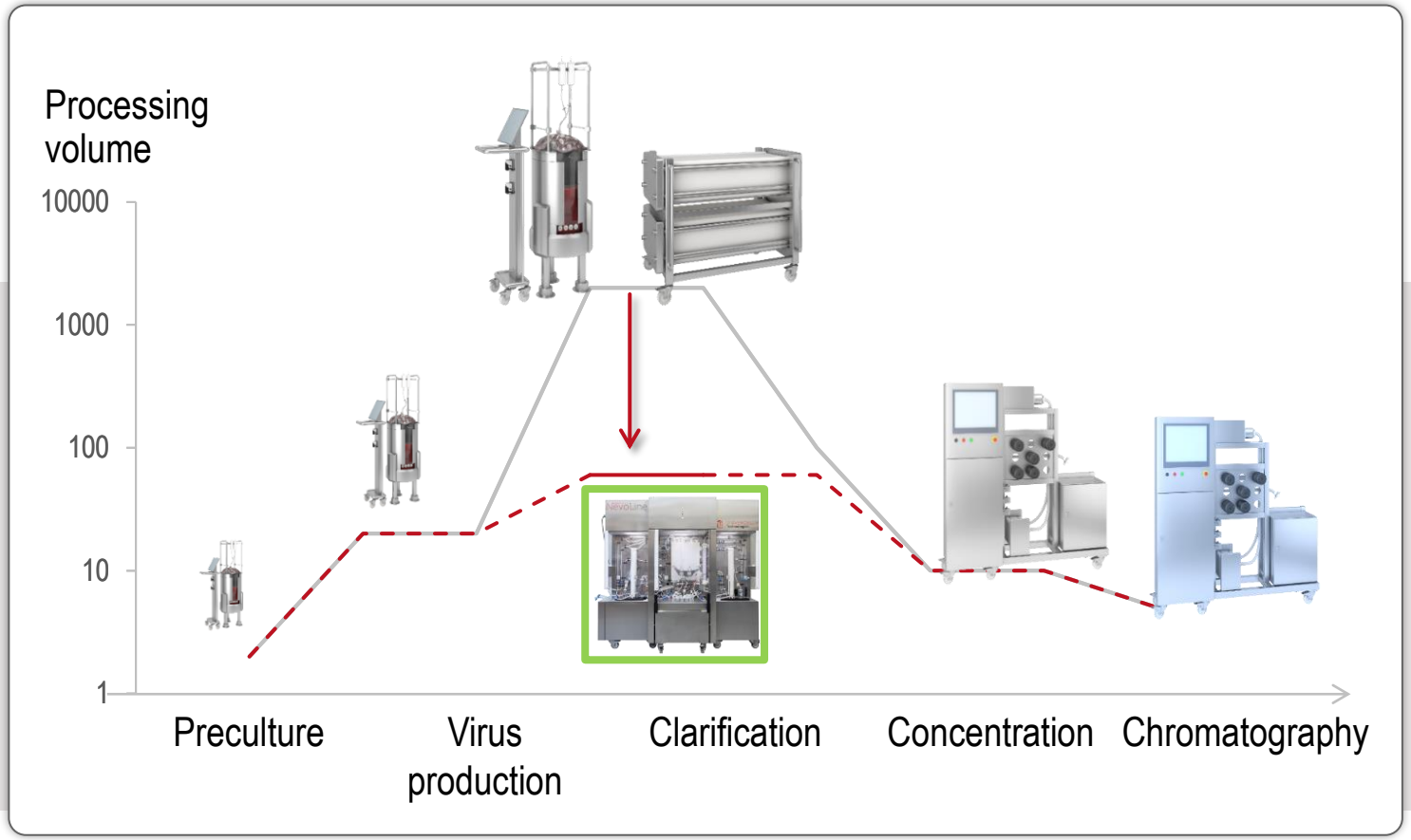
Need to be combined with cell retention devices (ATF/TFF system)

- > Added process complexity and cost
- > Added risk of failure (fouling)

STRs

Taking advantage of **intensified perfusion** in combination with **process intensification & integration** holds the key to address manufacturing bottlenecks

scale-X fixed-bed technology redesigns the workflows



Drastic reduction
of COGs due to a smaller number of batches required and more efficient use of DSP

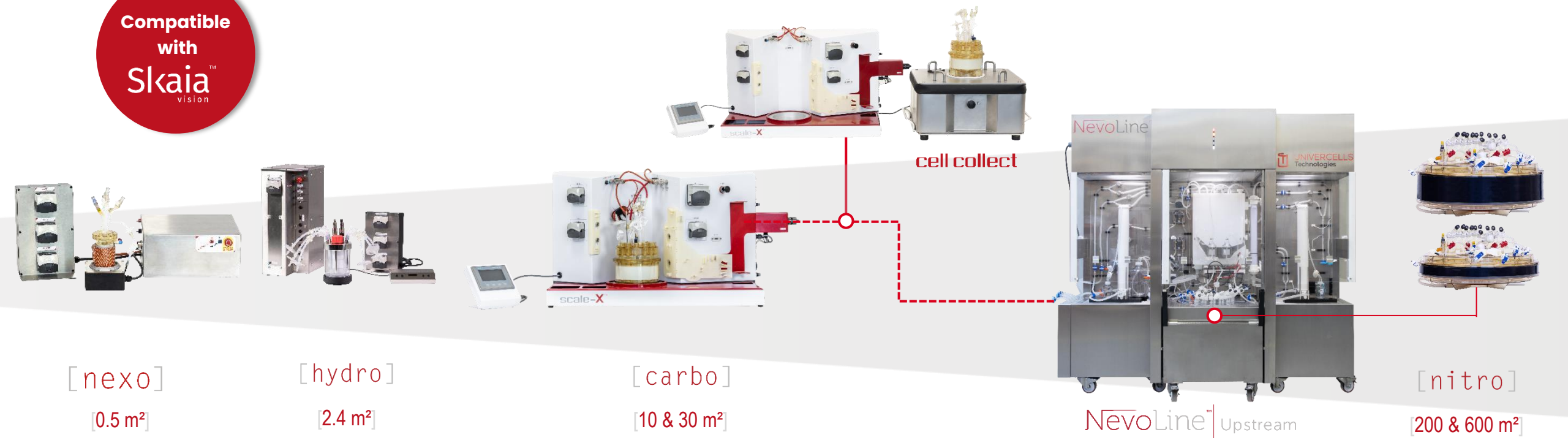
- **Process Intensification** → Low working volumes
- **Process Integration** → Reduced operational footprint
- **Intensified Perfusion** → Increased titer & Continuous processing

