Stability Considerations and Challenges in Autologous Cell Therapy

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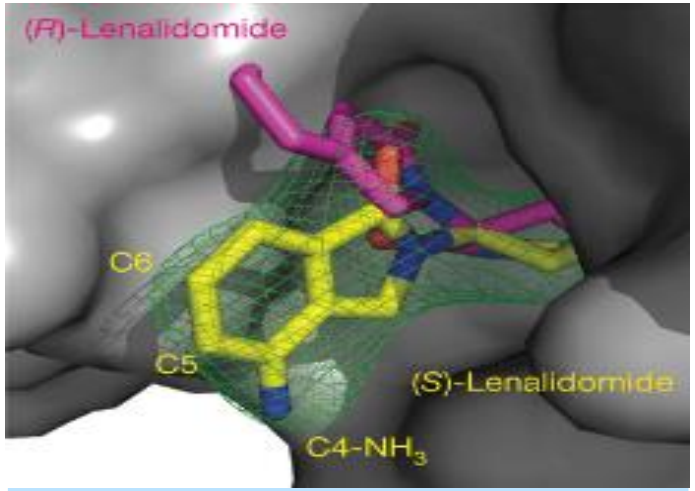
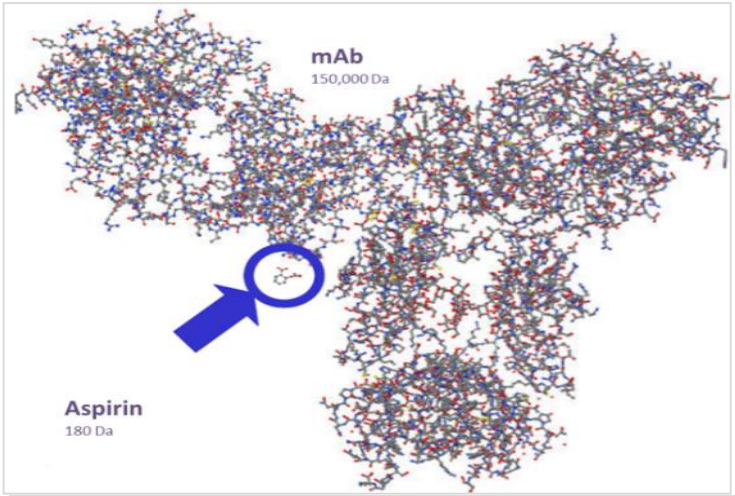
CAR T-cell Therapy Represents a Change in Paradigm

Pillar I: Small Molecule Drugs



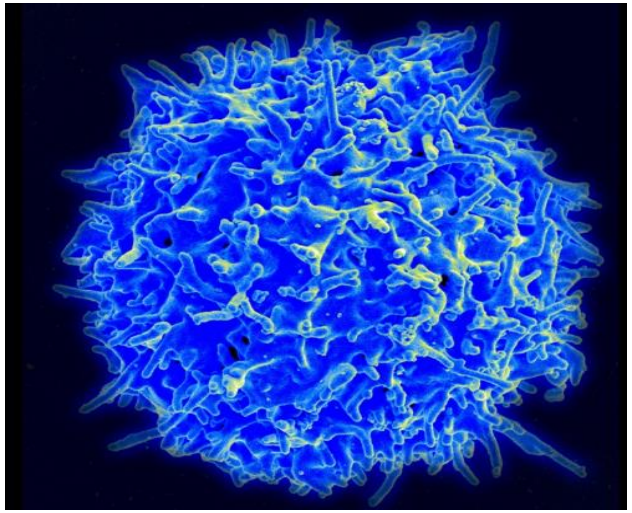
- Simple, single defined structure
- Predictable chemical synthesis
- Stable, easy to characterize
- Focused on specific targets

Pillar II: Biologics



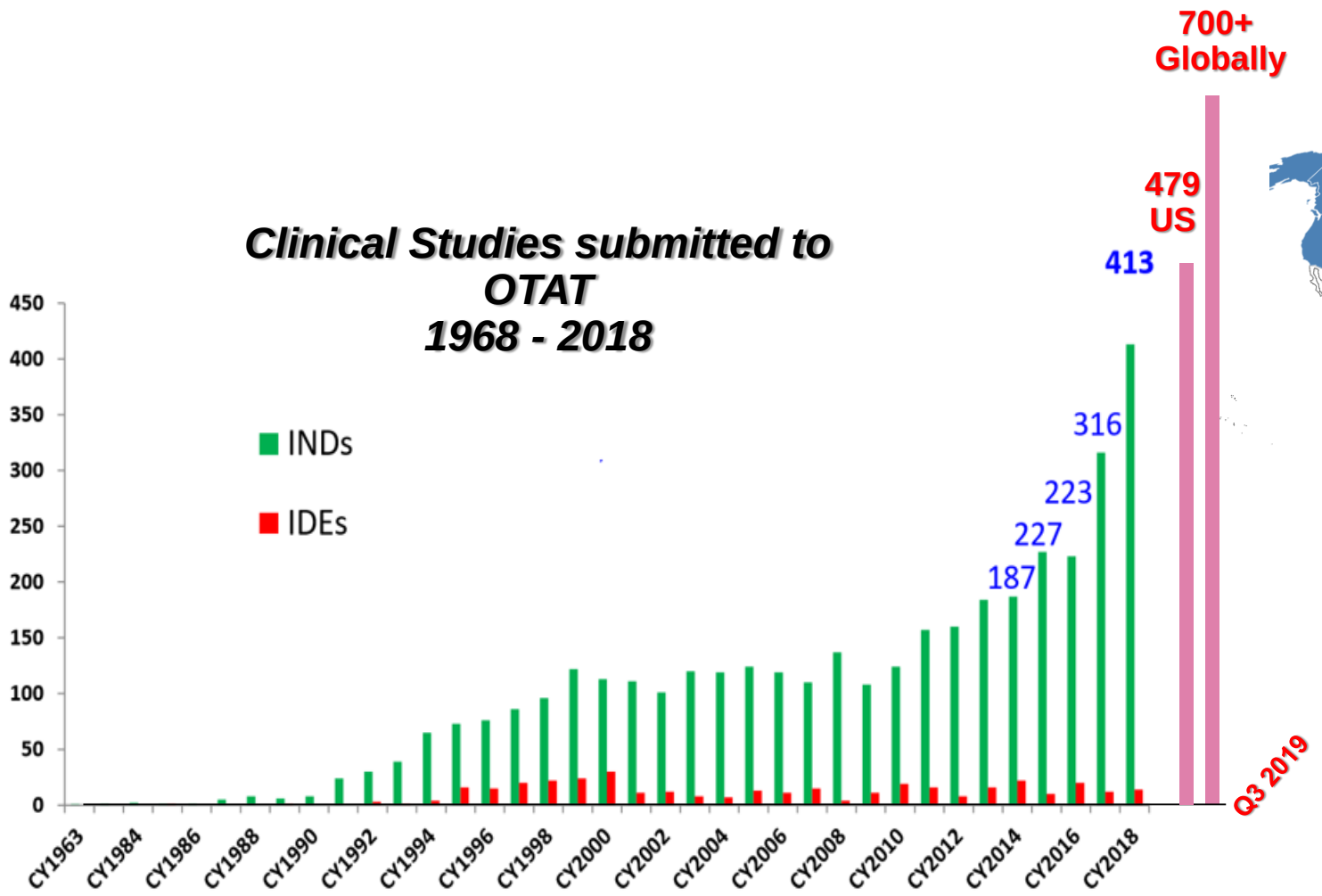
- Biomanufacturing of large, complex molecules
- Mature characterization and industry understanding
- Produced using recombinant DNA technology

