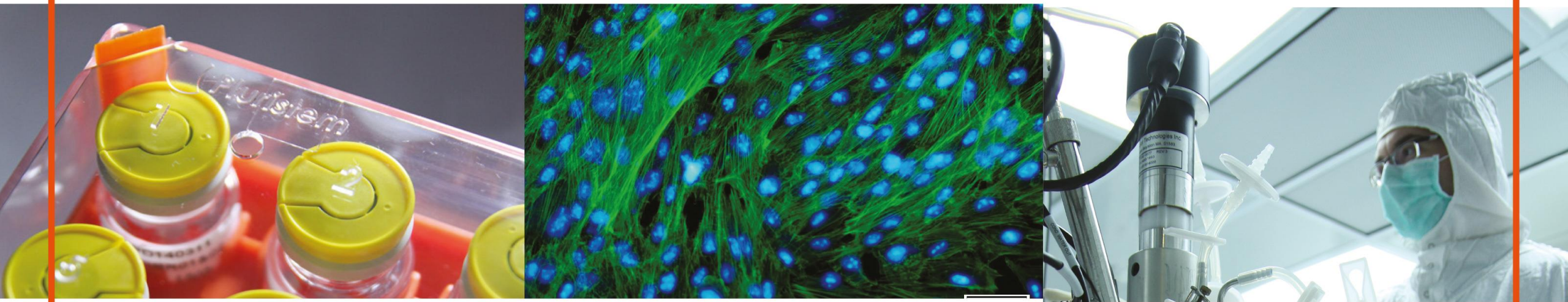
PROCESS DEVELOPMENT AND OPTIMIZATION USING PACKED BED BIOREACTOR SYSTEMS FOR ENSURING SUCCESSFUL LAUNCH INTO LARGE SCALE MANUFACTURING

LIOR RAVIV
VP DEVELOPMENT, PLURISTEM



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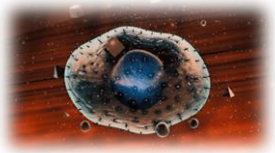
Forward looking Statement

This presentation contains express or implied forward-looking statements within the Private Securities Litigation Reform Act of 1995 and other U.S. Federal securities laws. For example, we are using forward-looking statements when we discuss the expected timing of obtaining regulatory approval for our various patient trials and clinical data readout, proposed trials that may occur in the future, the timing and implementation of our collaborations with various partners and the execution of definitive agreements relating to such collaborations and the potential benefits and impact our products could have on improving patient health care. These forward-looking statements and their implications are based on the current expectations of our management only, and are subject to a number of factors and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. The following factors, among others, could cause actual results to differ materially from those described in the forward-looking statements: changes in technology and market requirements; we may encounter delays or obstacles in launching and/or successfully completing our clinical trials; our products may not be approved by regulatory agencies, our technology may not be validated as we progress further and our methods may not be accepted by the scientific community; we may be unable to retain or attract key employees whose knowledge is essential to the development of our products; unforeseen scientific difficulties may develop with our process; our products may wind up being more expensive than we anticipate; results in the laboratory may not translate to equally good results in real clinical settings; results of preclinical studies may not correlate with the results of human clinical trials; our patents may not be sufficient; our products may harm recipients; changes in legislation; inability to timely develop and introduce new technologies, products and applications; loss of market share and pressure on pricing resulting from competition, which could cause our actual results or performance to differ materially from those contemplated in such forward-looking statements. Except as otherwise required by law, we undertake no obligation to publicly release any revisions to these forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events. For a more detailed description of the risks and uncertainties affecting us, reference is made to our reports filed from time to time with the Securities and Exchange Commission

PLURISTEM CORPORATE OVERVIEW

- Cell therapy company entering late-stage trials in 3 indications
- Multifactorial cell therapy releasing a range of therapeutic proteins in response to signals from the patient's body



- No tissue matching or immunosuppression is required to administer our placenta-derived cell products

- First in class 3D cell culturing technology allowing for efficient, controlled production of different cell products in commercial quantities
- Regulatory approval for clinical trials in US, EU, Japan, South Korea, Australia and Israel

FDA U.S Food and Drug Administration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pmda JAPAN

מדינת ישראל
משרד הבריאות
Ministry of Health Israel

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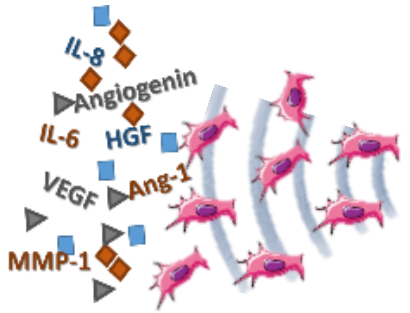
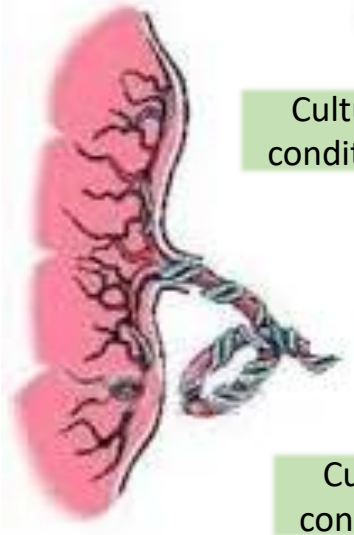
HUMAN PLACENTA- A PLATFORM FOR CELL PRODUCTS

Each PLX Product Secretes a Different Range of Proteins to Address Different Varieties of Indications



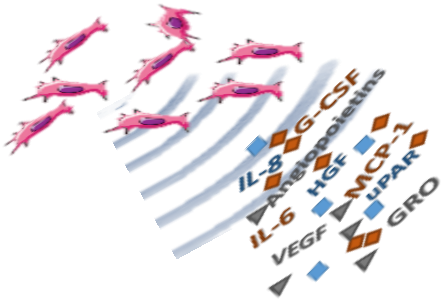
PLX-PAD
Angiogenesis

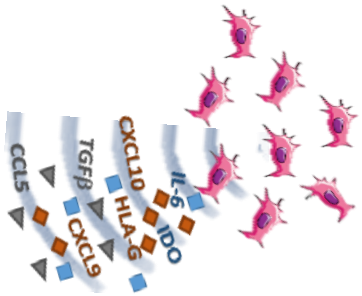
Culture conditions



Culture conditions

PLX-R18
Hematological
AKI



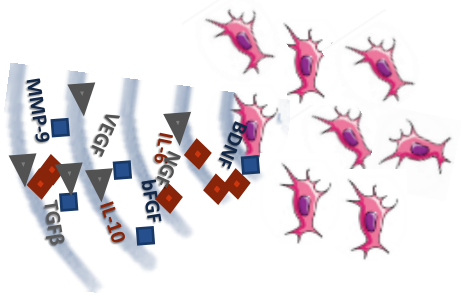


PLX-CNS
Neuronal

Culture conditions

Culture conditions

PLX-IMMUNE
Immunological



- Reduces inflammation
- Stimulates growth of collateral blood vessels
- Stimulates repair of damaged muscle

- Stimulates regeneration of damaged bone marrow to produce blood cells (white, red and platelets)