Source: Univercells Technologies

The scale-X bioreactor and NevoLine platform technology offer a complete range of solutions for viral manufacturing from proof of concept to GMP

Bioreactor product range from development to commercial manufacturing

Compatible with Skaia™ vision



[nexo]
[0.5 m²]

[hydro]
[2.4 m²]

[carbo]
[10 & 30 m²]

NevoLine™ Upstream

[nitro]
[200 & 600 m²]

POC

Clinical

R&D

Commercial

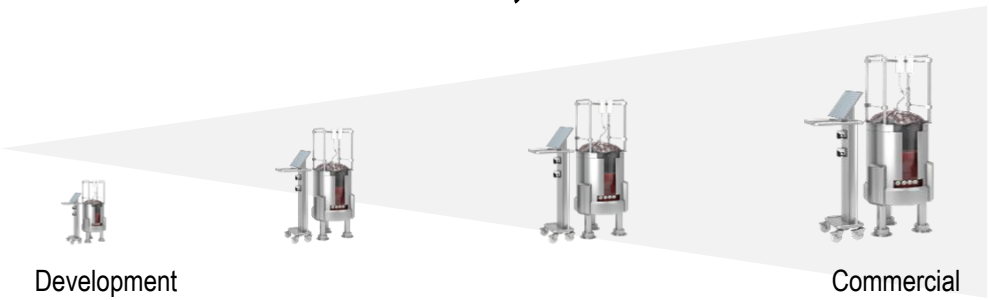
Source: Univercells Technologies

The scale-X bioreactors eliminates the complexity associated with **scale-up of key process steps**, leading to overall **faster process development time**

Key process parameters maintained across scales

Stirred tank technology

2 L ——— **x 1,000** ——→ 2,000 L



Scale-up parameters in STR

Operations
> P, V, N, U_T, vvm, kLa
Design
> D_v, H, d_I, N_D, impeller type, etc.

	Equal P/V	Equal N	Equal U_T	Equal Re	Equal k_LA & vvm
$P/V \propto N^3D^2$	1	100	0.1	10-4	0.8
N	0.22	1	0.1	0.01	0.3
$U_T \propto ND$	2.2	10	1	0.1	2.7
$Re \propto ND^2$	22	100	10	1	27.7
k_La at equal vvm	2	39.8	0.32	2.5x10 -5	1

Complex, non-linear, interdependent, multi-factorial design space upon scale-up

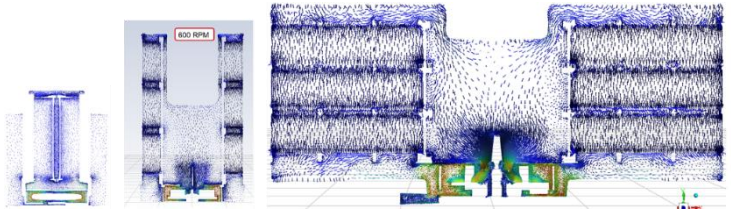
scale-X™

0.075 L → 0.8 L → 1.8-3.3 L → 30-60 L

POC | Clinical
R&D | Commercial

Scale-up parameters in scale-X

Operations
> k_La, V_{lin}
Design
> Compaction, V/S

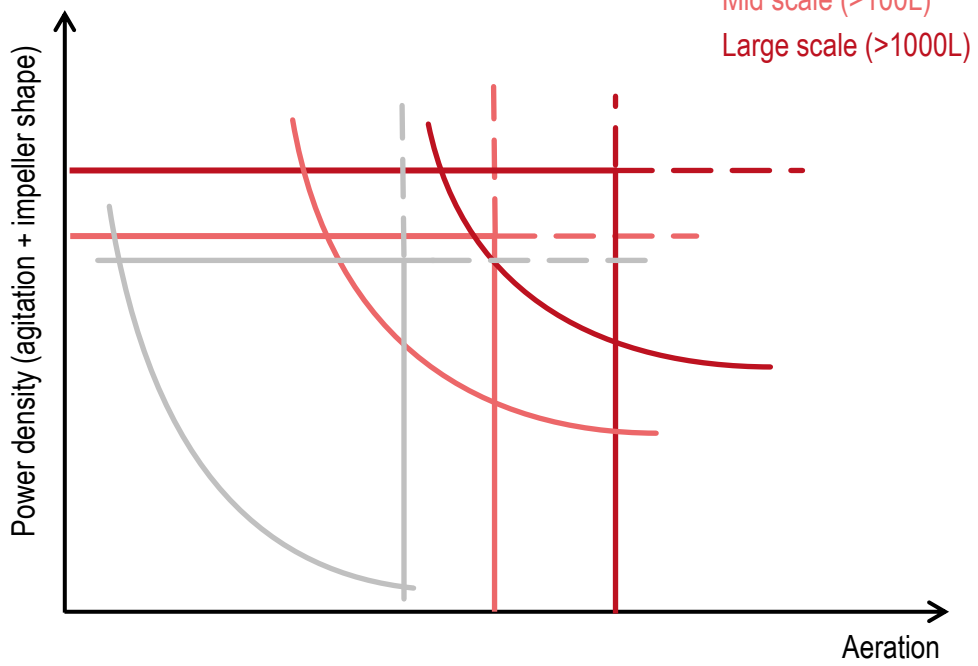


Smaller changes in volume between scales, simplified mixing, gas exchange and shear constraints

