Pharma&Biotech

Developing Commercializable Autologous Manufacturing Processes

SITC 2012

Robert Keefe / Lonza Walkersville, Inc., Walkersville, MD 21793 / 26 October 2012

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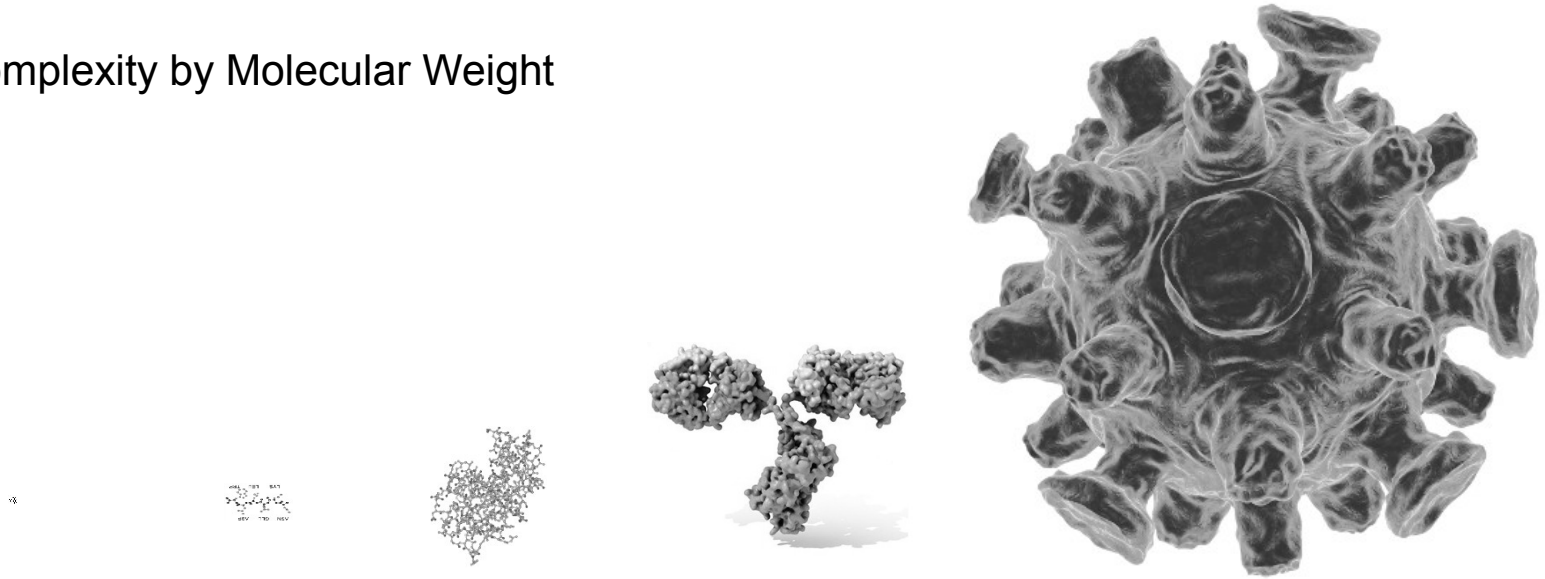
Lonza is a Life Science-focused Manufacturer

Complexity by Molecular Weight



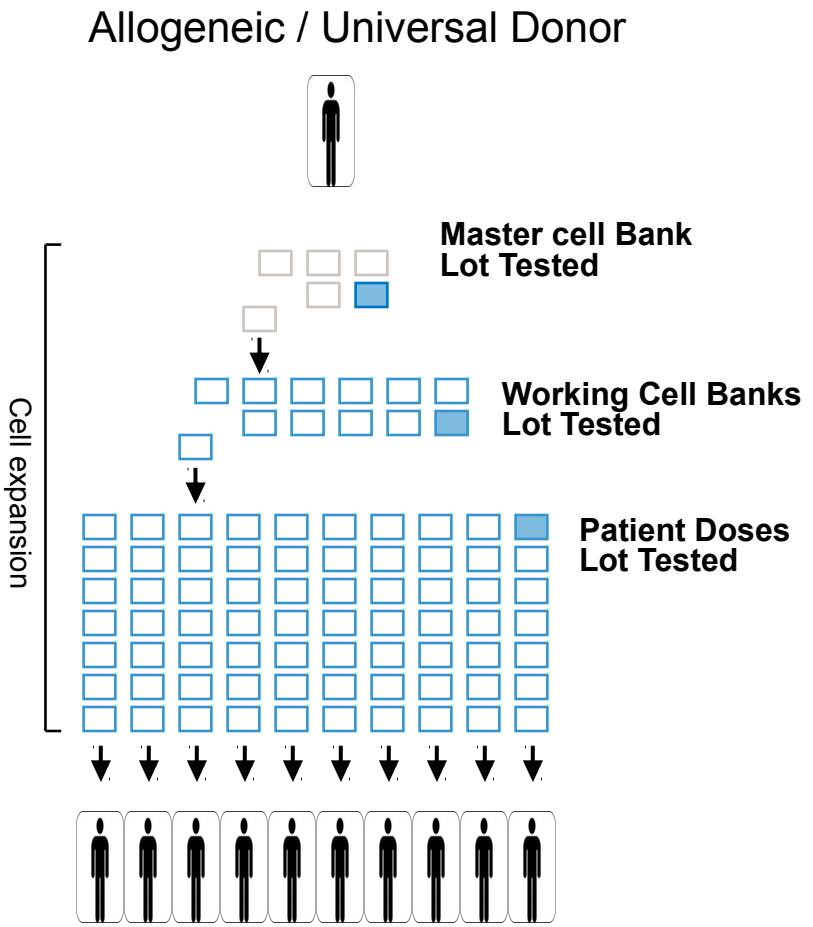
Chemical Molecule	Peptide	Protein	Antibody	Virus	Cell / Tissue
Aspirin (180 Da)	6mer (804 Da)	Lysozyme (14,700 Da)	Immunoglobulin G (150,000 Da)	Influenza (176 x106 Da)	Animal Cell Surface

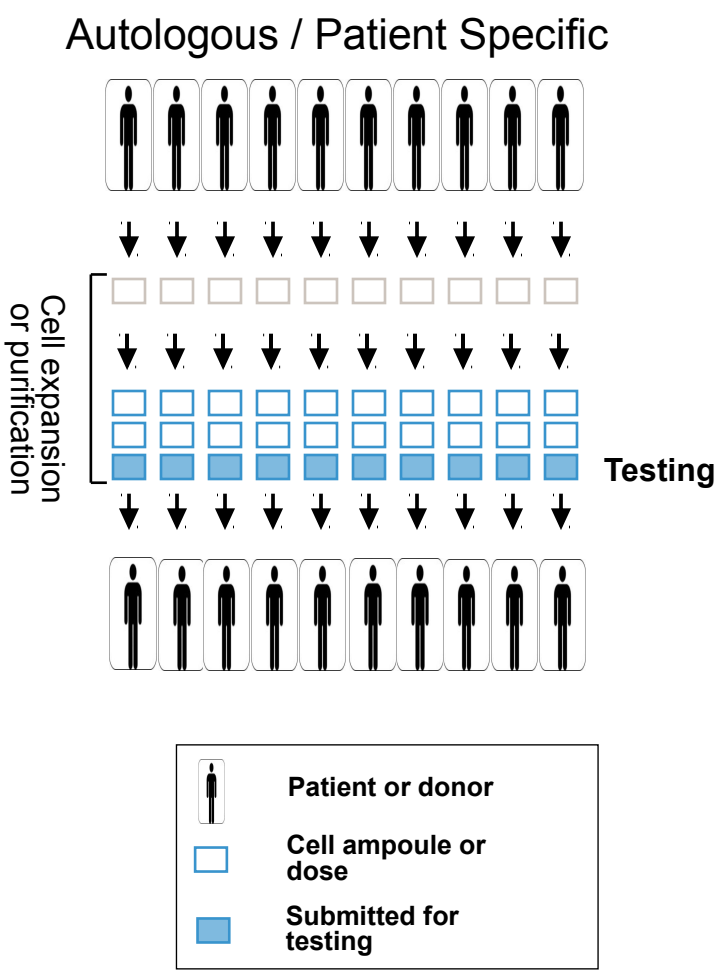
Increasing Molecular Weight (MW)

What Lonza Does

- Tissue acquisition
- Media formulation
- Process development and optimization
- cGMP manufacturing of viral vectors
- Assay development and validation
- Cell banking
- cGMP manufacturing of both **autologous** and **allogeneic** therapies
- Product testing and release
- Regulatory filing support
- Packaging
- Distribution

Allogeneic versus Autologous Manufacturing





A Framework for Cell Therapy Product Development

1. Know your cells; Know your product
2. Know your cost of goods
3. Know your process

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Know Your Cells – Cell Characterization

- Assays
  - Cell count and viability
  - Proliferation (MLR)
  - ELISA
  - Flow Cytometry
  - ELISPOT
  - Target Lysis (CTL)
  - CBA
  - Gene array/expression

