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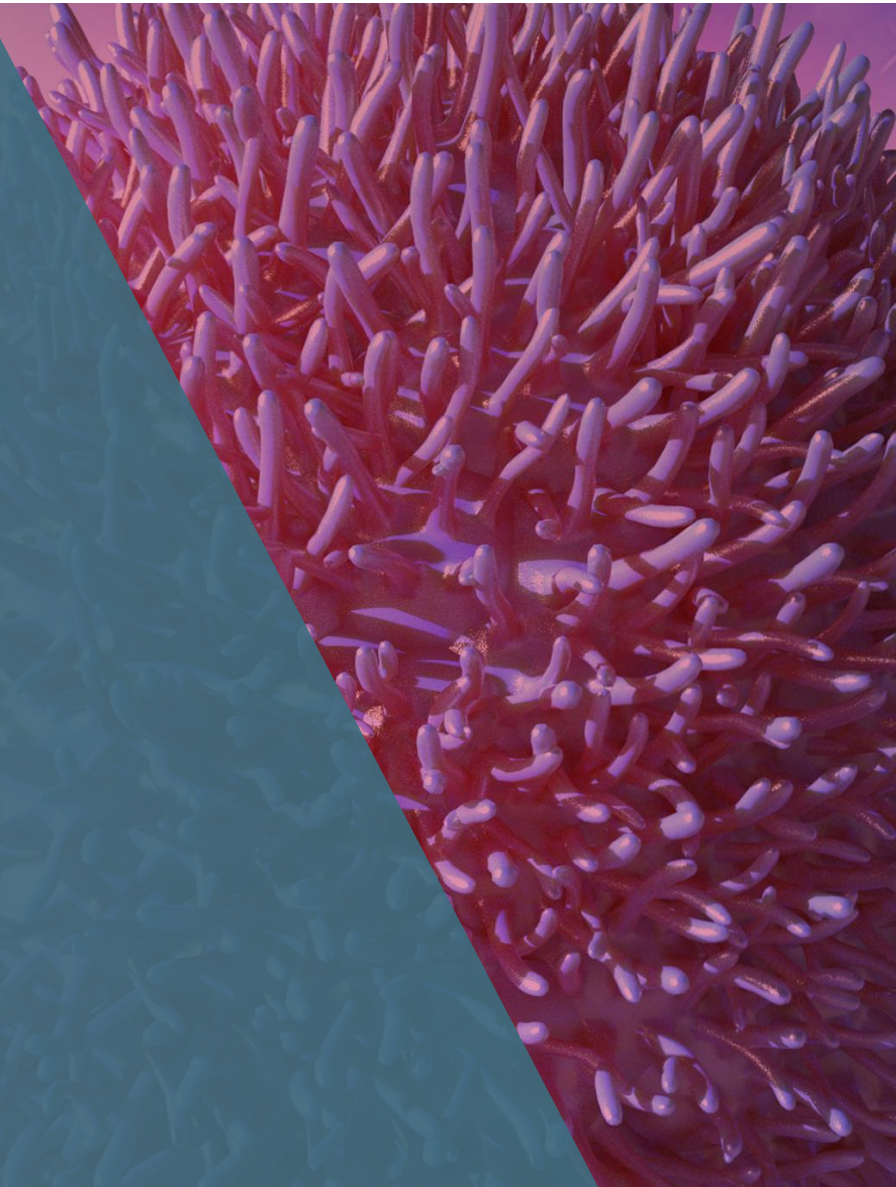
LASER FORCE CYTOLOGY™

Quantitative Cell Characterization Using Laser Force Cytology (LFC): The Future of Precision Analytics for Improved Manufacturing Success



Colin Hebert, PhD
Senior Vice President, Scientific and Business Operations

CASSS WCBP 2025
January 28, 2025

Biomanufacturing Advanced Therapies is Complicated

Starting materials are complex, variable, and difficult to characterize, reducing process and product consistency.

Delayed and imprecise analytics result in lost process and production efficiency, delaying delivery of life saving treatments.

Large biological variability throughout manufacturing processes results in batch-to-batch variability and potential for OOS/OOT and batch failure events.

Current Analytics ⇨ Slow ✚ ✚ ✚

Robust cellular characterization throughout a process paves the way for predictive insights, rapid optimization and adaptive manufacturing

LFC Technology Background | **Vaccines and Viral Vectors** | **Stem Cell Therapies** | **CAR T Cell Therapies**

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Real-time Label-free Single Cell Analysis Provides Solutions

- **Label-free cellular PAT analytics** reduce the need for antibodies, provide unbiased measurements and enable the sensitive measurement of cellular changes
- **Accurate, precise and non-subjective** multivariate data comprehensively characterize complex starting materials and products
- **Real-time analytics increase process knowledge**, enable improved process controls and optimization, and maximize product quality, yield, and shelf life
- **Quantitative precision analytics allows biological evidence** to be carried forward from early process development, production and QC
- **Reduced labor and waste** significantly lowering costs and accelerates time to patient

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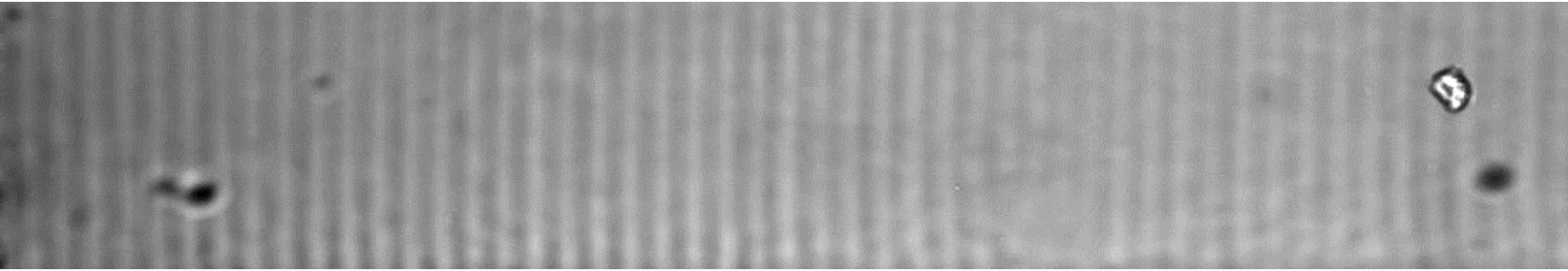
Laser Force Cytology™

Label-free, single cell analysis based on **intrinsic biochemical & biophysical properties** using a balance of optical and hydrodynamic forces in a microfluidic channel



Virally infected Vero cells

Laser (Optical Force) → Velocity ∝ $F_{Optical}$ ← Fluid Flow (Drag Force)

- An **optical force** is generated when a **laser beam reflects and refracts through a cell**
- Laser Force Cytology™ measures velocity (optical force) and other parameters to detect **subtle phenotypic changes in cells,** rapidly measuring **quantitative early indicators** of cellular response **to viral infection, activation, transfection and differentiation**
- Applications in **cell and gene therapy, vaccine development, and biomanufacturing**

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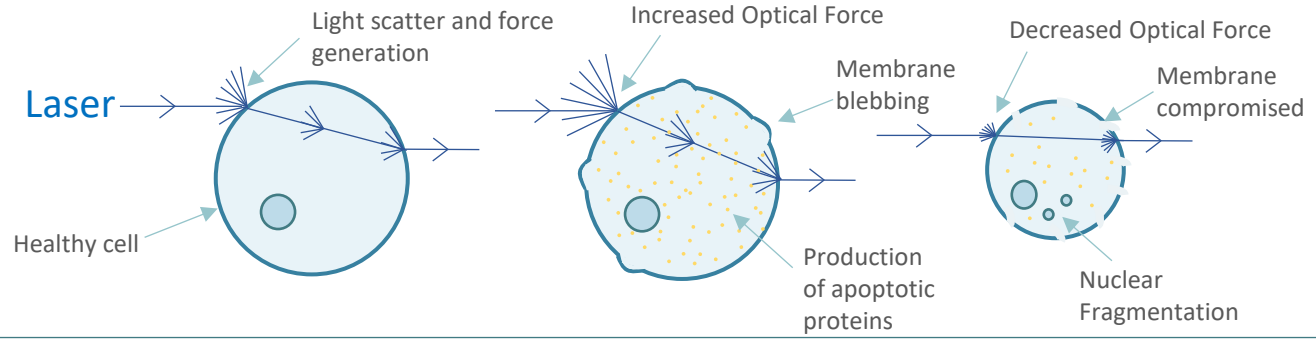
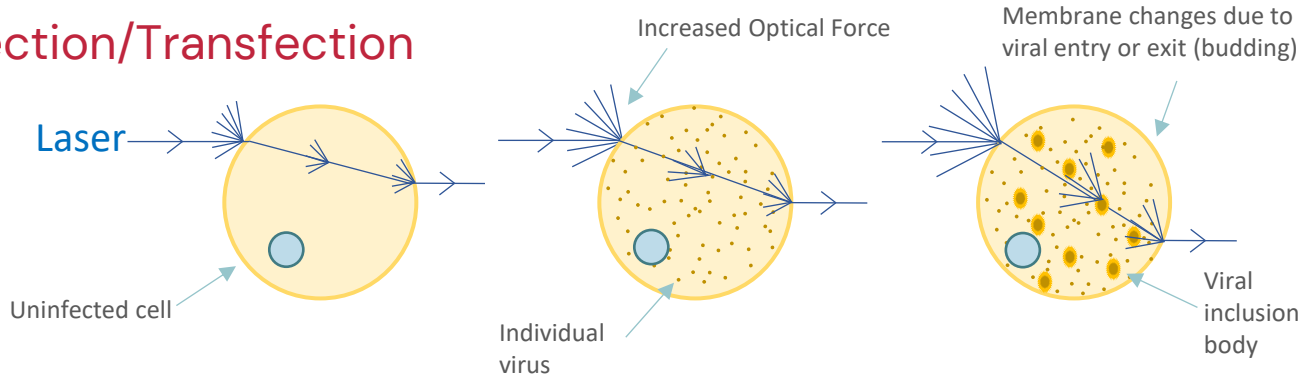
HOW DOES LASER FORCE CYTOLOGY™ CONNECT TO BIOLOGY?

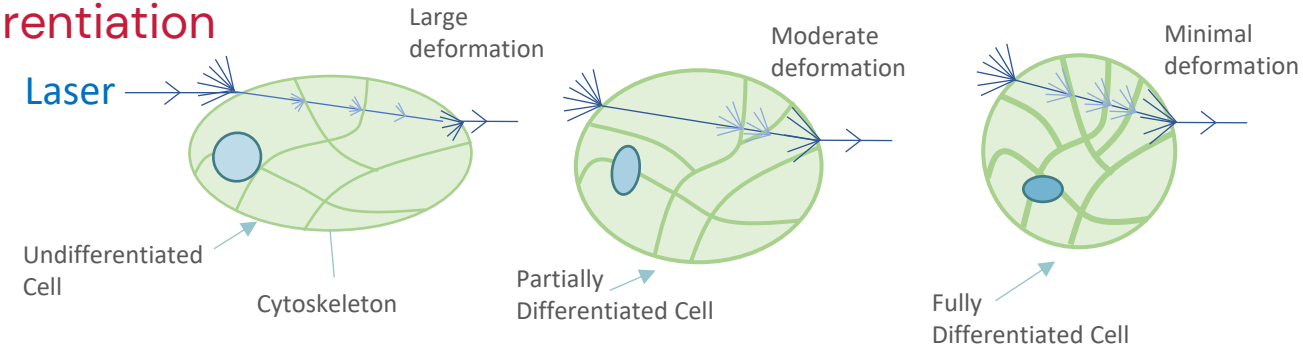
Cell Health Monitoring/Apoptosis



Viral Infection/Transfection



Cell Differentiation



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Laser Force Cytology™

Cellular Fingerprinting

Biological/Cellular Processes Affecting the LFC Fingerprint

Potency

Viral Infection and Neutralization

Oxidative Stress

Apoptosis

Cell health/viability

Contamination

Donor variability

Activation

Transfection

Differentiation

Transduction

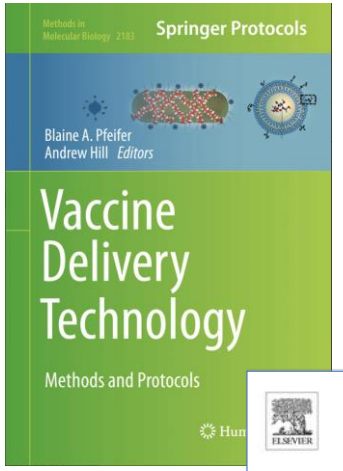
Media Composition

Electroporation

Metabolites

Cryopreservation

Formulation/Processing



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Hebert et al. 2018. *Vaccine*, 36, 6061–6069
Hebert et al. 2017. *Anal. Chem.* 89, 10296–10302
Hebert et al. 2011. *Anal. Chem.* 83, 5666-5672

Broad Applicability Delivering Robust Results

Cell, Virus and GOI Independent

Systems Tested with Laser Force Cytology to Date

Mammalian Cells and Viruses

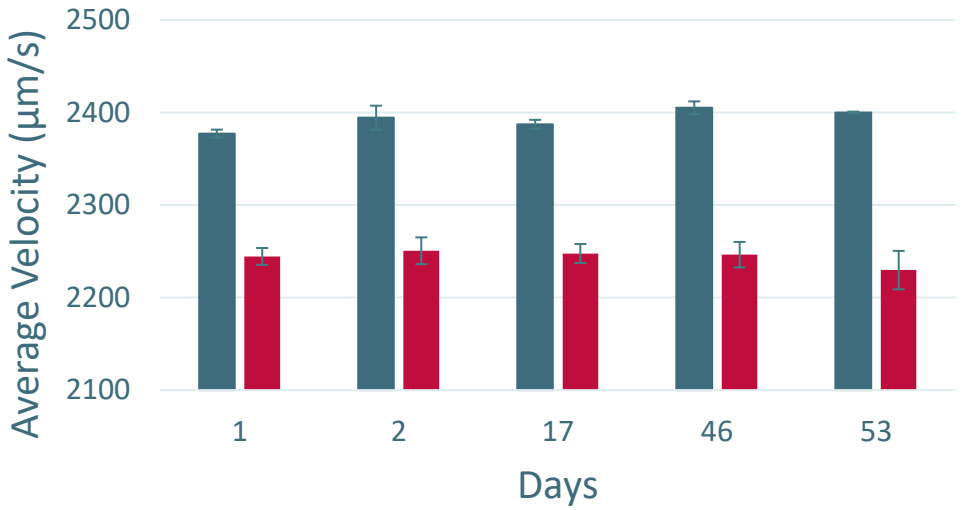
(partial list due to client confidentiality):

- Vero, MDCK, HEK-293, MRC-5, MARC 145, CRFK, A549, HL60, U937, SK-MEL-28, HCC2429, HEp-2, CHO, Primary Human Blood components including PBMCs, T-cells and RBCs, HeLa, NALM-6, iPSCs, hMSCs, cardiomyocytes
- Influenza, VSV, Zika Virus, VZV, PRRSV, Swine Influenza Virus, Pseudorabies Virus, Feline Calicivirus, Adenovirus, HSV-1 (T-Vec), RSV, Mouse Minute Virus, retrovirus, lentivirus, AAV, human coronavirus, Measles virus

Insect Cells

- Baculovirus infection of Sf9 cells for vaccine, VLP, protein, and AAV production

Reproducible measurements of the same samples over a 50+ day period demonstrate instrument consistency



