Improving The Success of Academia to Industry Transfer For Autologous Cell Therapies

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Background

- The number of cell therapy products in development continues to grow
- Many of these innovative products are spawned in academic settings
- Clinical testing and commercialization requires
  - Successful technology transfer from academia to industry
  - Routine and reliable manufacture
- Unfortunately, the challenges of these transfers are often underestimated

Successful Transfer And Production Requires

- Understanding the characteristics of academic to industry transfers
- Understanding of the unique challenges presented by autologous products

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- In a previous presentation we discussed some common transfer pitfalls & how to overcome
- Here we focus on two specific challenges & their consequences
  1. Misalignment of objectives and priorities
  2. High inherent variability

What is Misaligned? What Does it Mean?

Academic lab priority: Innovation, Publication, and sometimes outlicensing

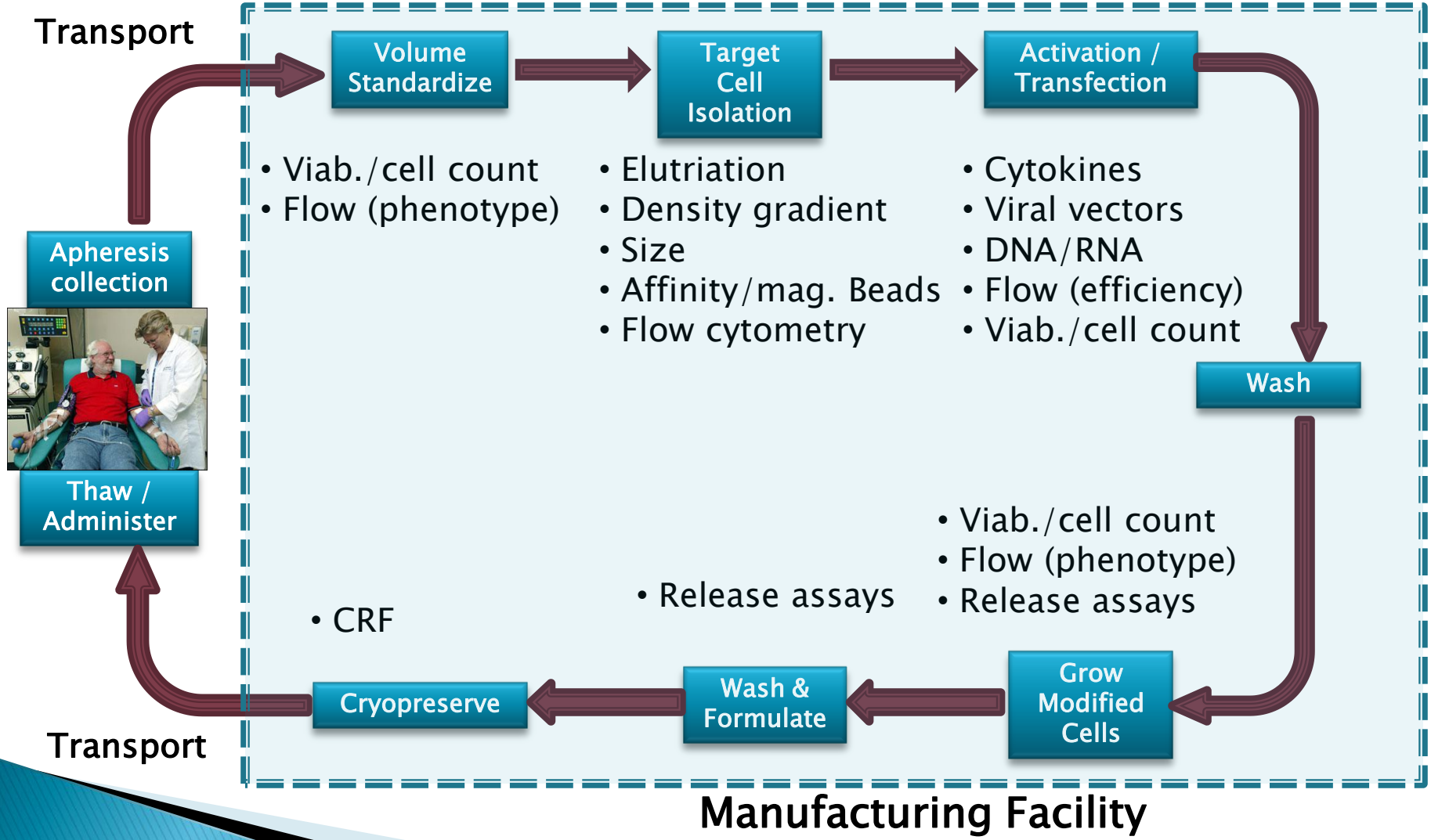
Requirement for successful transfer: Thorough understanding of production process, its limits & how to measure and control – This is not an academic priority!