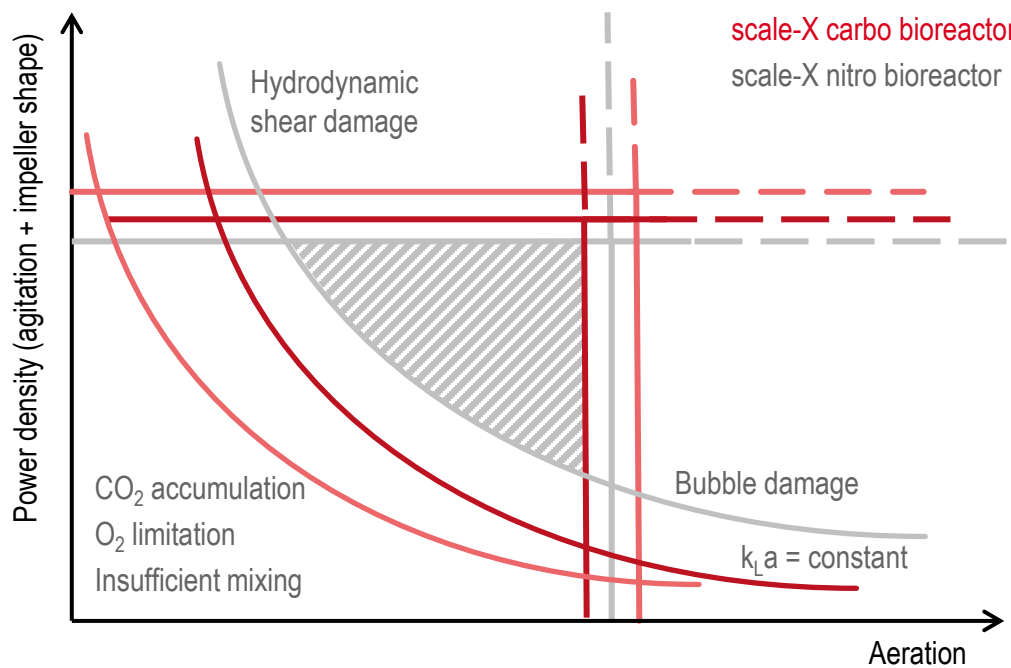
Source: Univercells Technologies

Every bioreactor system has a unique design space within the chosen process parameter allow cell cultivation

Comparing design spaces of different bioreactor scales shows how easy of complicated a scale-up is



The design spaces are not overlapping in one point meaning not the same parameter between the scales can be chosen for cell cultivation = non-linear scale-up



The overlapping design spaces = linear scalability
- same process parameters can be applied in all scales

Source: Univercells Technologies

D. Case Studies

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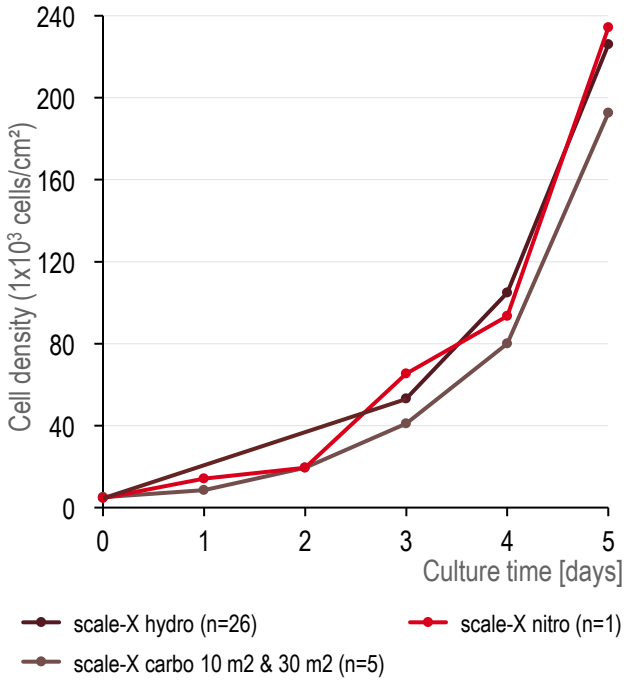
The next evolution of biomanufacturing

The scale-X bioreactor range has proven reproducible cell growth across scales and much higher titer of VSV-Ebola production

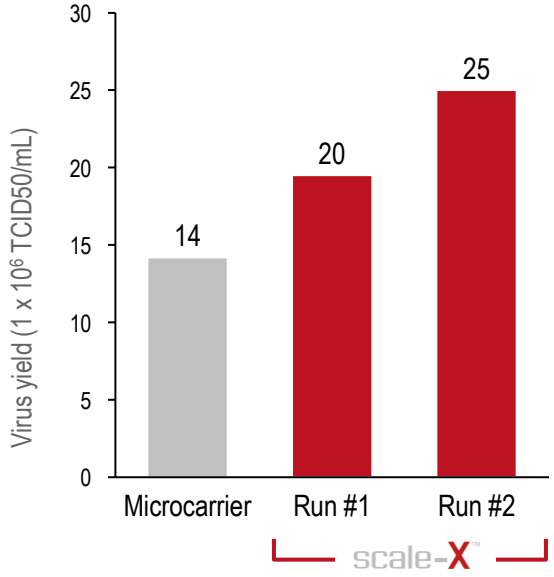
VSV-Ebola production with Vero cells | scale-X hydro (2.4 m²)