Average Velocity:
2393 ± 11 Uninfected Vero cells (0.46% CV)
2244 ± 14 VSV Infected Vero cells (0.36% CV)

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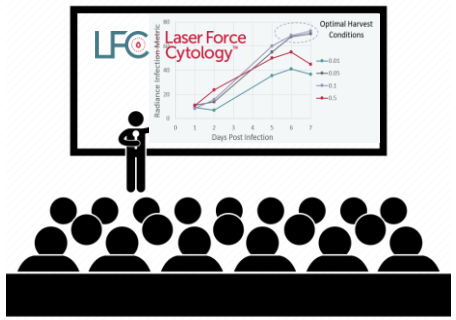
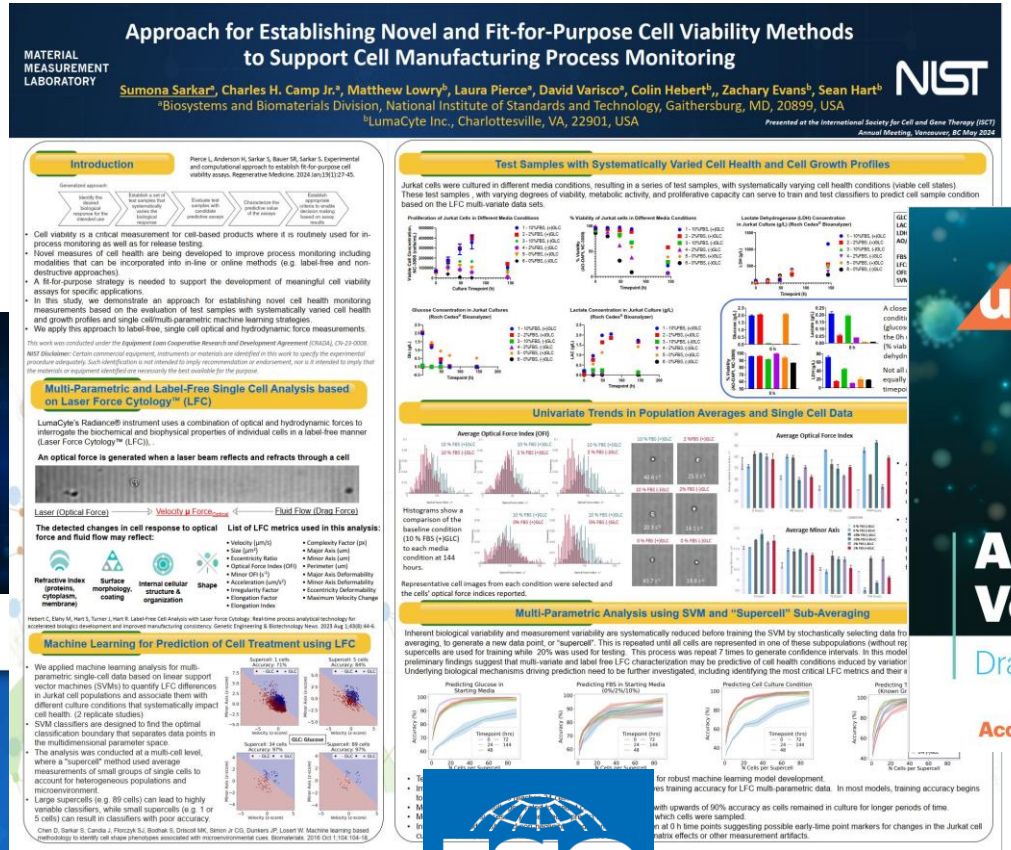
Regulatory Support for Novel PAT Analytics

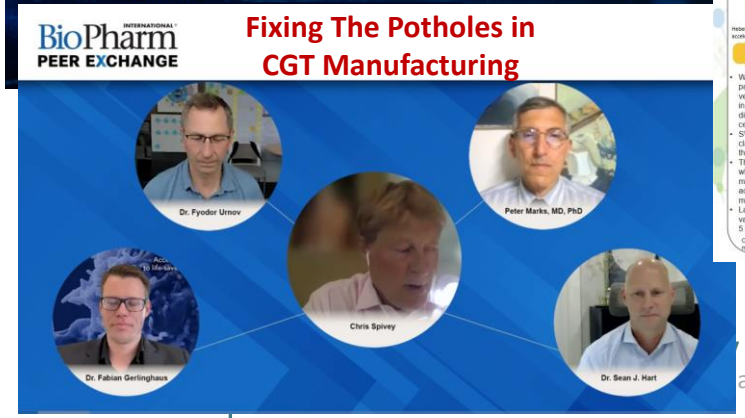
FDA

NIST

usp™







ISO

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Laser Force Cytology™

Vaccine and Viral Vectors

Cell Health, Potency, and Cell-Based PAT

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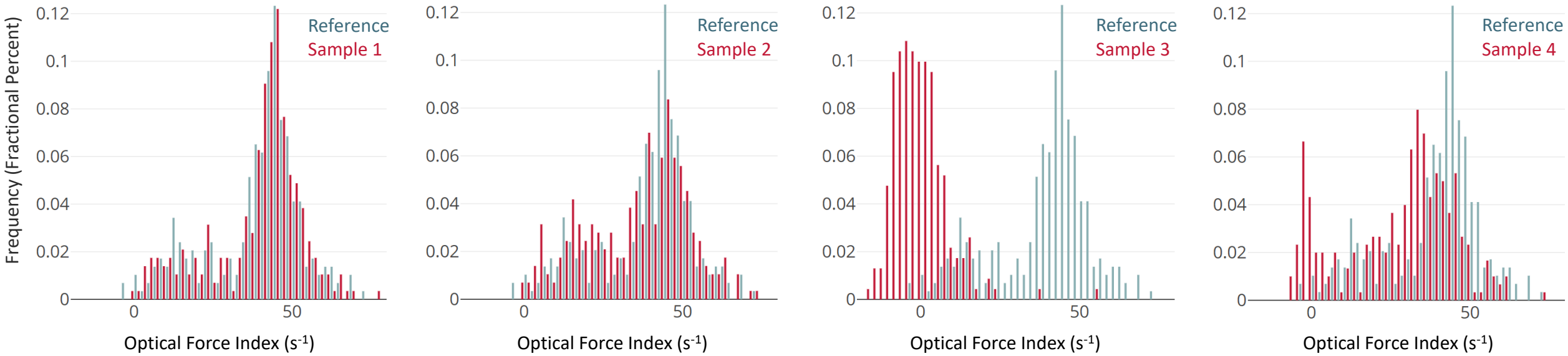
Cell Viable State Monitoring

Predictive Insights for Consistent Process Performance



- Radiance® can rapidly monitor cell health conditions and characterize changes in cell populations to ensure consistent process performance
- This study compares Vero cells frozen with different methods to the standard protocol, cells were then analyzed on Radiance® immediately post thaw
- Significant changes are seen in Radiance® Optical Force Index for samples without DMSO (Sample 3) and rapid (uncontrolled) freezing (Sample 4)

Sample	Condition
1	Standard/Same as reference
2	Higher FBS concentration
3	No DMSO
4	Uncontrolled freezing

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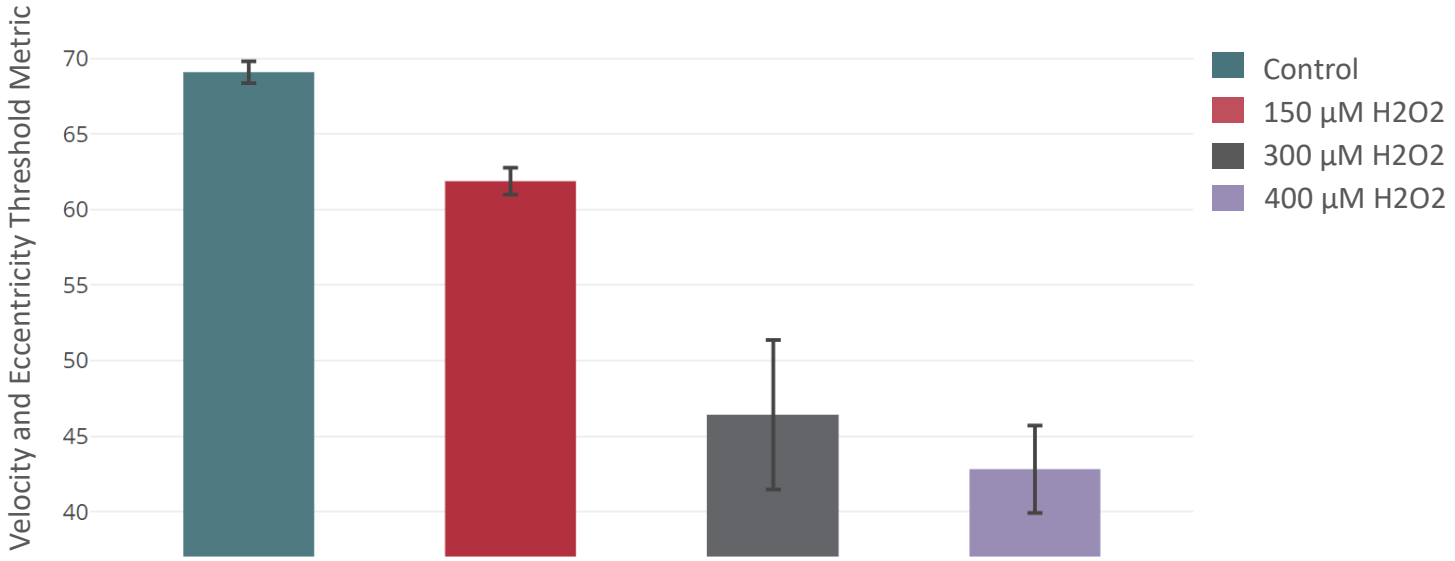
Measuring H_2O_2 Induced Oxidative Stress

Improving Cell Health Measurement with LFC



Viability (Trypan Blue)

Time (hours)	Sample	Average Viability (%)
24	Control	93±6%
	150 µM H_2O_2	89±4%
	300 µM H_2O_2	90±5%
	450 µM H_2O_2	56±3%

- Vero cells treated with various levels of H_2O_2 to simulate oxidative stress felt during bioproduction
- Radiance detects changes in velocity and eccentricity in all conditions compared to control, with no statistical difference seen in viability between untreated cells and up to 300 µM H_2O_2
- Caspase activity assay demonstrates that this LFC metric corresponds more closely with apoptosis, providing additional information beyond trypan blue viability

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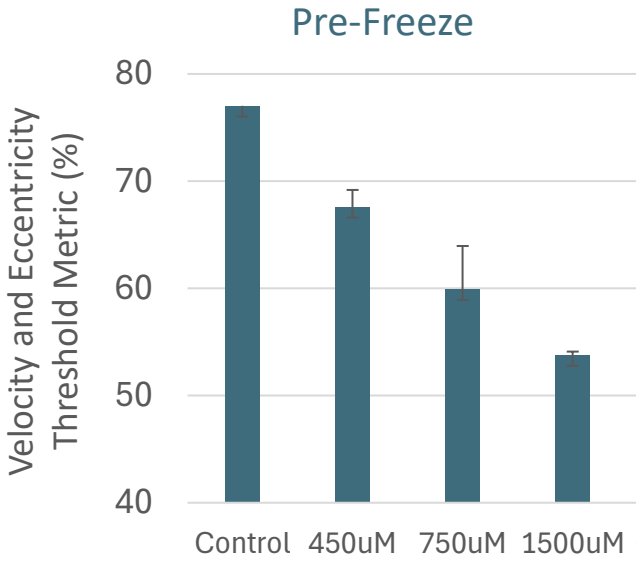
Reduced Viral Production Due to Oxidative Stress

Fit for Purpose Cell Health Measurements



24h Virus Production

Sample	VSV Production (TCID50/mL)
Control (0 µM H_2O_2)	1.31E10
450 µM H_2O_2	1.25E10
750 µM H_2O_2	4.22E9
1500 µM H_2O_2	1.31E9

- Vero cells treated with various levels of H_2O_2 to simulate oxidative stress felt during bioproduction
- Stressed and untreated cells frozen, thawed, and infected with vesicular stomatitis virus (VSV) ~6h post thaw
- Effects of the stress are visible at each stage of the process, including as a greater than 50% reduction in viral production at the 750 µM condition compared to unstressed cells

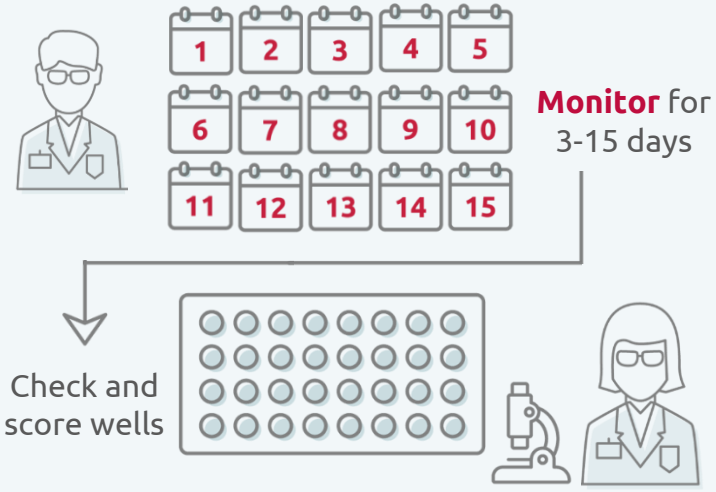
Compressing Time to Results

Rapid Viral Analysis with Radiance® vs TCID50

Virus Sample

TCID50

Infect cells with serial dilutions



Radiance® Infectious Titer

Infect cells with **1-3 dilutions**

3-8x shorter incubation (0.5-3 days)

NO MONITORING

Automated analysis (~5 minutes/sample)

- Faster infectivity / titer results: 1 day versus 10 days (adenovirus)
- Correlates with **plaque assay** or **TCID50 results**
- Absolute infectivity measurements **without correlation**
- **Direct results from bioreactor** with no further incubation (answers in 5 minutes)
- **Radiance® delivers** higher precision, **removing subjectivity to streamline assay transfer and comparability**

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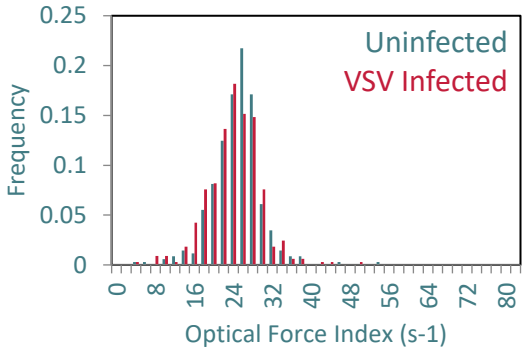
Rapid Viral Analysis

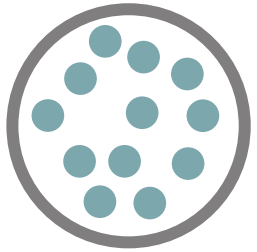
Vesicular Stomatitis Virus (VSV) Infectivity in Vero Cells

0h

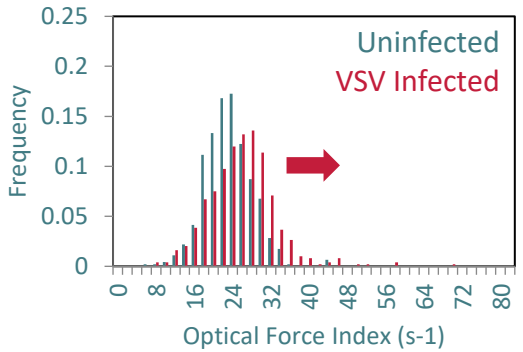
Infect cells

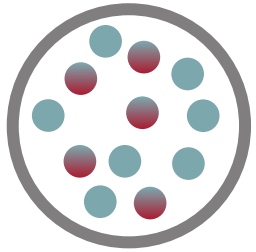
8h



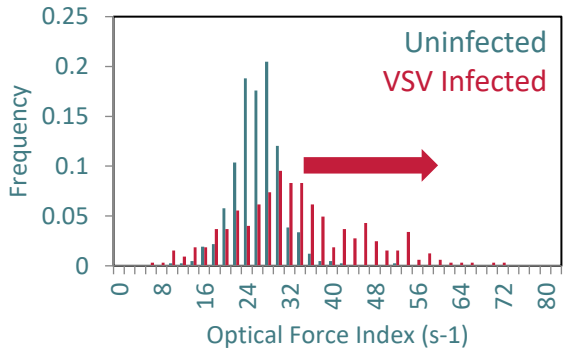


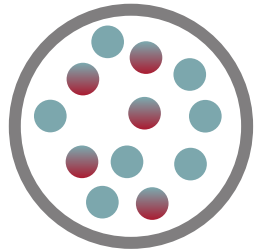
12h





16h





Titer Results!