Consequences:

1. Uncharacterized product/process, requiring changes during transfer, the sensitivity of which are typically not understood
2. Procedures, equipment and methods intended to demonstrate POC, not chosen with view toward commercialization

Implication: Longer timelines, increased costs, lost opportunity

Simplified Autologus Cell Therapy Production Process



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Some Examples of What is Too Often Overlooked Until Later

- Age of apheresis and conditions during transport
- Collection procedure and equipment used
- Suitability of procedures & equipment for GMP
  - What equipment used for processing?
  - Open operations?
- Availability of in-process data & controls
- Potency assay & it's sensitivity & variability
  - MOA based or surrogate measure?
  - If surrogate, how will you know if changes are impacting potency

Impact of Collection Equipment

Collection Equipment	Collected Volume (mL) Mean	SD	Distribution	N
Inst. #1	296	26	Normal	>100
Inst. #2	255	64	Normal	>100
Inst. #3	264	45	Normal	>100

Collection Equipment	Collected TNC ($x10^9$) Mean	Median	Distribution	N
Inst. #1	13.6	12.5	Non-Normal	>100
Inst. #2	11.3	10.9	Non-Normal	>100
Inst. #3	10.1	9.4	Non-Normal	>100

Things to think about:

- Will such differences matter for your product?
- Will there be similar or larger differences in collected cell phenotypes?

Impact of Apheresis Age

Does the age of apheresis have a material impact on your product/process?

- Compared MNC recovery on density gradient separation
- Two types of source for Apheresis
  - Sourced in close proximity to processing lab (Age-few hrs)
  - Sourced far away from processing lab (Age-overnight)

	Younger Aph		Older Aph	
	Mean	Median	Mean	Median
MNC recovery (%)	75	74	66	68

- Do these differences matter for your product?
- Does this suggest there may be other changes which matter?

Understanding The Sources & Implications of High Variability

High degree of variability inherent in Autologous Products

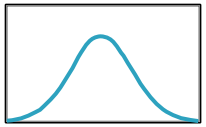
1. Typically manual processing
2. Biological & cell based assay variability
3. Variability of materials – (e.g. patient cells)

What are the implications?

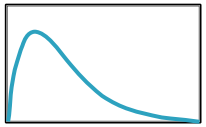
1. For successfully producing comparable product post transfer?
2. For running characterization experiments?

The Challenge of Autologous Cell Therapy Production

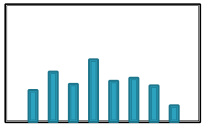
INPUT



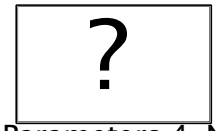
Parameter 1 – e.g.
Apheresis volume



Parameter 2 – e.g.
Cell density



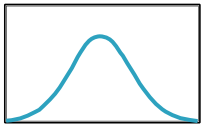
Parameter 3 – e.g.
Raw material properties



Parameters 4–N

Variability Of Input Parameters

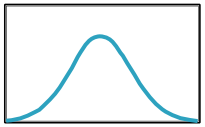
Process



Step 1– e.g.
Volume reduction

Step 2
Step 3

Step N

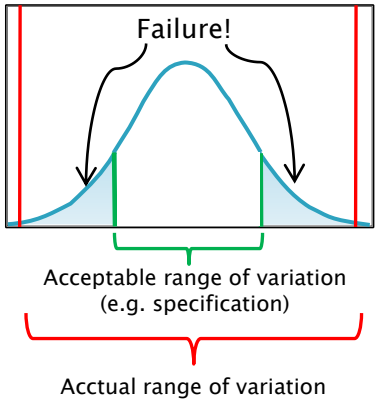


In-Process Methods

Variability Of Process Operations & Methods

Output

Product specifications
(e.g. Potency, strength, etc.)