COMPANY PIPELINE

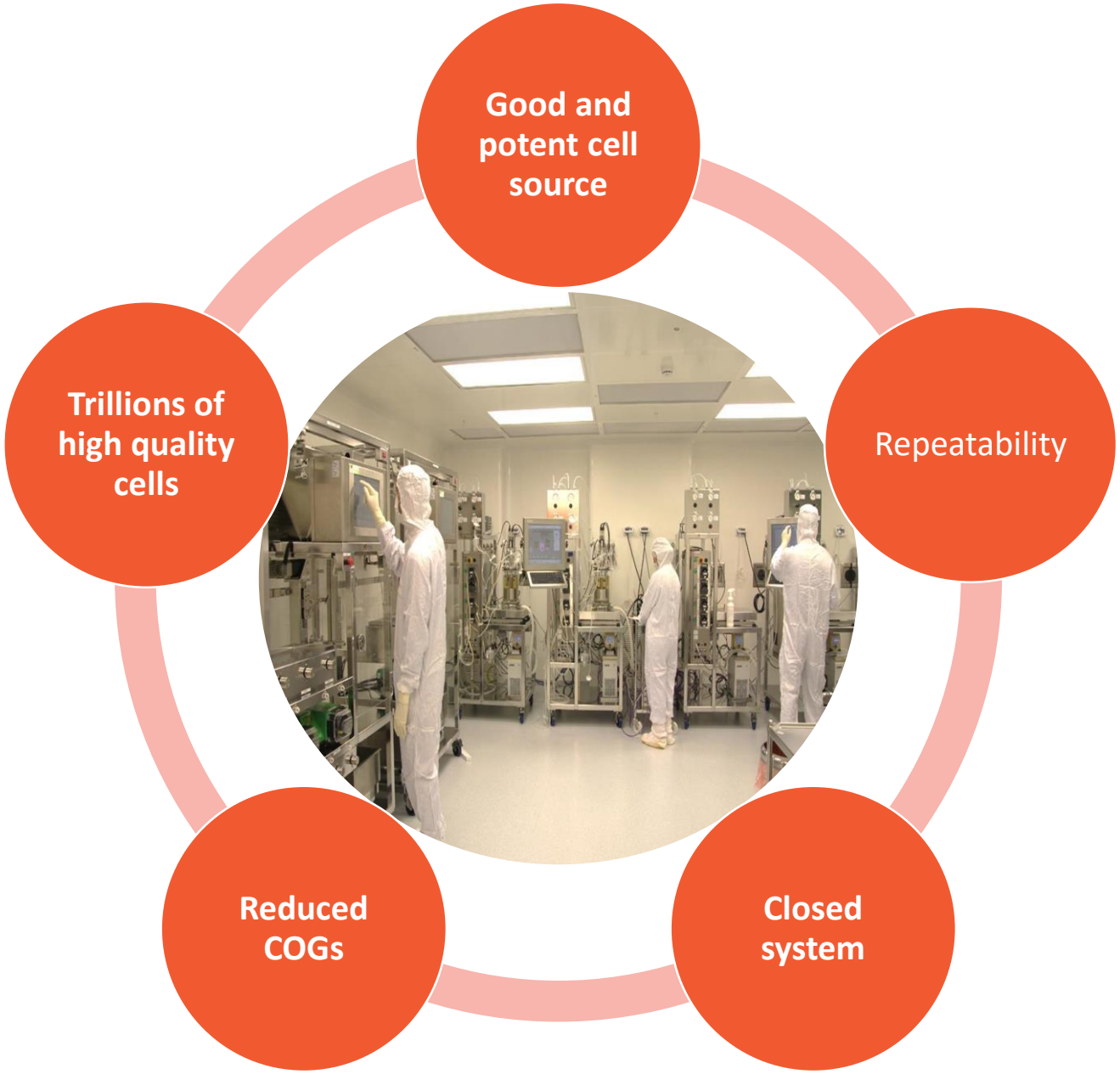
Pivotal pre-marketing trials

Indication	Product	Location	Pre-Clinical	Phase 1	Phase 2	Phase 3	Market
Critical Limb Ischemia (CLI)*	PLX-PAD	U.S.					
		Europe					
		Japan	Conditional Approval Pathway				
Femoral Neck Fracture**	PLX- PAD	U.S./ Europe					
Acute Radiation Syndrome (ARS)	PLX- R18	U.S.		Pivotal study via FDA Animal Rule			

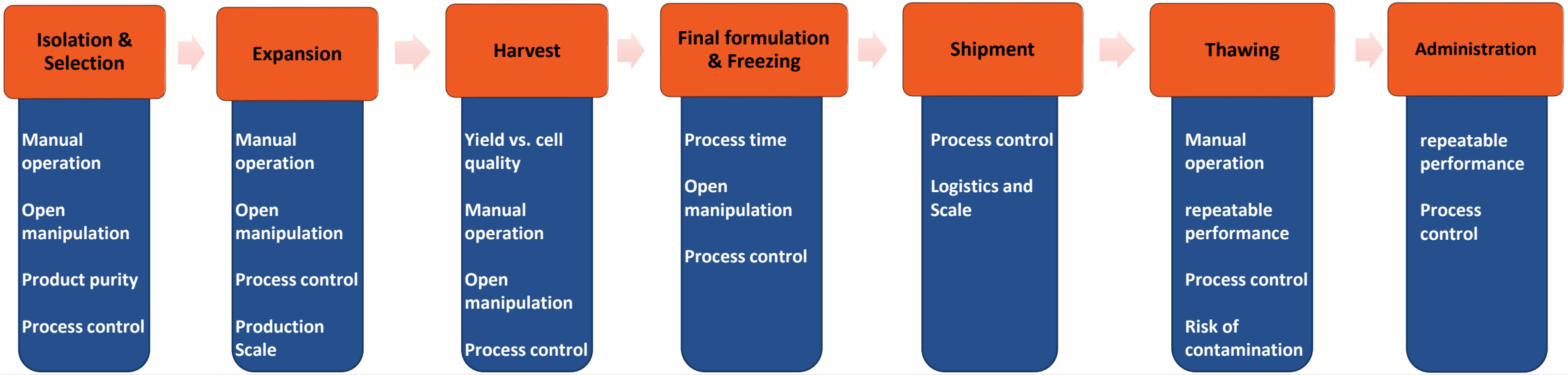
* One Multinational trial- U.S- phase 3, Europe- via adaptive pathway allowing early marketing approval

** Pending FDA/EMA approval

CELL THERAPY INDUSTRIAL PLATFORM



THE CELL THERAPY PROCESS



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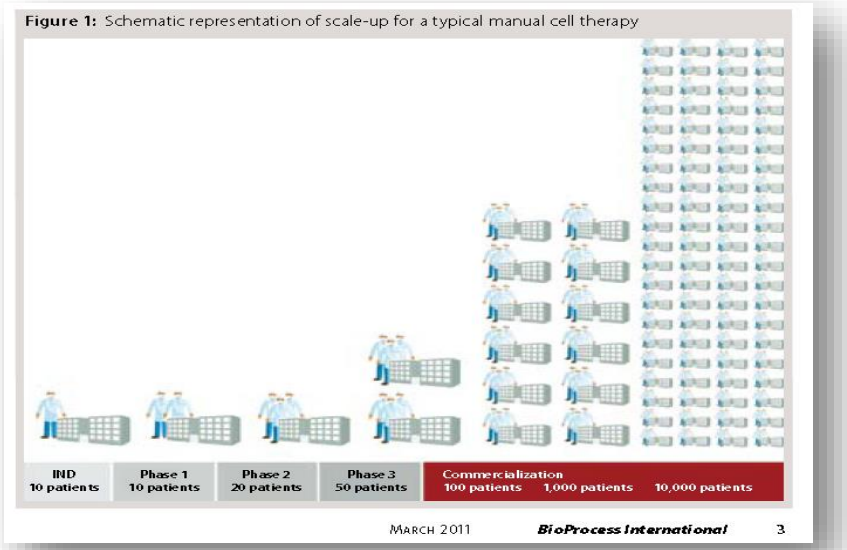
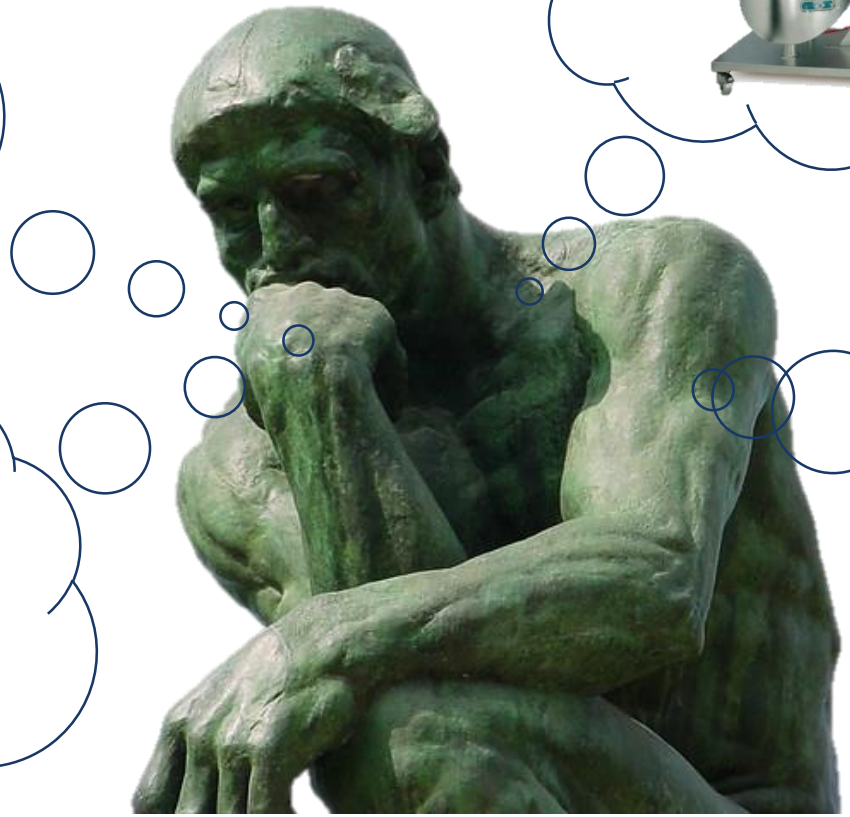
OPERATIONAL CHALLENGES OF CELL THERAPY

- Labor intensive
- High CoGs
- Large infrastructure
- Large overhead costs
- **What about cell quality?**
  - Hours of processing per step.
  - Layer to layer and vessel to vessel, room to room, site to site variation…..
  - No control of critical parameters (Glucose, Glutamine, PH, DO, Glutamate…..)



*THE GOAL OF PROCESS DEVELOPMENT IS TO **TRANSFORM IDEAS INTO PRODUCTS** THAT COULD BE MANUFACTURED IN AN **INDUSTRIALIZED PROCESS** WHILE **MAINTAINING PRODUCT SPECIFICATION***