Radiance® detects subtle phenotypic changes in virally infected cells, rapidly measuring quantitative early indicators of cellular response to viral infection.

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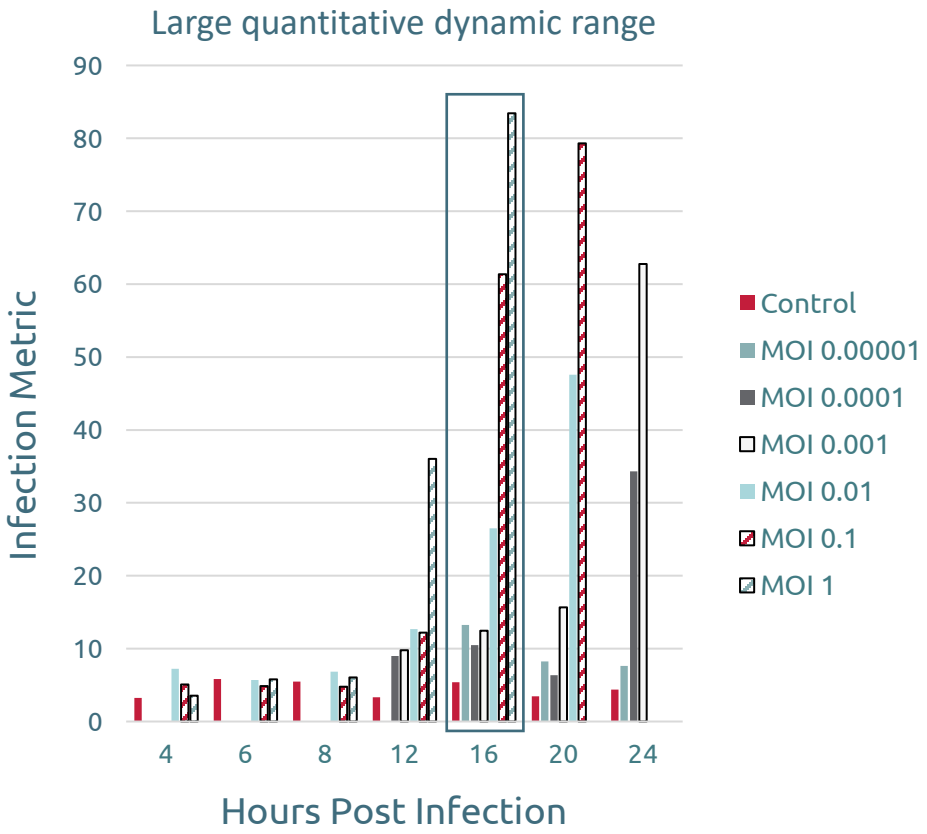
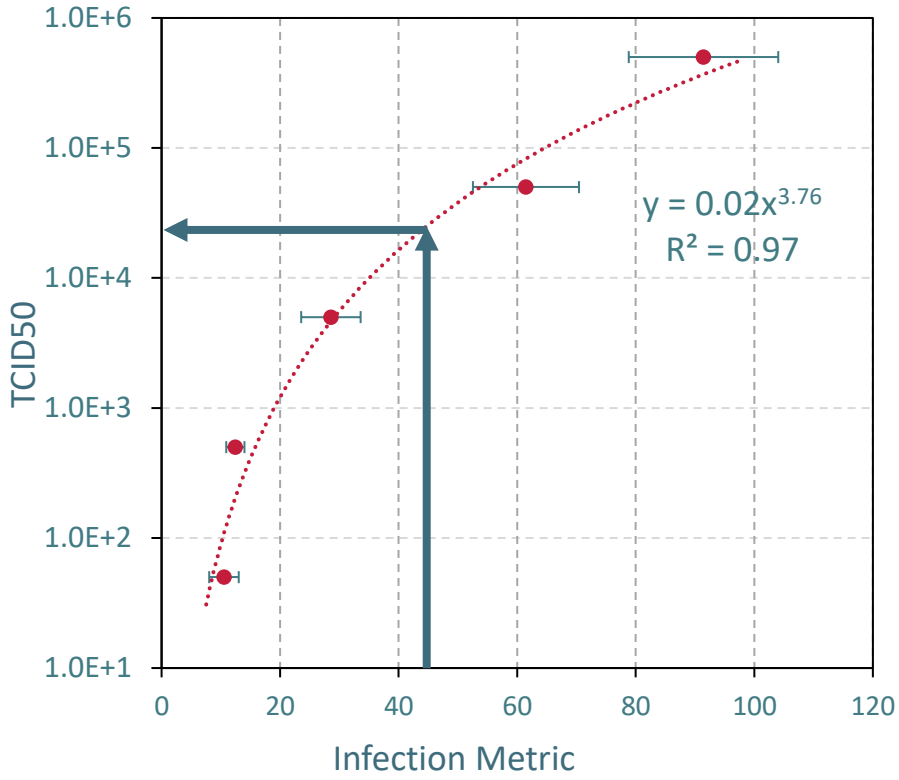
Calculating Viral Titer with Radiance®

VSV in Vero Cells



- Normal titer process with TCID50 takes 72h post infection
- Radiance takes only 16 hours for a MOI range of 0.0001 to 1
- Infection metric can be used directly or correlated to TCID50



Hebert et al. 2018. *Vaccine*, 36, 6061–6069

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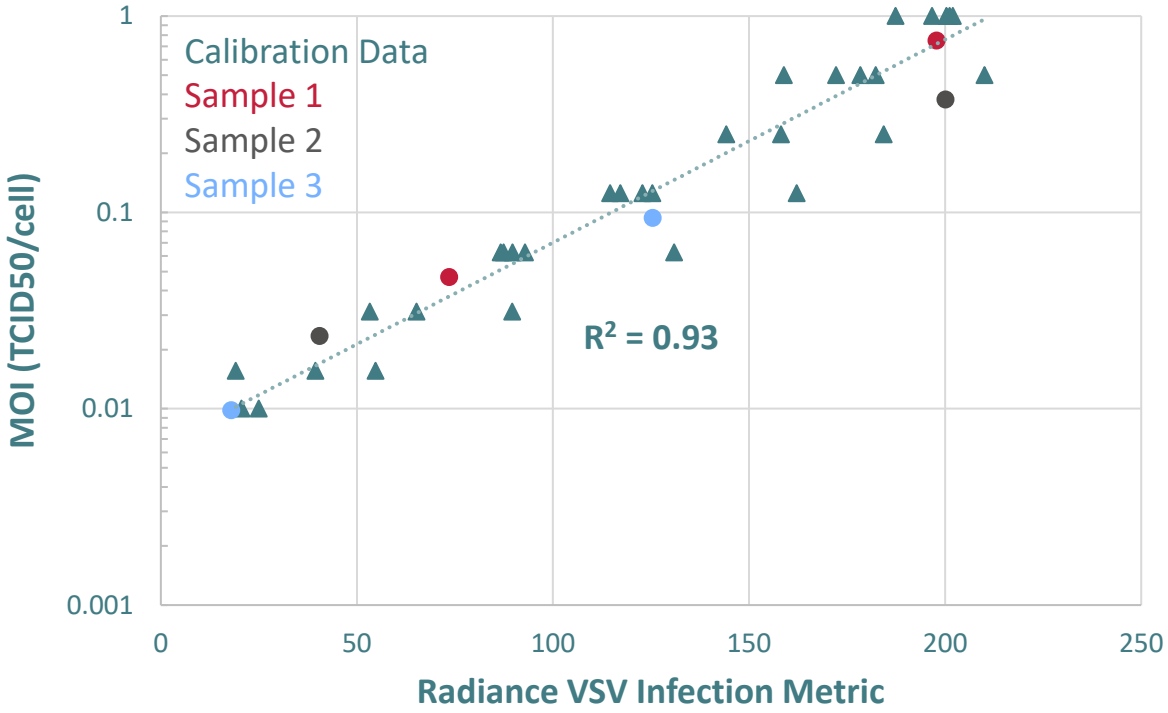
Infectivity Validation Data

VSV in Vero Cells



Stock TCID50/mL: 1.56E+8

Predictions	Actual MOI	Predicted MOI	Predicted TCID50/mL	Log10 Difference (% Error)
Sample 1 Dilution 1	0.750	0.721	1.37E+08	0.06 (12%)
Sample 1 Dilution 2	0.0469	0.0373		
Sample 2 Dilution 1	0.375	0.762	2.15E+08	0.14 (38%)
Sample 2 Dilution 2	0.0234	0.0170		
Sample 3 Dilution 1	0.0938	0.129	1.86E+08	0.08 (19%)
Sample 3 Dilution 2	0.0098	0.00994		
	Average Predicted Titer		**1.79E+08**	**0.06 (15%)**
	Titer Standard Deviation		**3.95E+07**	**22%**

- Composite calibration curve developed between Radiance® data and MOI across 5 independent experiments
- Separate unknown samples were predicted using the calibration curve with an average log10 difference of 0.06
- ✓ Demonstrates rapid analysis in <24h post infection with high accuracy and precision vs 72h for TCID50

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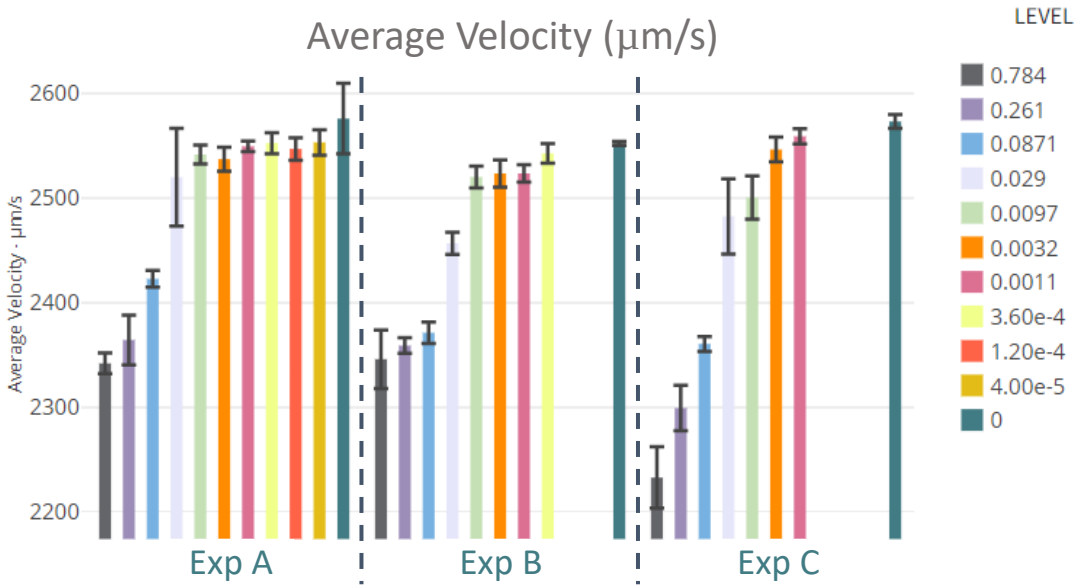
Adenovirus Absolute Titer Analysis

48 Hours Post Infection



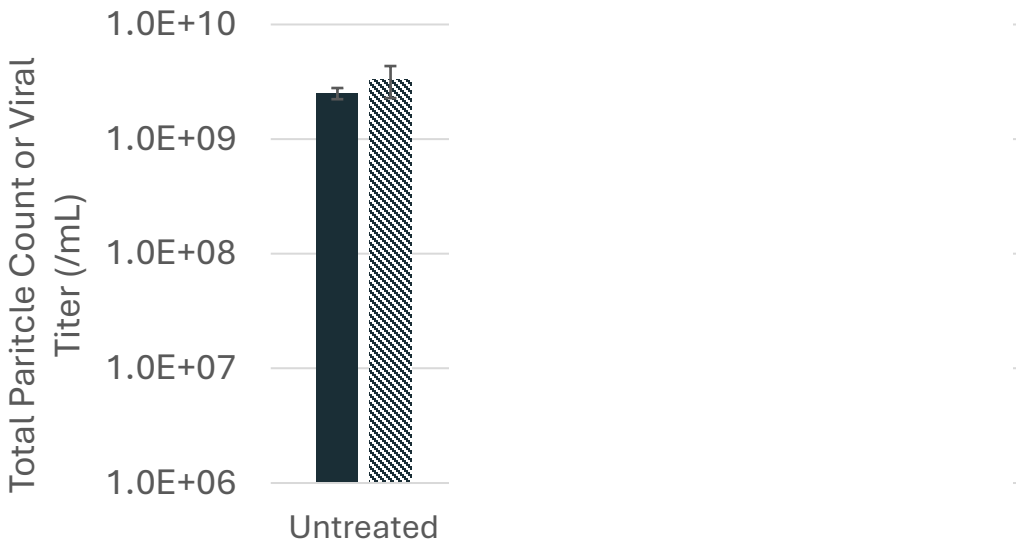
Plaque Assay Titer: 3.61E+09

	Radiance Absolute Titer	Log10 Difference
Exp A	3.51E+09	-0.012
Exp B	4.03E+09	0.048
Exp C	5.03E+09	0.144
Average	**4.19E+09**	**0.065**
St Dev (CV%)	**7.73E+08 (18%)**	

- Absolute titer algorithm can be used to calculate viral infectivity without correlation
- Results in table show absolute average $\log_{10}$ difference of 0.065 (14%) when comparing absolute titer and plaque assay results
- Absolute titer results in 48h post infection versus 7+ days for plaque assay

VSV Physical Count vs Infectious Titer

Results Summary



Treatment	NanoSight Pro: Total Particle Count (particles/mL)	Radiance: Infectious Viral Titer (TCID50/mL)	Log_{10} Reduction from Untreated
Untreated	2.51E9±2.80E8	3.31E9±1.03E9	N/A
Freeze Thaw	1.81E9±1.80E8	1.61E9±6.02E8	0.31
Low pH	1.74E9±4.70E8	6.83E6±4.95E6	2.69
High Temp	2.78E9±3.60E8	3.40E6	2.99