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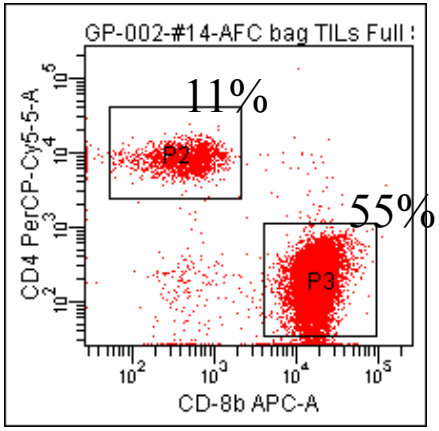
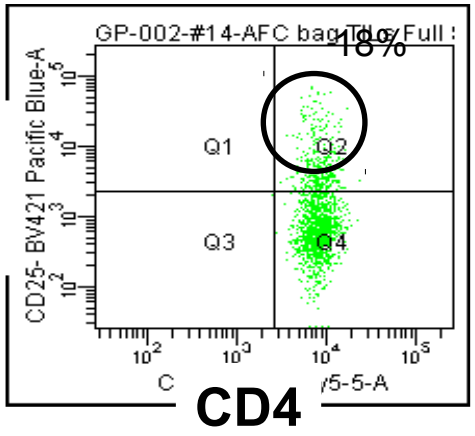
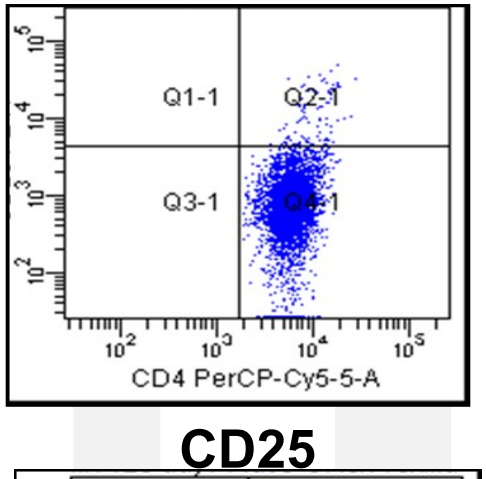
Know Your Cells – Cell Characterization

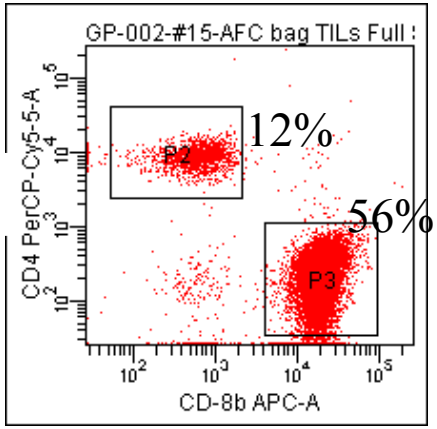
Process 1

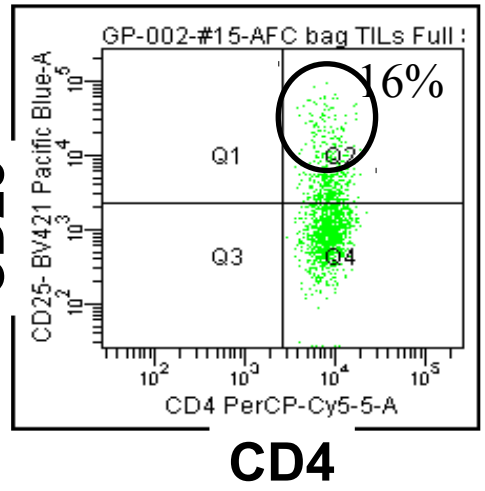


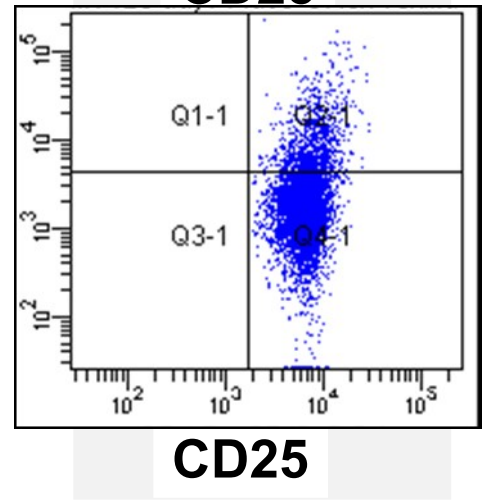




Process 2







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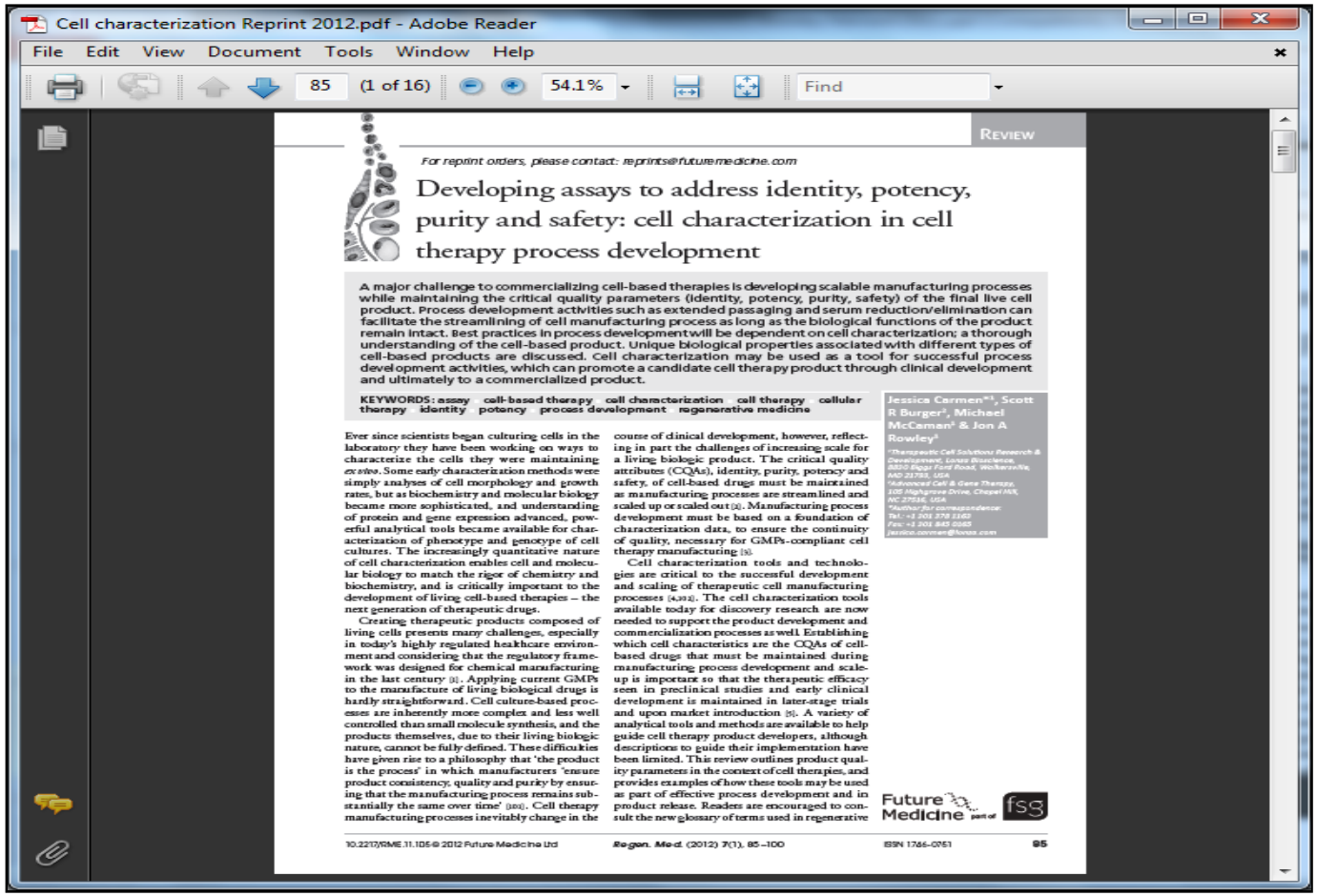
Know Your Cells


Cell characterization Reprint 2012.pdf - Adobe Reader

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REVIEW

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Developing assays to address identity, potency, purity and safety: cell characterization in cell therapy process development

A major challenge to commercializing cell-based therapies is developing scalable manufacturing processes while maintaining the critical quality parameters (identity, potency, purity, safety) of the final live cell product. Process development activities such as extended passaging and serum reduction/elimination can facilitate the streamlining of cell manufacturing process as long as the biological functions of the product remain intact. Best practices in process development will be dependent on cell characterization; a thorough understanding of the cell-based product. Unique biological properties associated with different types of cell-based products are discussed. Cell characterization may be used as a tool for successful process development activities, which can promote a candidate cell therapy product through clinical development and ultimately to a commercialized product.

KEYWORDS: assay cell-based therapy cell characterization cell therapy cellular therapy identity potency process development regenerative medicine

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Ever since scientists began culturing cells in the laboratory they have been working on ways to characterize the cells they were maintaining *ex vivo*. Some early characterization methods were simply analyses of cell morphology and growth rates, but as biochemistry and molecular biology became more sophisticated, and understanding of protein and gene expression advanced, powerful analytical tools became available for characterization of phenotype and genotype of cell cultures. The increasingly quantitative nature of cell characterization enables cell and molecular biology to match the rigor of chemistry and biochemistry, and is critically important to the development of living cell-based therapies – the next generation of therapeutic drugs.