DEFINE YOUR PROCESS WITH THE END IN MIND



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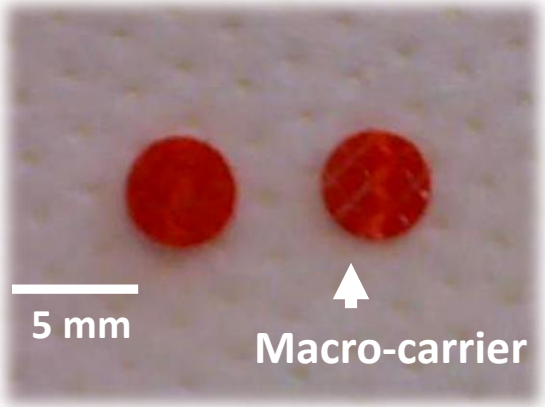
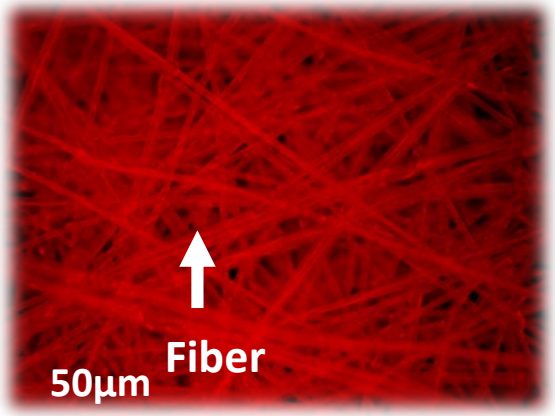
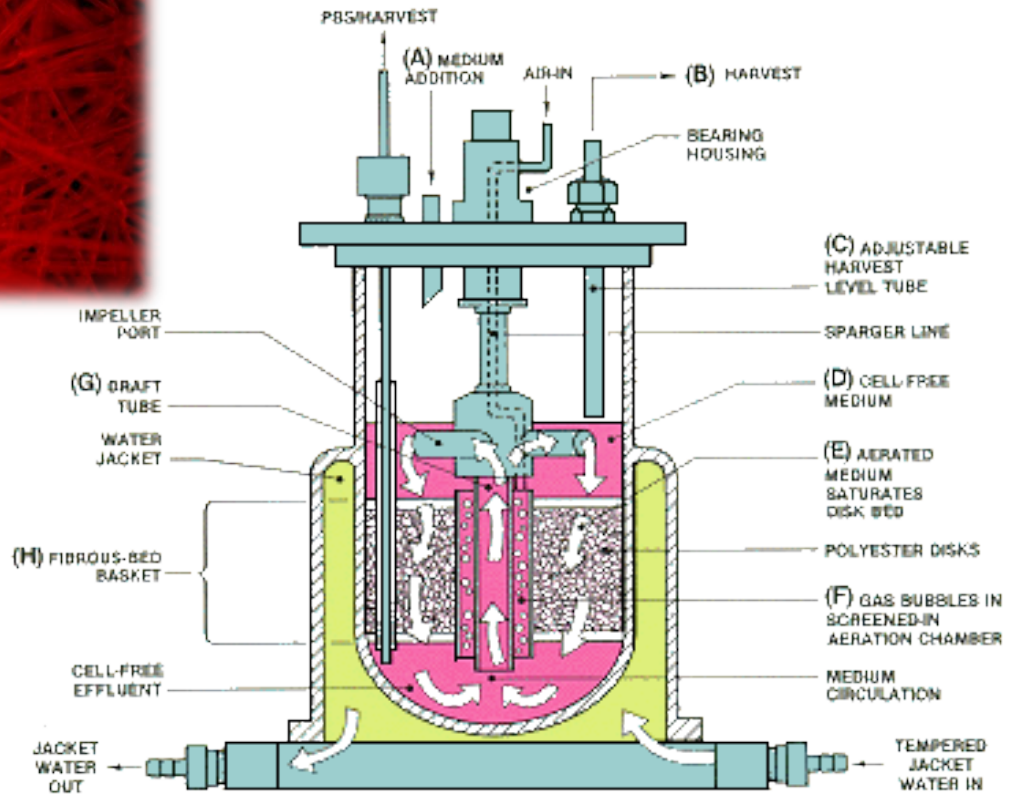
PACKED BED BIOREACTORS
3D NONWOVEN POLYESTER MACRO-CARRIER





Main Advantages

- ✓ Closed system
- ✓ Controlled
- ✓ Automated
- ✓ GMP compliant
- ✓ Scalable
- ✓ Rapid and high yield adherence of cells
- ✓ Low shear force on the cultured cells
- ✓ Enables sustained long-term periods of high-density growth in perfusion mode
- ✓ Allows perfusion and media optimization
- ✓ Relatively easy to engineer solutions around the carriers bed



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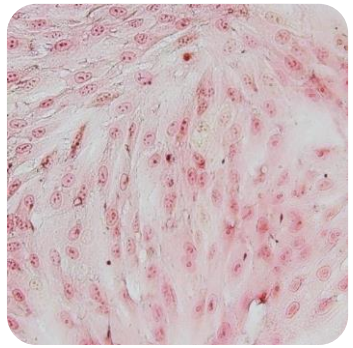
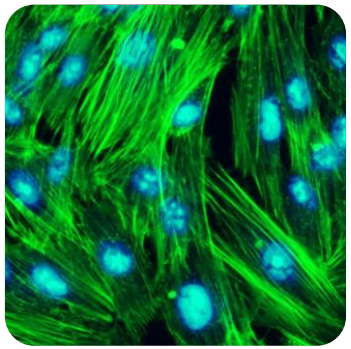
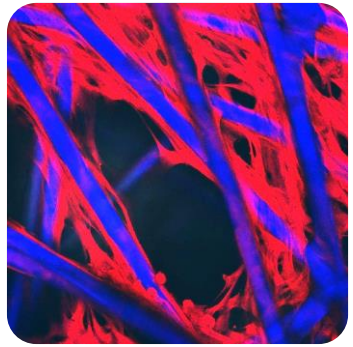
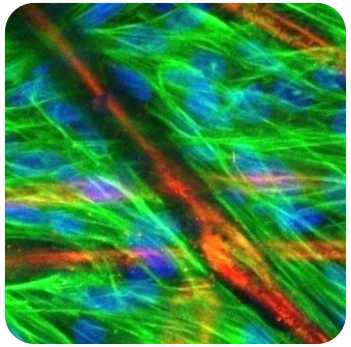
ALLOGENEIC MSC “THE PROCESS IS THE PRODUCT”

Monolayer Vs. Multilayer

- 3D Cell-Cell interaction
- PLX cells harvested following extracellular collagen-cells interaction
- High yield

Paracrine/endocrine effects leads to emphasis on the secretion profile

Proprietary 3D platform to enable controlled 3D culturing to ensure “batch to Batch” comparability and to modify the secretion profile as needed- PLX-PAD, PLX-R18 and others.

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DEVELOPMENT = MANUFACTURING TECHNOLOGY & SCIENCE

Mechanical

Industrial

Engineering

Electrical

Chemical

Biology/Cell Therapy

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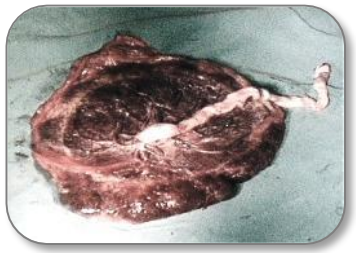
10 YEARS OF PROCESS DEVELOPMENT EVOLUTION

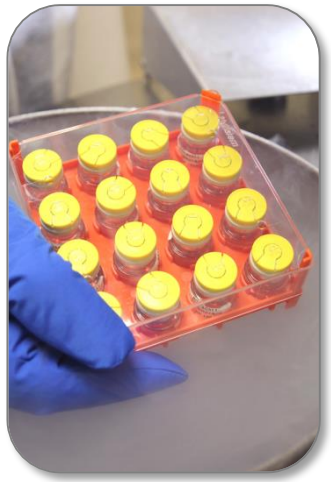


Placenta

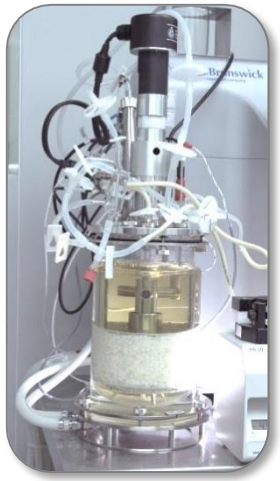
Cell Expansion 2D

ICS
Intermediate cell stock
250-400 vial

From one placenta 75,000 vials of 100 millions PLX cells



Downstream
Detachment, wash, formulation, freezing



Cell Expansion 3D

Cell Expansion 2D

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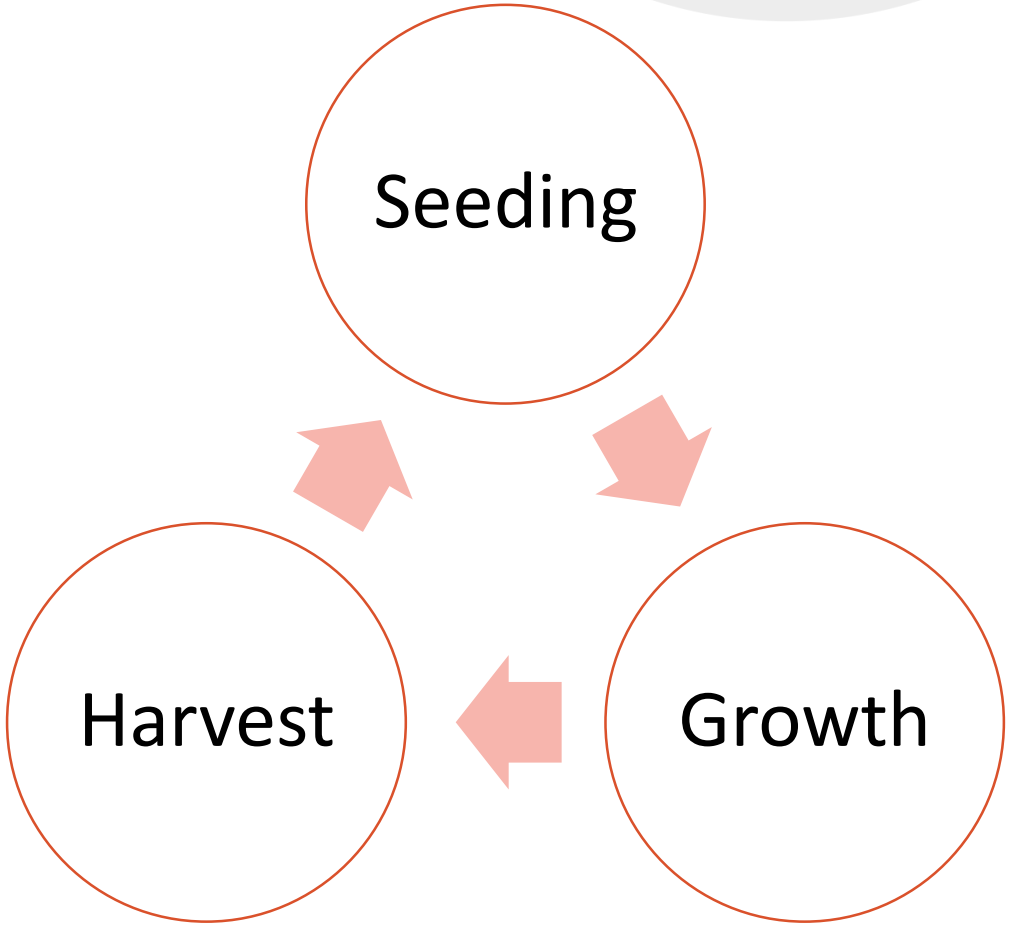
PROCESS DEVELOPMENT IN BIOREACTORS