Variability Of Final Product Properties

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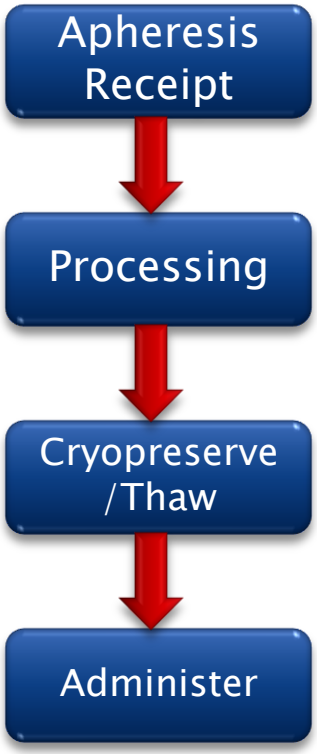
Understanding Impact Of Variability – A Simple Example

To illustrate the impact of variability, we setup a simple 2 step process



Assumptions

V=300 mL
WBC = $30x10^6$ per mL
Viability = 100%

Yield = 50%
Viability = 70%

Recovery= 50%
Viability = 70%

TPP :100 ± 30 $x10^6$ cells

Sanity Check

(do we have enough cells?)

$9 x10^9$ cells

$3.5 x10^9$ cells

$1.1 x10^9$ cells

vs

Administration
>> $130 x10^6$ cells

√

Process Ctl Assumptions

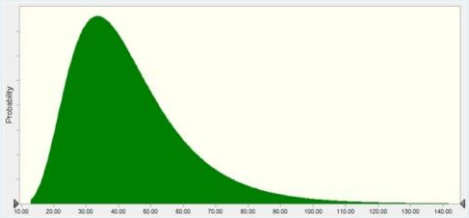
Start process with
$8.16 x10^8$ cells
100 / (0.5x0.7)/(0.5x0.7)

Final Product Post Thaw
$100 x10^6$ cells

√ So What's the Problem?

Understanding Impact Of Variability – Example Continued

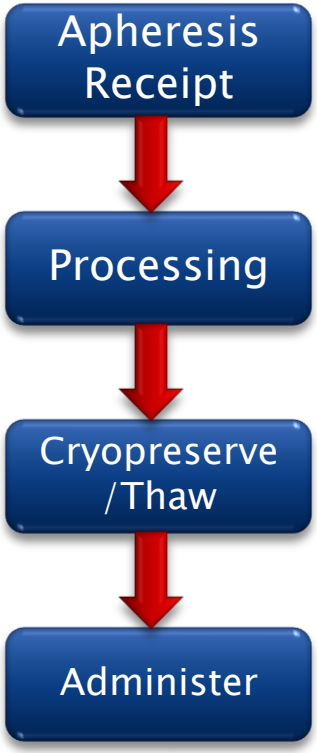
Injecting some reality into our assumptions

Assumption	Mean	SD	Distribution
Apheresis volume	300 mL	10%	Normal
Apheresis WBC	NA	NA	Non-normal 
Process Yield	50%	10%	Normal
Cryo-Recovery	50%	10%	Normal
Viability	70%	10%	Normal
Measurement error (viability & cell count)		5%	

Question – What is the probability of final product failing our specification of 70-130 $x10^6$ cells??

Understanding Impact Of Variability – Monte Carlo Simulations (N=3000)