Creating therapeutic products composed of living cells presents many challenges, especially in today's highly regulated healthcare environment and considering that the regulatory framework was designed for chemical manufacturing in the last century [1]. Applying current GMPs to the manufacture of living biological drugs is hardly straightforward. Cell culture-based processes are inherently more complex and less well controlled than small molecule synthesis, and the products themselves, due to their living biologic nature, cannot be fully defined. These difficulties have given rise to a philosophy that 'the product is the process' in which manufacturers 'ensure product consistency, quality and purity by ensuring that the manufacturing process remains substantially the same over time' [2,3]. Cell therapy manufacturing processes inevitably change in the course of clinical development, however, reflecting in part the challenges of increasing scale for a living biologic product. The critical quality attributes (CQAs), identity, purity, potency and safety, of cell-based drugs must be maintained as manufacturing processes are streamlined and scaled up or scaled out [3]. Manufacturing process development must be based on a foundation of characterization data, to ensure the continuity of quality, necessary for GMPs-compliant cell therapy manufacturing [3].

Cell characterization tools and technologies are critical to the successful development and scaling of therapeutic cell manufacturing processes [4,5]. The cell characterization tools available today for discovery research are now needed to support the product development and commercialization processes as well. Establishing which cell characteristics are the CQAs of cell-based drugs that must be maintained during manufacturing process development and scale-up is important so that the therapeutic efficacy seen in preclinical studies and early clinical development is maintained in later-stage trials and upon market introduction [6]. A variety of analytical tools and methods are available to help guide cell therapy product developers, although descriptions to guide their implementation have been limited. This review outlines product quality parameters in the context of cell therapies, and provides examples of how these tools may be used as part of effective process development and in product release. Readers are encouraged to consult the new glossary of terms used in regenerative

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Future Medicine part of fsg

Know Your Product

- **Target Product Profile (TPP)**
- Your cells of identity A, B, C and potency measures X, Y, Z
  - At a specified viable cell number per dose?
  - At what volume?
  - Suspended in what solution?
  - At what purity?
  - Stored in what container?
    - At what temperature?
    - For how long?
  - Administered to the patient by who, and with what?
- What is your target indication, and how many product doses are required per year?
  - By clinical phase and once on market
  - → Yearly production needs

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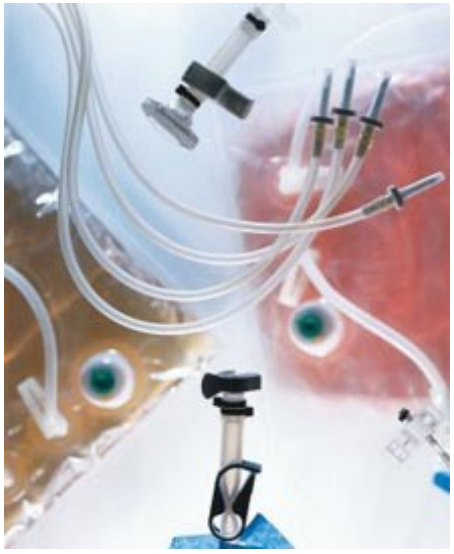
Know Your Cost of Goods (CoGs)



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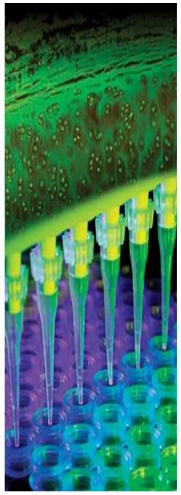
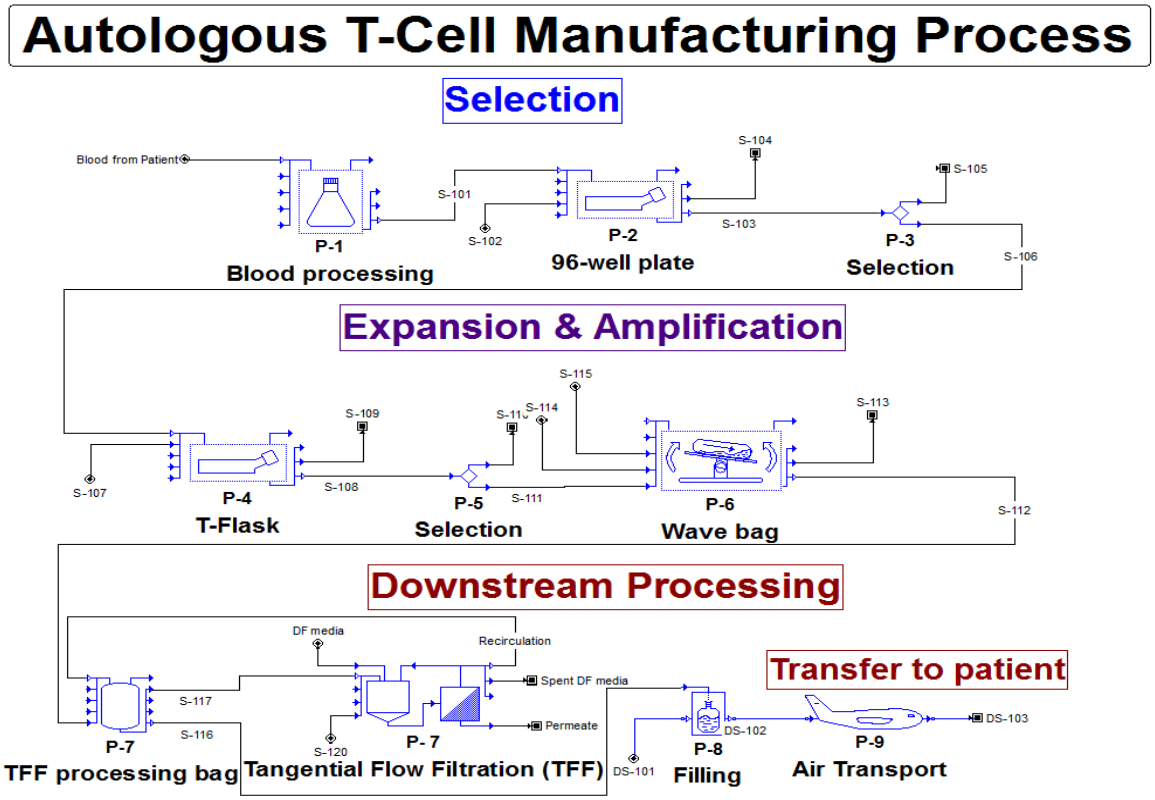


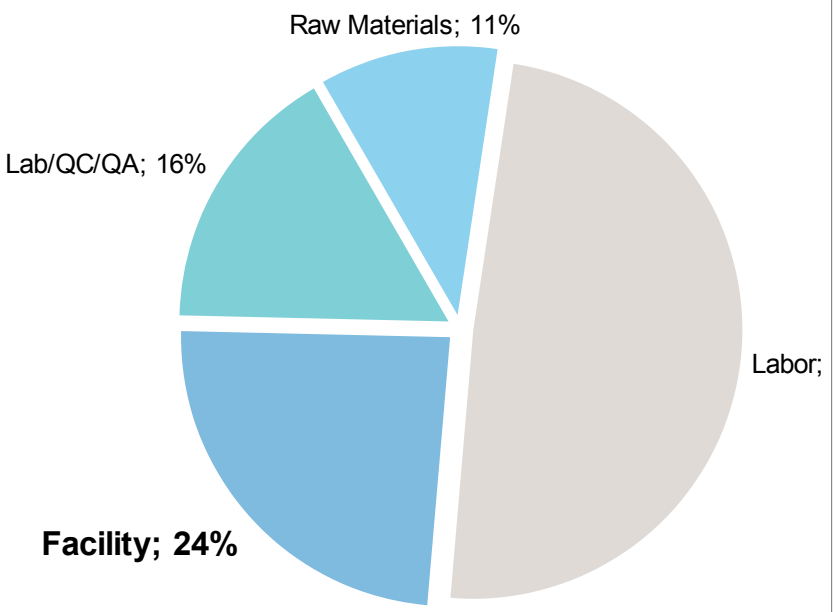
Know Your Costs: Process Modeling

Tool for process streamlining, capacity modeling and understanding CoGs impact



Know Your Costs –30 Day Process from Isolation to Scaled Up Wave

Isolation



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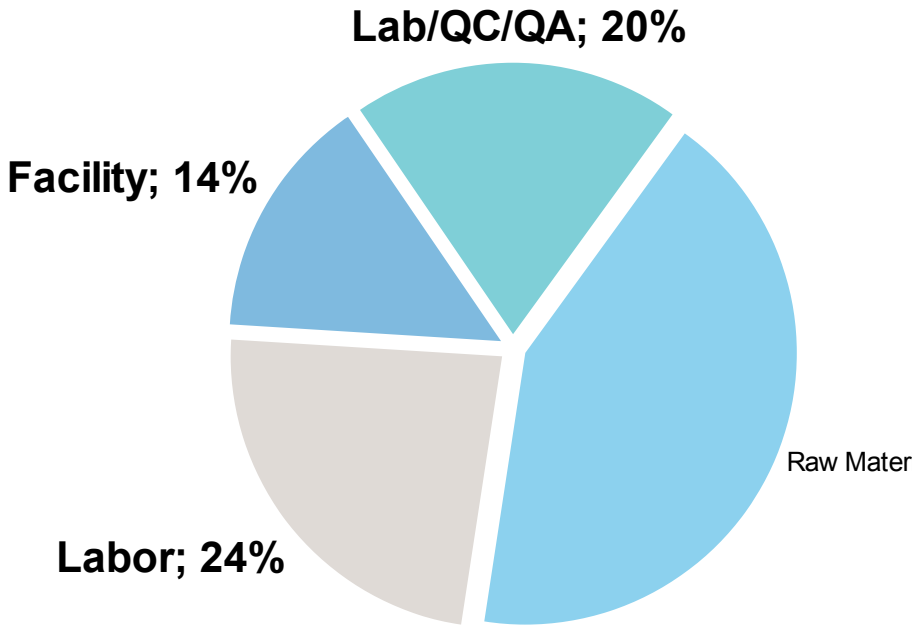
Expansion and harvest