Webinar Available on Demand

- Vesicular stomatitis virus (VSV) samples subjected to a variety of insults that may affect product quality
- Effects of the insults quantified by viral titration using Laser Force Cytology (Radiance) and particle counting using Nanoparticle Tracking Analysis (NanoSight Pro)
- No appreciable changes in total particle count, but Low pH and High Temperature show a significant reduction in viral titer, demonstrating the importance of measuring functional viral titer

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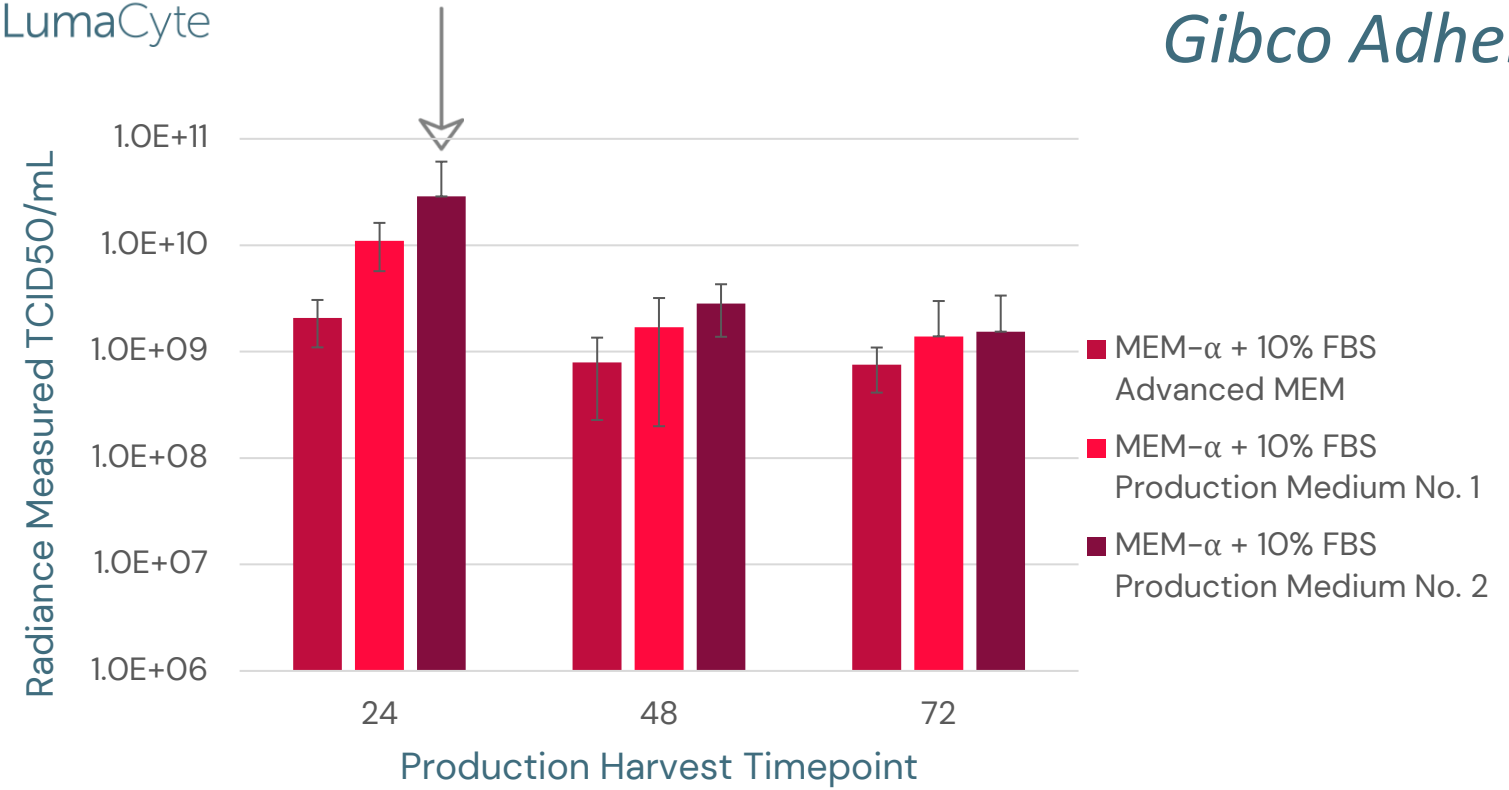
Rapid Media Screening to Maximize Production

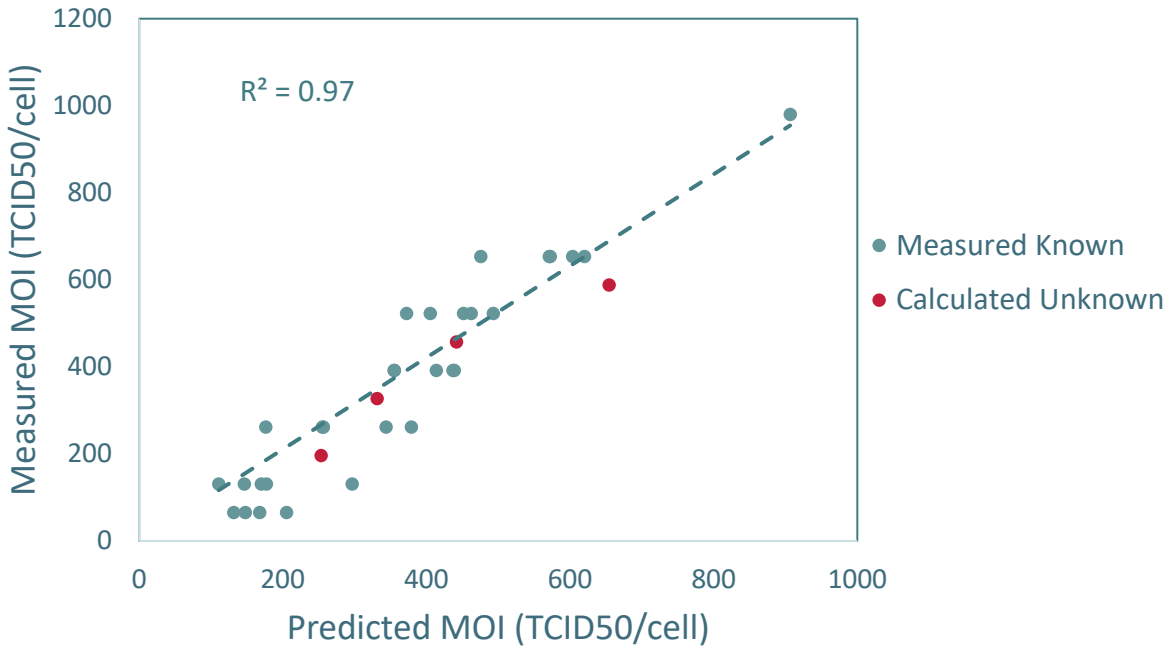
Gibco Adherent Kidney Media Panel



Webinar Available On Demand

- Under reduced serum conditions, Gibco Production Medium No. 1 and No. 2 show improved viral titer compared to Advanced MEM
- Highest viral titer achieved at 24h time point (~14X higher than standard conditions)
- Rapid infectivity assay enables screening of wide process design space

AAV Multivariate Transduction Curve



Stock Titer: 9.14E+9(TCID50/mL)

	Measured MOI (TCID50/cell)	Predicted MOI (TCID50/cell)	Predicted Titer (TCID50/ml)	Log10 Difference
Calibration Curve (Knowns)	979.5	906.42	8.46E+09	0.034
	653	568.48	7.96E+09	0.060
	522.4	436.81	7.64E+09	0.078
	391.8	399.87	9.33E+09	-0.009
	261.2	282.04	9.87E+09	-0.033
	130.6	180.11	1.26E+10	-0.140
		Average	**9.31E+09**	**0.008**
Unknown 1	587.7	654.41	1.02E+10	-0.047
Unknown 2	457.1	441.62	8.83E+09	0.015
Unknown 3	326.5	331.1	9.27E+09	-0.006
Unknown 4	195.9	253.32	1.18E+10	-0.112
		Average	**1.00E+10**	**0.045**
		Standard Deviation (%CV)		**1.32E+09 (14%)**

- Strong correlation developed between Radiance data and TCID50/mL titer

✓ Accurate and precise unknown prediction within 0.045$\log_{10}$ (9.4%) of the known stock titer with a CV of 14% across 4 unknows

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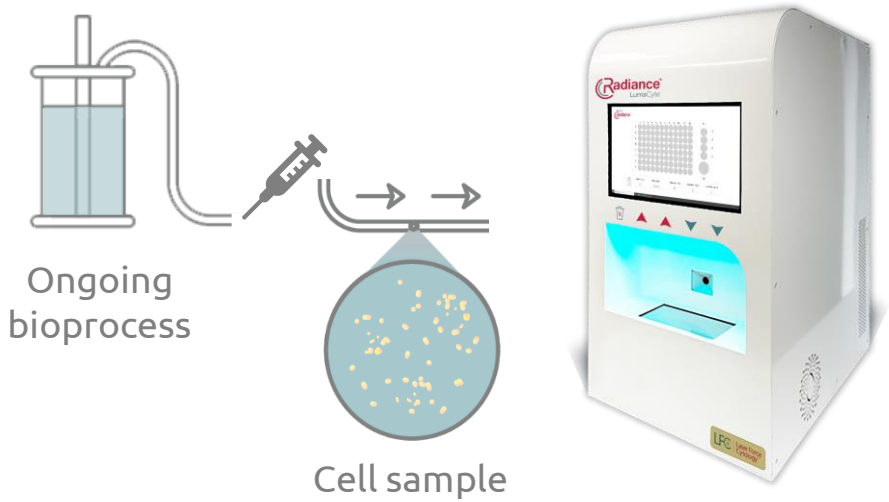
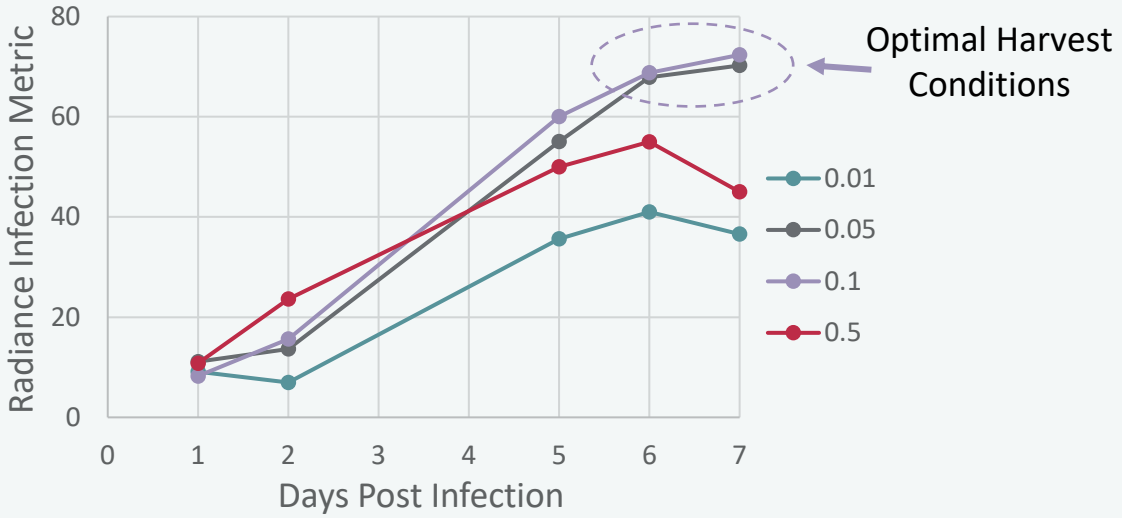
Process Analytics and Production

Rapid and Precise Process Analytics Enable:

- Real-time process optimization
- Increased process knowledge and understanding of process variability
- Real-time contamination monitoring and early mitigation of potential batch failures
- Significant increases in product yields





- Example viral process optimization experiment to determine the optimal multiplicity of infection (MOI)
- Relative response of Radiance infection metric can be monitored in real-time to rapidly screen process conditions without having to perform lengthy and resource intensive assays such as plaque/TCID50, PCR, or ELISA

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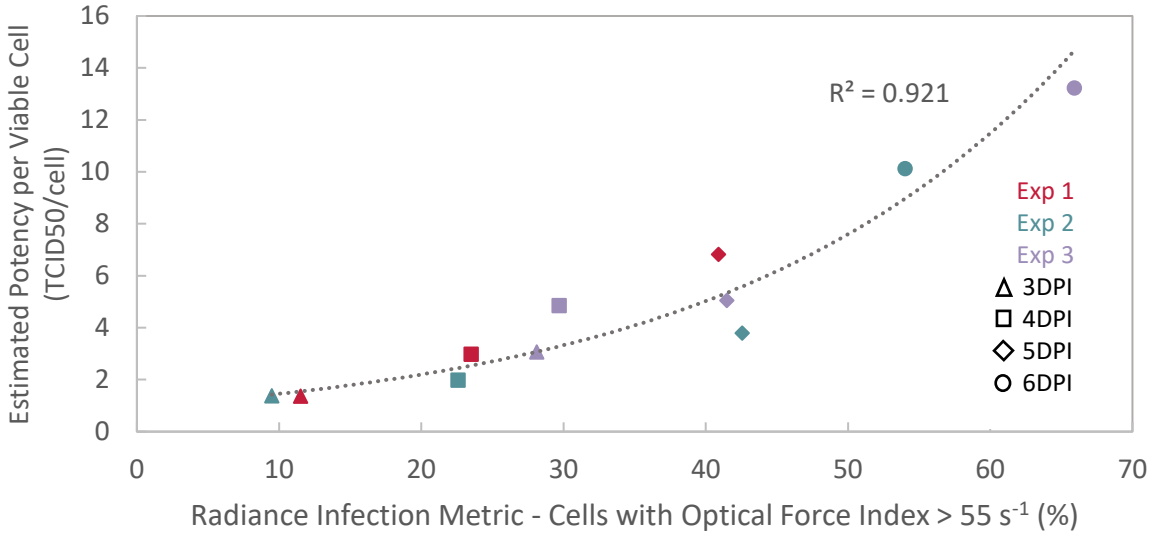
Live Virus Vaccine Production Monitoring

Estimated Potency Correlation



Experiment	Time Point (h)	Radiance Infection Metric (% OFI>55 s^{-1})	Estimated Potency (TCID50/viable cell)	Calculated Potency (TCID50/viable cell)	Log_{10} Difference
Exp 1	72	11.53	1.36	1.55	0.056
	96	23.52	2.97	2.54	-0.068
	120	40.92	6.81	5.22	-0.116
Exp 2	72	9.49	1.38	1.42	0.015
	96	22.60	1.98	2.45	0.093
	120	42.57	3.79	5.59	0.169
	144	54.02	10.11	8.97	-0.052
Exp 3	72	28.12	3.06	3.08	0.002
	96	29.69	4.85	3.28	-0.169
	120	41.48	5.04	5.34	0.025
	144	65.92	13.22	14.67	0.045
				Absolute Average	**0.074**

McCracken et al. 2022. Vaccines 10(10), 1589

- Work conducted by Merck to monitor real-time viral infectivity from a bioreactor
- Strong correlation demonstrated between estimated potency measurements and Radiance data
- Calibration curve can be used to accurately calculate the estimated potency throughput the production process and provide real time feedback to improve the speed of process development and manufacturing consistency
- Additional data in publication demonstrates monitoring of another virus, real-time contamination monitoring, and rapid analytics (TCID50 replacement) for measles virus