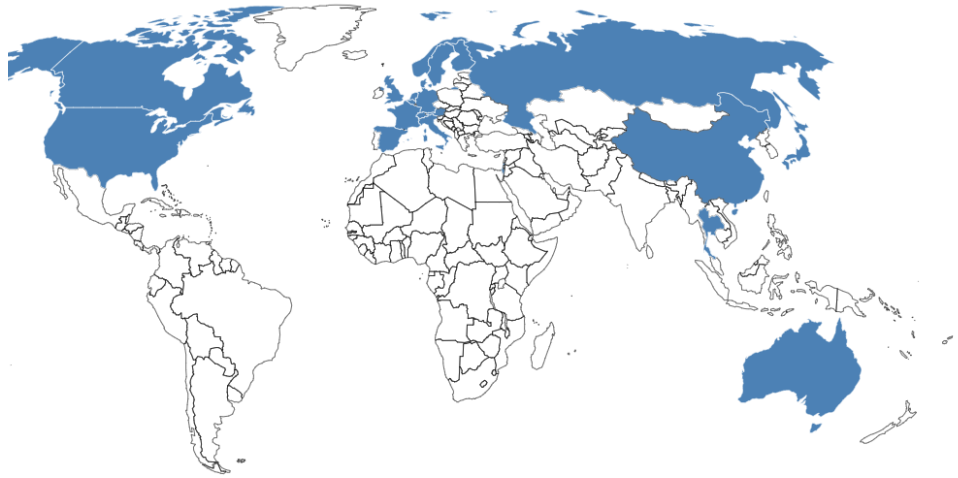
Pillar III: Cell & Gene Therapy



- Complex structure
- Potentially curative and regenerative therapy
- Personalized Medicine
- Gene editing, cellular & molecular biology