Scalability of Vero cell growth in scale-X bioreactors*



> **Reproducible** cell growth during process scale-up
> High cell density at infection **200,000+ cells/cm²**, or ~30 M/mL

Production of VSV-Ebola in scale-X hydro



> Higher TCID50 shows **higher productivity** and **higher potency** of virus produced in scale-X

Impact

> The compact design of the fixed-bed allows a **reduction in equipment footprint by factor 5** compared to microcarrier process

> Structured scale-X fixed-bed bioreactor system is a **suitable alternative to traditional scale-out technologies**

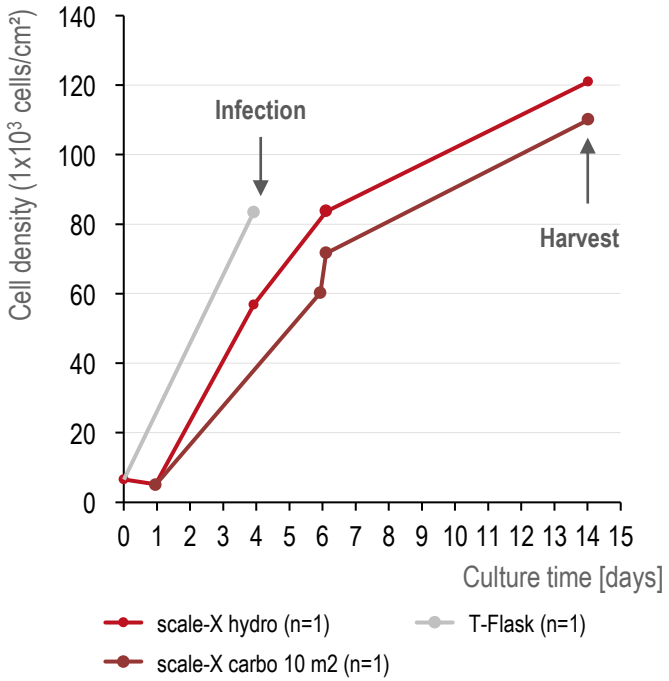
*Repeated growth studies with Vero cells in different scale-X bioreactor systems, performed at Univercells.

Source: S. Kiesslich et al., Journal of Biotechnology, 2020.

Production of Rubella in a scalable solution demonstrating faster viral production and comparable results across scales

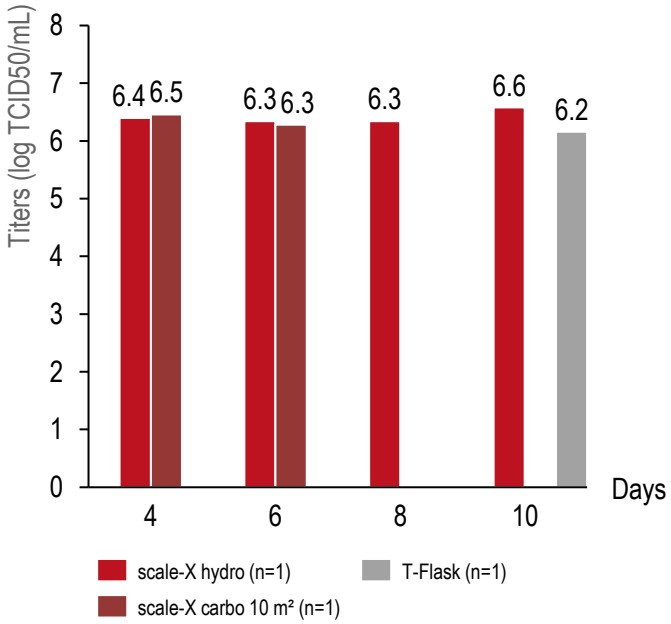
Rubella production with MRC5 cells | Cell growth and productivity results

Scalability of MRC5 cell growth in scale-X



> **Equivalent MRC5 cell growth** profile between scale-X and classic flatware technology
> Cell growth observed after infection at day 4
> High cell density harvested of **120,000 cells/cm²**

Production of Rubella



> Goal of **6 log Rubella titer achieved within 4 days** compared to 10 days for flatstock
> Similar Rubella titer per mL obtained in hydro and carbo scales

Impact

> **Consistency** in viral productivity **across scale-X range** for a reliable scale-up

> **Projected productivity** in scale-X bioreactors:
- 1.03 M doses/batch in scale-X carbo 30m²
- 20.6 M doses/batch in scale-X nitro 600m²

Source: A. Chatel et al., Univercells Technologies & Batavia Biosciences, App. note, 2021.

Successful implementation of tech transfer, optimization, and scale-up for an adenovirus-based vaccine, achieving increased productivity and reduced COGs

Adenovirus production with HEK293 suspension-adapted cells | scale-X hydro, carbo & nitro bioreactors

Case study suspension-adapted cells

HEK293
Adenovirus

Highlights

Successful tech transfer
Adenovirus production from suspension to fixed-bed bioreactor

Scale-up to 200m² (scale-X nitro)
Straightforward scale-up and optimization in fixed-bed architecture

High titer and reduced CoGs
Reduced media consumption and increased productivity

Source: Exothera & Reithera, Advanced Therapies Week 2023

Three different process designs were assessed in the scale-X bioreactor during the PoC study

Adenovirus production with HEK293 suspension-adapted cells | Materials and methods in scale-X hydro bioreactor