DEFINE YOUR PRODUCT – TPP & CQA

Target Product Profile - The properties of the end product desired for clinical use
Critical quality attribute – Quantitative properties that ensure product quality

Table 2 Quality target product profile considerations for four CTPs

Property	CAR-T cells immuno-therapy (T-cell derived)	Umbilical cord blood expansion (HSPC derived)	Crohn's disease therapy (MSC derived)	Myocardial infarction (PSC-derived cardiomyocytes)
Therapy type (patient specific or off-the-shelf)	Autologous	Allogeneic, matched	Allogeneic, unmatched	Allogeneic, unmatched
Identity (cell phenotype, morphology)	$CD3^+$ Average vector copy number	$CD34^+$ $CD133^+CD90^+$ CD45RA	$CD105^+CD166^+CD45^-$ $CD73^+CD90^+CD80$- $HLA\text{-}DR^-$	$cTNT^+$ $VCAM^+$ $SIRP\alpha^+$
Viability	High cell viability (typically >70–80%)			
Potency (ability of cells to perform desired action)	*In vitro* anti-tumor activity	Identity-based surrogate assay (high correlation between identity and potency in xenograft model)	Secreted factor profile	Force-of-contraction and electrophysiology measure-ment
Cell expansion (quantity of desired cells)	Sufficient cell expansion to meet target dosage		Meets number of doses needed	
Cellular impurity to minimize (cells in final product to minimize)	Residual $CD5^+CD19^+$ tumor cells & retrovirus	$CD3^+$ T cells $CD19^+$ B cells	Unknown	Residual pluripotent cells
Impurities and microbiology (below threshold)	Endotoxin, mycoplasma, bacteria, viruses, particulates, ancillary materials			
Karyotype (as expected)	CAR present	Normal		
Storage and stability (assessed by potency assay)	Fresh product, stable >24 h	Frozen product, stable >6 months		
Reference	Hollyman *et al.*[9]	Reviewed in ref. 43	Reviewed in ref. 47	Reviewed in ref. 46

Although target levels for many elements of the QTPP are essential, these evolve with the progression of clinical trials and corresponding clinical data. Targets are provided here as examples.

Lipsitz, Yonatan Y., Nicholas E. Timmins, and Peter W. Zandstra. "Quality cell therapy manufacturing by design." *Nature biotechnology* 34.4 (2016): 393-400.

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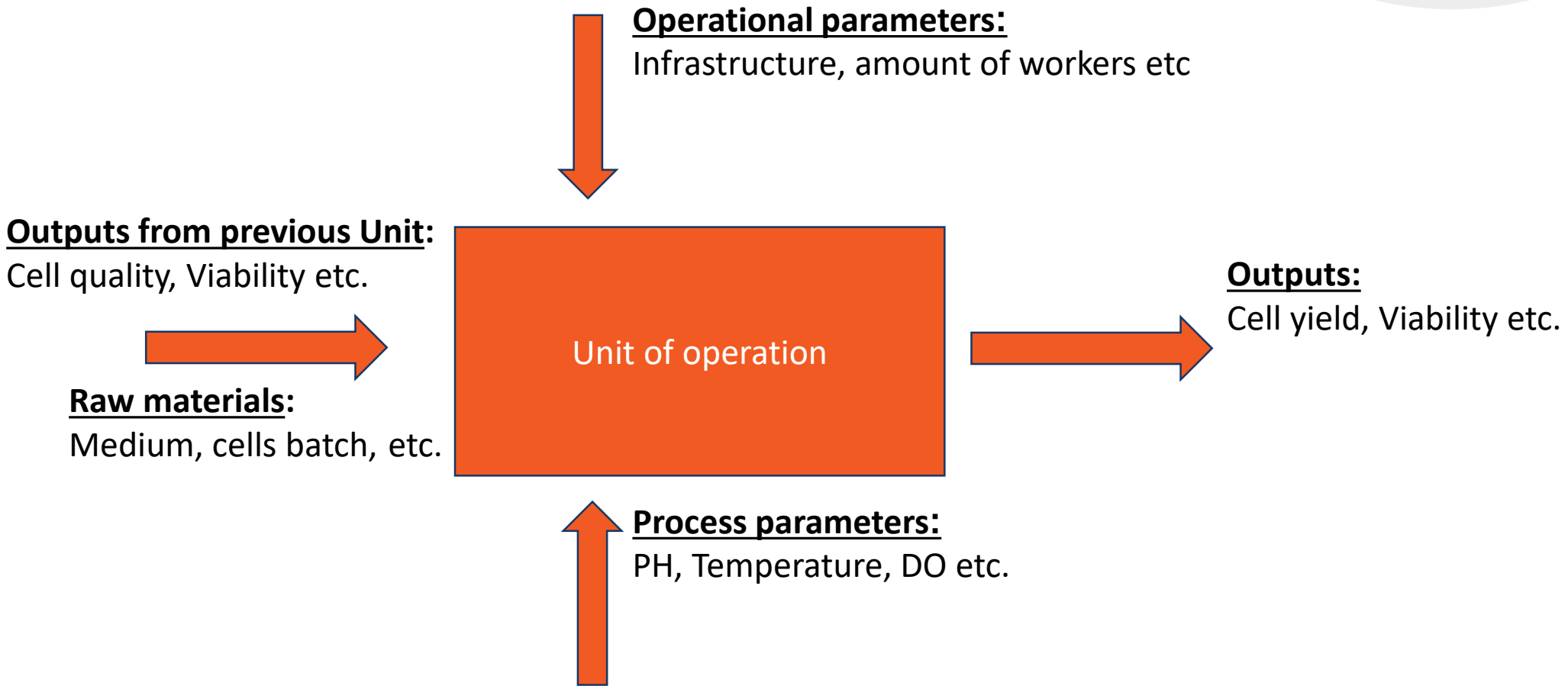
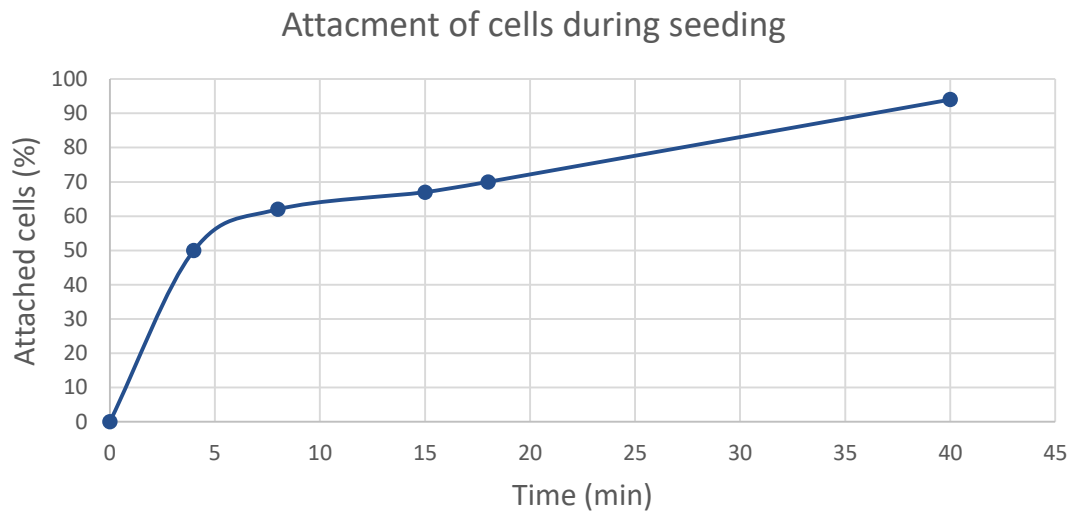
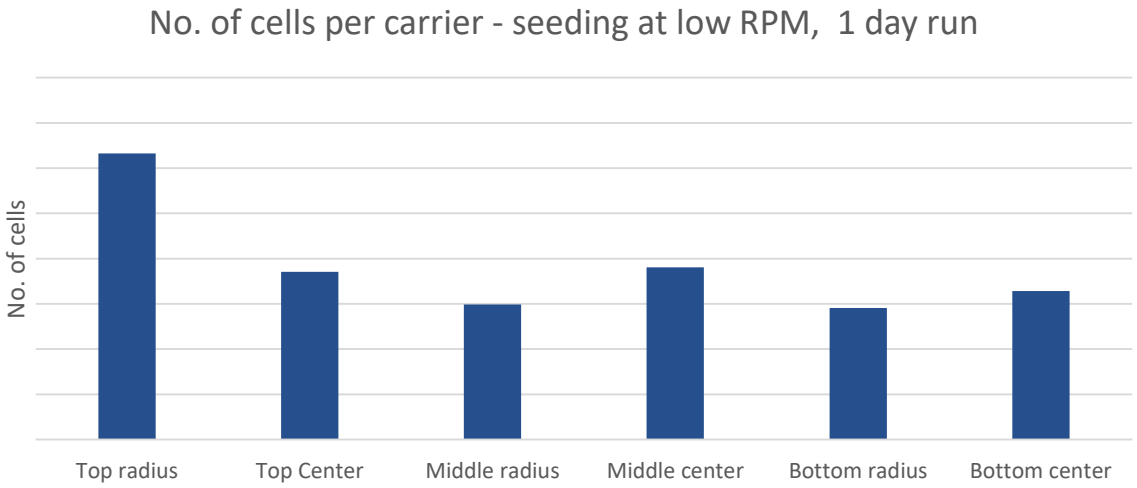
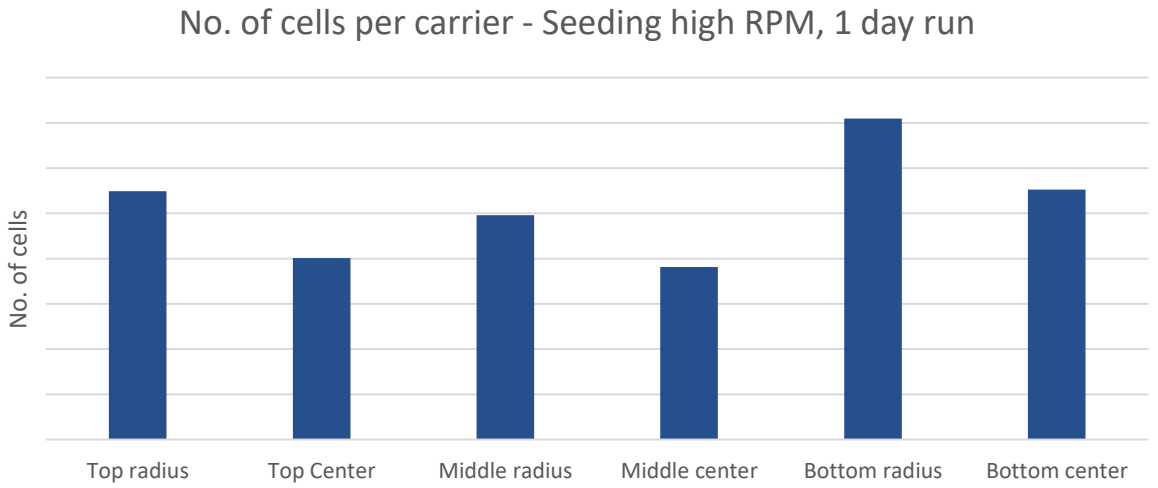
DEFINE YOUR UNIT OF OPERATION