~70%

Know Your Costs: Opportunity to Streamline Raw Materials in Late Expansion Phase of Process

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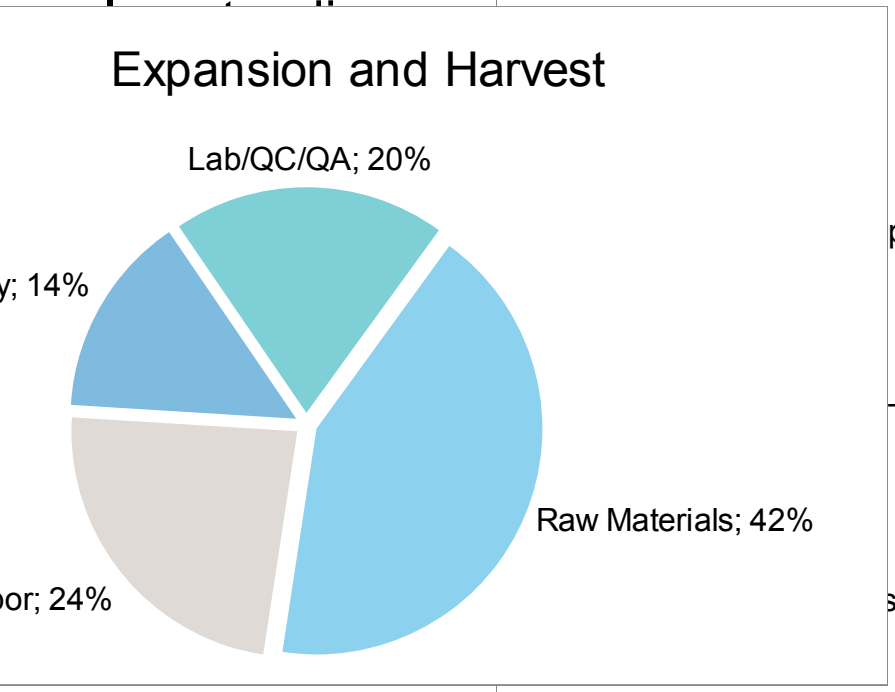

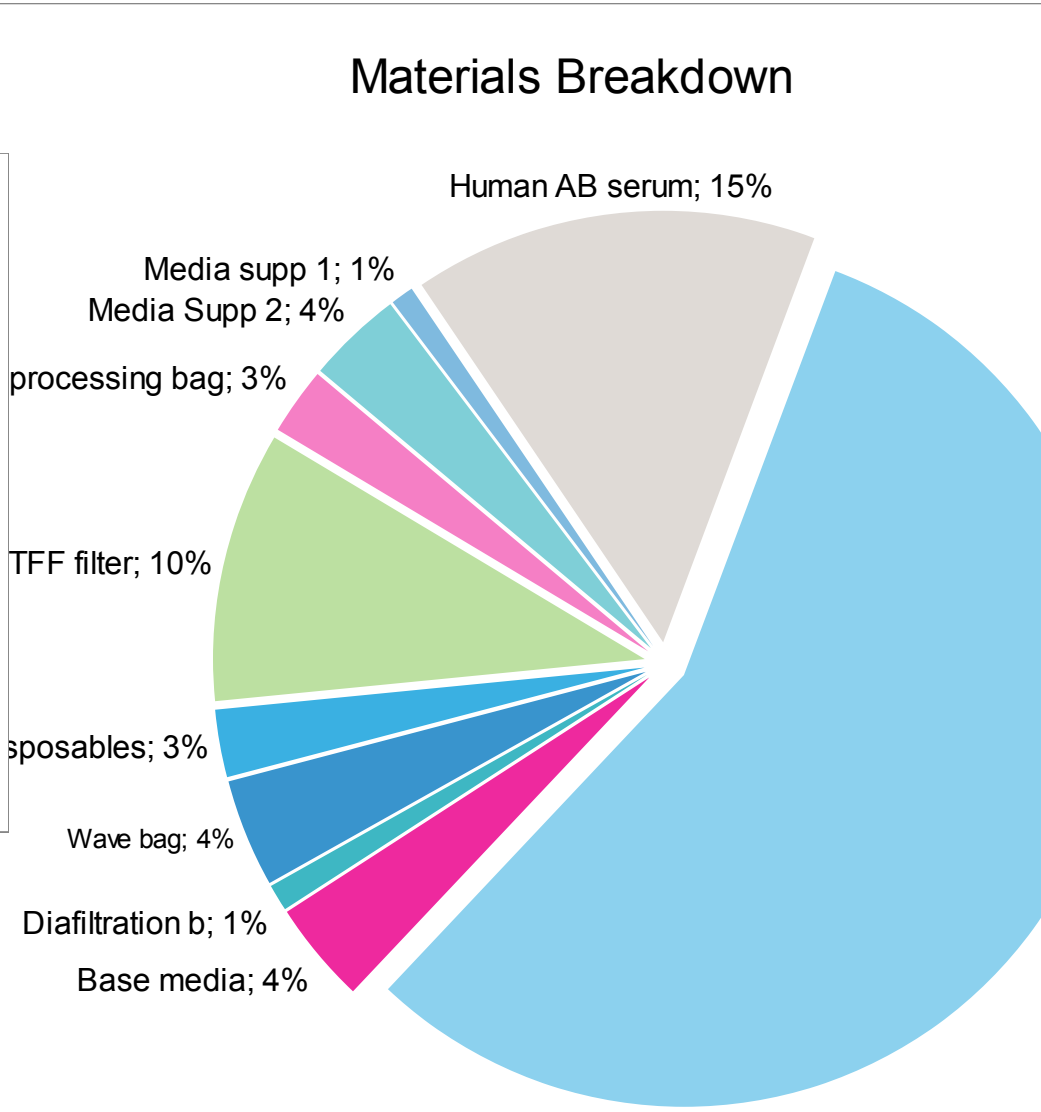

Know Your Costs: Reducing One Cost Driver Highlights Additional Targets for Process Improvements

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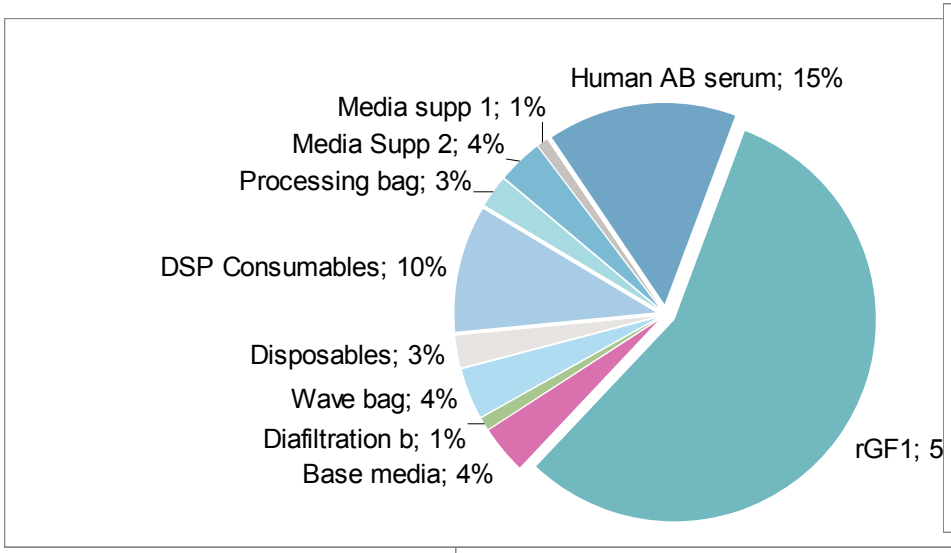
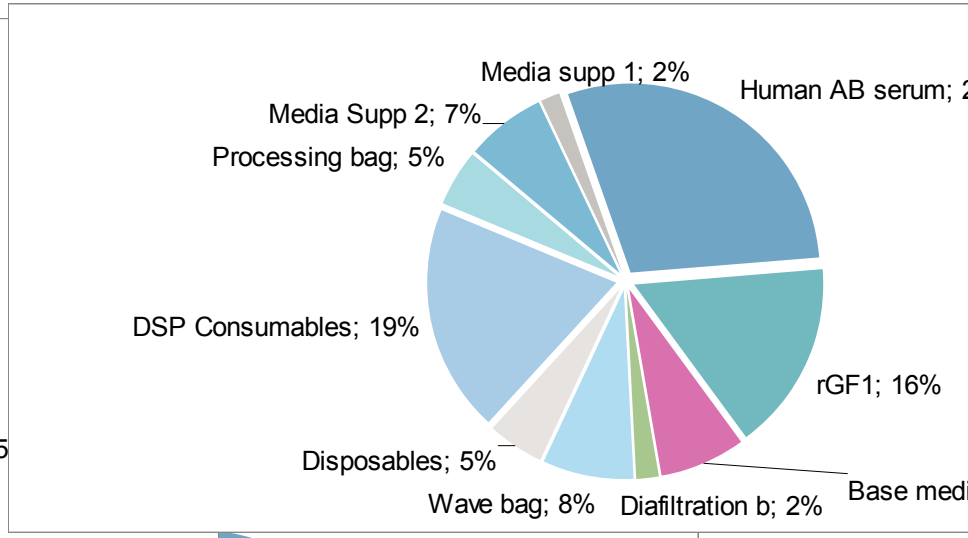
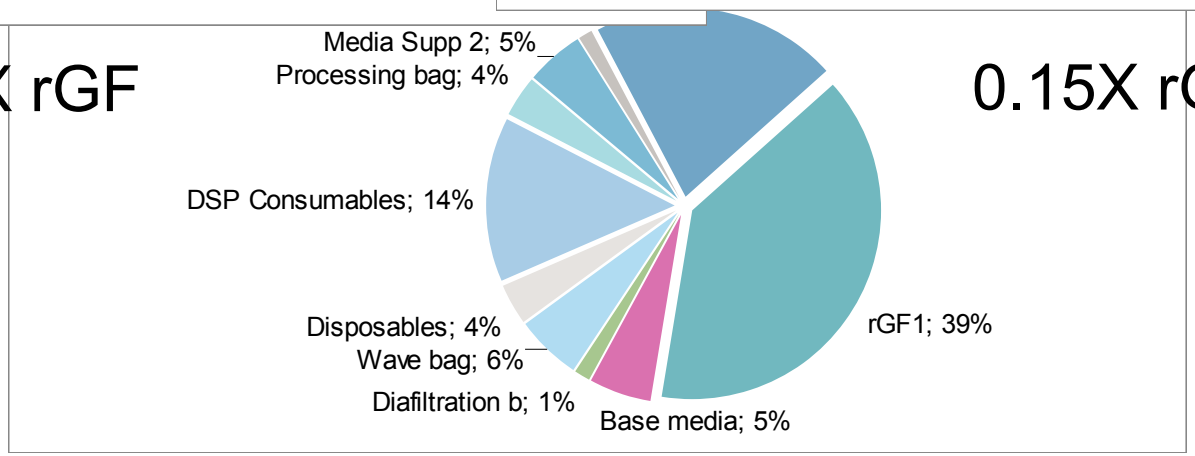