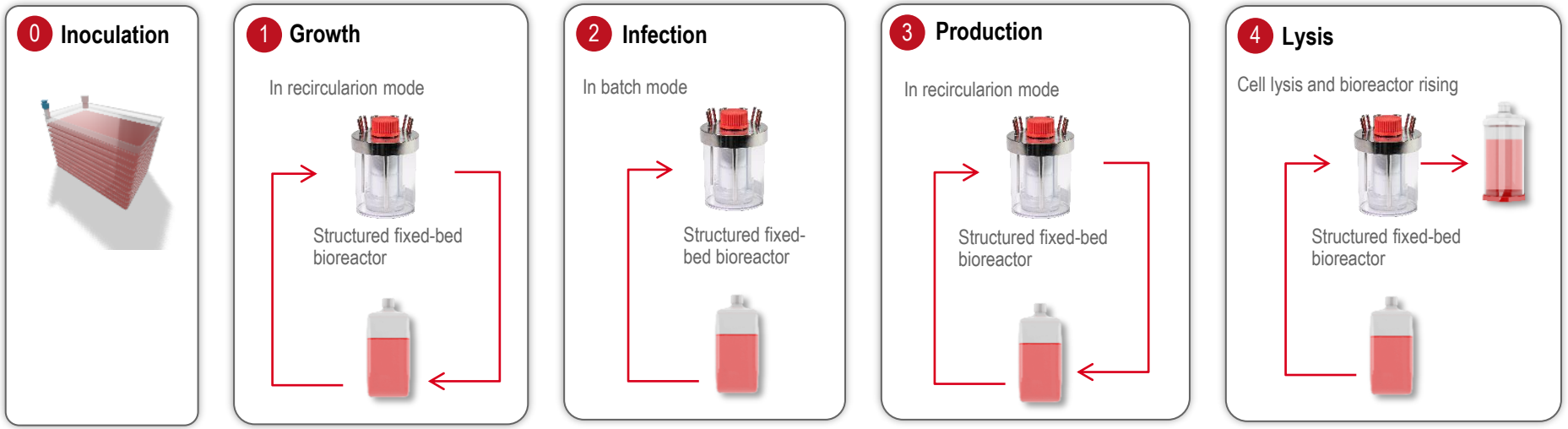
Before infection | **After infection**

Control process

Vessel: 2L bioreactor

Process
Seeding density: 5x105 cells/mL
Growth phase: 3 days
MOI: 200
Production phase: 3 days

Controlled parameters
DO ≥ 40%
pH = 7.00
Temperature = 37°C



Bioreactor #1	Process transfer: Adjust the cell densities into the FB bioreactor and ensure satisfactory cell entrapment with PDT of 42±5h
Bioreactor #2	Increase in production phase: Assess whether the production phase can be extended past 3 days or the productivity plateaus after this period
Bioreactor #3	Increase cell density at infection: Assess whether the increasing the biomass at the point of infection has an impact on productivity

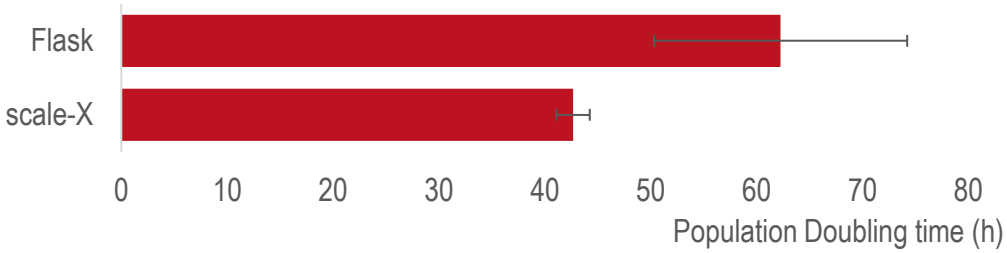
Source: R. Carvalho et al., Univercells Technologies, Exothera & ReiThera, App. note, 2021.

Higher specific cell productivities have also been evidenced in processes developed using suspension adapted cells

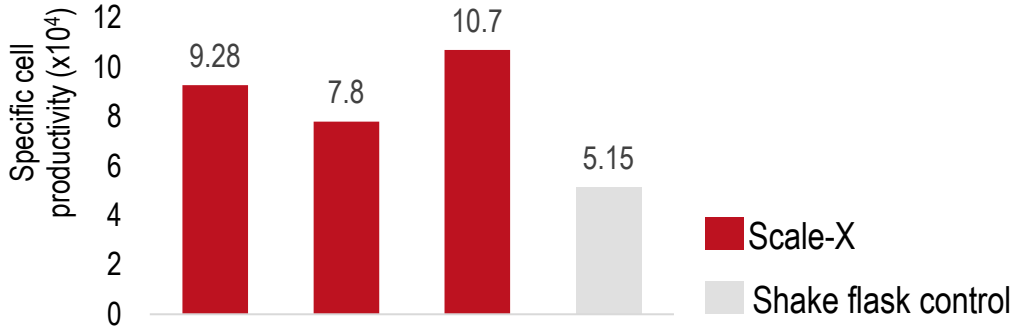
Adenovirus production with HEK293 suspension-adapted cells | Experimental results

Experimental Results

Cell growth



Productivity



Capacity and reagent usage Impact

Unit	nitro600	Control shake flask (extrapolated 2000L)
Vp/mL	4.8E+10	3.15 E+10
Vp/cm²	1.4E+10	N/A
Vp TOT	**8.4E+16**	**6.3E+16**
Total medium used	**1,750L**	**2,000L**

Source: R. Carvalho et al., Univercells Technologies, Exothera & ReiThera, App. note, 2021.