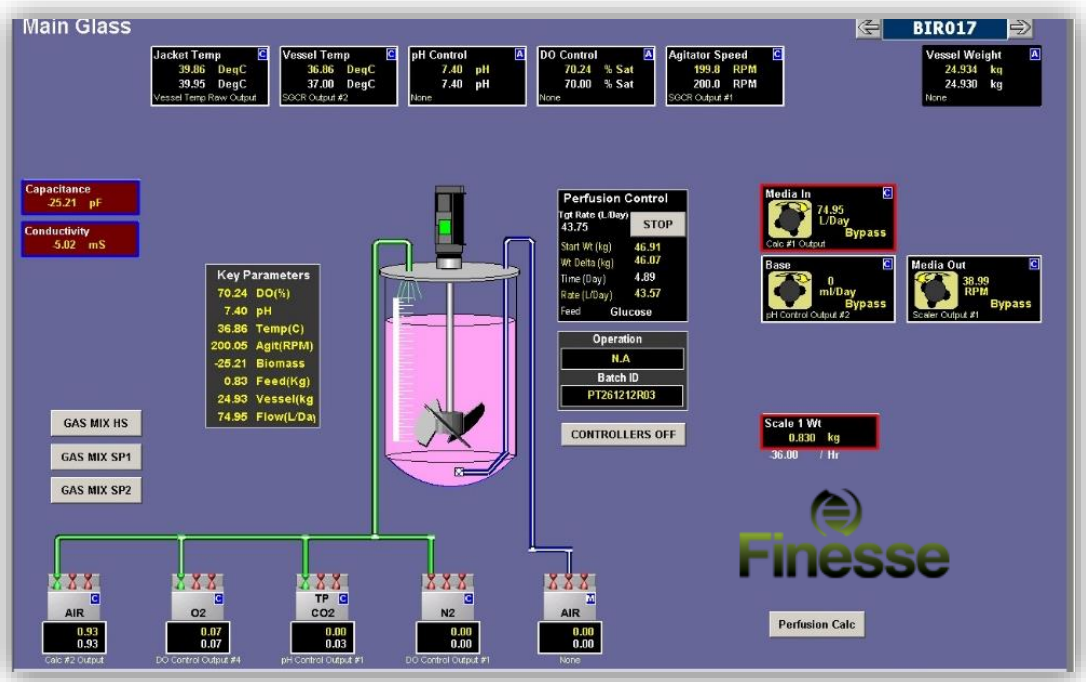
CELL SEEDING – ATTACHMENT AND DISTRIBUTION