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Stem Cell Applications

Label free characterization of differentiation

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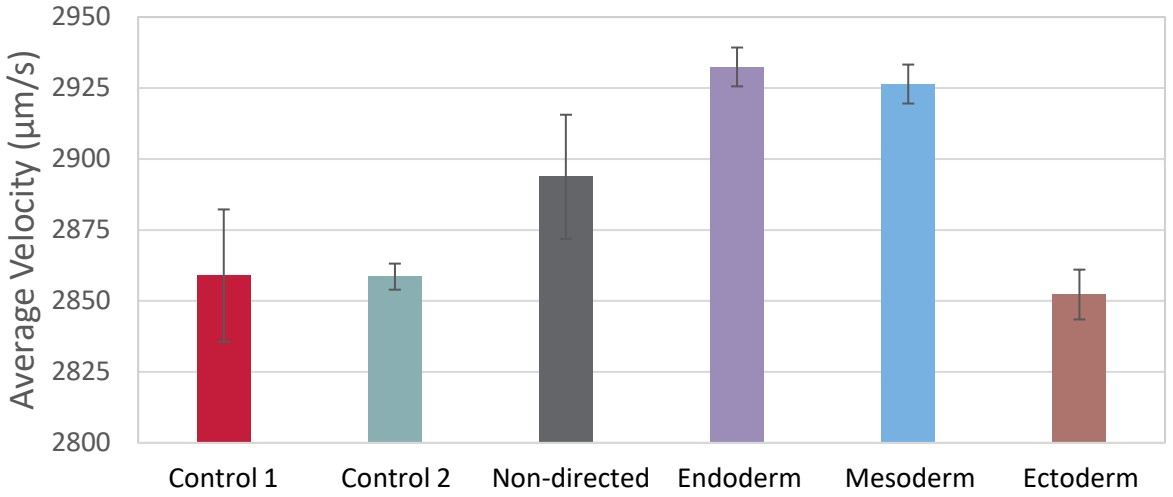
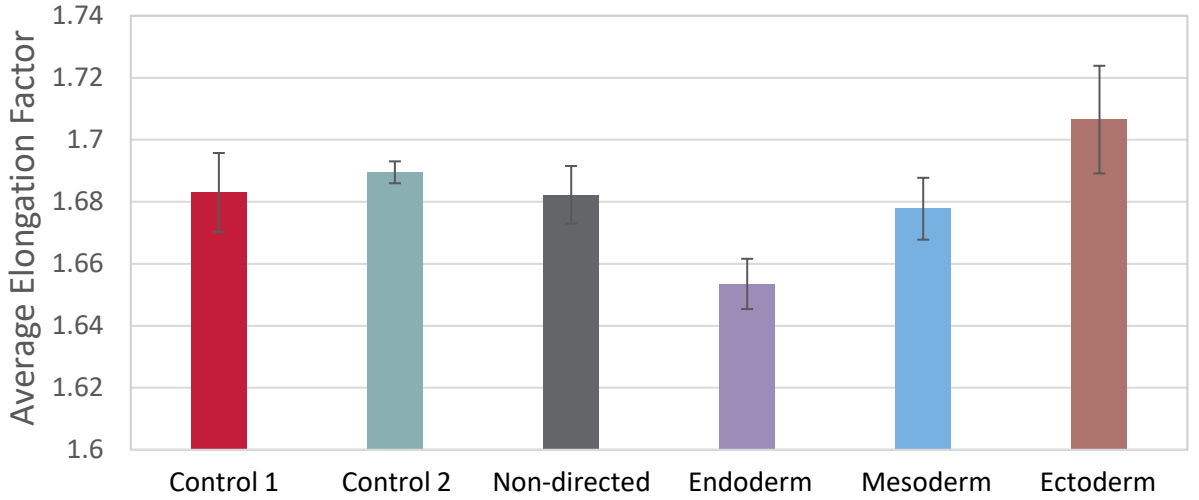
Label-free iPSC Differentiation Monitoring

LFC Metric Changes

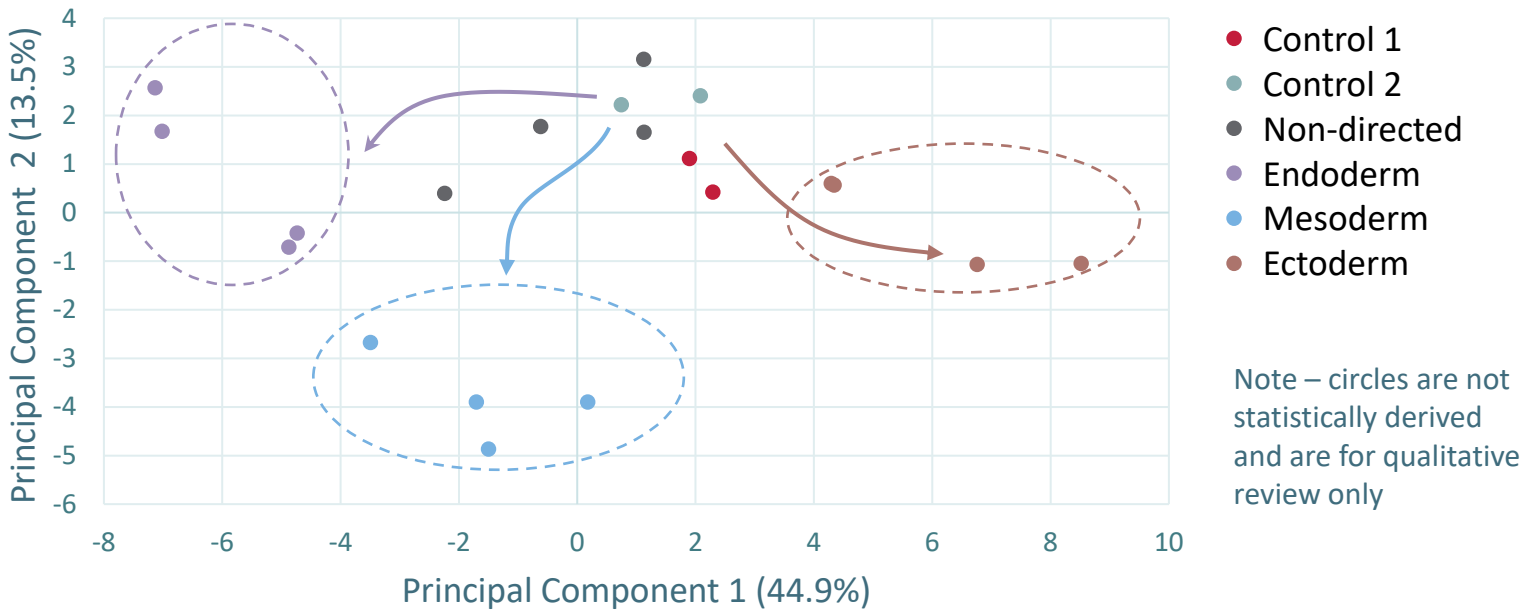




- Induced pluripotent stem cell (iPSC) samples were directed into three different lineages (endoderm, mesoderm, and ectoderm) and compared to undifferentiated controls as well as non-directed/spontaneous samples
- Multivariate analysis can be used to visualize changes seen in multiple parameters

Label-free iPSC Differentiation Monitoring

Principal Component Analysis

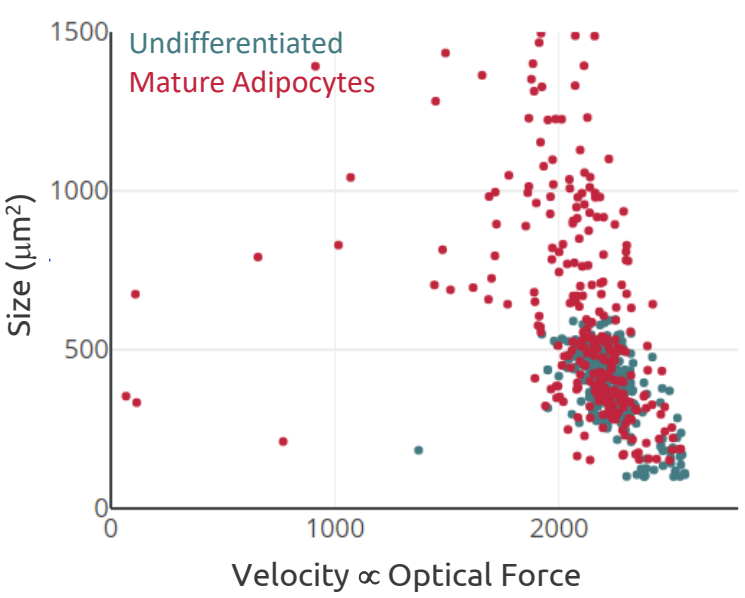


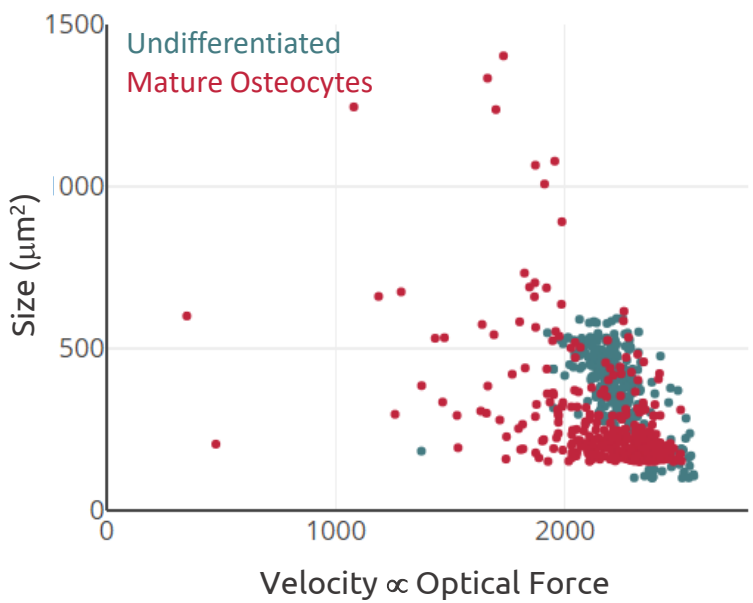
PCA: Multivariate dimensionality reduction technique to easily visualize multidimensional data

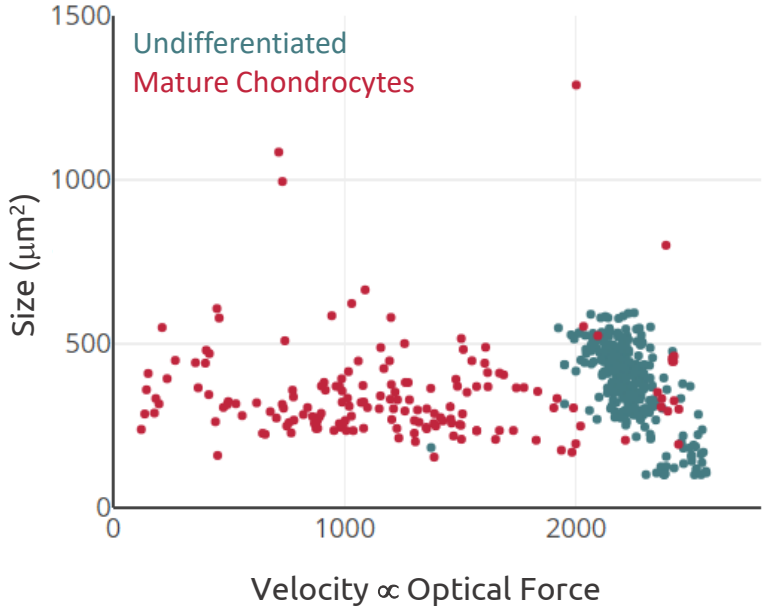
Note – circles are not statistically derived and are for qualitative review only

- Principal component analysis (PCA) uses multiple Radiance data parameters to assess cell populations – each point represents a population of cells
- Radiance can be used to monitor iPSC and other cell differentiation pathways in a label-free manner, allowing for unbiased characterization of cells without the limitations of antibodies that only indicate the presence of a specific marker or protein
- Allows for quantitative and universal characterization of cell differentiation

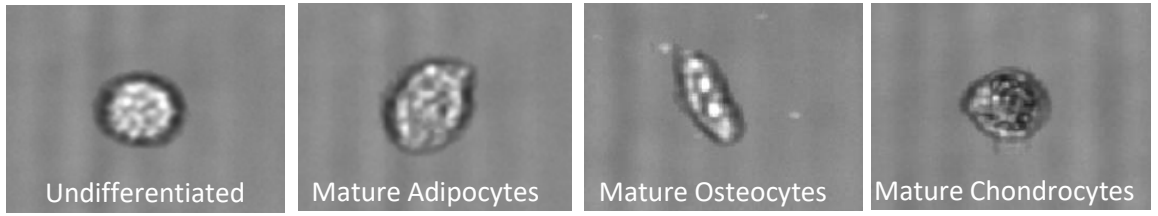
Label-free hMSCs Differentiation Monitoring







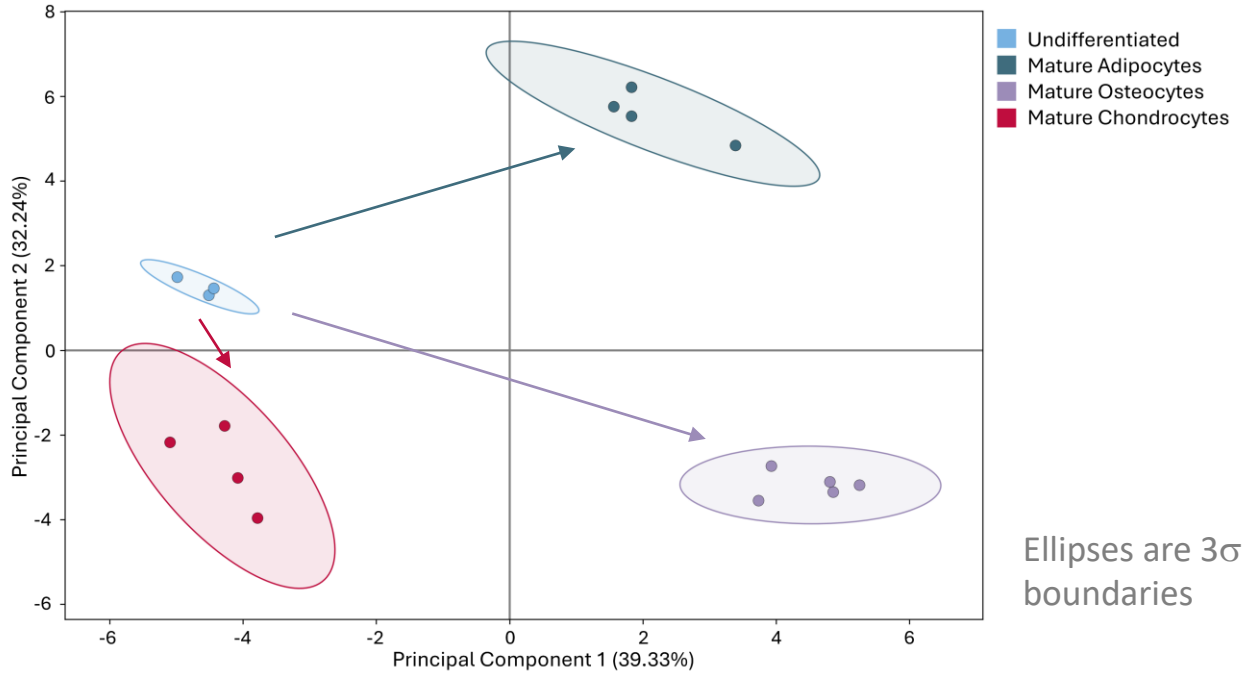
Representative Radiance Cell Images:



✓ LFC single cell data can be used to monitor hMSC differentiation by tracking population shifts and identifying specific sub-populations of interest

Radiance® LumaCyte Label-free hMSCs Differentiation Monitoring

Principal Component Analysis

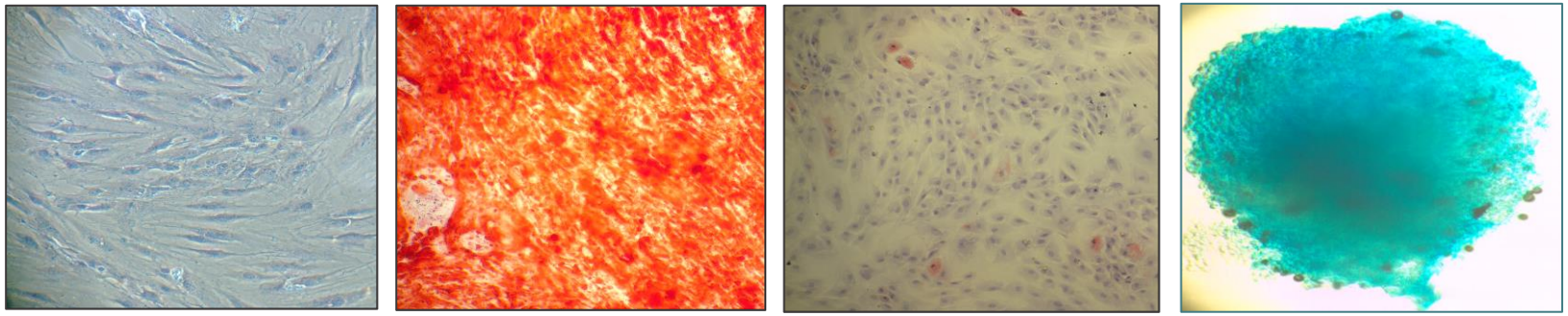


Ellipses are 3σ boundaries

- Study to monitor the expansion and differentiation of human bone marrow derived mesenchymal stem cells into osteoblasts, adipocytes and chondrocytes

- ✓ Radiance can be used to monitor MSCs differentiation in a label-free manner at different time points enabling a rapid and label-free indication of commitment towards a specific lineage

Undifferentiated (0d) | **Mature Osteocytes (21d)** | **Mature Adipocytes (14d)** | **Mature Chondrocytes (21d)**



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Monitoring hMSC Changes due to Passage

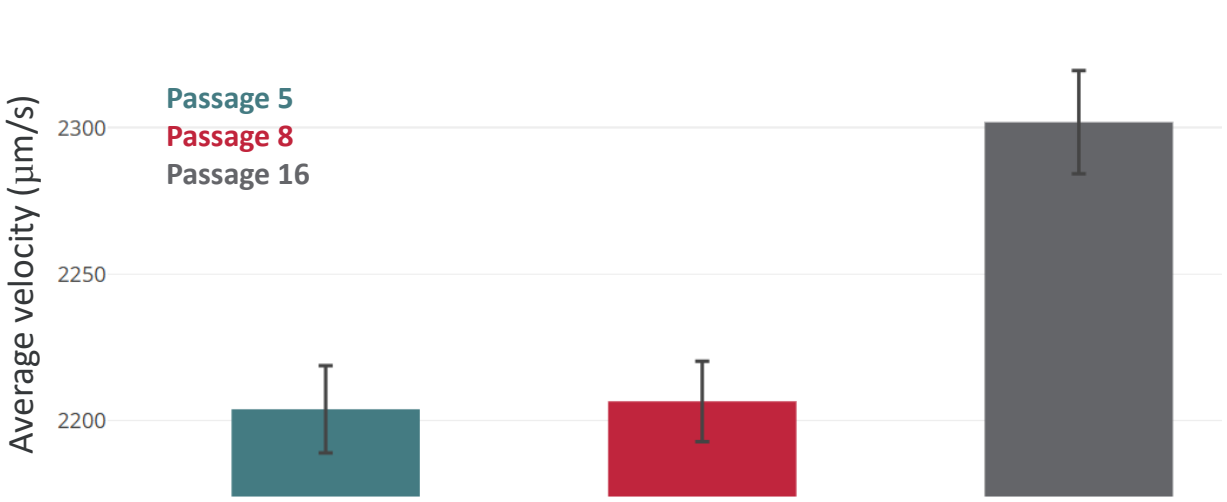
Experimental Summary

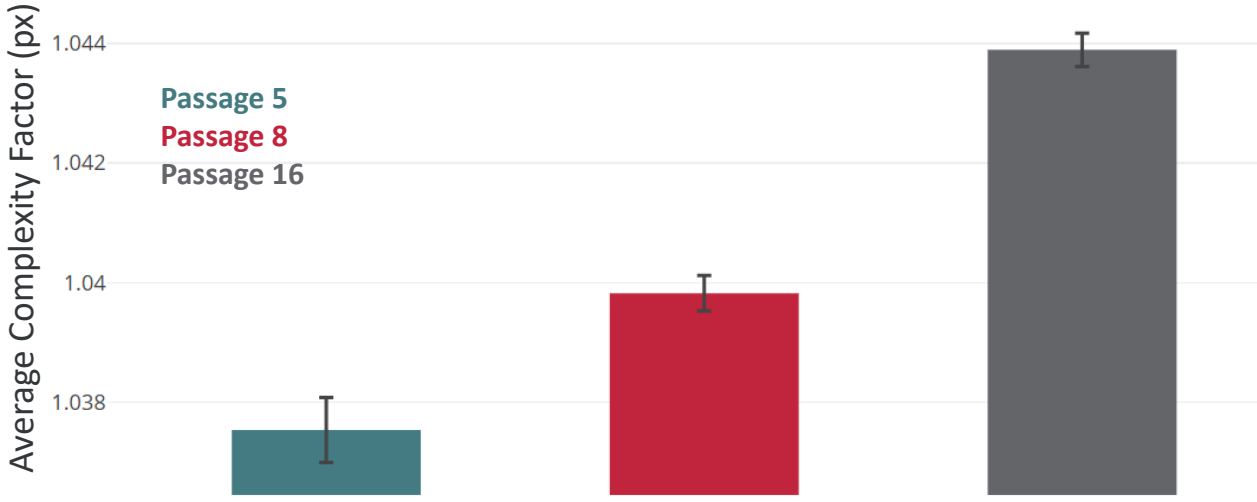
- Study conducted to investigate how hMSCs differentiation changes as passage number increases
- Undifferentiated cell samples analyzed using Radiance at passage numbers 5, 8, and 16
- At each of the three passages, cells were induced to differentiate into adipocytes and stained 14 days post differentiation

- Objective: determine if differences in undifferentiated cells can be measured using LFC that could be used to predict success or failure of differentiation

Monitoring hMSC Changes due to Passage

LFC Population Data

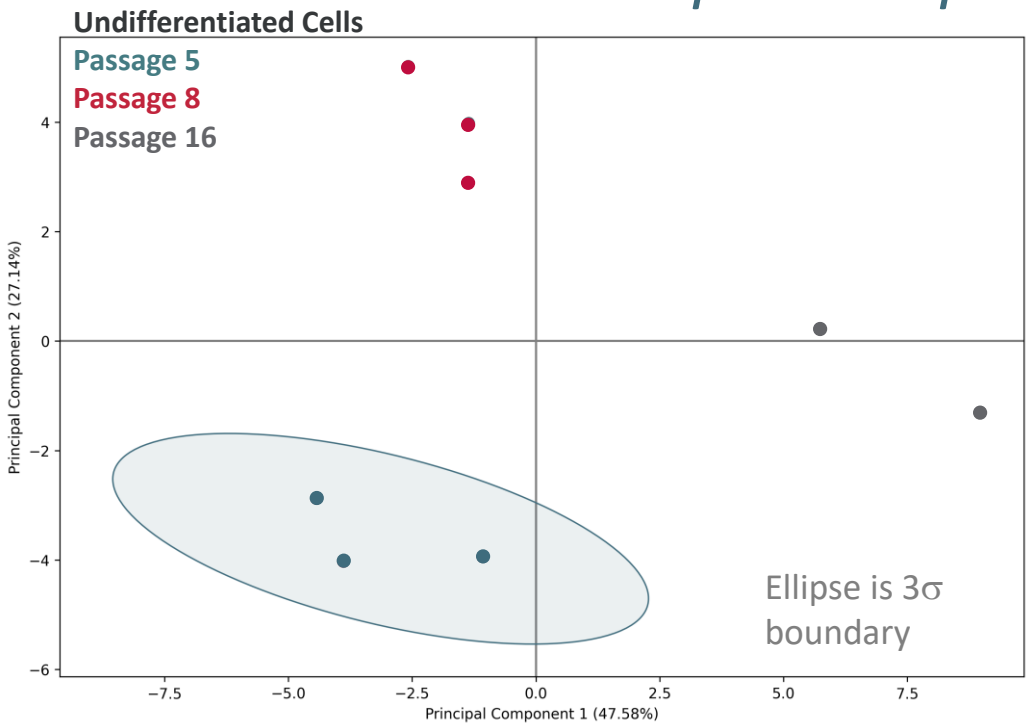


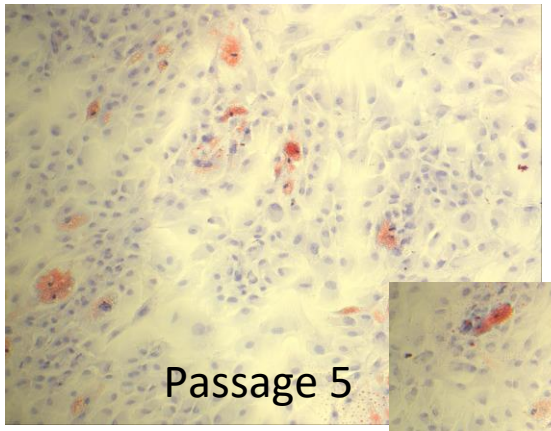


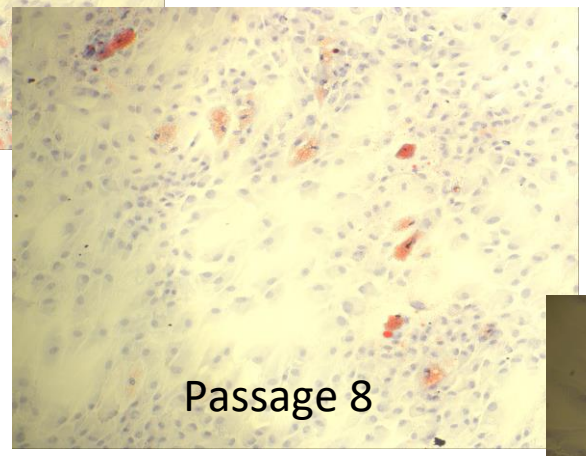
- Changes seen in multiple LFC metrics, including both average velocity and average complexity factor as passage number increases
- Velocity is proportional to the cell's optical force, while complexity factor is a shape metric related to the cell's circularity
- As shown on the next slide, multivariate methods can be used to measure population wide changes in multiple metrics

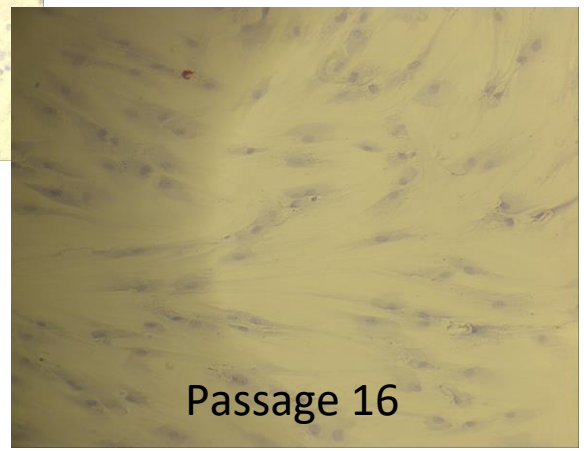
Monitoring hMSC Changes due to Passage

Principal Component Analysis









Differentiated Cell Images (14 days post induction) - show a general decrease in differentiation as passage number increases

- PCA plot of undifferentiated cell populations at different passage numbers shows statistical separation between samples
- LFC data could be used to predict future differentiation quality

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CAR T Cell Therapy

Co-culture killing, in-process phenotype, and predictive donor characterization

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LFC Analytics in Manufacturing – CAR T Cell Therapy Example

In Process Contamination Monitoring

Sterility for Batch Release

Rapid transfection monitoring & optimization

Donor qualification to predict manufacturing success

T cell process monitoring and road mapping (process optimization and consistency)

Cellular phenotype monitoring (correlation with offline assays)

CAR T Killing Potency Assay / QC for release

Cryopreservation/Formulation

Cellular viability/fitness

Viral Vector Production → Patient Apheresis → T Cell Selection → T Cell Activation → Transduction → Expansion → Harvest and Final Formulation → Infusion

* Day 0 | Day 1 | Day 1-12 | Day 12 | Day 12-13

Indicates where Radiance can be used across complex cell therapy manufacturing processes

* CAR T manufacturing process can vary between developers (4-12 days)

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LFC Analytics in CAR T Cell Therapy Manufacturing

In Process Sterility Monitoring

Sterility for Batch Release

Rapid transfection monitoring & optimization

Donor qualification to predict manufacturing success

T cell process monitoring and road mapping (process optimization and consistency)

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Indicates where Radiance can be used across complex cell therapy manufacturing processes