1X rGF



0.15X rGF



0.5X rGF

Know Your Process

- Explore process changes that target high cost areas
- Minimize raw material risks
  - Animal origin reagents
  - Supply risks – secondary suppliers, peak serum

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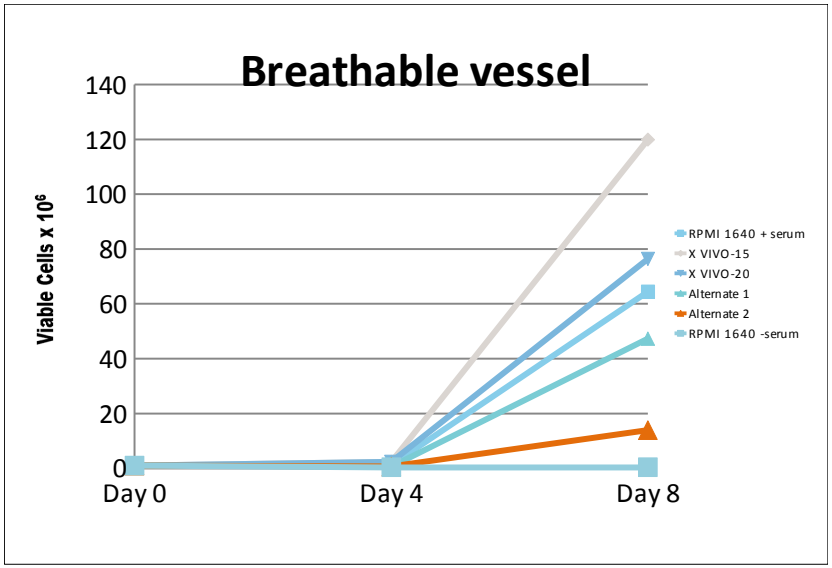
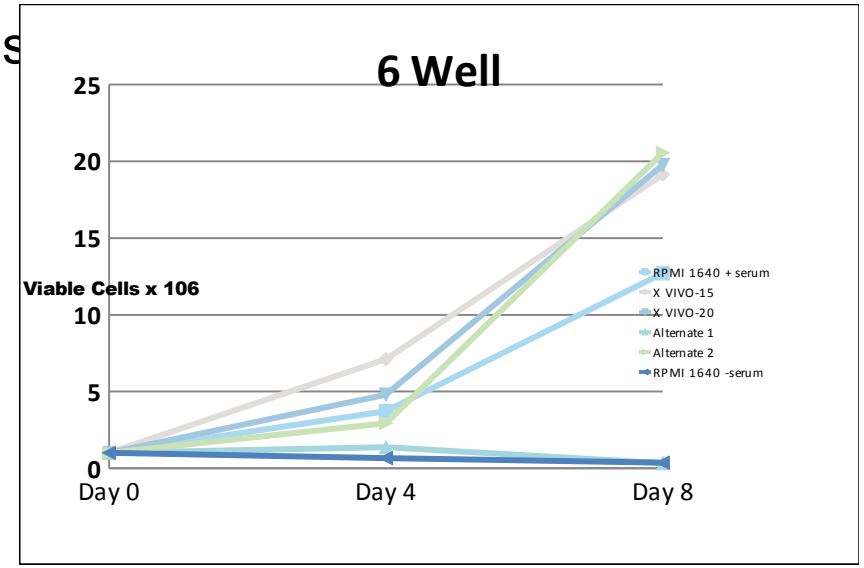
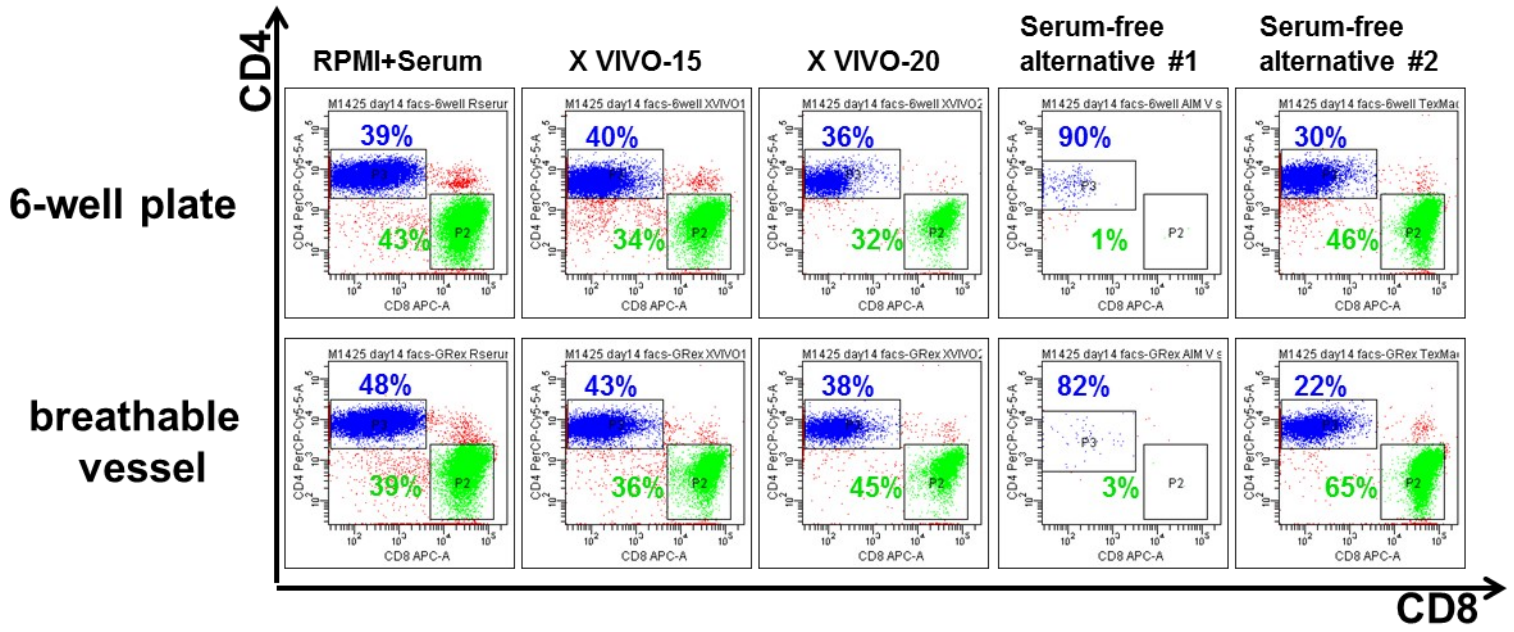
Media Selection can Produce T-cells with Reduced Cost and Regulatory Risk





- Serum free media can reduce cost with improved or comparable performance, better regulatory profile, and supply de-risk.