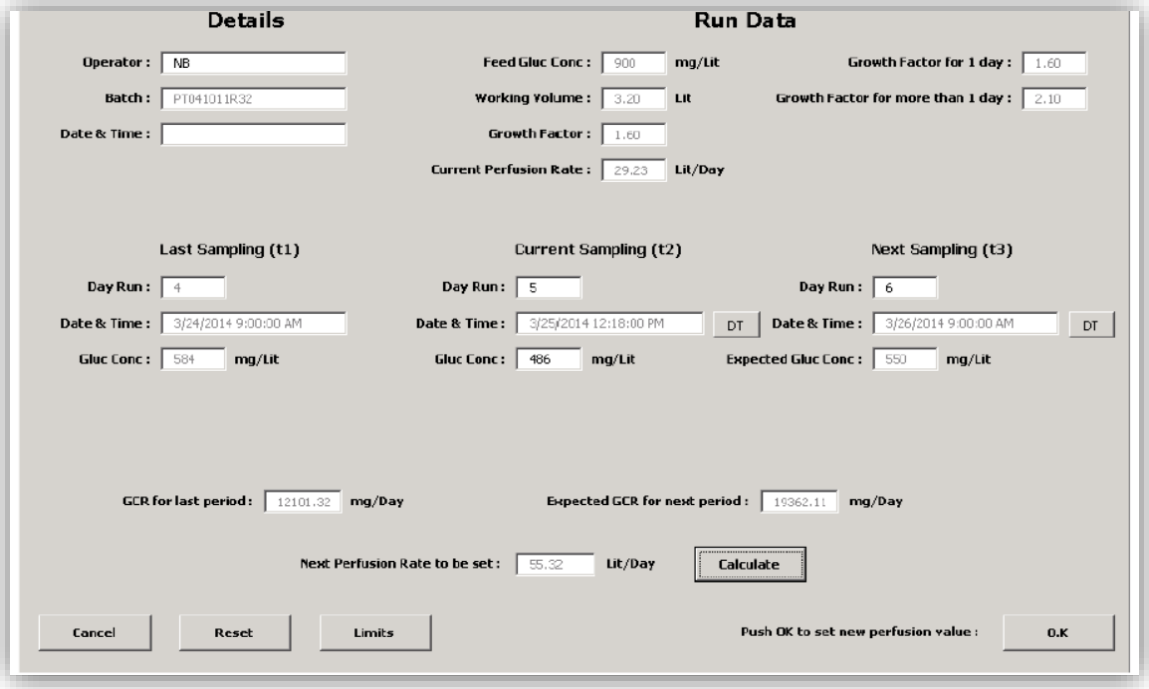




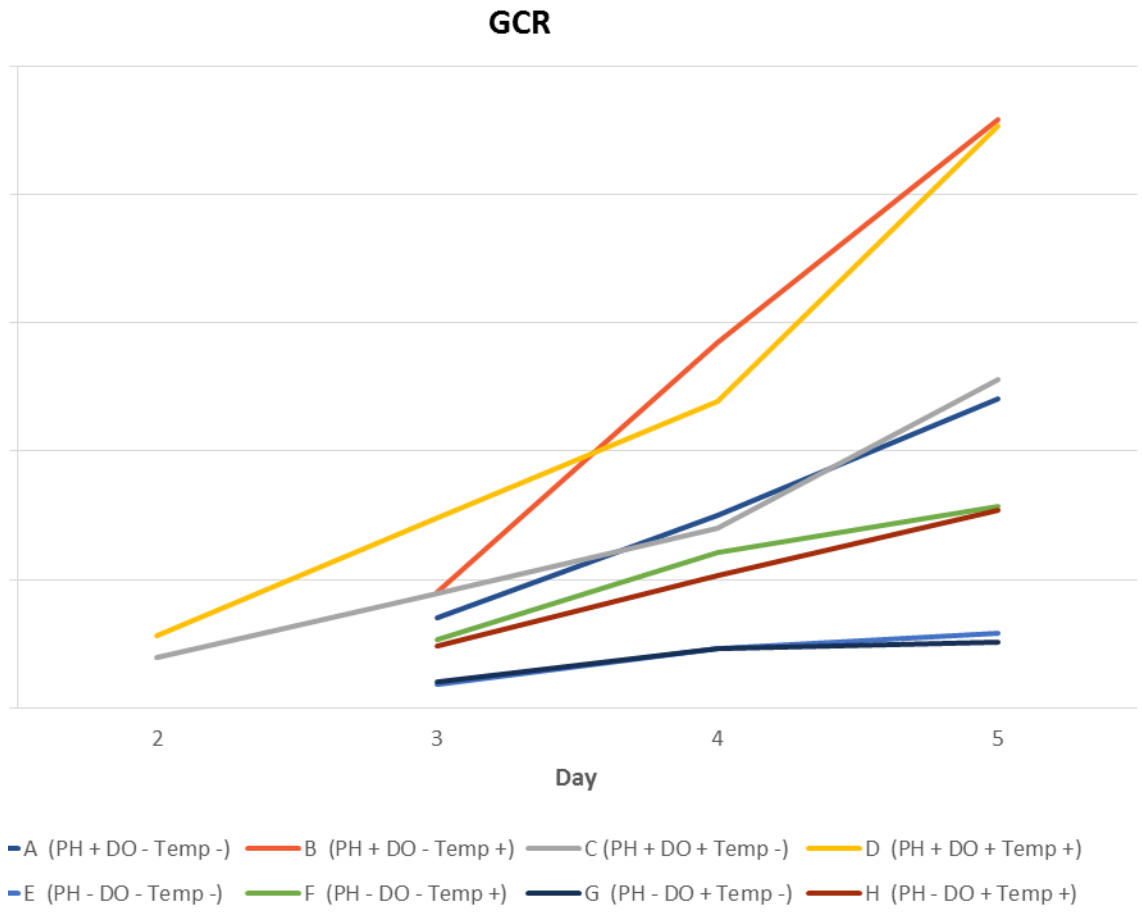


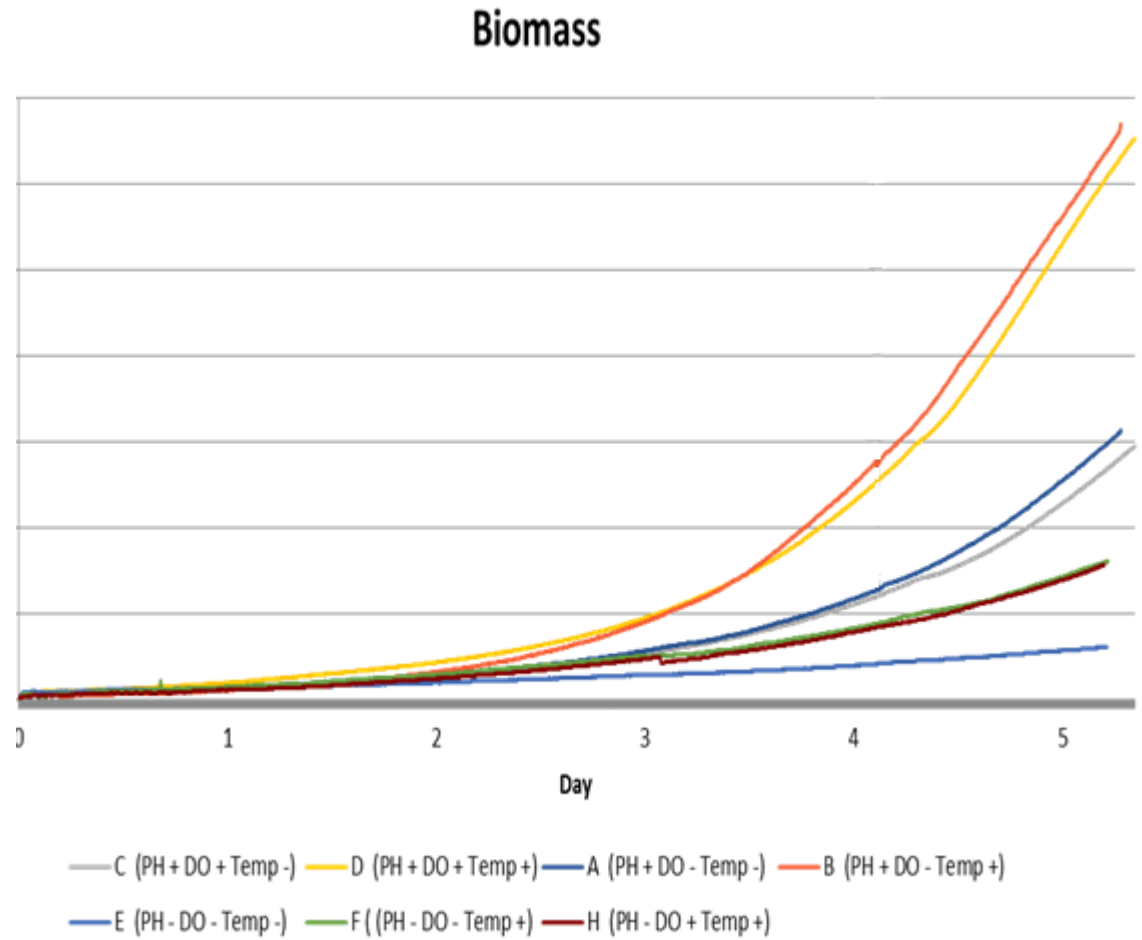
CELL GROWTH - PARAMETERS CONTROL





PROCESS PARAMETERS EFFECT ON GROWTH





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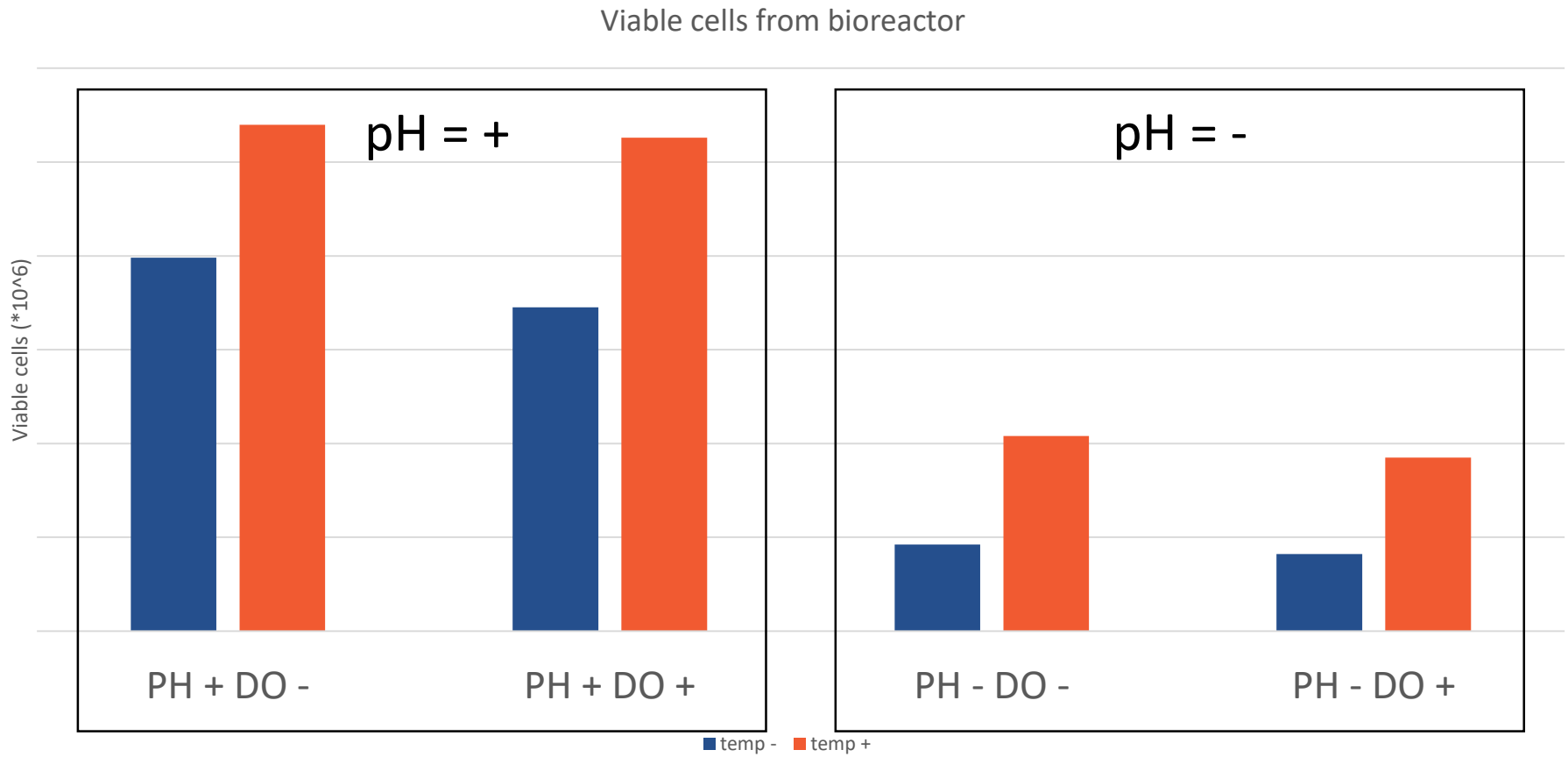
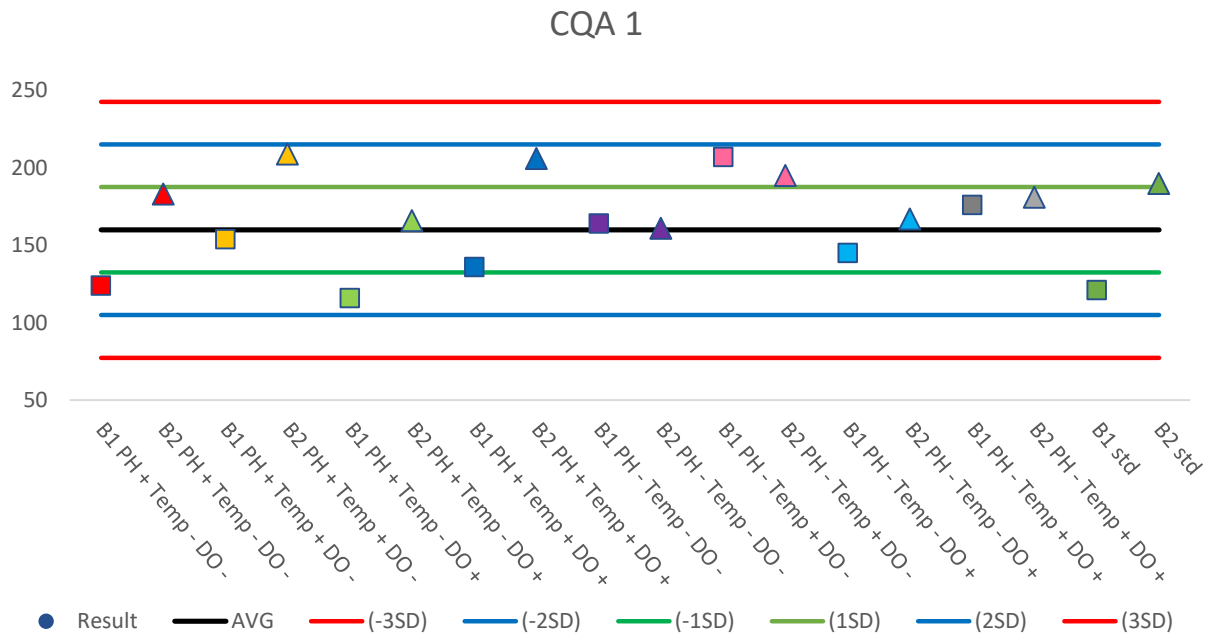
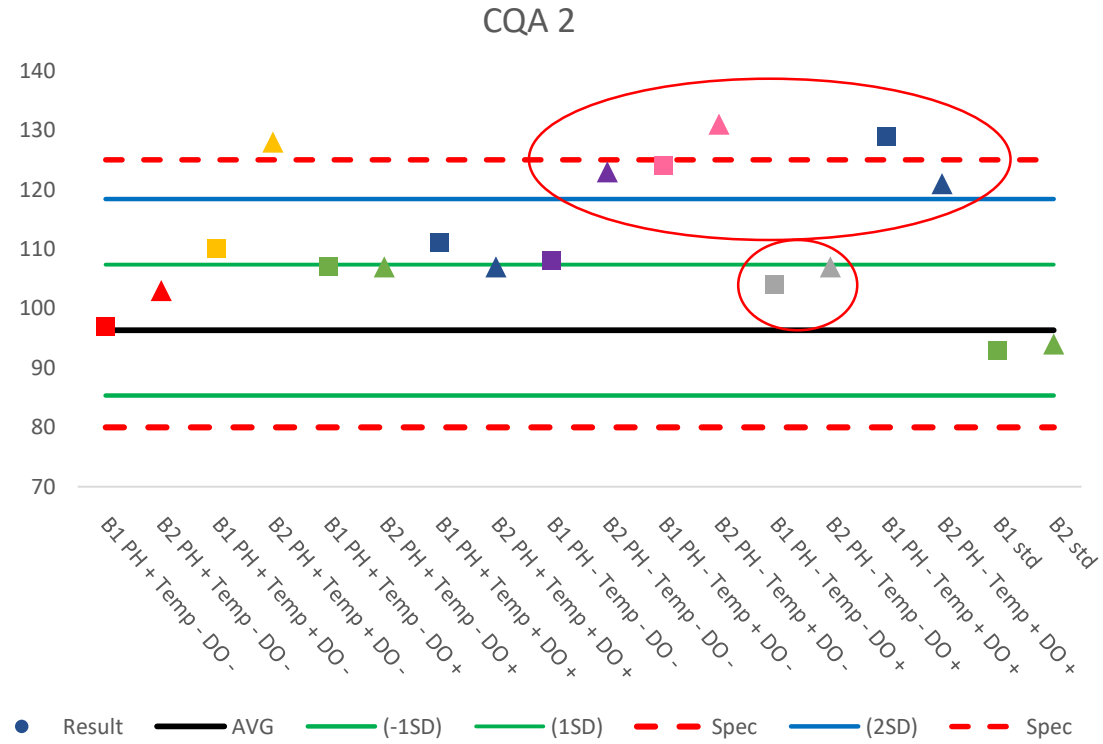
PROCESS PARAMETERS EFFECT ON YIELD