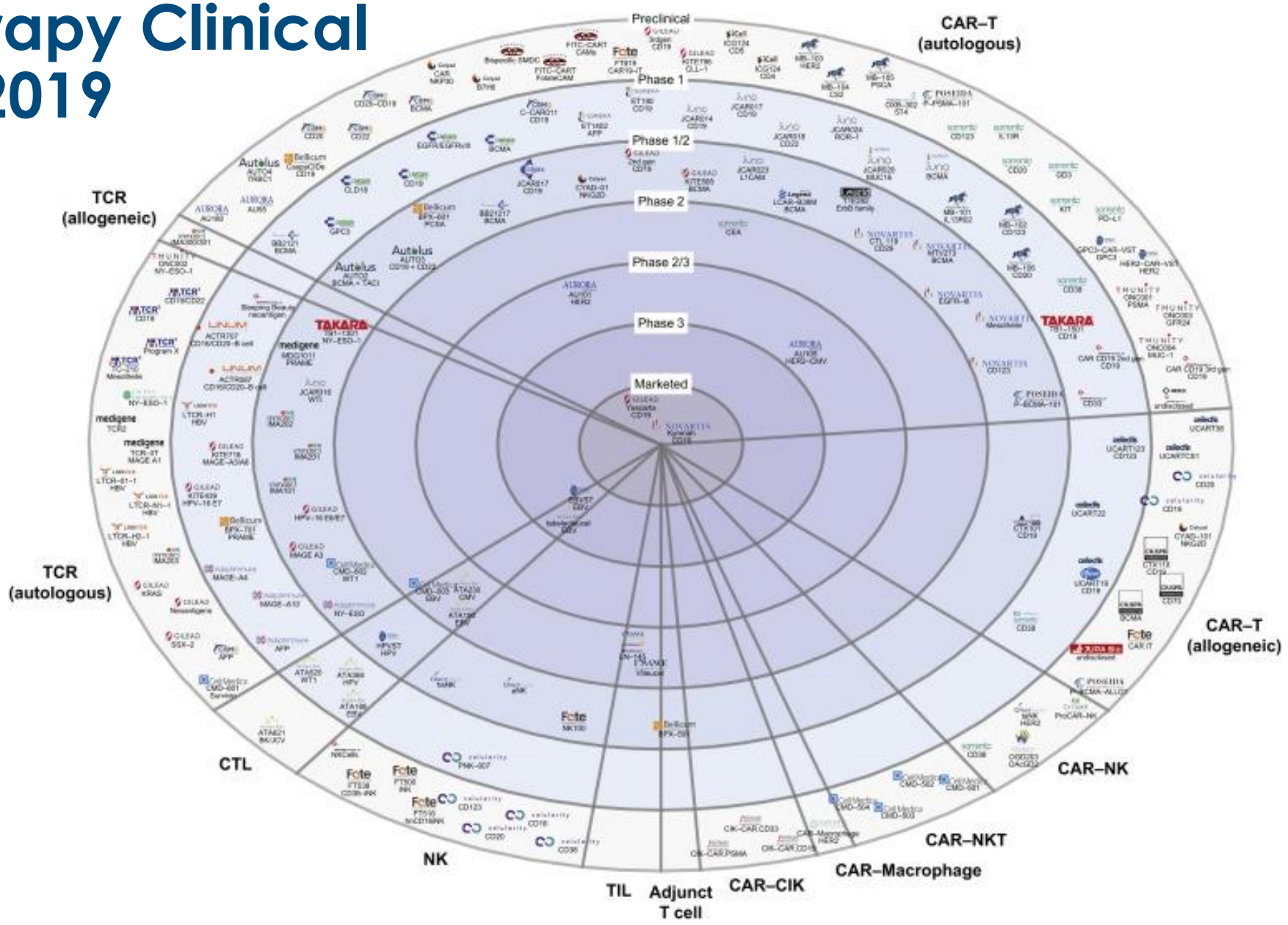
Increasing Number of CAR T-cell Trials





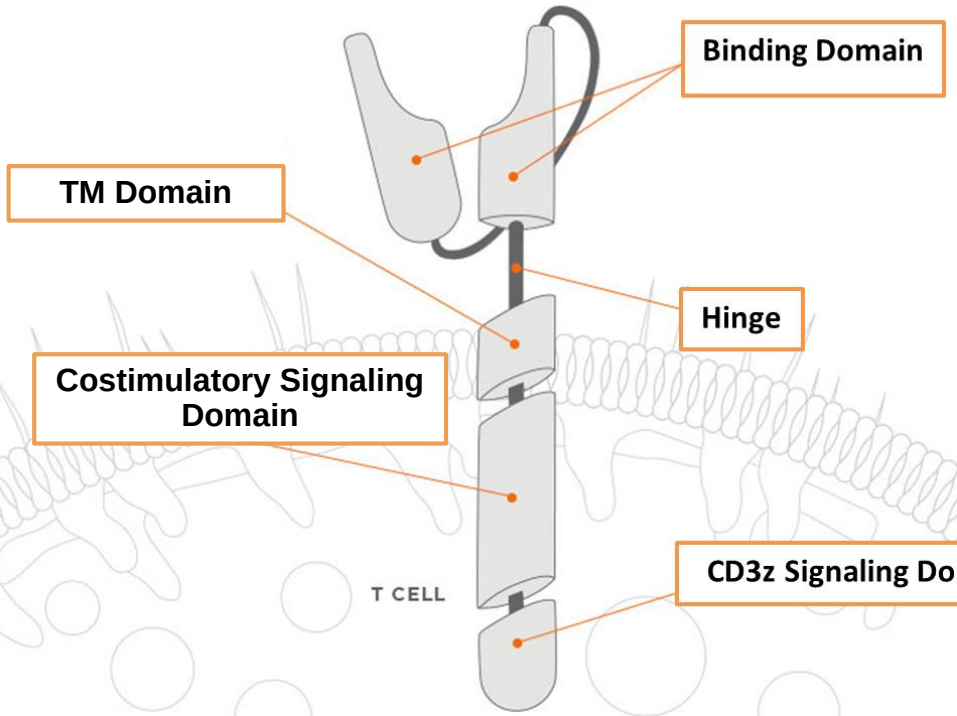
[CASSS Cell & Gene Therapy, Steven Oh, June 10, 2019](www.clinicaltrials.org)