Serum Reduction Maintains Critical Quality T-cell Phenotype



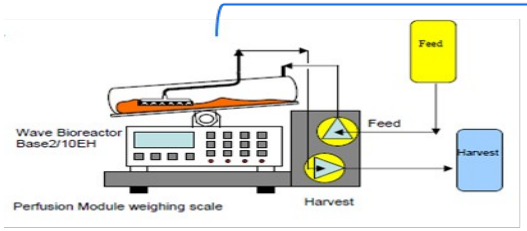
Know Your Process

- Explore process changes that target high cost areas
- Minimize raw material risks
  - Animal origin reagents
  - Supply risks – secondary suppliers, peak serum
- Implement closed systems and automated technologies

Insert a picture by clicking on the symbol

Know Your Process – Large Scale T-cell Expansion – Closed Systems

4 x 



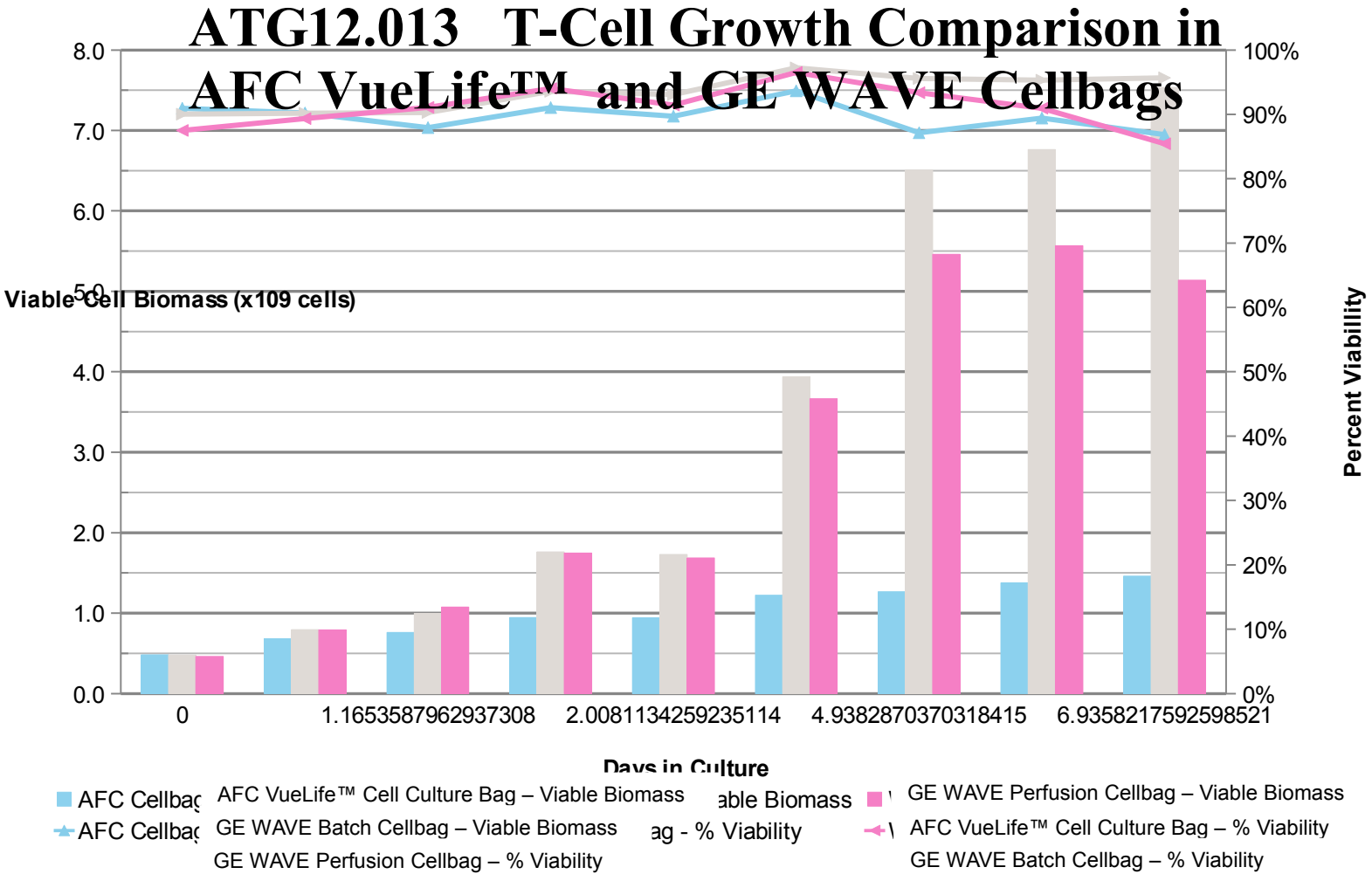
2L GE WAVE Perfusion Cellbag

2L GE WAVE Cellbag

1L AFC VueLife™ Cell Culture Bag

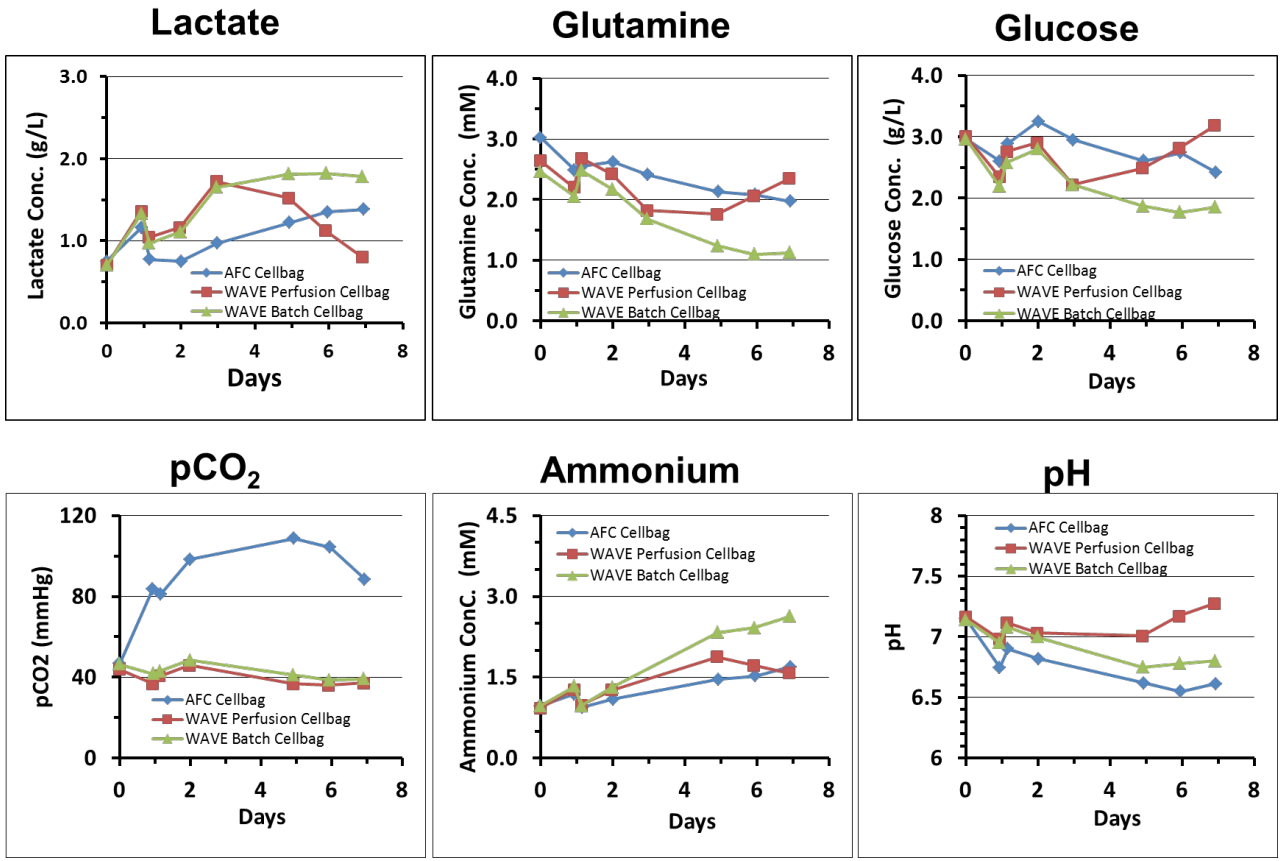
- Closed System culture reduces
  - Cost (through labor)
  - Risk (of contamination)

Large Scale T-cell Expansion. Closed System with Perfusion Reduces Labor, Increases Media



Closed System Easily Allows Monitoring Metabolites

This is critical to optimizing feed schedules, perfusion rates, and nutrient levels



Know Your Process

- Explore process changes that target high cost areas
- Minimize raw material risks
  - Animal origin reagents
  - Supply risks – secondary suppliers, peak serum
- Implement closed systems and automated technologies
- Don’t underestimate downstream process development

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Downstream Processing
Single-use Tangential Flow Filtration (TFF)