PROCESS PARAMETERS EFFECT ON CQA



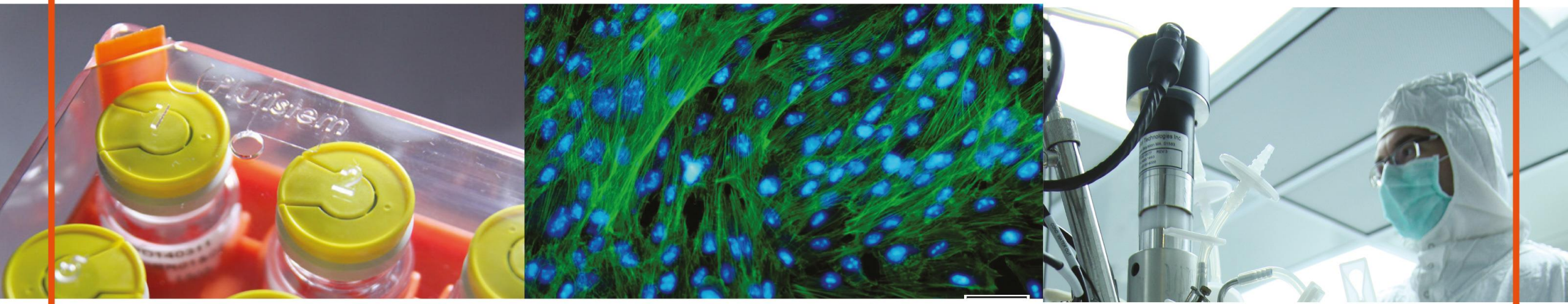


AUTOMATED CLOSED HARVESTING SYSTEM

- **Closed system**
- **Combination of enzymatic reaction and mechanical forces**
- **Efficient – high yield**
- **Maintaining the cell quality**
- **Full CFR 21 Part 11 compliant**

✓ **Proprietary innovative technology** to release and collect the adherent cells from the carrier in a closed and controlled system

SCALE UP AND SCALE OUT



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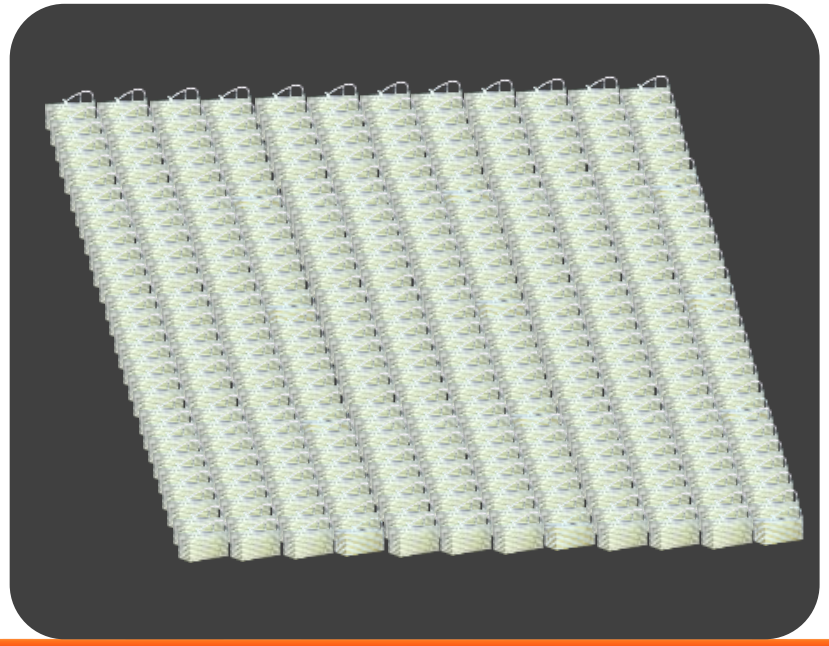
3D CULTURING – SCALE UP

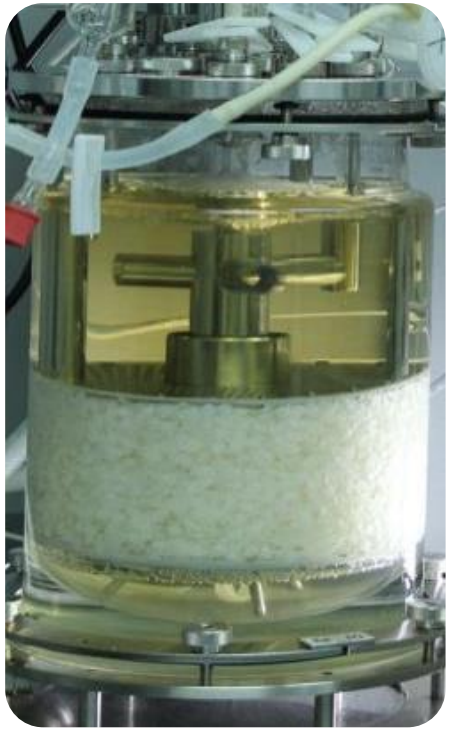
~10-15* Multi 10 Trays
~30-50* Multi 10 Trays
~100-160 *Multi 10 Trays



X 70 more efficient

=

2.5L bioreactor with **30g** scaffold
5L bioreactor with **100g** scaffold
15L bioreactor with **375g** scaffold



L – Liter | g – gram | SA – Surface Area | V – Volume
* Harvest Density Dependent