Project strategy to transfer, optimize and scale-up production until 200m² scale

Adenovirus production with HEK293 suspension-adapted cells | Exothera's tech transfer & scale-up approach

CONTEXT

> Adv process in suspension
> HEK serum free cell line
> Process not fully optimized

OBJECTIVE

> Scale-up to large scale
> Reduce CoGs
> Increase productivity
> Improve process flexibility and degree of automation

STRATEGY

> Tech transfer of adenovirus production from suspension to fixed-bed
> Up to 200 m^2 (scale-X nitro)
> Bioreactor with suspension as reference process

	scale-X™ [hydro]	scale-X™ [carbo]	scale-X™ [nitro]
2 L Suspension	**2.4 m²**	**10 & 30 m²**	**200 & 600 m²**
			
POC	R&D	Clinical	Commercial

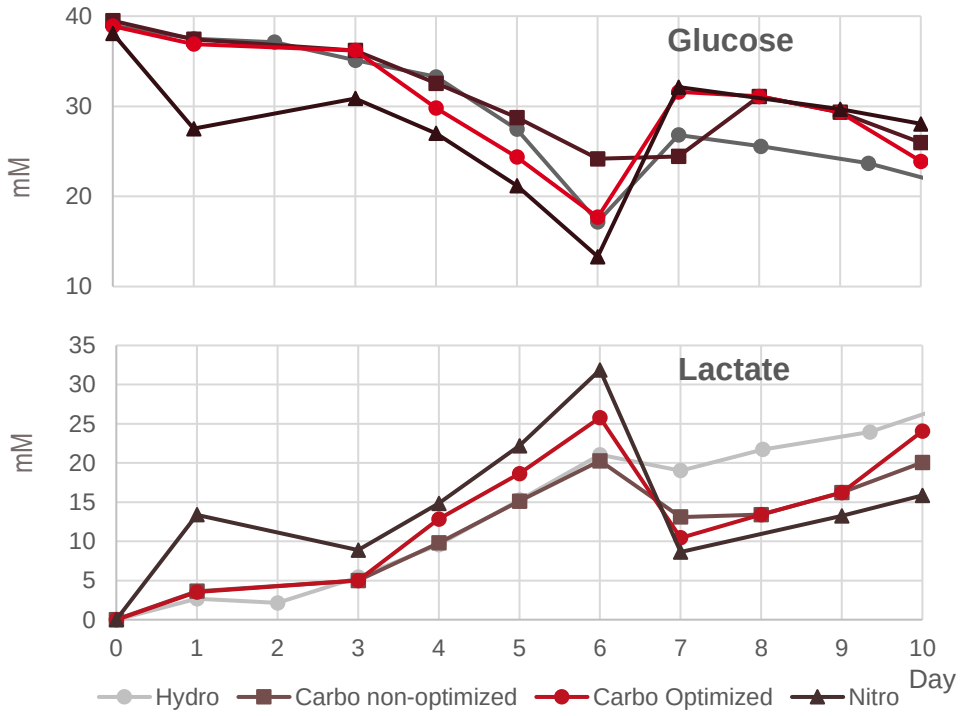
Source: Exothera & Reithera, Advanced Therapies Week 2023

Scalability by design enables cell growth profiles and productivities to be maintained across scales

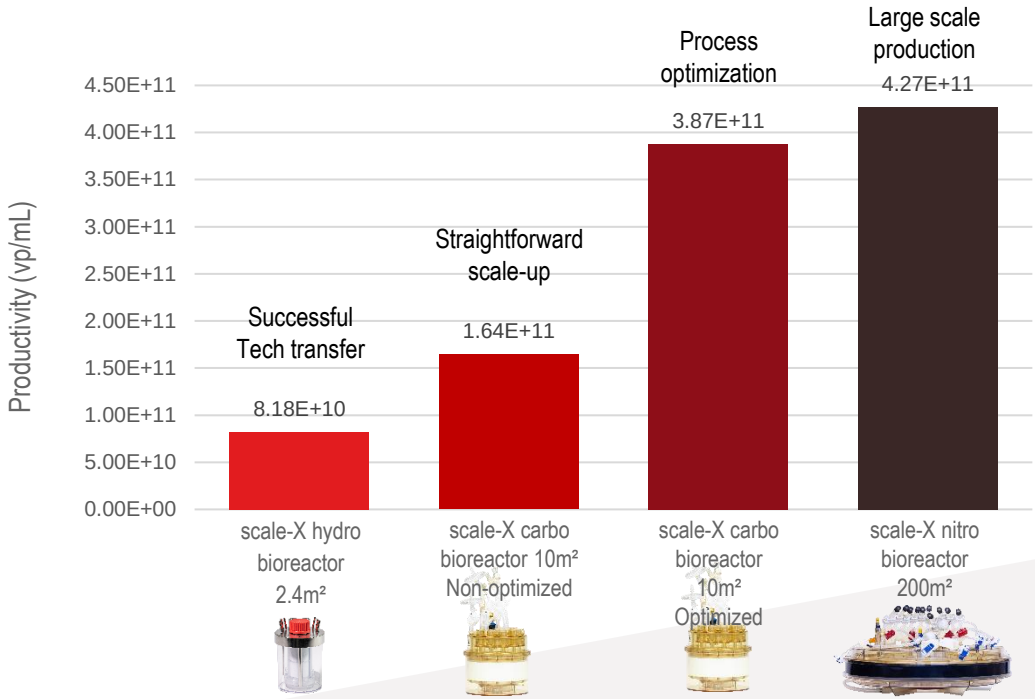
Adenovirus production with HEK293 suspension-adapted cells | Scale-up