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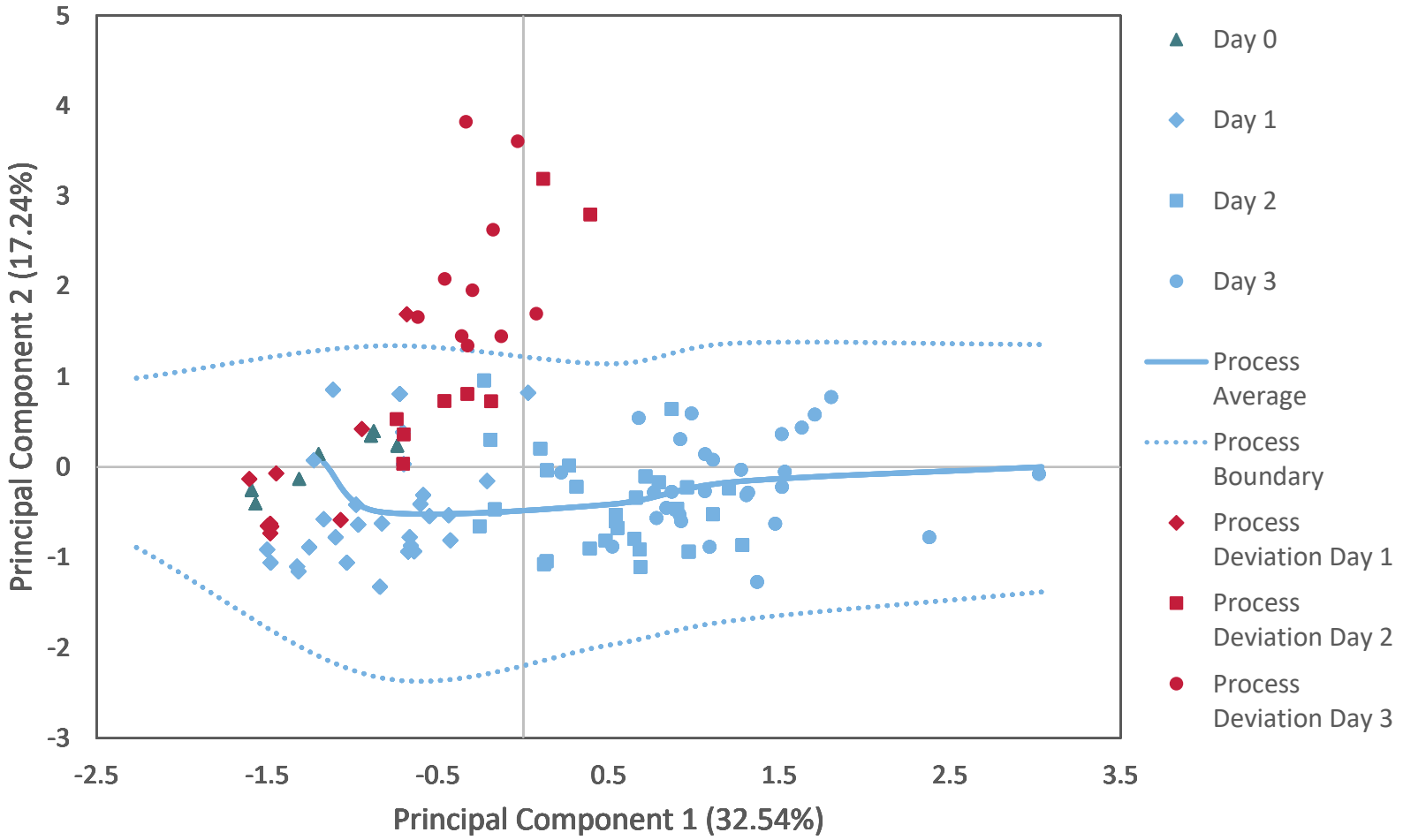
Process Tracking using PCA

T-cell Activation



- T-cell data across 5 experiments and 3 different donors used to create process "road map" using LFC data
- Deviation in process detected outside boundary as early as 1 day post activation and continues down alternate path

Process average and standard deviation:
3.2 σ in PC1
3.0 σ in PC2

- **Deviation: Doxorubicin treated T Cells**

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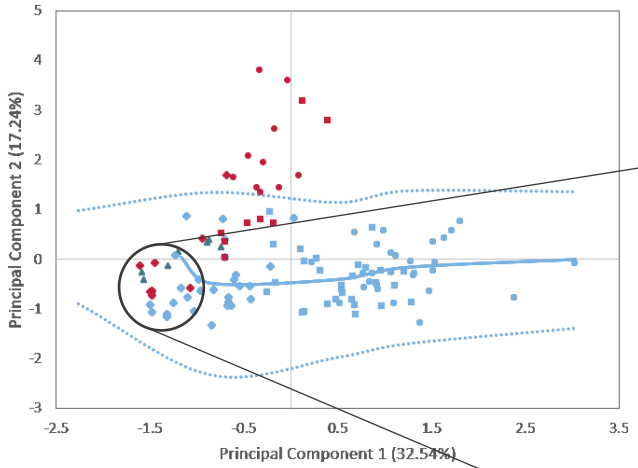
Process Prediction using PCA
T-cell Activation

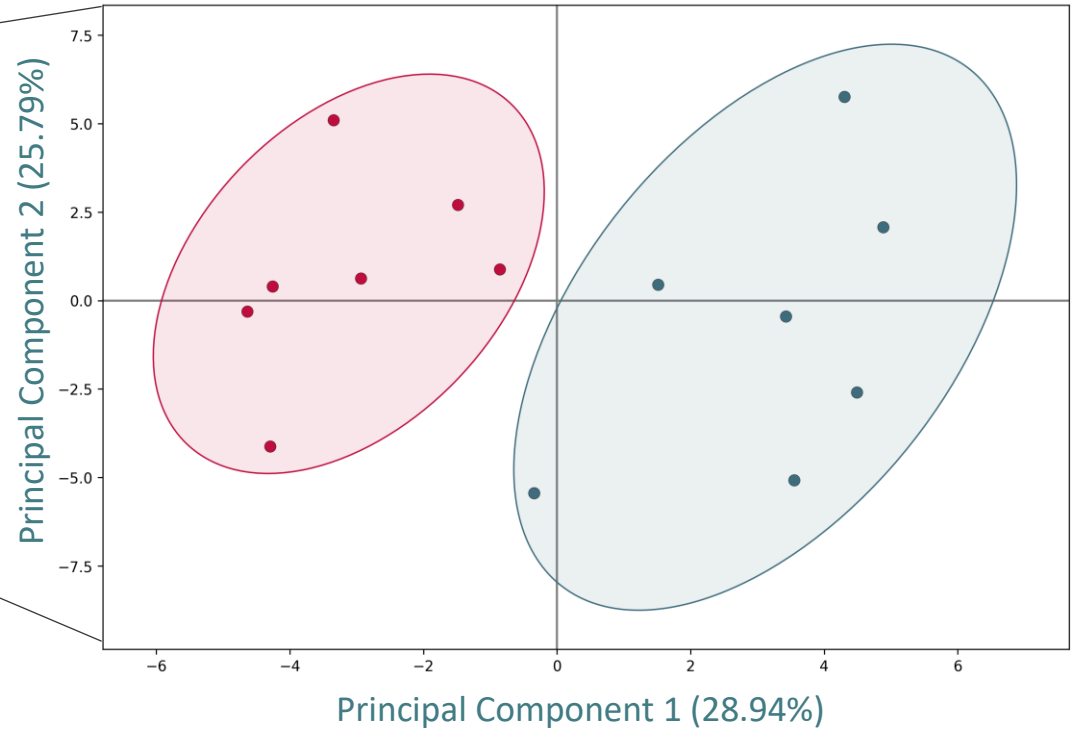
- Analysis of cells at early timepoints can predict future process failure
- 24 hr PCA model shows differences in cell populations affected by treatment with a chemotherapeutic agent versus untreated cells, providing near real-time feedback of a process variation



24 Hour Timepoint

Activated T Cells

T Cells previously treated with 5 mM Doxorubicin



Ellipses are 2σ boundaries

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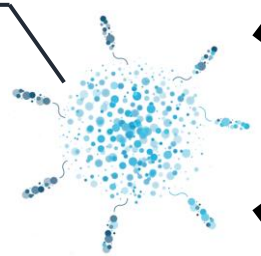
Poseida Therapeutics using ML models to predict cell state based on LumaCyte Radiance® data

Label-free, single cell optical force measurements with LumaCyte Radiance®
20+ parameters (e.g. velocity, size, eccentricity)

In-process sample collection at various timepoints

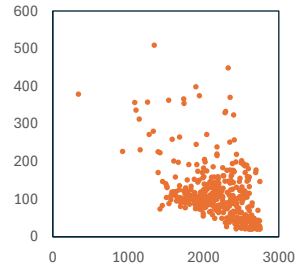
Paired flow cytometry data
Cell health, phenotyping

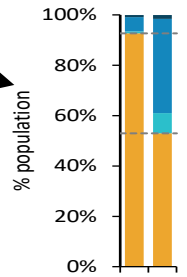


Model development
Samples on both Radiance and Flow cytometry

Predictive ML modeling

ML model: Radiance® → Flow





Accurate mapping of Radiance® data to cell health and cell phenotype.

Enables real-time monitoring of cell state in process

Model Application
Model outputs interpret/predict the result without the need to run flow cytometry

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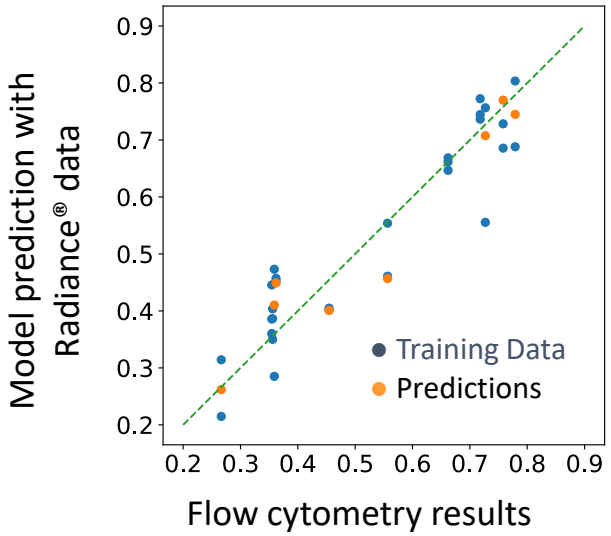
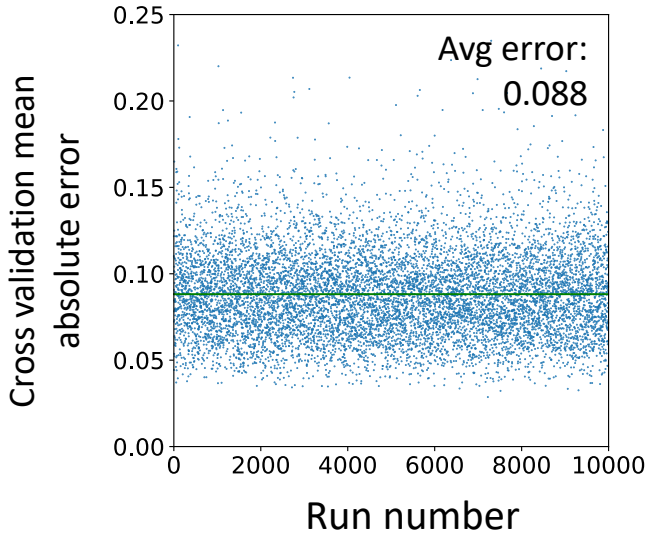
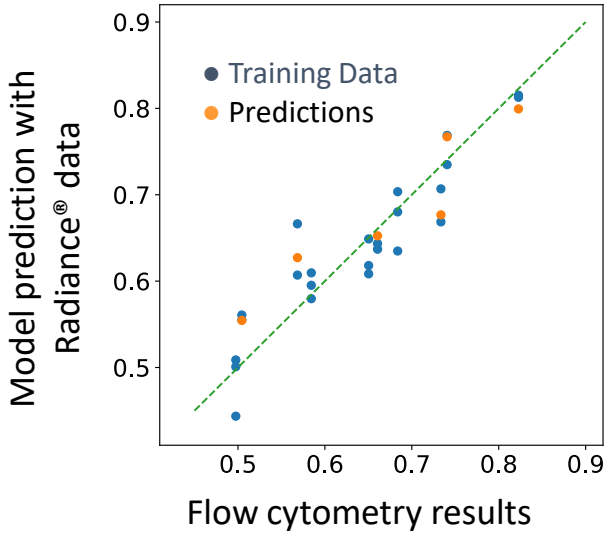
Poseida Therapeutics utilization of LFC Process Analytical Technology (PAT) and AI in developing a control strategy

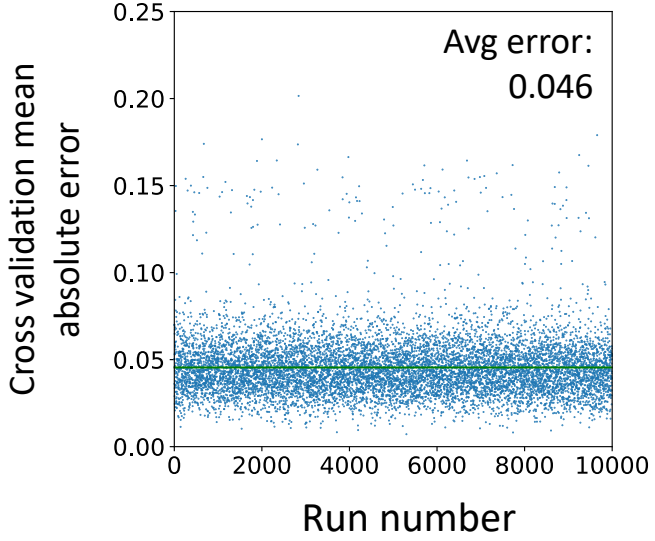
ML model:
Radiance → Cell health





ML model:
Radiance → Phenotype

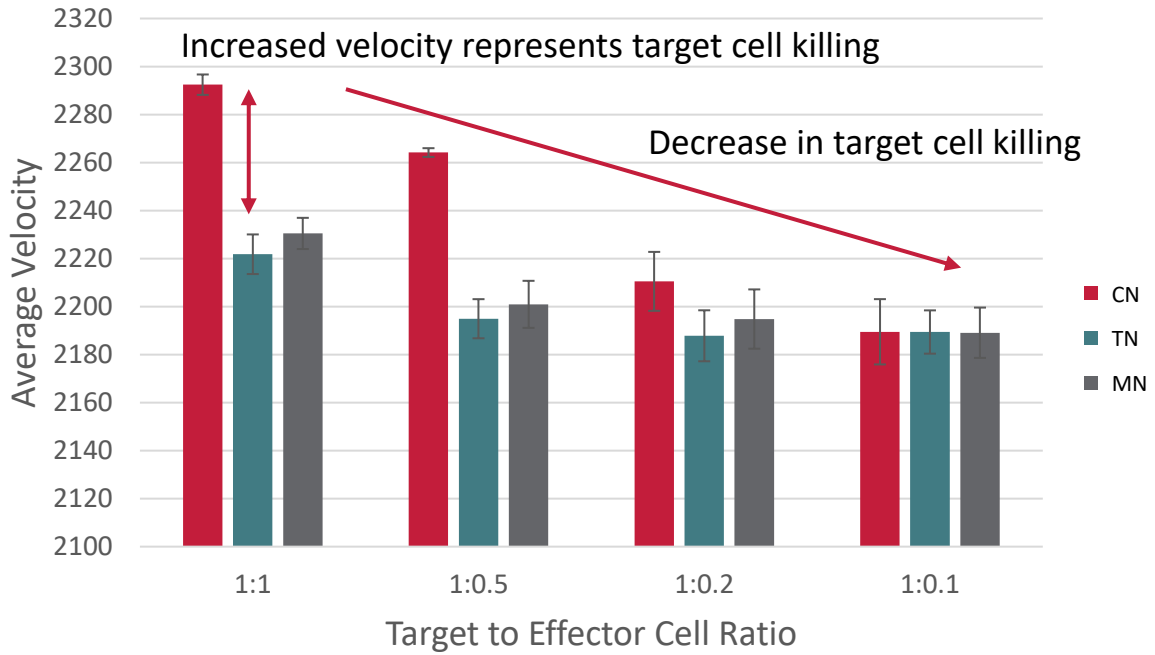




- ***ML models exhibit excellent predictive power on cell health and phenotype across multiple in-process timepoints and donor starting material.***
- ***Correlations between certain product attributes or process performance with input parameter or combination of input parameter(s) (e.g. PCA principal component analysis) can be made***
- ***These correlations can be utilized for control strategy***
- ***Results from PAT can be applied to guide manufacturing decisions at critical process steps***

Detection of CAR T Mediated Cell Killing

Average Velocity (∝ optical force)



CN = NALM6+CD19 CAR
TN = NALM6+T cells
MN = NALM6+Mock Transduced

- CD19 CAR T cells were produced from healthy donors and killing efficacy was determined using a 24h co-culture assay with NALM-6 luciferase target cells at a variety of target to effector cell ratios
- Specific detection of cell killing in CN population when compared to TN and MN populations was detected as an increase in velocity
- A decrease in killing response is seen as fewer effector cells are added to the co-culture