Cell Therapy Clinical Studies 2019



Journal of Pharmaceutical Sciences, 108 (2019) 2207-2237

Chimeric Antigen Receptor (CAR) Modified T Cell Therapy



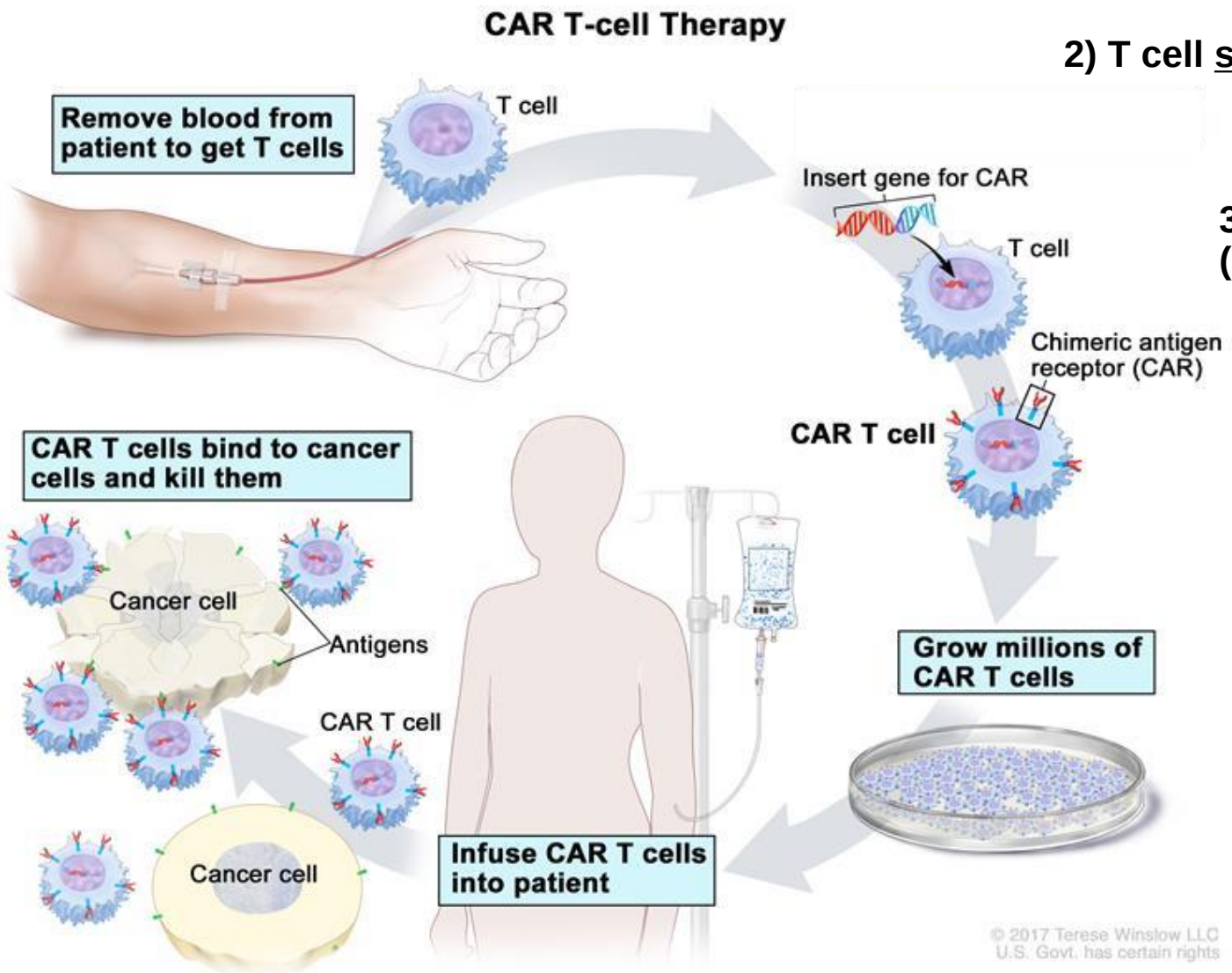
Anatomy of a CAR (example):

- Binding Domain (specificity)
- Hinge Domain
- Transmembrane Domain
- Cell Signaling Domain (costimulation and activation)

<u>Potential Signaling Domains</u>
CD3ζ, CD27, CD28, ICOS,
4-1BB, OX40

General Autologous CAR T- Cell Manufacturing Process

1) Patient's T cells are collected via leukapheresis (starting material)



2) T cell selection / purification

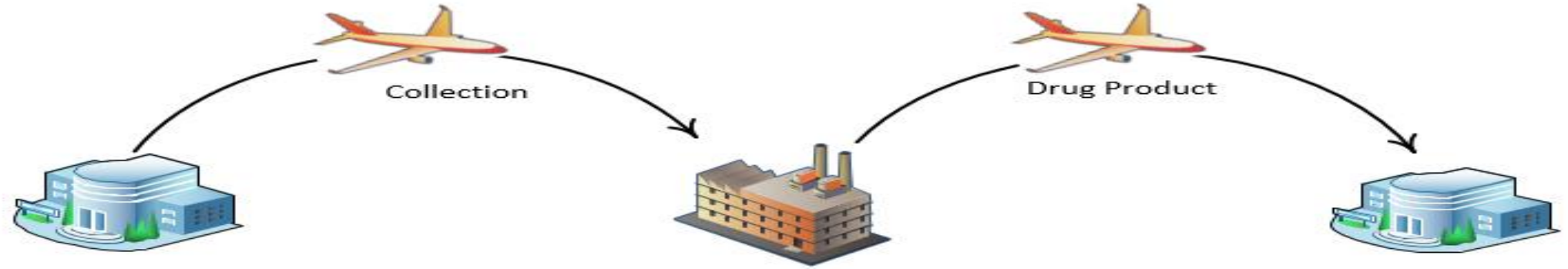
3) T cell specific activation (induce T-cells to proliferate)

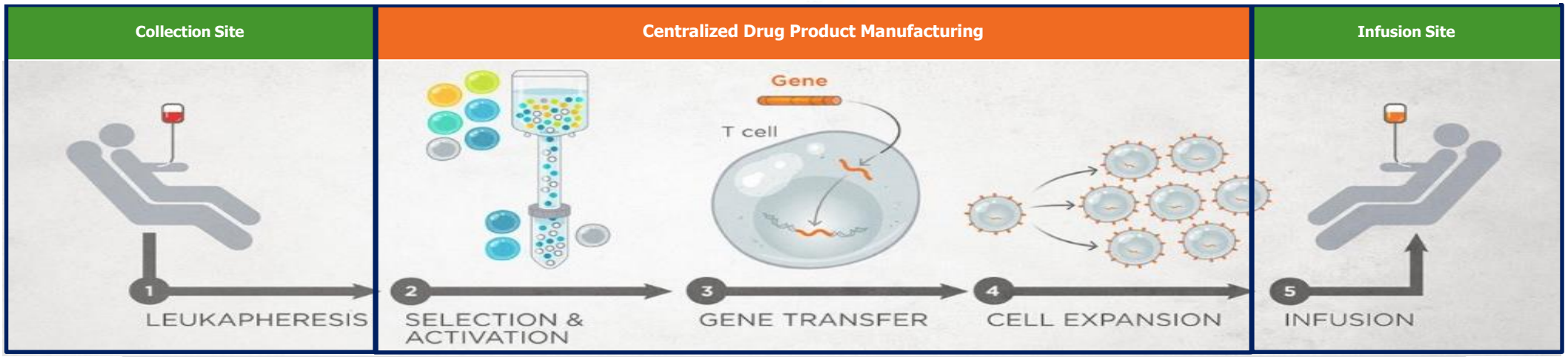
4) Transfer gene to T cells via transduction to provide specificity of T cell to target antigen