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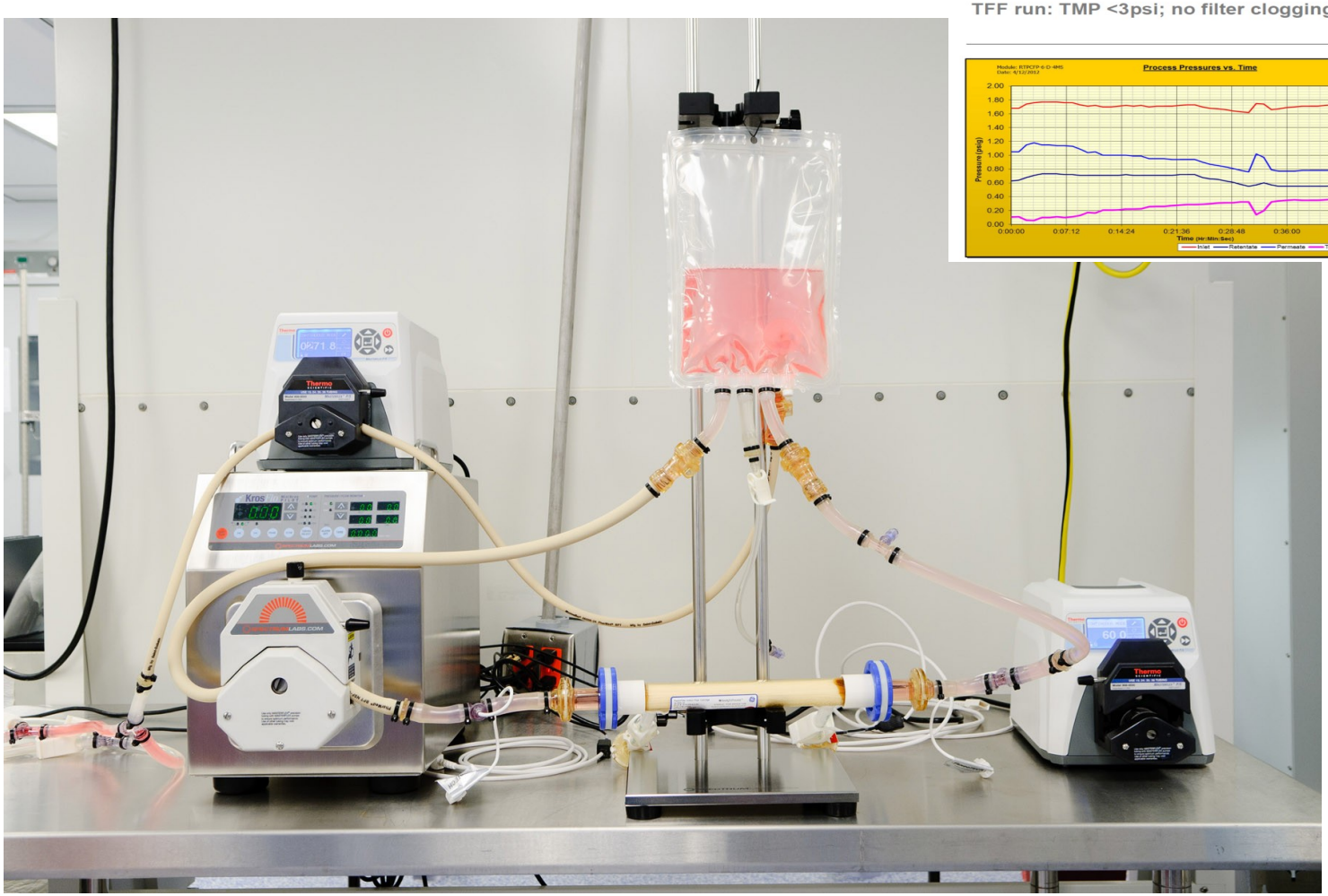

TFF run: TMP <3psi; no filter clogging

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Shear Rate is a Critical Parameter that Significantly Affects Cell Viability

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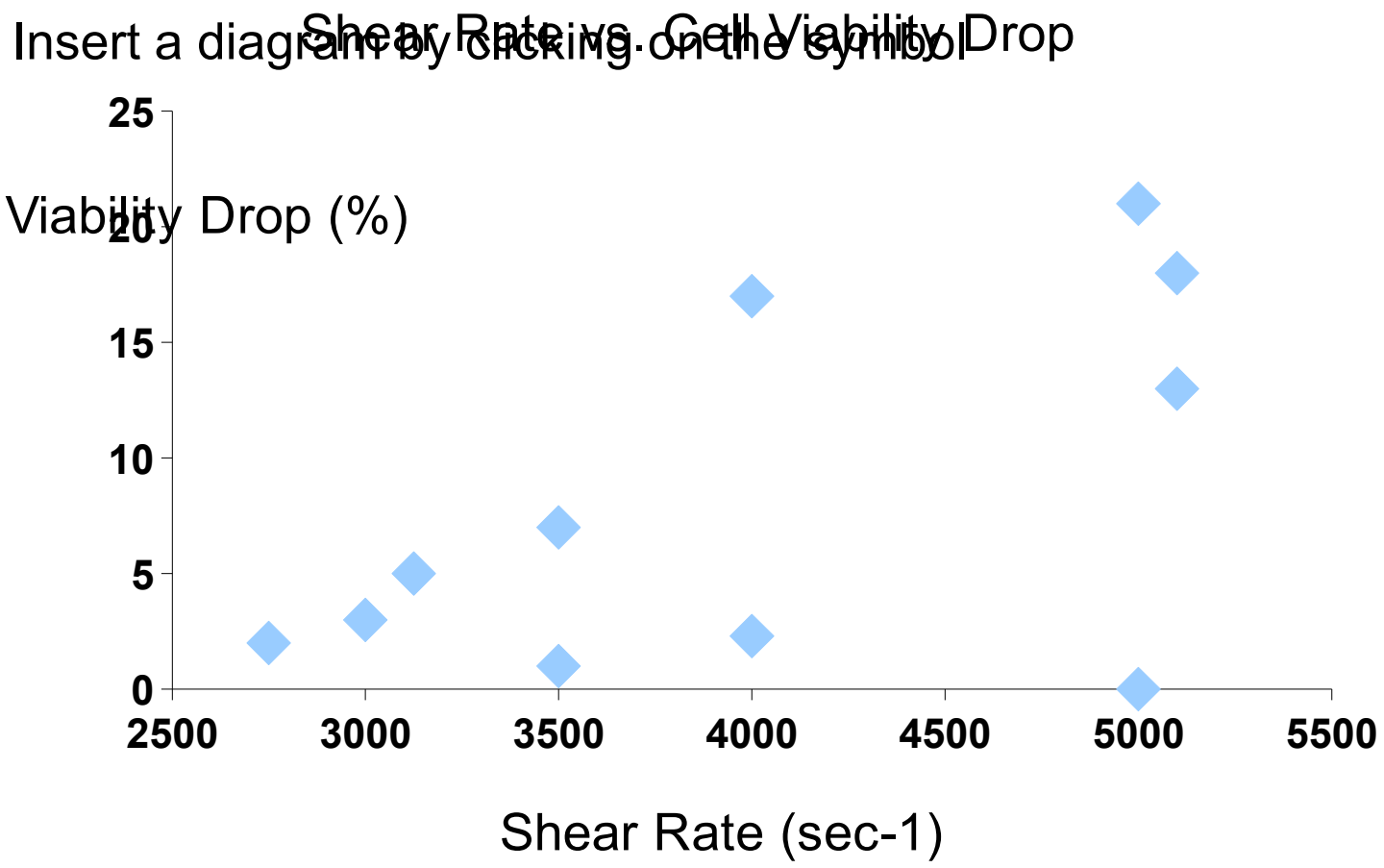
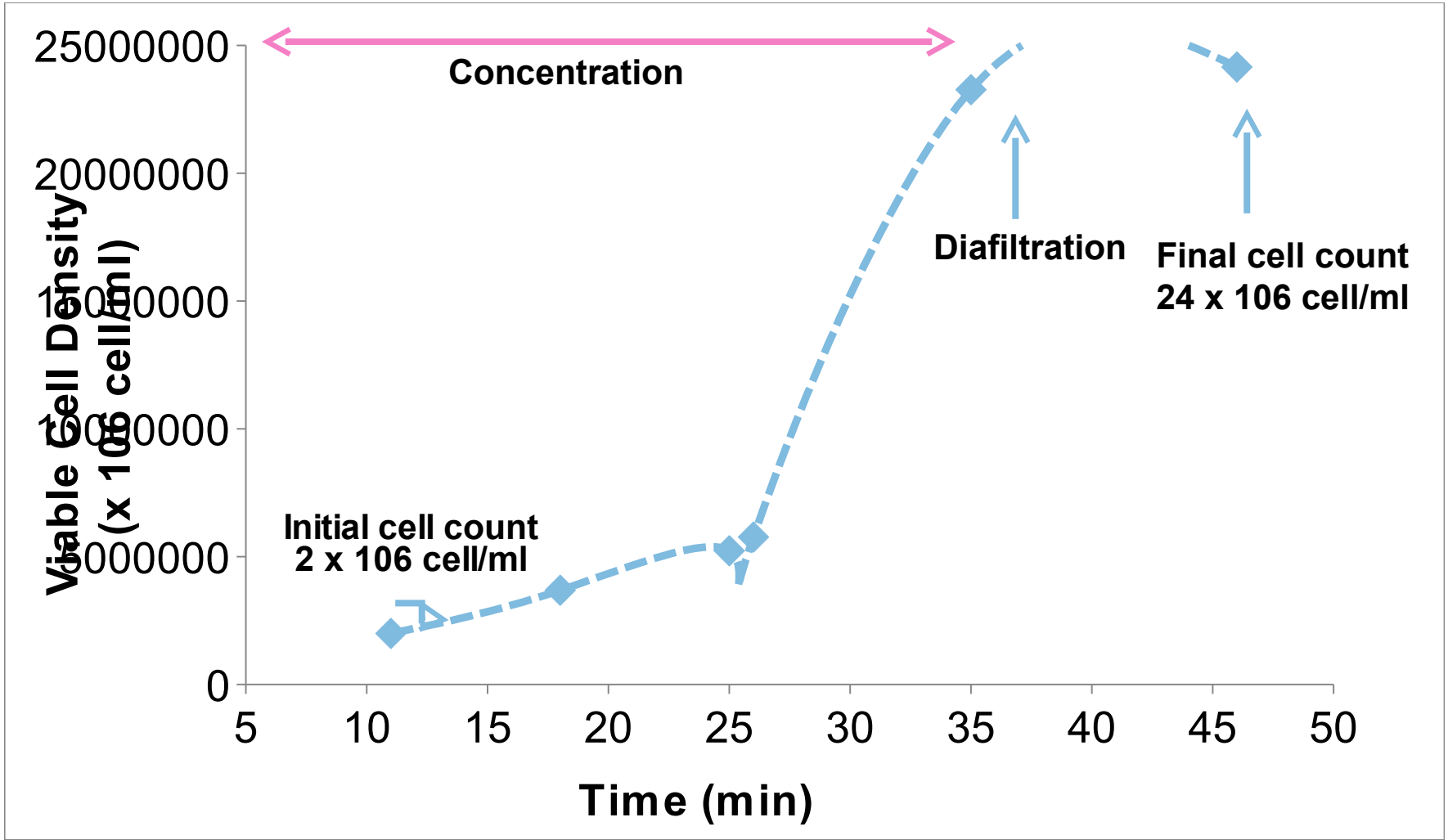
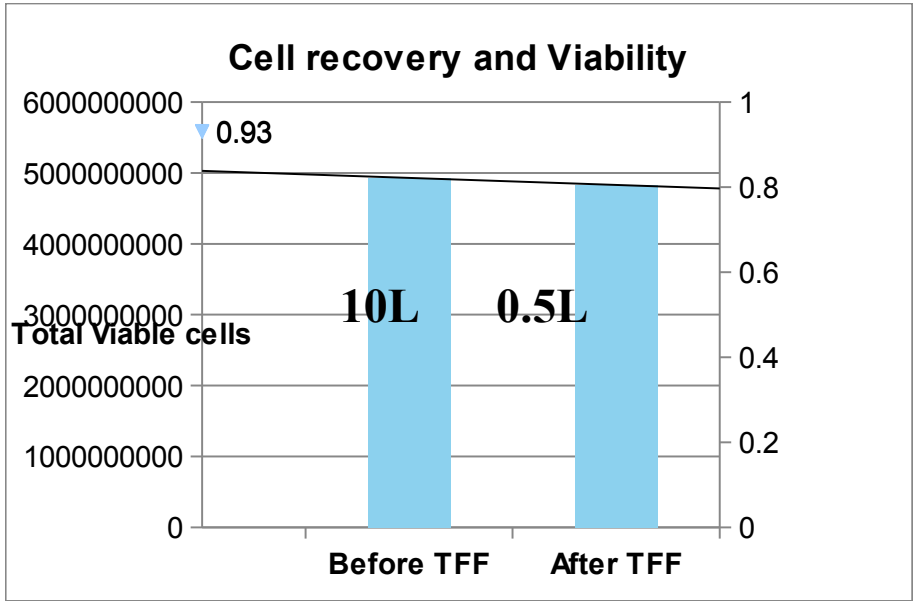