Titer improvement and smooth process scale-up to scale-X nitro 200m²

Comparable metabolites profile



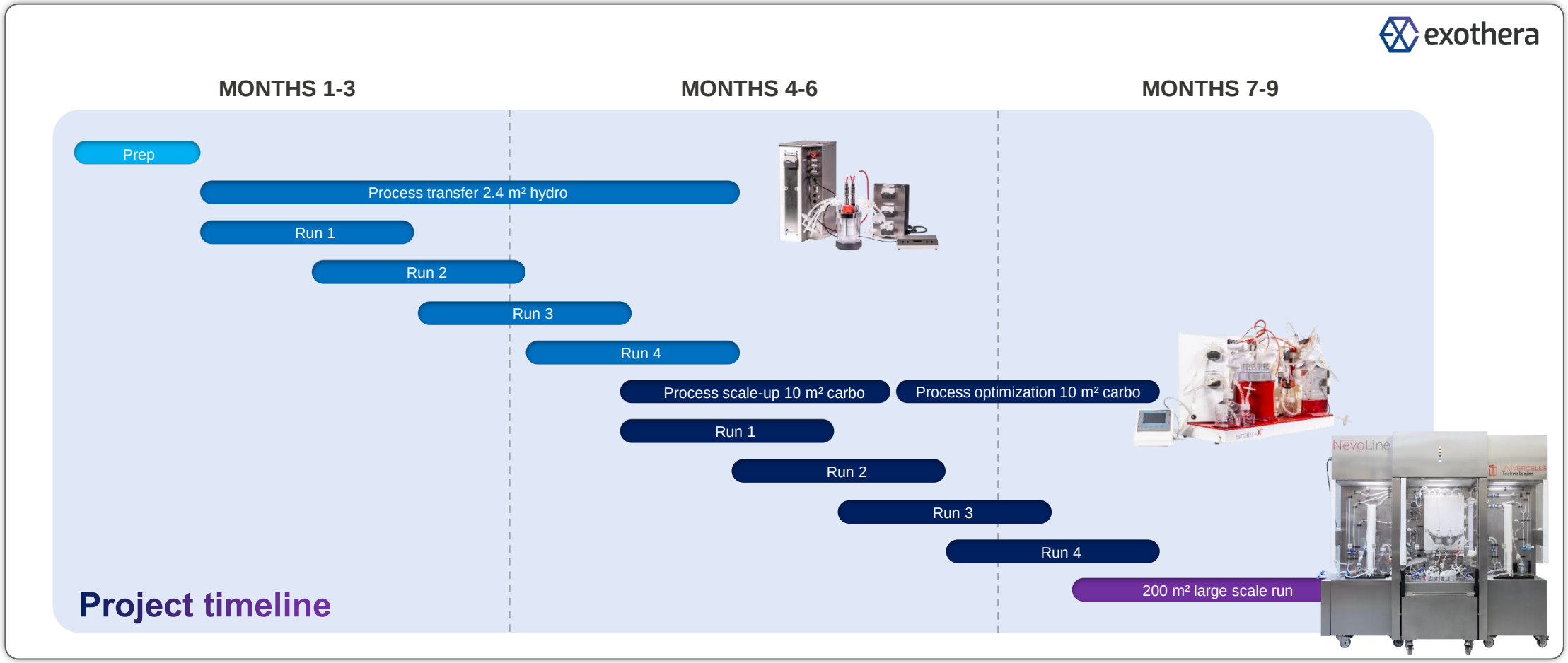
Productivity increase: **1,5-fold (vp/mL)** | **4-fold vp/cell**



Source: Exothera & Reithera, Advanced Therapies Week 2023

Exothera achieved a technology transfer, optimization and scale-up in 8 months

Adenovirus production with HEK293 suspension-adapted cells | Tech transfer & scale-up project timelines

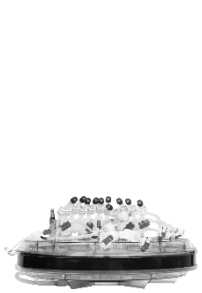


Source: Exothera & Reithera, Advanced Therapies Week 2023

The experimental result were used in a process economics study to assess the economic benefits of process intensification for an Ad-based vaccine

COGs comparison for a throughput of 35M doses / year

Scenarios
COGDS from seed to formulation

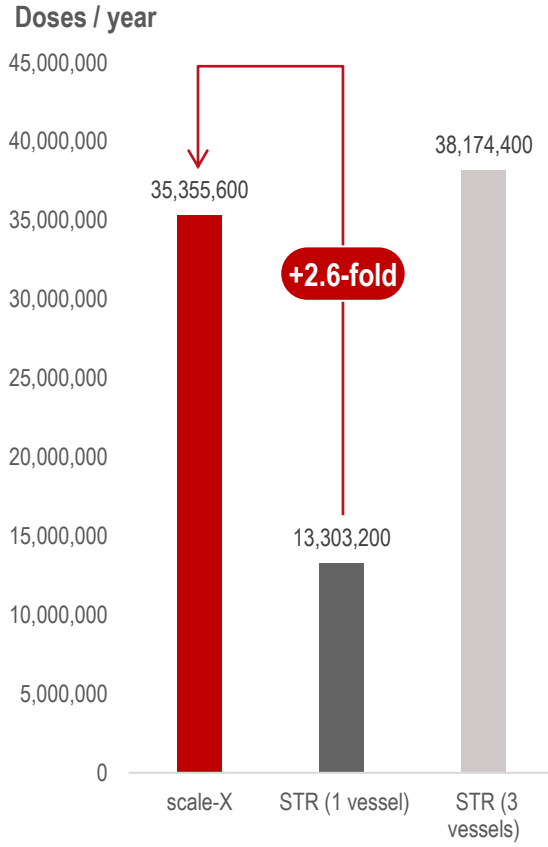


600m²

1*2,000L

3*2,000L

Unit	scale-X 600m²	STR 2,000L
Viral vector	Adenovirus (intra & extracellular)	
Dose size	2e 11 vp / dose	
Cell line	HEK293 adapted to suspension	
Bioreactor size (tested)	200 m²	200 L
Final scale	600 m²	2,000 L
Total media	1,560 L (360 L growth)	2,000 L
Productivity (VP / mL)	4.27 e 11 vp / mL	9.64 e 10 vp / mL
Cell density at infection	200,000 cells / cm²	2 e 6 cells / mL