5) Controlled and consistent expansion to produce consistent T cell phenotype (dose)

6) Infusion back to patient following lymphodepletion

Complexities of the CMC Manufacturing and Supply Chain





Apheresis & Shipping → Selection Operation → Cryo-preservation (if required) → Manufacturing (transduction, expansion) → QC Testing → Drug Product Release → Shipping & DP Infusion

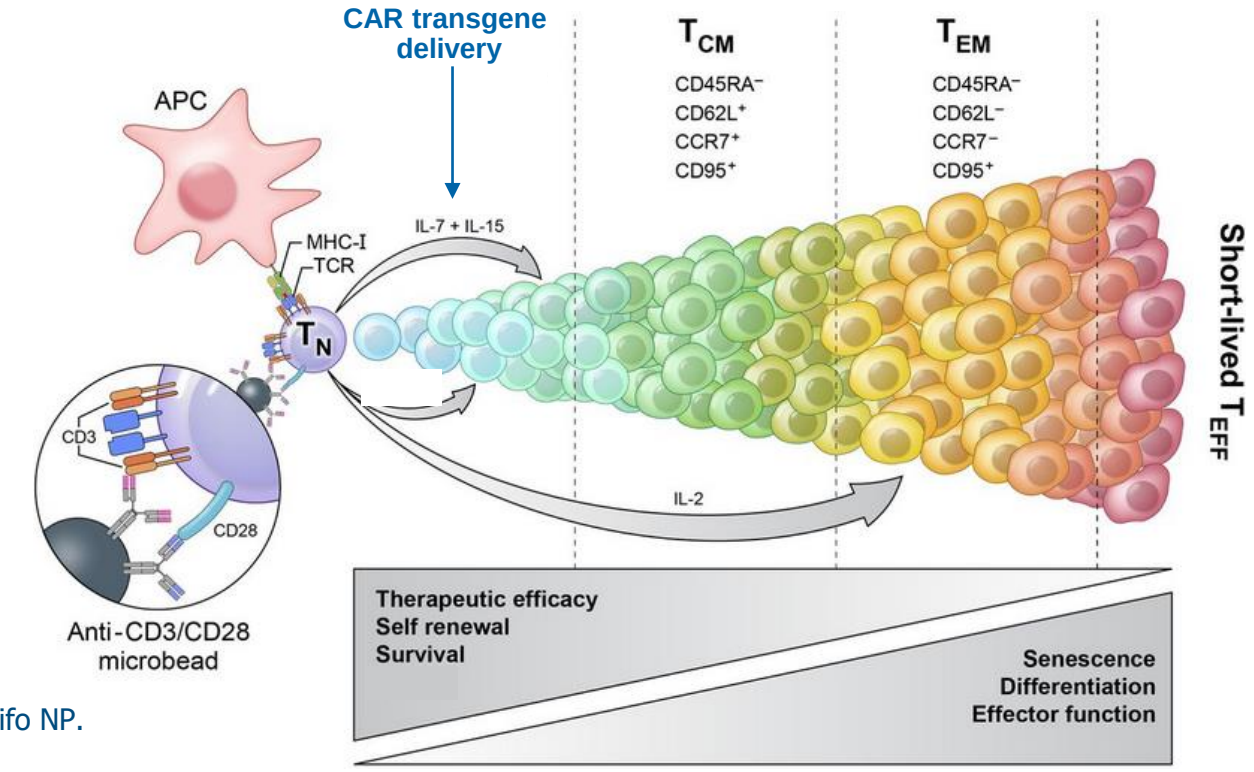
Minimize Vein – to – Vein time…

Development Considerations influencing Stability Strategy

Development Consideration	Well Characterized Biologics	Autologous Cell Therapy Programs
Product understanding	• CQAs well defined • Product and process understanding can be well characterized	• Preliminary CQAs established, correlation to clinical outcome in early stages of understanding (process, analytics) • Patient heterogeneity is complex, influences T-cell biology (T_N, T_{CM}, T_{EM}) and process understanding

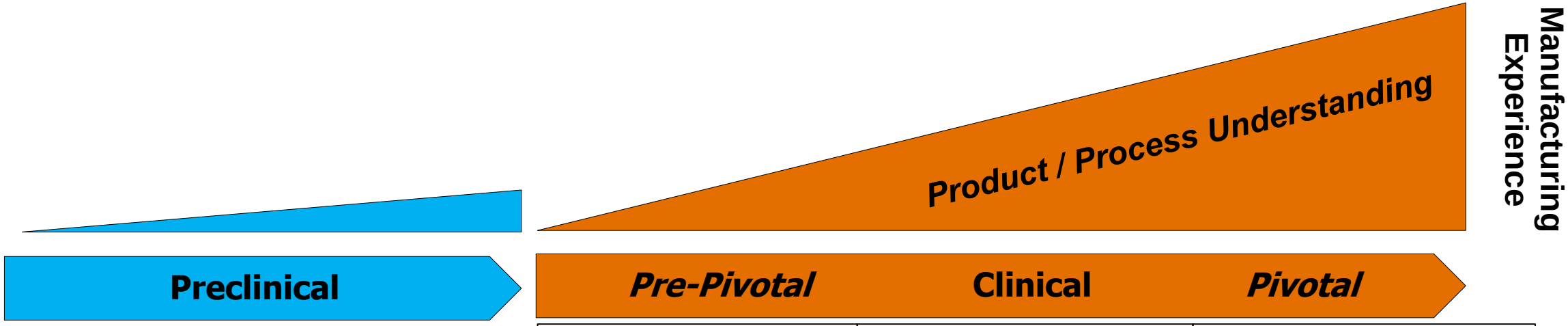
Clinical and pre-clinical evidence supports a role for early memory T cells in CAR T cell mediated efficacy