Process Design

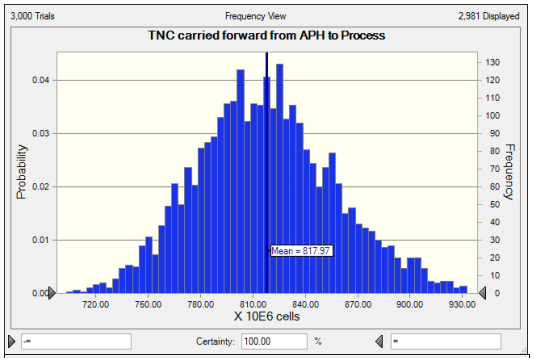


APH Carry Forward to Process target TNC- 816x10^6 Cells

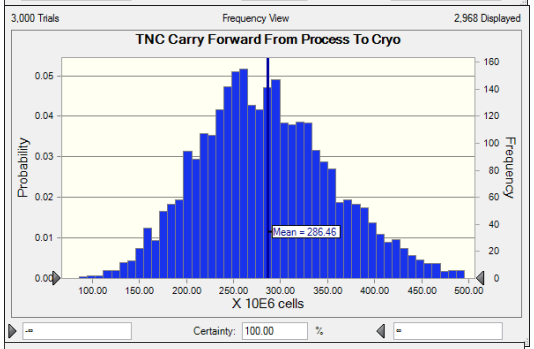
Target TNC to Cryo 290x10^6 Cells

Final Product Target TNC
100±30 x10^6 cells

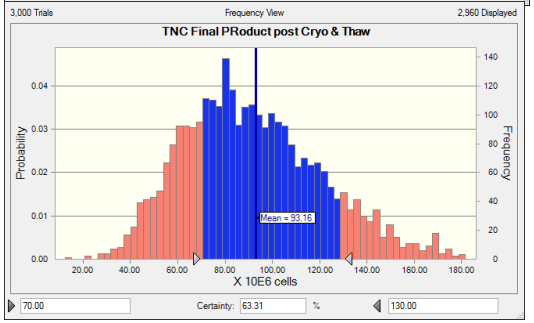
Monte Carlo Prediction



Predicted Mean TNC
Carry forward to process
817x10^6 Cells
Range:700-930x10^6 Cells



Predicted Mean TNC to Cryo
287x10^6 Cells
Range:86-495x10^6 Cells



Predicted Mean FP TNC
93x10^6 Cells
Range:13-182x10^6 Cells

Probability of failure: 37%

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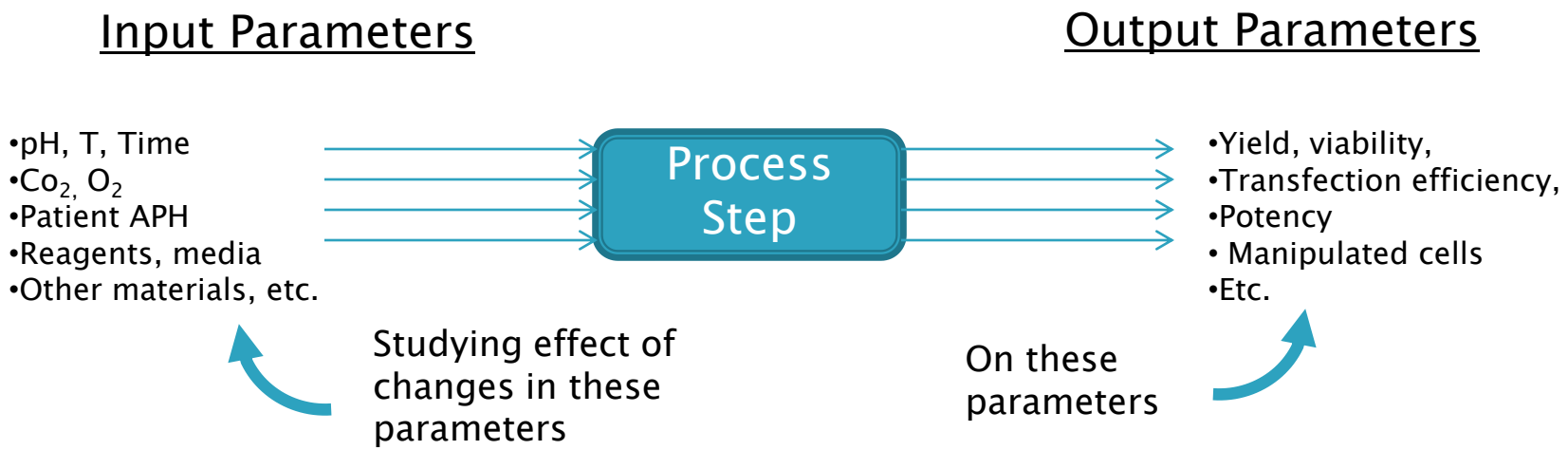
Other Implications Of Variability For Your Characterization Studies

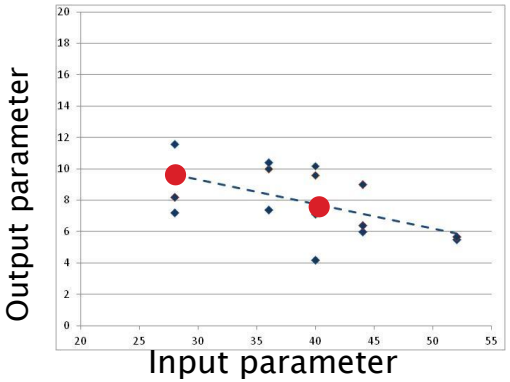
- Successful transfer will require characterization studies
- What are the implications of variability on your studies?