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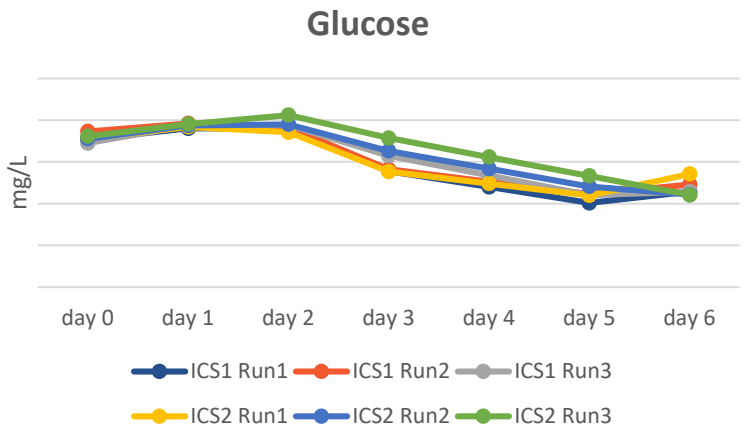
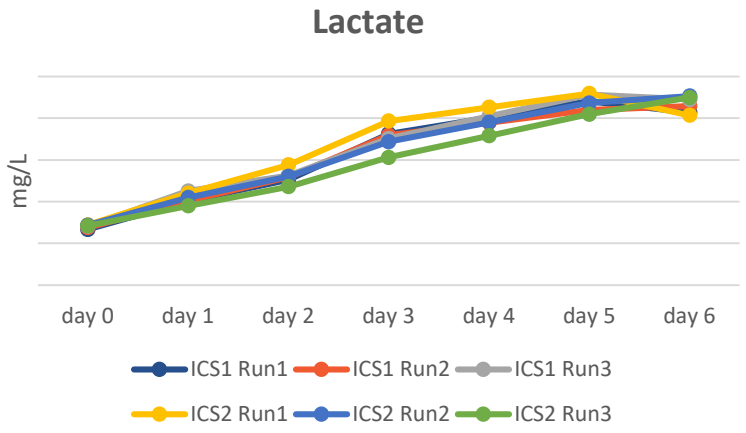
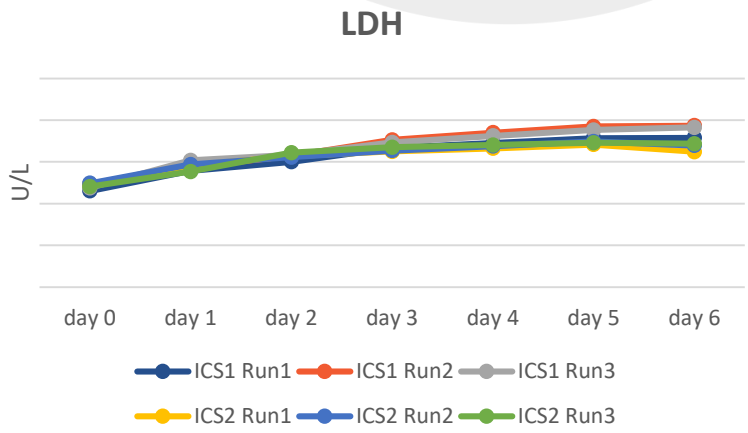
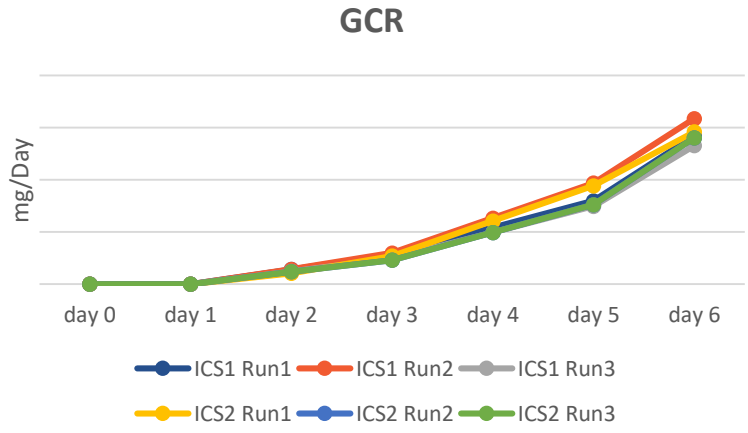
HIGH PROCESS CONTROL LEADS TO COMPARABILITY AND EFFICIENT SCALE OUT





Two ICS batches
6 Runs
12 Bioreactors

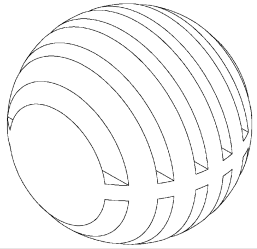


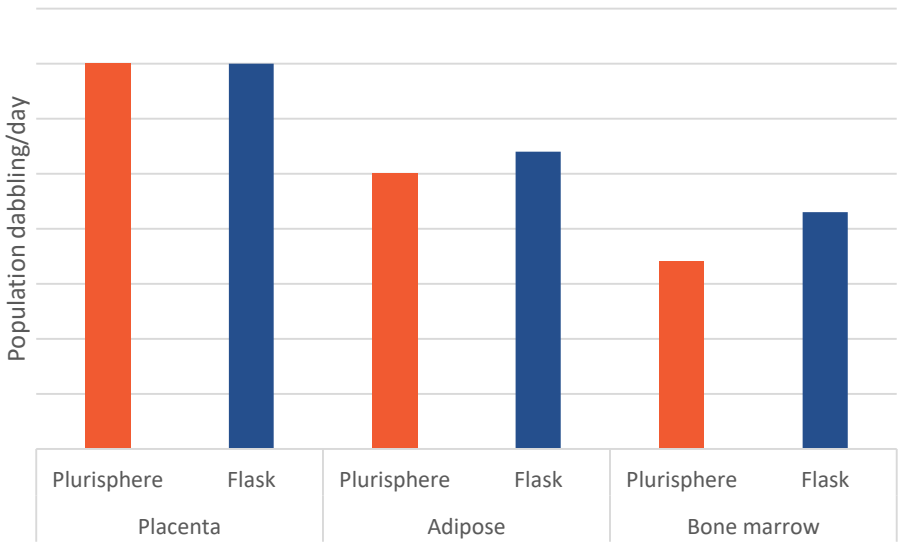


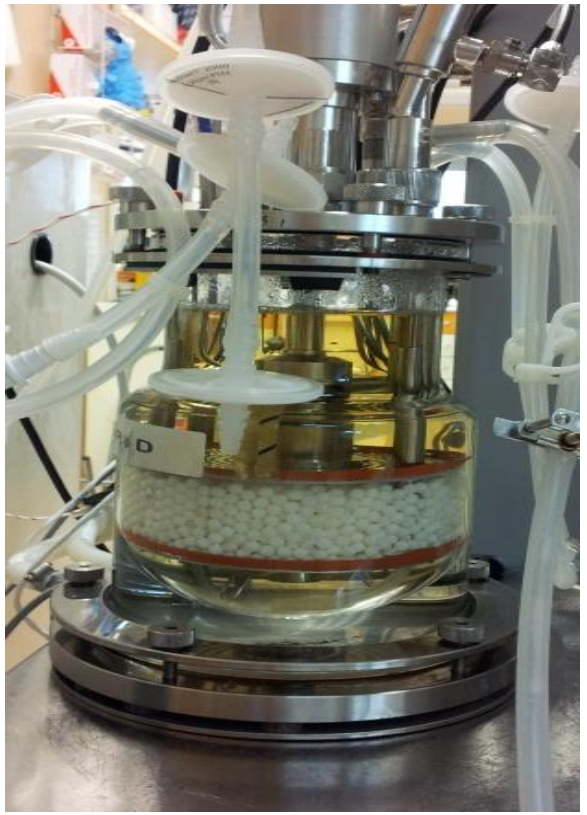
FUTURE WORK: 2D ADHERENT AUTOMATED AND CONTROLLED CELL SYSTEM

The Plurisphere carriers are designed to allow highly available surfaces with perfect media flow and low shear forces.

- ✓ Proven comparability on PLX cells
- ✓ Tested on human MSC's from Placenta Bone marrow and Adipose.
- ✓ Homogenous seeding
- ✓ Closed harvesting system
- ✓ Highly active and viable cells
- ✓ Reduction of media by 30-50%







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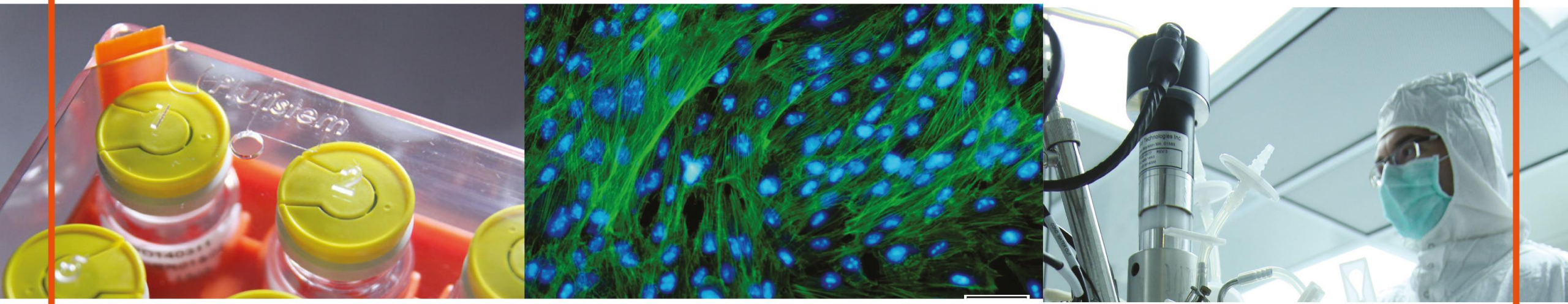
QUESTIONS?



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