Cohen et al, ASH 2018 (Multiple Myeloma)
Fraietta et al, Nature Medicine 2018 (CLL)
Larson et al, AACR 2018 (NHL)
Ghassemi et al, Cancer Immunology Research 2018 (preclinical mouse model)
Sabatino et al, Blood 2016 (preclinical mouse model)



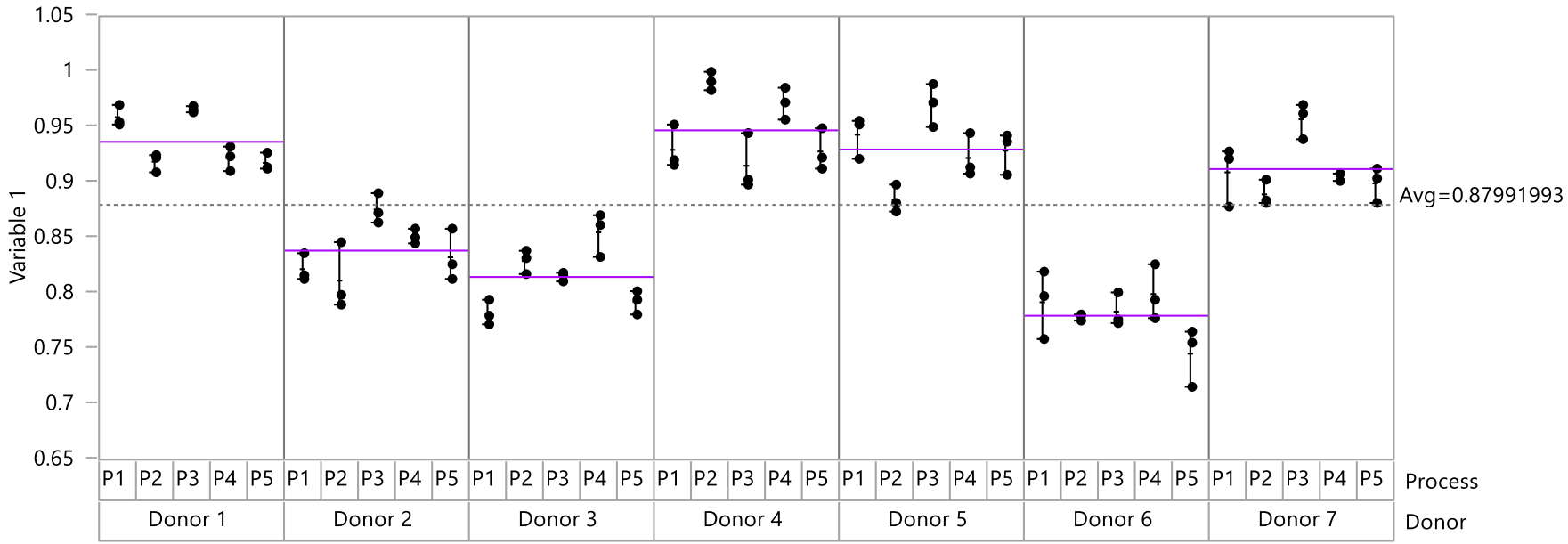
Adapted from Gattinoni L, Restifo NP. Blood. 2013;121(4):567-568.

CQAs evolve throughout Development – Tied to Clinical Outcomes



Correlative Analysis: Statistically correlate CQAs directly to clinical outcomes (safety / efficacy) → Establish commercial control strategy

Patient / Donor Dominated Variance in Cell Therapies impacts Stability Strategy



Donor variability

Process variability

Analytical variability

Total variability

Variance Components

Component	Var Component	% of Total	20 40 60 80	Sqrt(Var Comp)
Donor	0.00439270	82.4		0.06628
Process[Donor]	0.00065038	12.2		0.02550
Within	0.00029072	5.5		0.01705
Total	0.00533380	100.0		0.07303

Donor variance makes up 82.4% of the total variance

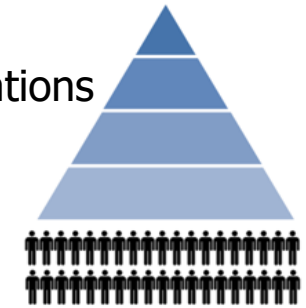
Variability as a standard deviation for each of the variance components

$$\sigma^2_{Total} = \sigma^2_{Donor} + \sigma^2_{Process} + \sigma^2_{Analytical} = 0.00439 + 0.00650 + 0.000291 = 0.00533$$