Viable Cell Density during T-cell TFF Process

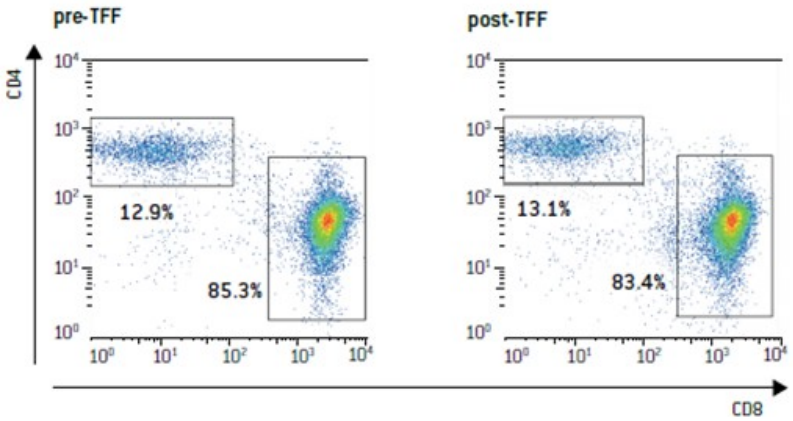


Viable Cell Density during T-cell TFF Process

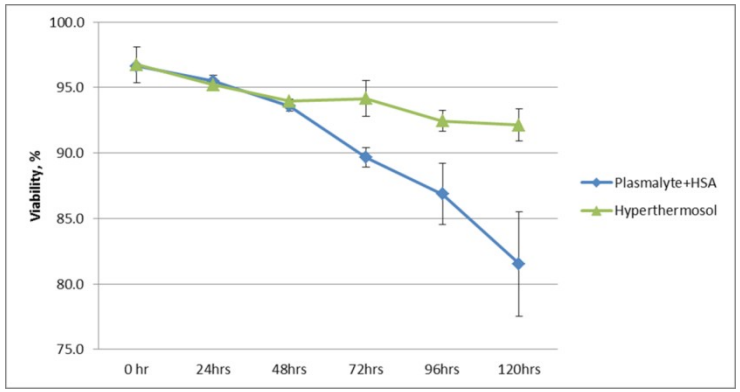
No drop in cell viability



Phenotype is maintained

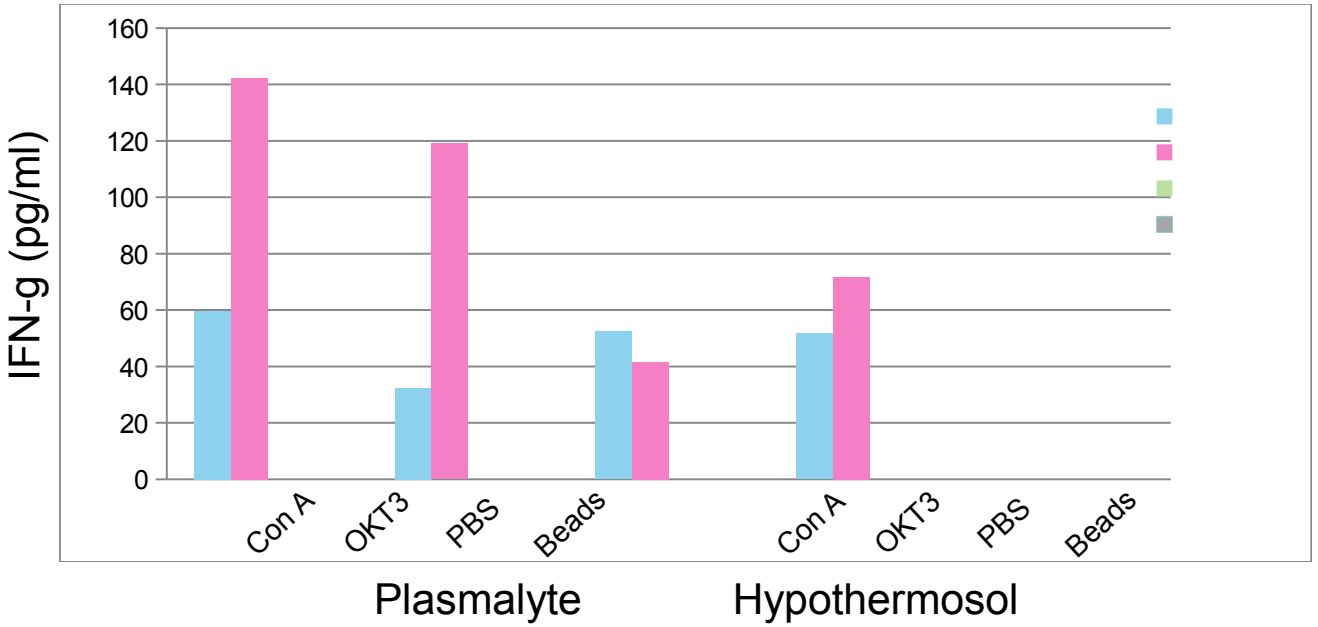


Large Scale T-cell with Functional Data at 120 Hours



Cells are stored at 1x10 8/ml in Hypothermosol or Plasmalyte with HSA at 4C. Vials are sampled at intevals and counted for cell number and viability

Cells at 120 hours are plated for 24 hours and measured for IFN-g release



Know Your Process

- Explore process changes that target high cost areas
  - Reducing Growth Factors levels
- Minimize raw material risks
  - XVIVO-20/15
- Implement Closed technologies
  - Wave Cellbags
  - TFF
- Biospreservation
  - Hypothermosol

Insert a picture by clicking on the symbol

Designing High Impact Cell Therapy Process Development Programs

- Know your cells; Know your product
- Know your cost of goods
- Know your process

Insert a picture by clicking on the symbol

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Thank You!