> A facility fitted with only 1 * 2,000L STR bioreactor can not meet the target throughput

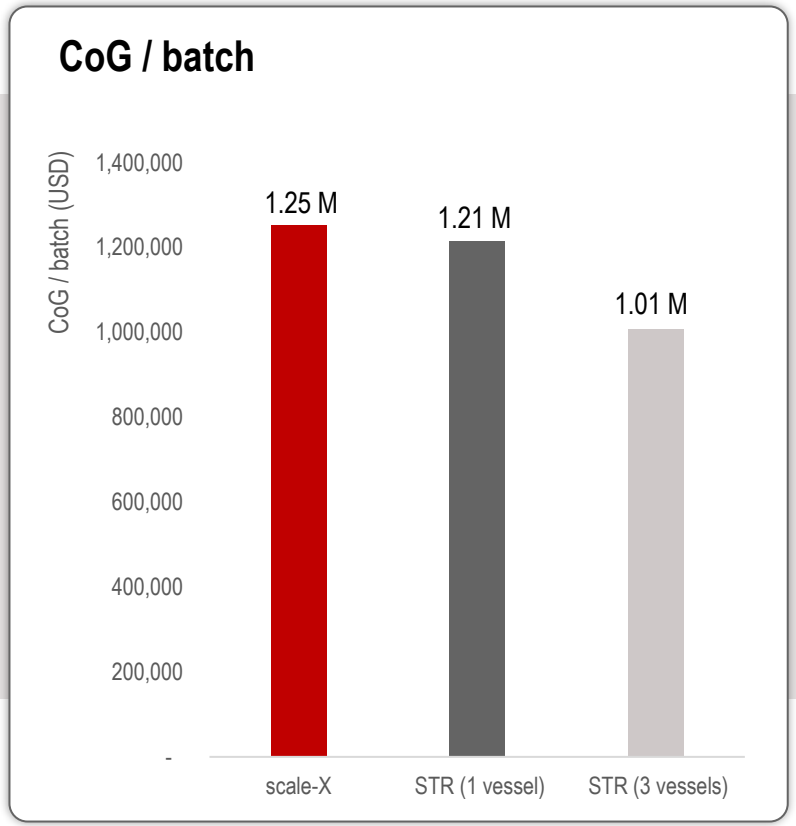
> A scenario with 3 * 2,000L STR bioreactors sharing a DSP train can achieve the yearly throughput, matching the 1 * scale-X nitro 600m² bioreactor

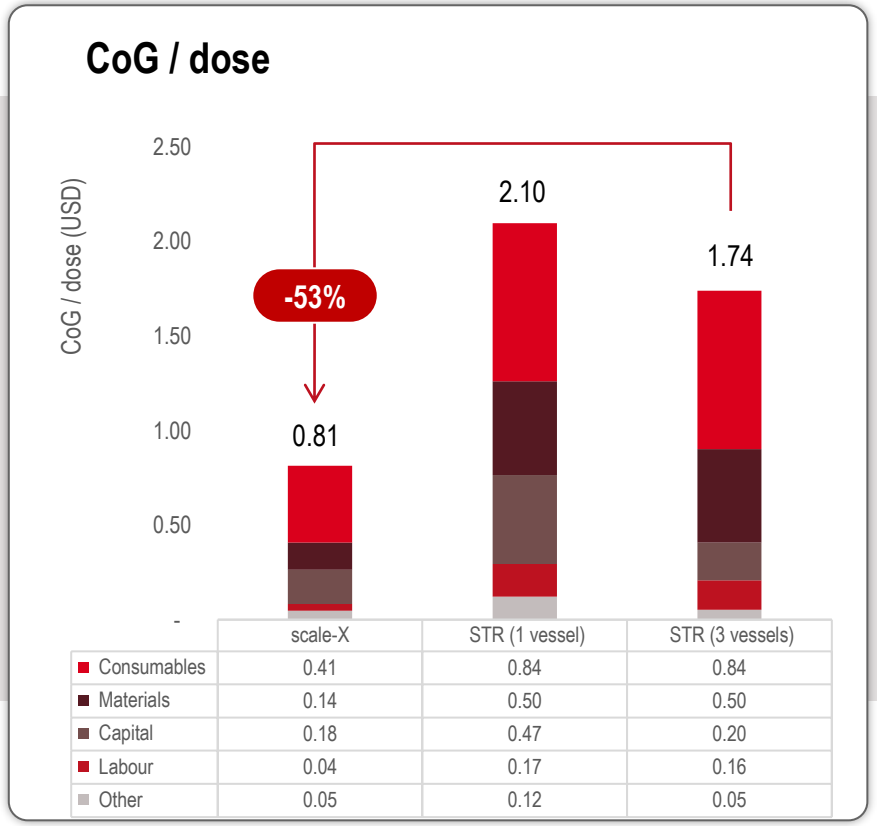
> **To reach same output as 1 x scale-X nitro (1.5m dose / batch), the equivalent STR volume is 5,315L**

Source: Univercells Technologies

The scale-X not only offer > 2.6x productivity increase but CoGs more than half of a comparable facility running with STR technology

CoG per dose and per batch





	scale-X	STR (1 vessel)	STR (3 vessels)
Consumables	0.41	0.84	0.84
Materials	0.14	0.50	0.50
Capital	0.18	0.47	0.20
Labour	0.04	0.17	0.16
Other	0.05	0.12	0.05

- CoG / batch is higher for scale-X as the CAPEX is being amortized over less batches. Else, labour is much cheaper (42% data not shown). This is compensated by the much larger doses / batch in scale-X
- Which leads to **a 53% reduction in the CoGs / dose** in scale-X when compared to equivalent throughput STR facility

Source: Univercells Technologies

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Thank you
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