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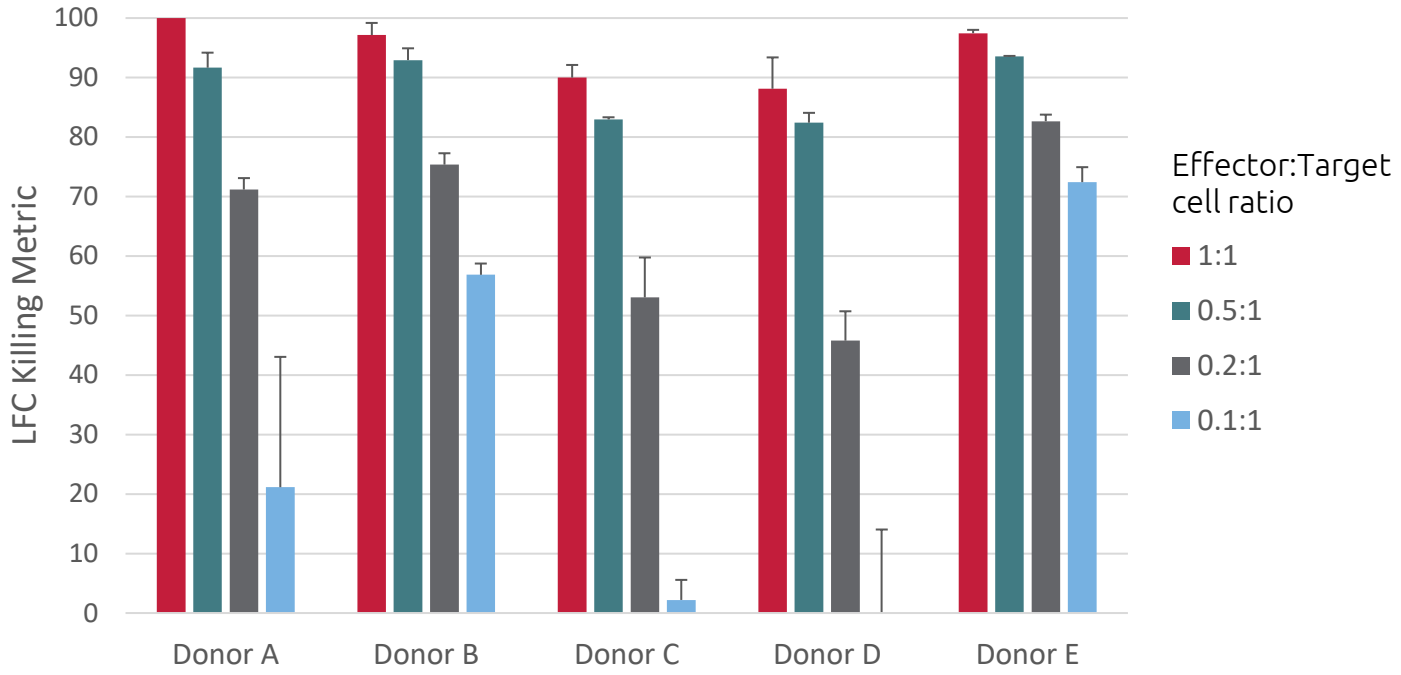
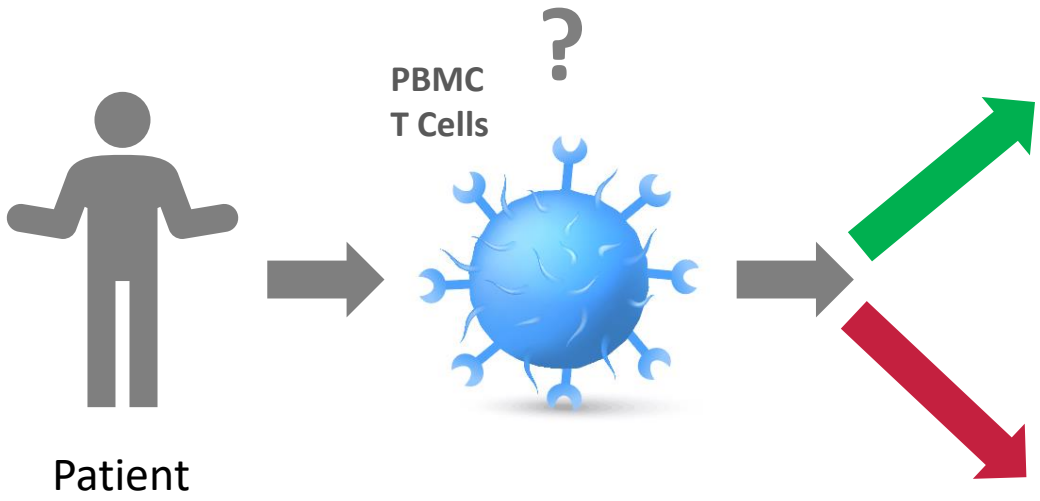
Variation of Cell Killing Across Donors



- Changes in LFC metrics across populations can be used to measure cell killing across donors
- Variation in target cell (NALM6) killing as a function of number of CAR T cells across 5 healthy donors after a 24h co-culture period
- Highest overall killing shown in Donors B and E, especially at the lower ratios

What if you could predict CAR T potency based upon the starting materials?



Successful CAR T production ✓

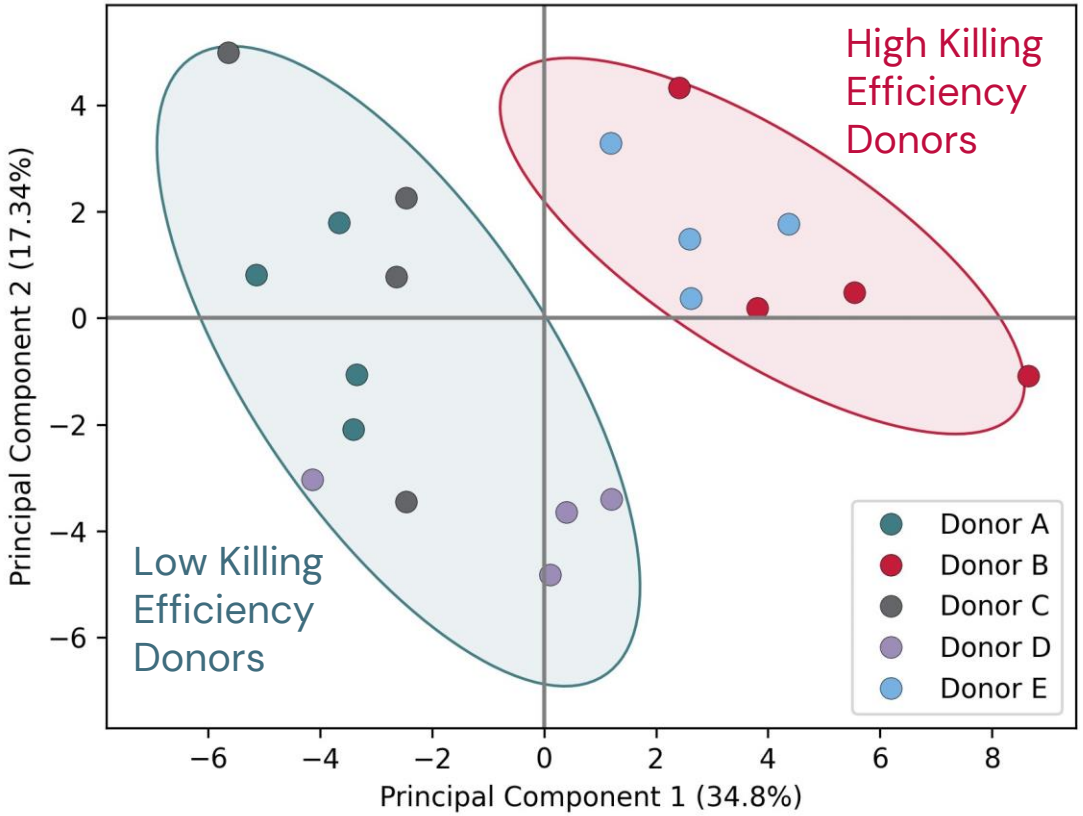
Outcomes-based reimbursement (OBR) for high $ therapies[1]

Unsuccessful CAR T production ✗

- Ineffective treatment
- Wasted effort and $
- Delays
- Negative prognosis

1. Jesper Jørgensen, Eve Hanna, and Panos Kefalas, "Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries", J Mark Access Health Policy. 2020; 8(1): 1715536.

Correlation of CAR T Potency with Cellular Starting Material



Ellipses are 2σ boundaries

	Percent Killing (%)				
Ratio (CAR T:NALM6)	Donor A	Donor B	Donor C	Donor D	Donor E
1:1	97.32	99.68	98.69	93.02	98.56
0.5:1	95.57	99.43	96.83	87.53	97.48
0.2:1	51.59	82.14	41.54	35.23	78.16
0.1:1	0.50	67.62	0.50	5.49	54.14

- PCA model created using Radiance data collected from donor PBMC samples
- Donors B and E are the high killing donors and the others are the lower (see table)
- ✓ Radiance may be used to estimate the killing efficiency of donor T-cells prior to manufacturing of the therapy

What if we could use Prescriptive Analytics for Adaptive Manufacturing?

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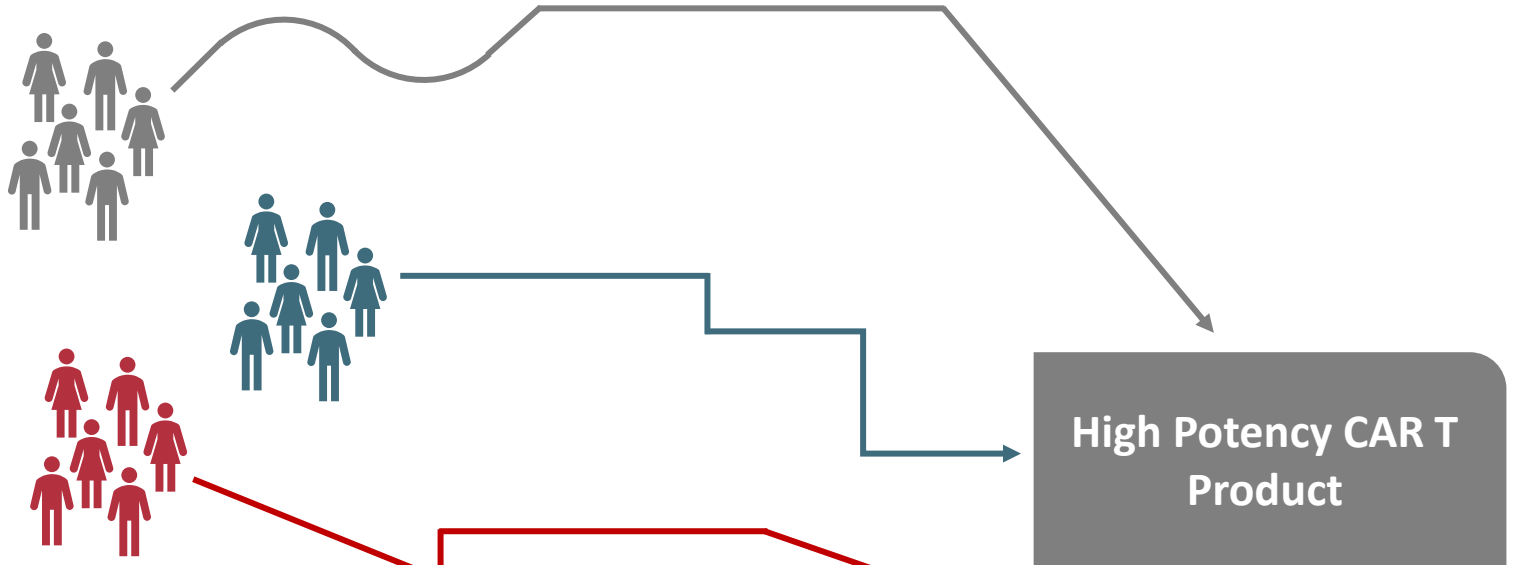
"When feasible, risks to potency caused by material variability should be mitigated by designing a manufacturing process with **adaptive steps** that compensate for variations in the material."

FDA Potency Assurance for Cellular and Gene Therapy Products - Draft Guidance for Industry, December 2023, 338 – 340



Different patient phenotypes May require distinct manufacturing pathways to achieve expansion & high potency result

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RESULTS SUMMARY & CONCLUSIONS

- The development and manufacturing of cell-based products is complex and requires precision analytics to reduce costs and increase access
- Current analytical tools are often slow, laborious, and do not always predict or indicate manufacturing or clinical success, especially when characterizing cellular material
- Laser Force Cytology (LFC) uses a combination of optical and fluidic forces to sensitively and rapidly measure cellular properties and responses in a label-free manner
- LFC can be used throughout the development and manufacturing process, including correlation of cellular starting material quality to predict manufacturing success
- LumaCyte's Radiance® instrument enables rapid assessment of cell health, phenotype, viral infectivity and cytotoxicity to facilitate rapid optimization and adaptive manufacturing

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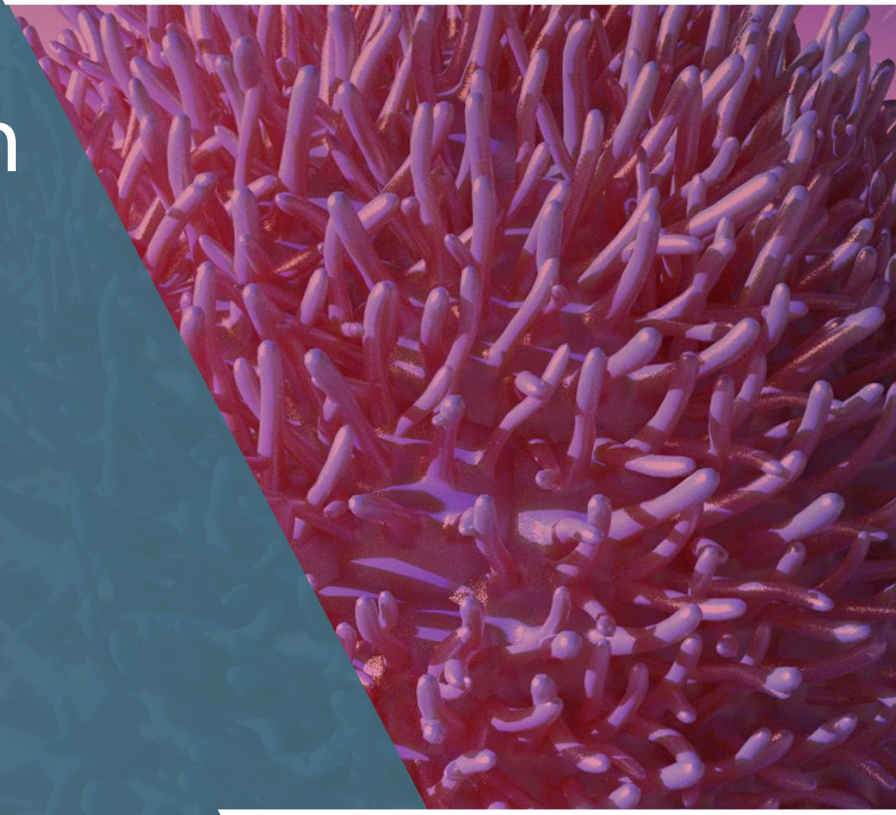
Thank You For Your Time & Attention



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