R. Ashton, Juno Therapeutics – CASSS Cell and Gene Therapy Products, June 10, 2019

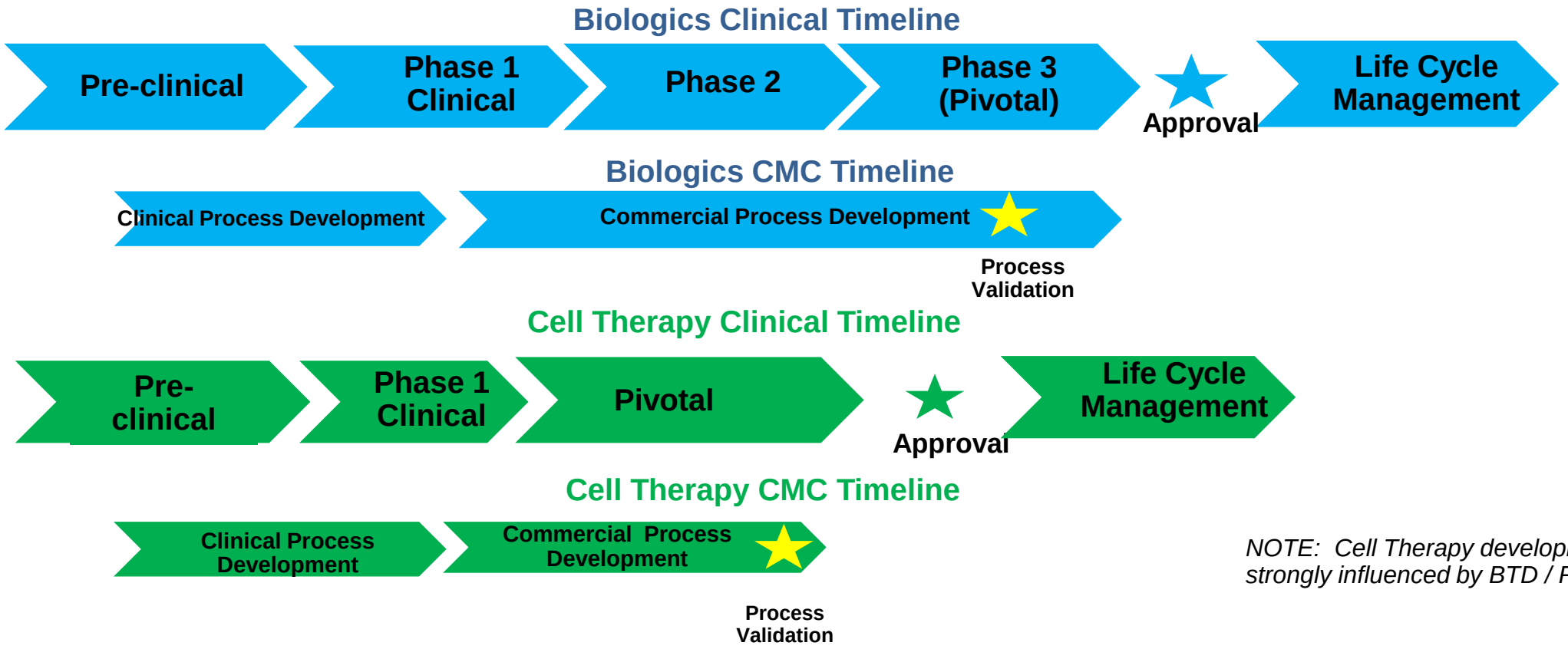
Development Considerations influencing Stability Strategy

Development Consideration	Well Characterized Biologics	Autologous Cell Therapy Programs

Manufacturing Process	• Platform unit operations
	• Scale-up
	• Large batch size
	 
		• Technology continuing to evolve
		• Scale-out (1 patient = 1 batch)
		• Small batch size
		• Need robust process in early development
		  • Minimize changes (if possible)
		• Develop robust analytical assays
		  • Suitable bioassay earlier in development
		 

Starting Materials	• Well characterized and consistent (WCB)	• Limited quantity of starting materials (apheresis material), each batch is unique (patient / disease state) • Vector material (critical component of DP)
Clinical Manufacturing Experience	• Low "n" • Challenge to link to direct clinical outcomes	• High "n" • Directly correlate with clinical outcomes (safety / efficacy)
Development life-cycle	• Longer development • Limited batches	• Shorter development • Extensive manufacturing experience

Product Development Timeline Considerations



NOTE: Cell Therapy development timeline strongly influenced by BTD / RMAT designations.

Cell Therapy Development can be significantly shorter than typical Biologics Development therefore…

Stability Studies for Critical Materials in Phase 1 may support Pivotal /Commercial Studies

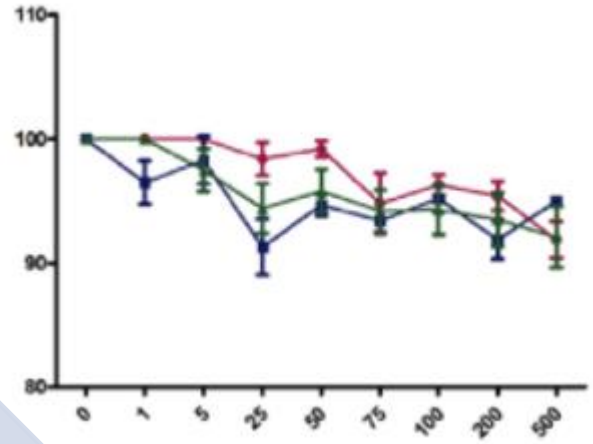
STABILITY CHALLENGES FOR AUTOLOGOUS CELL THERAPIES

Vector

- Manufacturing & Supply constraints
- Phase 1 → Pivotal changes
- "Critical Component" of DP
- Limited Stability (timepoints/duration)
- Stability indicating methods (viral vector)
- Stressed conditions

Drug Product

- 1 batch/patient, cryopreserved DP
- Limited volume / sample availability
- Patient vs. Healthy Donor correlation
- Full stability (bracketing / matrix)
- Stability indicating methods
- Stressed conditions



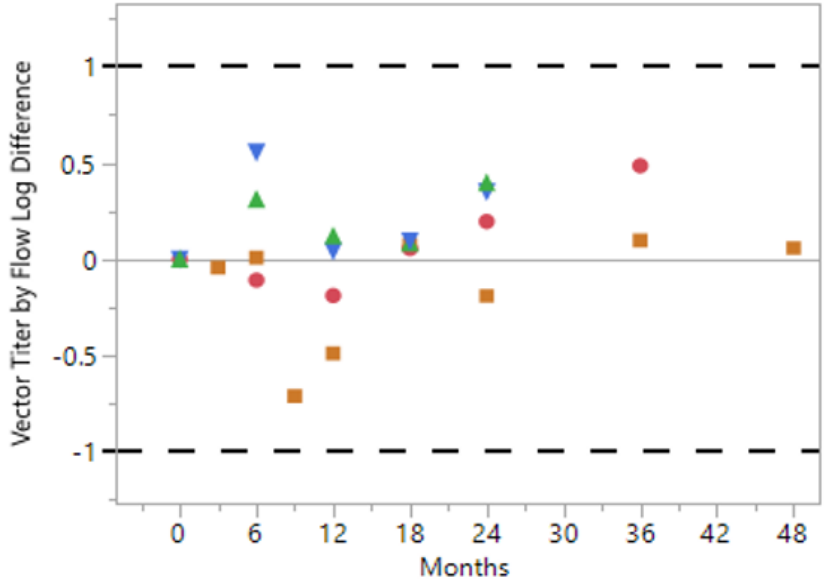
VECTOR

- Subset of release specifications
  - Limits are the same as the release specification
  - Testing Frequency: Long term study frequency according to ICH Q1A recommendation