- **Question:** How many replicates do we need in order to know if the measured effect is real? Statistically significant?

What Are the Implications for Your Studies – Continued

Example Study



- At any given condition, the "effect Size" (ε)

$$\varepsilon = \frac{(\mu_1 - \mu_2)}{\sigma}$$

- Where

μ_1 = True mean at condition 1
μ_2 = True mean at condition 2
σ = SD of measurements, assuming equal variances

Estimating for our example

$\mu_1 = 9$
$\mu_2 = 7.8$
$\sigma = 2.2$
$\varepsilon = 0.54$

N ≈ 27–44

Effect Size (ε)	70% power	80% power	90% power
3	2	3	4
2	4	5	5
1	9	10	13
0.5	27	34	44
0.25	100	128	170

N required at any given (ε) and power

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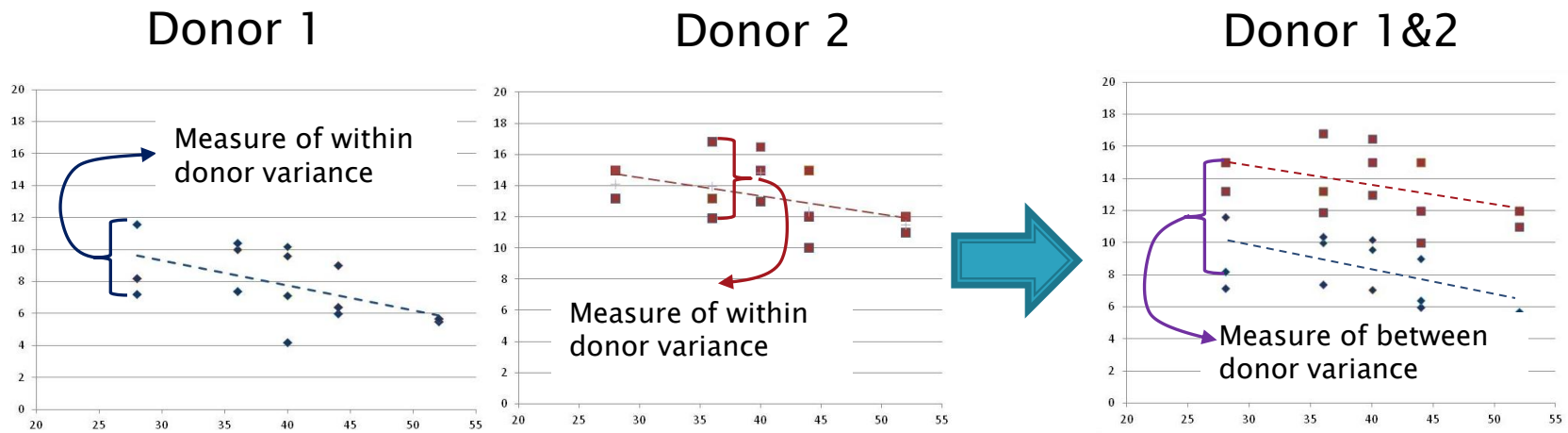
Let Us Now Take Donor to Donor Variability Into Consideration



- Donor to donor variability can be greater than other variables
- Increasing “N” by adding donors typically increases variance at each condition, hence requiring a disproportionately larger “N”
- Can reduce variability by using single donor & splitting cell
  - Finite donor material limits number of splits
  - Necessitates availability of “scale down” models

Take Home Messages – How To Improve Your Success Rate?

- Characterization likely required- Plan for it
- Take time to understand limitations of process & methods -> gives leads to duration of transfer
- Good potency assay very important very early on
- Need for appropriate in-process controls
- Need to know variability of your methods
- Statistical design of experiments is a must
- Make use of tools such as Monte Carlo simulations to improve your design & success rate

Thank you for you time

Contact us if you have questions we did not cover here
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