Example

Attribute	Time Points (Months)							
	0	3	6	9	12	18	24	36
Appearance	X	X	X	X	X	X	X	X
pH	X	X	X	X	X	X	X	X
Vector Titer	X	X	X	X	X	X	X	X
Potency (direct or indirect)	X	X	X	X	X	X	X	X
Sterility / CCI	X				X		X	X

- Storage condition: -70°C, Accelerated conditions: -20°C, 5°C
- Data trending (raw data vs. log transformed)
- Stability Commitment
  - Vector is critical component (not active DS)
  - May not warrant annual stability commitment
  - Assess stability impact during process / site changes (comparability)

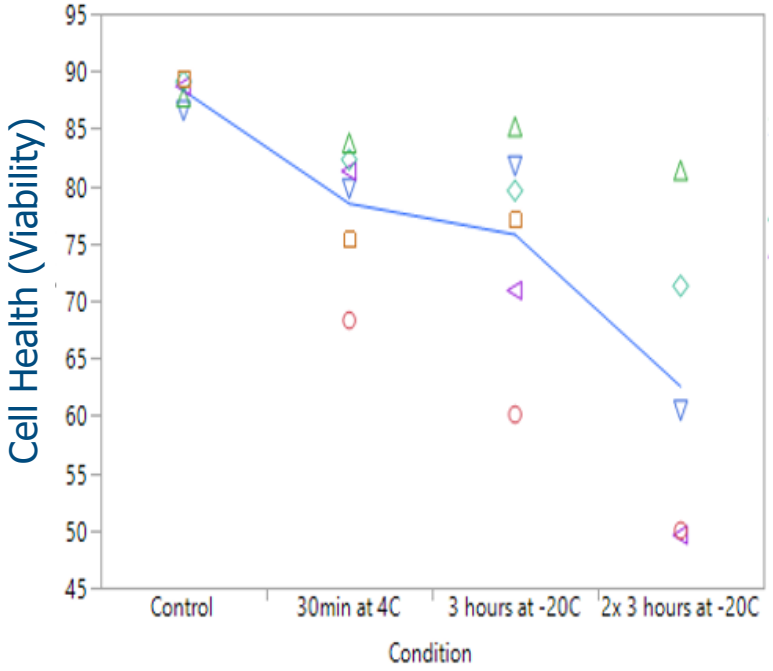


AUTOLOGOUS CAR-T CELL THERAPY DRUG PRODUCT

- Subset of release specifications
  - Limits are typically the same as the release specification

- Full stability studies (limited sample volume)
  - Bracketing Approach: multiple primary containers and/or fill volumes
  - Matrix Approach: multiple lots to capture cumulative stability time-points
  - Testing Frequency: Long term study frequency according to ICH Q1A recommendation
  - Leverage healthy donor material as a surrogate (Patient material is confirmatory)

Stability Methods	Safety (sterility) Cell Health (viability) Strength (cell count) CAR Frequency (%CAR+) Potency



- Storage condition: LN2 (≤-130°C), Stressed Conditions (F/T)

- Stability Commitment
  - No annual commitment as a potential option
  - DP demonstrated to be successfully cryopreserved at DP release
  - Assess stability impact during process / site changes (comparability)

BRACKETING AND MATRIXING

- Bracketing
  - Only samples on the extremes of certain design factors are tested at all time points
  - May be full design or reduced design (below) or sub-set based on surface area:volume ratio
  - Assumes stability of intermediate levels is represented by the stability of the extremes

Strength	Dose 1			Dose 2			Dose 3		
Batch	1	2	3	1	2	3	1	2	3
Container Size (50 mL)	Test	Test	Test				Test	Test	Test
Container Size (250 mL)									
Container Size (500 mL)	Test	Test	Test				Test	Test	Test

BRACKETING AND MATRIXING

- Matrixing
  - Stability study design where a subset of batches are tested at a specified time point. Another subset of batches are tested at other time-points.
  - Cumulative design covers all possible combinations across multiple stability batches.
  - Assumption: stability of each subset of samples tested represents the stability of all samples at a given time point.

Example

Batch Number	Time Points Analyzed for Each Batch												
	0	1M	2M	3M	4M	5M	6M	9M	12M	13M	18M	24M	36M
XXX001	X					X		X		X			
XXX002	X			X			X			X	X		
XXX003	X			X			X	X					
XXX004	X			X			X			X			
XXX005	X			X			X			X			
XXX006	X								X		X		
XXX007	X								X		X		
XXX008	X								X		X		
XXX009	X						X		X		X		
XXX010	X			X			X		X		X	X	X
XXX011	X			X			X		X		X	X	X
XXX012	X			X			X		X		X	X	X

CONCLUSIONS

Stability considerations for autologous cell therapy products are complex

- Rapid development timelines may reduce "phase appropriate" stability strategies
- Stability methods detecting CQAs can be directly correlated to clinical safety and efficacy
- Limited batch size may require utilizing matrix stability strategy
- Increased patient heterogeneity has the potential to drive more stability studies
- Leverage Healthy Donor DP stability vs. Patient DP stability
- Stressed conditions differ from conventional biologics

Scientific knowledge should be leveraged to justify adapted or custom stability strategies that may be required to support autologous CAR T-cell therapies

- Thank you